Optimisation of CML therapy

MD (Res) Thesis

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I dedicate the work to my grandfather, my mom and dad whose
dream was to see me achieve big in life and my wife because of
whom this has become possible
Acknowledgement

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would like to profusely thank my parents whose dedication to help me achieve my dreams
over the years can never be overstated.

DECLARATION OF ORIGINALITY

I, Pratap Neelakantan, declare that the work presented in this thesis is my own and
that it has not been submitted elsewhere. I have referenced all other material, and
clearly indicated the work of others whenever possible.

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CONTRIBUTIONS FROM OTHERS

The first part of the work included in this thesis was carried out at department of
haematology, hammersmith hospital, imperial college london during the period from
August 2011 until Sep 2013 under the supervision of Dr. David Marin and Professor
Katayoun Rezvani. Patients were followed up by the consultants and physicians at
the hammersmith hospital. Data collection was done by me and others that
contributed as the database is almost 13 years old. The pcr data was provided by the
mrd research unit at the hammersmith hospital headed by Prof Letizia Foroni. The
second part of the work included a questionnaire study done across 5 other hospitals.
The data was collected by the consultants and research nurses at the respective
sites.
Abstract:

TKI inhibitors have revolutionised CML therapy and the goals for management have shifted from finding newer therapies to optimising existing treatment approaches. We have tried to optimise CML therapy by identifying poor responders early by molecular monitoring, improve adherence by using self reported adherence and optimise intolerance by actively changing TKIs to overcome side effects. BCR-ABL PCR of <10% at 3 months and <1% at 6 months have become an accepted standard after the publication by Marin et al. We tried to combine the two measurements and showed that 3 month milestone predicts poor responders and is sufficient to consider changing therapy and that an additional measurement at 6 months does not add any further value. Most existing methods of determining adherence to medications are financially impossible to replicate on a day to day basis or too labour intensive. We tried to measure adherence by 4 different questionnaire based methods (visual adherence scale, Lu’s scale, Haynes method and DAMS scale) and correlate it with clinical responses. We have showed that adherence by all methods correlated with clinical responses and Haynes method which quantifies adherence based on number of doses of medications missed over the last 7 days was the best indicator of adherence amongst all. We further looked at the interactions of daily routine, communication with the physician; access to internet and patients views on taking the medications with adherence to therapy and adherence was shown to be influenced by all of them. Majority of the patients on TKI therapy appeared to be anxious and nearly half of them depressed. Patients with a better QOL had improved adherences. We propose a model based on 4 questions with the most significance on multivariate analysis to be possibly used as a surrogate for adherence methods. It has been shown that intolerance affects adherence and hence outcomes. We have tried to improve intolerance by switching TKI therapy in patients who had attained CCyR and with chronic low grade side effects and showed that the side effects improved and all patients had further improvement in the molecular milestones with deepening responses.
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List of abbreviations

2G-TKI  Second generation tyrosine kinase inhibitor
ABCB1  ATP-binding cassette, sub-family B (MDR/TAP), member 1
ABL1   Human homologue of the Abelson leukaemia virus oncogene
AE     Adverse events
ALL    Acute lymphoblastic leukaemia
AML    Acute myeloid leukaemia
AP     Accelerated phase
Ara-C  Cytarabine
aRR    Adjusted relative risk
ATP    Adenosine triphosphate
BC     Blast crisis
BCR    Breakpoint cluster region
BP     Blastic phase
CA     Chromosomal abnormalities
CBA    Chromosome banding analysis
CCyR   Complete cytogenetic response
CE     Clonal evolution / additional cytogenetic abnormalities
CHR    Complete haematological response
CI     Cumulative incidence
CML    Chronic myeloid leukaemia
CMR    Complete molecular response
CMV    Cytomegalovirus
CNS    Central nervous system
CP     Chronic phase
CYP3A4 Cytochrome P450 family
DLI    Donor lymphocyte infusion
DNA    Deoxyribonucleic acid
EBMT   European group for blood and marrow transplantation
EFS    Event free survival
ELN    European Leukaemia-Net
EUTOS  European Treatment and Outcome Study
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>EVI-1</td>
<td>Ecotropic virus integration site-1 protein homolog</td>
</tr>
<tr>
<td>FBC</td>
<td>Full blood count</td>
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<tr>
<td>FDA</td>
<td>Food and drug administration</td>
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<tr>
<td>FISH</td>
<td>Fluorescence in situ hybridisation</td>
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<tr>
<td>GIST</td>
<td>Gastrointestinal stromal tumour</td>
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<tr>
<td>GVHD</td>
<td>Graft versus host disease</td>
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<tr>
<td>GVL</td>
<td>Graft versus leukaemia</td>
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<tr>
<td>VAS</td>
<td>Visual adherence scale</td>
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<td>DAMS</td>
<td>Diagnostic adherence to medicines scale</td>
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Chapter I. Introduction

Chronic myeloid leukaemia is a clonal myeloproliferative disorder characterised by a balanced translocation of chromosomes 9 and 22, resulting in a Philadelphia chromosome\(^1\). The research that led to treatments for CML has over the years resulted in a much deeper understanding of the biology behind it and has formed the basis and blueprint for targeted therapies in oncology. Today, with improved cure rates, CML is considered more of a chronic condition with the aims directed more towards optimising therapy to improve outcomes even further.

I.1 Aetiology & Incidence

The aetiology behind chronic myeloid leukaemia is unknown\(^2,3\). But there have been many postulations like effects of radiation, especially when increasing numbers of CML cases were seen in Japan after the Hiroshima bombing in 1945. The other evidence towards ionising radiation as a causative is from increased incidence in people with ankylosing spondylitis and others who have received radiotherapy and radiologists from their occupational exposure\(^2\).

The incidence of CML worldwide has been quoted at 0.6 to 2 per 100,000 population\(^4\). The numbers seem to be slightly higher in the western world. Caucasians and afro-Caribbeans appear to be more prone to the disease as compared to other ethnic races\(^5\). The incidence increases with age and appears to be skewed towards men than women with a ratio between 1.3 & 1.8. The prevalence of the disease is increasing worldwide due to the tremendous success and increasing life span of CML patients. In the USA, 4870 new cases are estimated to be diagnosed annually and around 700 new cases in the UK\(^6\). Overall, CML accounts for 7 - 20 % of all leukaemias.
I.2 History of CML:

Chronic myeloid leukaemia (CML) was the first leukaemia to be described\textsuperscript{7}. Dr. Alfred Donne, a French physicist first possibly described a condition similar to CML way back in 1842\textsuperscript{2}.\textsuperscript{8}. It was not until 3 years later that a physician from Scotland, Dr. David Craigie described a patient with fever, leucocytosis and Splenomegaly and later after 3 more such cases, with the help of his colleague and pathologist, Dr. John Bennett performed an autopsy and described their findings in 1845 in the \textit{Edinburgh Medical and Surgical Journal}\textsuperscript{9}. Simultaneously the German physician Virchow described a similar patient with autopsy findings in a journal soon after the British pair. Virchow coined the descriptive term “Weisses Blut” or “white blood”; this was based on the Greek (\textit{λευκός} and \textit{όμα}) and became in German “Leukämie.” Virchow is also credited with the view that the cause of the disease was a primary alteration in hematopoiesis\textsuperscript{10-12}.

There was a further 30 years following on from the discovery of CML, when Ernst Neumann recognised that the leukaemia originated in the bone marrow\textsuperscript{13, 14}. There was a further 100 years following this before any serious development with regards to understanding the disease really began. It started in Pennsylvania in the 1960’s with two cytogeneticians Peter Nowel and David Hungerford, who made a groundbreaking discovery that eventually led to the discovery of the molecular abnormalities associated with CML, potentially enabling its cure\textsuperscript{15}. They discovered abnormally small G-group chromosome that we now call the Philadelphia chromosome (Ph). The name Philadelphia was given by some colleagues from Scotland in appreciation for their work. The chromosome was initially labelled as Ph1 in the hope that it was the beginning of many, but eventually on realisation that it was the only causative, became Ph.
Thirteen years later, with introduction of improved banding techniques the Ph chromosome was further characterised by Janet Rowley and colleagues, who were able to show in 1973 that it was a truncated version of chromosome 22 (designated 22q-) and was the result of reciprocal translocation of genetic material between chromosomes 9 and 22 [designated t(9;22)]\textsuperscript{16}.

The early 1980s saw the identification of the two genes that flank the translocation breakpoint. The \textit{ABL} gene (now renamed \textit{ABL1}) from chromosome 9 had been known as the human homolog of a murine leukaemia virus; while the translocation partner from chromosome 22 was termed \textit{BCR} for breakpoint cluster region, since DNA breaks occurred in a relatively small genomic region\textsuperscript{17, 18}. It was later confirmed the relation between the \textit{BCR-ABL1} fusion gene and the Ph chromosome in CML patients.

Of great importance was the discovery that the protein derived from the \textit{BCR-ABL1} gene had protein-tyrosine kinase (TK) activity that was deregulated compared with normal \textit{ABL1} and correlated with its ability to transform cells to a malignant phenotype\textsuperscript{19}. Several groups later reported that a CML-like disease could be induced in mice transplanted with bone marrow infected with a \textit{BCR-ABL1} retrovirus. This proved that \textit{BCR-ABL1} is the causative agent of the disease and not just a marker\textsuperscript{20, 21}.

\textbf{I.3 Biology & pathogenesis of CML:}

A single, pluripotent, haematopoietic stem cell (HSC) acquires the Philadelphia (Ph) chromosome carrying the \textit{BCR-ABL1} fusion gene, provides its progeny with a proliferative advantage over normal haematopoietic elements and thus allows the Ph-positive clone gradually to displace residual normal haematopoiesis, resulting in CML is well established\textsuperscript{8}.
The Ph chromosome is a shortened chromosome 22 (22q-) that results from a balanced, reciprocal translocation between the long arms of chromosome 9 and 22, designated t(9;22)(q34;q11)\textsuperscript{16}(figure 1).

**Figure 1- Schematic diagram of the translocation that creates the Ph chromosome**

The translocation results in the bulk of the \textit{ABL1} (Abelson) proto-oncogene normally found in chromosome 9 translocated into a relatively small, 5.8Kb genomic region on chromosome 22, that was named the breakpoint cluster region or \textit{BCR}\textsuperscript{22}.

The classic BCR-ABL1 gene of CML results from the fusion of parts of two normal genes: the ABL gene on chromosome 9 (now renamed ABL1) and the BCR gene on chromosome 22 \textsuperscript{8}. The breakpoints within the ABL1 occur either upstream of exon Ib, downstream of exon Ia, or more frequently, between exons Ib and Ia\textsuperscript{23} (Figure 2).

In most patients with CML and in one-third of those with Ph-positive B-cell acute lymphoblastic leukaemia (Ph+ B-ALL) the breakpoints within BCR occur at a 5.8-kilobase (kb) area spanning exons e12-e16 (formerly called b1-b5), referred to as the major breakpoint cluster region (M-bcr). Alternative splicing gives rise to fusion transcripts with either b2a2 or b3a2 junctions that generate a 210-kDa protein (p210BCR-ABL1)\textsuperscript{24}.

**Figure 2- Schematic representation of the ABL1 and BCR genes**
The resulting BCR-ABL1 kinase contains a series of functionally distinct domains (figure 3). The tyrosine kinase encoded by the SRC-homology 1 (SH1) domain of the ABL1 component is undoubtedly the most crucial for oncogenic transformation. Other important motifs in the ABL1 portion are the protein interaction SRC-homology 2 (SH2) and the C-terminal actin-binding and DNA binding domains.

Figure 3- Functional domains of p210BCR-ABL1

On the BCR moiety, the coiled-coil motif encoded by the first BCR exon is responsible for the dimerization of the oncoprotein; a tyrosine at position 177 is crucial for the binding of adaptor proteins such as growth factor receptor bound protein 2; the N-terminal phosphoserine and phosphothreonine residues are required for interaction with SH2 containing proteins, including ABL1 itself (figure 3). The leukaemogenic potential of p210BCR-ABL1 resides in the fact that the normally regulated tyrosine kinase activity of the ABL1 protein is constitutively activated by the juxtaposition of ‘alien’ BCR sequences. BCR
acts by promoting dimerization of the oncoprotein, such that the two adjacent BCR-ABL molecules phosphorylate each other on tyrosine residues.

The uncontrolled kinase activity of BCR-ABL1 then supersedes the physiologic functions of the normal ABL1 enzyme by interacting with a variety of effector proteins. The key pathways implicated are those involving RAS, mitogen-activated protein (MAP) kinases, signal transducers and activators of transcription (STAT), phosphatidylinositol 3-kinase (PI3K) and MYC.

Most of the interactions are mediated by tyrosine phosphorylation and require the binding of BCR-ABL1 to adapter proteins such as growth factor receptor-bound protein 2 (GRB2), DOK, CRK, CRK-like proteins, SHC and casitas B lineage lymphoma protein. The net result is deregulated cellular proliferation, decreased adherence of leukaemia cells to the bone marrow stroma and a reduced apoptotic response to mutagenic stimuli.

**I.4 Clinical picture and manifestations:**

CML is characterized by a triphasic course that includes a chronic phase (CP), an intermediate or accelerated phase (AP) and an acute or blastic phase (BP). These days with the advent of TKI therapies and earlier diagnosis, the middle stage has become quite rare. At the time of diagnosis, more than 80% of patients are in CP, which is asymptomatic in approximately 40% of patients, being discovered during routine laboratory workup.

From historical data, patients diagnosed with CP had a median survival of approximately 5 years, and unless the disease was controlled or eliminated, they eventually transformed to a terminal or BP after a median of 3 to 5 years.
The prognosis for patients with BP is poor, with a median survival of 3 – 6 months. Prior to introduction of TKI’s, approximately two thirds of the patients go through an intermediate phase known as AP before progressing to BP with a median survival of 1 – 2 years².

As a result of routine examination, the incidence of asymptomatic presentations in CP-CML has increased dramatically from 15% to 40% – 50%. There has been also a decrease in the presenting features of advanced phase disease².

**Chronic Phase**

The commonest physical finding present in more than three-quarters of CML patients is an enlarged spleen and symptoms at the time of presentation are often attributed either to it or to anaemia²⁵. These include fatigue and left upper abdominal pain or mass. Patients with CML are often diagnosed with leukocytosis, with white blood cell counts > 50 x 10⁹/L. In rare situations, the leukocytosis can lead to retinal haemorrhage and signs of hyper viscosity such as priapism, cerebrovascular accidents, tinnitus, confusion, and stupor.

**Advanced phase (accelerated and blastic phases)**

In contrast to patients in chronic phase, patients in the advanced phase are more likely to experience symptoms, including weight loss, fever, night sweats and bone pains. Anaemia, infectious complications and bleeding are also common among these patients²⁶. Subcutaneous nodules or haemorrhagic tender skin lesions, lymphadenopathy and central nervous system (CNS) leukaemia may also occur. Other features of progressive disease include increased blasts and basophils, resistance to therapy, increasing splenomegaly, cytogenetic clonal evolution, thrombocytosis or thrombocytopenia²⁷. In the majority of patients, the progression in between phases is relatively insidious but distinct.
I.5 Prognostic factors:

Sokal

The Sokal prognostic score arose from a study of 813 patients with non-blastic Ph+ CML, which was designed to distinguish between patients with good and poor prognosis\(^{28}\). This study was conducted at a time when busulfan was the most common treatment modality. Clinical parameters (spleen size; blast-cell, platelet, and white cell count; and haemoglobin) were assessed as possible prognostic indicators. Importantly, all of the variables were assessed prior to the commencement of any therapy. Using a hazard ratio analysis, the most discriminatory factors were found to be spleen size, blast-cell percentage, patient age, and platelet count. The hazard ratio was then calculated for each patient, and patients were grouped into low-risk (Sokal score < 0.8), intermediate-risk (Sokal score 0.8–1.2), and high-risk groups (Sokal score > 1.2). In the busulfan era, the Sokal score was found to be predictive of long-term survival and became a universal prognostic indicator for CML; it remains in use today.

Hasford

The Hasford prognostic score was developed in the interferon era\(^ {29}\). It was based on the analysis of 908 patients and generated an algorithm based on several covariates: age, spleen size, blast count, platelet count, eosinophil count, and basophil count. The score was found to be predictive of survival in interferon-treated patients.

Eutos

The European leukaemia net came up with a prognostic score for CP CML patients treated with imatinib first line\(^ {30}\). 2060 patients gathered from 5 national studies to make the “European Treatment and Outcome Study” (EUTOS) for CML in order to provide a score
that predicts the probability of achieving a CCyR within 18 months. The simple formula for calculating the new (EUTOS) score can be shortened into:

**Equation 1- Eutos score**

\[
\text{EUTOS score} = (7 \times \text{basophils}) + (4 \times \text{spleen size})
\]

The spleen was measured in centimetres below the costal margin and basophils as a percentage at baseline. A EUTOS score of > 87 indicates high risk and < 87 low risk. The reliability of the score could not be fully ascertained from studies published based on single institution experiences. For example Marin et al and Jabbour et al using patients treated at their respective institutions showed Sokal and Hasford prognostic indices to be superior to EUTOS in predicting survival outcomes\(^{31, 32}\). On the other hand, a study by Tiribelli et al showed that EUTOS score was predictive of long term survival of imatinib treated patients but not predictive of cytogenetic and molecular milestone achievements\(^{33}\). A large study by Hoffmann et al showed EUTOS score to be predictive of achievement of cytogenetic and molecular milestones as well as survival outcomes\(^{34}\). In the face of a number of publications showing both the merits and inadequacies of the EUTOS score, it is difficult for this to be universally acceptable as a replacement for the time tested sokal and Hasford prognostic scoring methods.

I.6 Treatment:

**Historical treatment approaches:**

Arsenic has been mentioned as a possible treatment approach for cancer in Ramayana, an Indian epic written 1000’s of years ago. In modern age, the earliest documented attempts at treating CML using arsenic was reported by Heinrich Lissauer in 1865, an effective therapy
in the treatment of CML when 2 patients were treated\textsuperscript{35}. Author Conan Doyle has mentioned in his works of using arsenic to treat a patient with CML. Subsequently, the discovery of X-rays by Wilhelm Roentgen in 1895 brought a new treatment for leukaemia and results seemed to be similar to those produced by arsenic\textsuperscript{36}. In the 1920s, splenic irradiation was introduced for symptomatic relief.

Effective control of blood counts became feasible with the introduction of busulphan by David Galton, from London\textsuperscript{37}. In 1968 he published a paper reporting that busulfan-treated patients lived longer than those who received radiotherapy and thereafter busulfan became the standard treatment for CML in the UK. The down side to busulphan was that it regularly rendered women infertile and men azoospermic. In those days the median survival from diagnosis was about 5 years. This became the standard of care until the better-tolerated hydroxyurea became available, probably the first intervention with a (modest) prolongation of survival.

Development of treatment methodologies leading to present treatment:

Research conducted during the 1980’s showed that allogeneic stem cell transplantation, although hazardous and even sometimes fatal, could if induce long term remissions and probably cure some patients\textsuperscript{38}. Investigators at Seattle had shown that CML patients transplanted with marrow cells collected from their identical twins could expect a number of years without evidence of leukemia detectable in their body, paving the way for transplant to be considered the standard for eligible patients. Therefore, from the 1990’s onwards, the treatment of choice for all relatively young patients (i.e., under the age of 50) who presented in chronic phase was an allogeneic stem cell transplant (SCT)\textsuperscript{2}.

The next big treatment to arrive on the CML scene was interferon. Moshe Talpaz, at the MD Anderson centre in Houston pioneered the use of IFN to treat CML\textsuperscript{39, 40}. Some of the
patients who received this treatment achieved Philadelphia chromosome negativity and a small number of patients who achieved this status did not relapse when the IFN was discontinued. Interferon was associated with modest prolongation of life when compared with the use of hydroxyurea. Later on, evidence from France suggested that the best treatment for CML patients who aren’t eligible for allografting was a combination of IFN-α plus cytarabine (Ara - C)\(^41\), subsequently data from Italy has refuted some of these claims\(^42\).

It was in 1996, when Druker and colleagues described CGP57148, a highly specific pharmacologic inhibitor of the \( ABL1 \)-tyrosine kinase that selectively suppressed the growth of \( BCR-ABL1 \)-positive cells that CML therapy was changed\(^43, 44\). This compound, first renamed STI571 and then imatinib (Novartis, Basel, Switzerland) revolutionized the treatment of CML and set an example for the development of more potent, newer second and subsequent generation of tyrosine kinase inhibitors like dasatinib, nilotinib, bosutinib, ponatinib and radotinib.

**Current Therapies:**

**Hydroxycarbamide (hydroxyurea):**

Introduced in 1972, a cell cycle–specific inhibitor of DNA synthesis became available for the treatment of chronic myelogenous leukaemia. It allowed rapid but transient haematologic control, was well tolerated, and had few side effects (nausea, vomiting, diarrhoea, mucosal ulcers, and skin manifestations). Hydroxyurea was given orally at 40 mg/kg daily, and doses are adjusted to maintain a leukocyte count of 2 to 10 cells \(x10^9/L\)\(^45\). Although hydroxyurea is effective in controlling the white blood cell count and reduces the splenomegaly of CML, it does not eradicate the Ph clone. Its current role is limited to the initial normalisation of counts in newly diagnosed CML at doses ranging from 0.5g to 3g daily.
Interferon Alfa:

The use of Interferon-α in CML has been pioneered by the MD Anderson cancer centre\textsuperscript{39, 40}. It was introduced in the backdrop of highly myelosuppressive drugs that did not lead to Ph negativity. IFN-α can not only induce Ph negativity without drastic myelosuppression, but there was convincing evidence that it prolongs survival by delaying the onset of the blastic phase CML\textsuperscript{46}. Sensitive molecular analysis revealed underlying Bcr-Abl transcripts in patients who attained CCyR on IFN-α, showing that IFN causes a reduction in the transcript level rather than eliminating it altogether. IFN-α induced complete cytogenetic response in 5% to 20% of patients. This was associated with a survival greater than 10 years. In fewer than 1% of patients the \textit{BCR-ABL1} transcripts became undetectable by the most sensitive PCR technique and many of these patients could be considered as operationally cured as the leukemia did not appear to relapse after prolonged discontinuation of the therapy. IFN was associated with significantly increased side effects with 15 to 25% of patients discontinuing treatment and 30% to 50% requiring dose reductions. The most common immediate side effects were “flu-like” symptoms including fever, shivers, myalgia, and tiredness. In most patients these effects wore off after a few weeks. The main haematological side effect was thrombocytopenia.

Stem cell transplantation (SCT):

Allogeneic stem cell transplant from a suitably fully matched sibling resulted in the high cure rates\textsuperscript{47}. The possibility of obtaining fully matched sibling donor in this day and age in “developed” countries is about 25% to 30%. The probabilities of 5-year overall survival and leukemia-free survival are 60% to 80% and 55% to 70%, respectively, with a 10% to 20% relapse rate\textsuperscript{48}. Majority of the relapses occur early and within the first three years following which they are rare. The initial attempts at a fully matched volunteer unrelated donor
transplant was associated with increased mortality and morbidity from graft vs. Host disease, graft failure and increased transplant related mortality. Subsequently improved donor selection was able to show rates of survival in the first few years to be equivalent to the fully matched sibling donors.

Transplantation risk assessment:

Although allo-SCT offers a clear benefit of providing a cure to a rather lethal condition, one clear disadvantage is that it is associated with a high rate of morbidity and mortality\(^48\). Outcome has been improved over the years by selecting those patients who are most likely to benefit from the procedure. The European Group for Blood and Marrow Transplantation (EBMT) developed a risk score system for patients with CML undergoing transplant\(^49\).

The EBMT score is based on 5 variables: donor type, disease phase, recipient age, donor/recipient sex combination, and interval from diagnosis to transplantation \(^49\). These five factors provide a score from 0 as lowest up to 7 as highest risk.

Risk assessment can be further adjusted by integrating additional elements known to influence transplant related mortality (TRM), such as cytomegalovirus (CMV) serological-status of the recipient, cytokine polymorphisms or the co-morbidity score\(^50-52\). Expression of the polycomb group gene BMI-1 was shown to reduce TRM in patients with CML\(^53\).

A defined natural killer receptor, KIR2DS5, was shown to be associated with a higher risk for relapse despite allogeneic SCT\(^54\) and recently, C-reactive protein level less than 10mg/L (regardless of infective status) has been also shown to be an independent predictor for survival\(^55\).

Graft-versus-host-disease and T-cell depletion:
The major causes of morbidity and mortality during SCT are infections and graft-versus-host disease (GVHD). Now GVHD could be prevented using a combination of methotrexate and cyclosporine post-transplant. This combination offers good protection without a significant increase in relapse\textsuperscript{56}. The 1980s saw the introduction of T-cell depletion, which was effective in decreasing the severity and frequency of GVHD, but was associated with a higher frequency of graft failure\textsuperscript{57}.

**Donor lymphocyte infusions**

Donor lymphocyte infusions have been remarkably successful in treating post transplant relapses in CML patients. Its principle relying on the evidence that donor T lymphocytes can exert a graft vs. Leukaemia (GvL) effect, potentially able to eradicate the residual host disease. In order to restore remission to transplanted patients who have relapsed, additional donor lymphocytes were given\textsuperscript{58}. Their therapeutic principle relies on the evidence that donor T lymphocytes can exert a graft-versus-leukaemia effect (GVL), potentially able to eradicate the residual host disease\textsuperscript{58}.

Administration of DLIs can re-induce remission in 60\% to 90\% of patients with CML who underwent transplantation, and relapsed in chronic phase. The use of escalating doses in case of persistent disease limits the risks for GVHD\textsuperscript{59,60}. A European study showed a 69\% 5-year survival in 328 of patients who received DLI for relapsed CML\textsuperscript{61}.

DLI-related mortality was 11\% and disease related mortality was 20\%. Some form of GVHD was observed in 38\% of patients. Risk factors for developing GVHD after DLI were T-cell dose at first DLI, time interval from transplantation to DLI, and donor type. In a time-dependent multivariate analysis, GVHD after DLI was associated with a risk of death of 2.3-fold compared with patients without GVHD \textsuperscript{62}. With the advent of targeted therapies like imatinib, stem cell transplant has been replaced as the primary option for cure.
Currently available targeted therapies:

Imatinib:

The collaboration between Druker, his colleagues and Ciba-geigy (now Novartis) resulted in a phenyl-aminopyrimidine molecule, then called CGP57148B, that occupied the kinase pocket of the \textit{BCR-ABL1} protein and blocked access to ATP, thereby preventing phosphorylation of any substrate\textsuperscript{44}. Preclinical studies showed that the molecule was highly effective in blocking the tyrosine kinase activity of \textit{ABL1}; the stem-cell factor receptor, c-kit; and the platelet-derived growth factor receptor (PDGFR) but had little effect on other tyrosine kinases. The addition of a benzamide group and a polar side chain enhanced the molecule’s efficacy against tyrosine kinases and also improved its bioavailability significantly\textsuperscript{43}.

The molecule was known as (STI1571) Imatinib mesylate, binds to the amino acids of the \textit{BCR-ABL1} tyrosine kinase ATP binding site and stabilizes the inactive, non-ATP-binding form of \textit{BCR-ABL1}, thereby preventing tyrosine auto- phosphorylation and, in turn, phosphorylation of its substrates, resulting in “switching off” the downstream signalling pathways that promote leukaemogenesis\textsuperscript{43}.

\textsuperscript{44} Implication of tyrosine phosphorylation in the regulation of cell growth and differentiation. 

\textsuperscript{43} Significant improvement in the bioavailability of the drug.
The excellent in vitro data led to subsequent in vivo and rapidly onto phase 1 and 2 clinical trials. Imatinib was administered once daily and pharmacokinetics showed a half-life of 13 to 16 hours and was fairly well tolerated with minimal side effects. In June 2000, the landmark IRIS phase 3 trial comparing upfront 400mg imatinib to a combination of IFN-α with Ara-c (cytosine arabinoside), which was considered a standard treatment at that time was initiated. With a median follow-up of 19 months, patients randomized to imatinib had significantly better results than patients treated with IFN-α plus Ara-C in all parameters measured, including rates of CHR (97% vs. 56%, \( P < 0.001 \)), MCyR and complete cytogenetic responses (CCyR) (85% and 74% vs. 22% and 8%, respectively, \( P < 0.001 \)), discontinuation of assigned therapy due to intolerance (3% vs. 31%), and progression to AP or BP (3% vs. 8%, \( P < 0.001 \)).

The most recent data from an 8 year follow up of IRIS trial, the estimated event free survival (EFS) at 8 yr was 81% and freedom from progression to AP/BP was 92%. Estimated OS was 85% at 8 yr and 93% when only CML-related deaths and those prior to SCT were considered. Imatinib is known to be associated with a few side effects, most of which are mild to moderate in intensity and settle after the first few months of treatment. Most patients don’t require dose reduction or interruption of therapy. The main haematological side effects
are neutropenia and thrombocytopenia. The main non haematological side effects are fatigue, deranged LFT's, rash, oedema (including peripheral and periorbital), muscle cramps, diarrhoea, nausea and musculoskeletal pain. These non haematological side effects sometimes tend to stay on as chronic low grade side effects.

**Nilotinib:**

Nilotinib (AMN107, Tasigna®; Novartis) is an orally bio available, rationally designed, derivative of imatinib designed to overcome its resistance in CML and was found to be 30-35 times more potent than imatinib in inhibiting BCR-ABL1 in pre clinical models. In earlier phase I and II studies nilotinib showed good tolerability in adult patients with Ph+ CML who have been resistant or intolerant to at least 1 prior line of treatment. The phase III trials have shown that nilotinib induces deeper responses more rapidly and in more patients than imatinib when compared upfront in newly diagnosed patients. Nilotinib has shown remarkable efficacy in chronic and accelerated phase of the disease but the evidence is lacking when it comes to its efficacy in blast transformation phase of CML. It is currently approved for use both in a front line setting and for subsequent lines of therapy. Whilst nilotinib can overcome the majority of the mutations resistant to imatinib, the T315i (gate keeper) mutation has proven to be resistant.

The main side effects related to nilotinib apart from the myelosuppression is its non haematological side effects. The main ones are rash, pruritus, deranged LFT's (especially hyperbillirubinemia), GI symptoms, cardiovascular toxicity like cardiac failure, arrhythmias, peripheral arterial occlusive disease and hyperglycemia especially in diabetics. Cortes et al showed in a study on patients who switched over to nilotinib from imatinib that there was very little cross intolerance amongst the different the two meaning that the side effects could potentially be overcome by switching TKI therapy.
**Dasatinib:**

Dasatinib is a potent orally available ABL kinase inhibitor with 325-fold greater in vitro selectivity for un-mutated \( BCR-ABL1 \) than imatinib. In addition to blocking \( BCR-ABL1 \) kinase activity, it also inhibits a wide spectrum of other kinases, including SFKs, c-Kit, platelet-derived growth factor-receptor (PDGFR), and ephrin-A receptor\(^ {74, 75} \). The effectiveness of the early phase clinical trials brought about an FDA approval for second line use in 2006 and upfront in 2012\(^ {76, 77} \). The most recent update on the phase III trials show patients attaining molecular and cytogenetic milestones (CMR, MMR & CCyR) earlier when compared to standard imatinib therapy\(^ {78} \). The various trials have so far failed to show an improvement in overall survival when compared to the Imatinib data. The argument for using dasatinib upfront is similar to nilotinib in that a greater suppression of the Bcr-Abl clone early on leads to fewer progressions and more patients are likely to attain the early molecular monitoring cut offs at 3 and 6 months.

The side effects from dasatinib are related to its off target effects. The main side effects of dasatinib are pleural effusion and myelosuppression. There have been a number of reports with regards to pleural effusion and old age, Lymphocytosis, advanced phase of the disease and higher dose are thought to be its risk factors. The other side effects that have been reported of late include pulmonary arterial hypertension and it is not clear if it is reversible on stopping the drug. Some of the other side effects include fluid retention, GI disturbances including colitis, headache, musculoskeletal disorders, rash, and infection.

**Bosutinib:**

Bosutinib (formerly known as SKI-606; Wyeth/Pfizer, New York, New York, USA) is a dual \( ABL1/SRC \) TKI which, like nilotinib and dasatinib, is more potent than imatinib and offers activity against several imatinib resistant \( ABL1 \) mutations\(^ {79} \). After its efficacy was
demonstrated in imatinib resistant patients in a second line setting, a phase III trial compared standard dose of 500mg bosutinib to 400mg imatinib\textsuperscript{80, 81}. This trial failed to meet its primary end point (superiority of attainment of CCyR). There was no difference in CCyR rates at the end of 1 year although the trial did show earlier attainments of cytogenetic and molecular milestones. Treatment interruptions and dose reductions were higher in bosutinib treated patients on imatinib.

The main side effects associated with bosutinib was GI toxicity in the form of diarrhoea, vomiting and abdominal pain. The other side effects which are common to a majority of the TKIs (edema, musculoskeletal pains, fatigue, elevated transaminases and myelosuppression) were also noted with bosutinib.

**Ponatinib:**

Ponatinib (AP24534; Ariad Pharmaceuticals, Cambridge, MA) is a novel TKI of $\text{BCR-ABL1}$ with activity against all known $\text{BCR-ABL1}$ mutants, including T315\textsuperscript{I} \textsuperscript{82}. A phase I trial showed clear evidence of anti-leukaemia activity, with major cytogenetic responses in 46\% of chronic-phase patients resistant to second-line tyrosine kinase inhibitors, including 67\% of those with the T315I mutation\textsuperscript{83, 84}. The Phase II trial trail data has been presented at ASH 2012 recently and has confirmed the efficacy shown in the phase I trial in patients both intolerant and resistant to second generation TKIs\textsuperscript{85}. Over half the patients in the trial had received all three approved TKIs (53\%) previously. The findings showed MMR rates of 25\% in patients with T315i mutation and 28\% of patients overall had attained MMR at the end of 9 months. The estimated probability of remaining in MMR at 6 months and 1 year is 87\% and 84\% respectively. A phase III trial comparing ponatinib at a dose of 45mg to upfront imatinib 400mg in newly diagnosed CP CML patients is underway.
The major side effects noted with ponatinib was myelosuppression and this was in a heavily pre treated population. The other major non haematological side effects included pancreatitis, dermatological side effects including rash, pruritus, and other constitutional symptoms like nausea, vomiting, fatigue and arthralgia.

**Radotinib:**

Radotinib is a novel, selective Bcr-Abl tyrosine kinase inhibitor (TKI) developed by IL-YANG Pharm, South Korea. Radotinib showed a good efficacy and safety profile to chronic myeloid leukemia (CML) in preclinical and phase 1 clinical studies. It has been approved for second line and beyond CP CML patients in South Korea. The interim results of a phase II trial of Radotinib usage in a second line setting with a median follow up of 10.5 months was presented at ASH 2012\(^86\). The results from 77 patients who received at least 3 months of therapy showed fewer than half the patients (45.4%) attained a complete cytogenetic response and 18.2% attained a partial cytogenetic response. A phase III trial comparing upfront usage (300mg BD or 400mg BD of Radotinib vs. 400mg OD of imatinib) is currently underway. Radotinib appears to be effective in patients who have either been intolerant or resistant to imatinib but is not active against the T315i mutation.

**Omacetaxine:**

Omacetaxine mepesuccinate (formerly known as homoharringtonine) is a reversible inhibitor of protein translation. It’s activity therefore is not inhibited by the mutational status of Bcr-Abl. There have been a number of publications over the years to support the clinical effectiveness of omacetaxine in CML over the last 25 to 30 years\(^87\). It fell out of favour in the last decade owing to the tremendous success of TKI inhibitors. Recently Cortes et al reported the findings of a phase II study showing the effectiveness of omacetaxine in CML patients bearing the T315i mutation and having had prior TKI therapies which has in a way
brought it back to the forefront as a possible alternative\textsuperscript{88}. The CHR in this heavily pretreated population was 77%. The rates of the Major and complete cytogenetic responses were 23% and 16% respectively. This drug represents a possible alternative along with ponatinib for CML patients bearing the T315i mutation. The drug is given as a subcutaneous injection, with the induction dose of 1.25mg/m\textsuperscript{2} twice a day for 14 days in a 28 day cycle. Once the patients reach a CHR, they are then switched on to the maintenance cycle comprising 1.25mg/m\textsuperscript{2} twice a day for 7 days in a 28 day cycle. The main side effects were related to myelosuppression.

\textbf{I.7 Current issues in CML}

CML has been transformed in the last decade and half from a near fatal condition with median survival of around 3 to 5 years to well over 25 years and counting. All of this has been made possible with the advent of the TKI therapies from imatinib to the third generation ponatinib. The most recent updates from the long term follow up of the IRIS trial looking at the survival figures of the imatinib treated patients puts OS in excess of 93% for CML related deaths at 8 years\textsuperscript{67}. The newer TKI's have shown improvement in the early response rates compared to imatinib. Second and third generation TKI's when used upfront show improved and earlier attainment of milestones like CCyR and MMR when compared to imatinib and is postulated to improve already excellent OS rates obtained with imatinib. The improved early responses have also shown lower progression to advanced phase of the disease and the reasoning behind it is thought to be a greater suppression of the Bcr-Abl clone early on. With such excellent cure rates, the focus of CML management has shifted from finding newer therapies to trying to improve outcomes to the existing therapies and improve patient experience on them.
Early molecular responses to TKI therapy has been shown to be predictive of excellent outcomes by a number of groups. Branford et al showed in 2006 from an analysis of the IRIS trail data that Bcr-Abl transcript numbers of less than 10% at 3 months predicts patients like to attain higher rates of CCyR\textsuperscript{89, 90}. Subsequently Marin et al showed that a transcript cut of 9.84% at 3 months and 1% at 6 months are likely to identify patients at risk of poor clinical outcomes\textsuperscript{91}. Hanfstein et al from the German collaborative group shown similar findings using cut offs of 10% and 1% at 3 and 6 months and that failure to attain them results in inferior clinical outcomes\textsuperscript{92}. These results helped focus attention firmly on identifying patients who may do poorly using the cut offs. It was however not clear if the patients need to fail the 3 and 6 month cut off to be predictive of poor responses or simply failing to attain the 3 month cut would predict poor responders on its own. To answer this question we tried to analyse the data from patients who attended the Hammersmith hospital for management of their CML.

The key to maintaining good clinical outcomes lies in good adherence to therapies over a long period. Patients not adhering to prescribed medications are not only confined to CML alone. Indeed, the problem is pervasive across chronic conditions. The average adherence to long term therapies according to a 2003 WHO report in diseases like asthma, diabetes, hypertension, and tuberculosis was only about 50% in developed countries, and possibly even lower in developing countries where the access to resources like healthcare is very variable and unpredictable.

Adherence to TKI therapy has gained importance following a number of publications showing poor adherence correlating with inferior clinical outcomes like attainment of CCyR, MMR and CMR. The adherence to TKI therapy has been varyingly shown to be between 20 to 100% by a number of groups. Marin et al showed that only 60% of people were 90%
adherent to their Tki therapy\textsuperscript{93}. A similar study by Noens et al showed that only 14\% of patients took their TKI therapy all the time\textsuperscript{94}. Efficase et al showed adherence rates of 53\% using a questionnaire based study\textsuperscript{95}. There are a number of ways to monitor adherence. The gold standard would be a directly monitored continuous observation of the patients taking the medications, a method that would be practically impossible and economically unviable in most healthcare settings. Marin et al showed that adherence of <90\% correlated with failure to attain CCyR, MMR and CMR using a microelectronic monitoring device (MEMS)\textsuperscript{93}. MEMS was a device fitted to bottle caps to record opening and closing of medicine containers and is considered the most practical gold standard method of monitoring adherence. The downside of such a method is the cost implications and the fact that MEMS records only the opening of the containers and the actual pill taking\textsuperscript{96, 97}. The other methods that have been used over the years are measurement of blood levels. Imatinib blood levels have been shown to be an useful method of estimation of recent imatinib dosage and was initially developed to test the appropriateness of the dosage for a particular patient\textsuperscript{98}. The levels are done in a clinic prior to seeing a clinician. Apart from the information that imatinib was recently taken by the patient it does not shed any more light on the long term adherence of the drug similar to HbA1c measurement of glucose in diabetic patients. The other method would be pill counting which is labour intensive and does not correlate with actual everyday pill taking rather than just long time estimation\textsuperscript{96}. Medication possession ratios and pharmacy refills have also been used in some studies to determine adherence to TKI therapies. A lot of these measures are practically difficult to be used continuously in a clinic setting to monitor adherence behaviour over a period of time. In this background we tried to study the practical feasibility of using simple self reported measures of adherence and correlate them with clinical outcomes. If successful, they could become a useful tool to study a pattern of adherence over a period of time. There have been various
possible theories that have been put forward as to the reasons for non adherence to TKI therapies\textsuperscript{99}. In a cancer setting with patients on oral medications it has been postulated that patient related factors like daily routine, communication with the clinical team, anxiety, depression, beliefs about medicines could play in important role in determining a patients behaviour to taking the medications long term\textsuperscript{95, 100}. We have tried to study the impact of such factors on self reported adherence and clinical outcomes using a questionnaire based study. The eventual goal would be to try to generate surrogate markers of adherence based on patient related factors which could be used to monitor adherence as the self reported adherence questionnaire involves direct questions pertaining to adherence.

Compliance to TKI therapy can depend on a number of factors including tolerability. All TKI therapies from imatinib to the recent ponatinib have side effects even though they are fairly well tolerated. Side effects can be one of the main reasons for treatment interruptions and possible inferior clinical outcomes\textsuperscript{96}. Chronic low grade side effects often persist for a long term, not necessarily leading to treatment interruptions, but can often end up with interference to the quality of life of the patient. A lot of the side effects are thought to be a class effect of the particular type of TKI in the sense that all therapies can give rise to the same side effect of varying degrees. In this background we were interested in seeing if changing TKI on the basis of their side effect profile would be a helpful measure to not only alleviate the low grade side effects but also improve upon their molecular responses further. We tried to study the effect of changing TKI therapy after patients have attained a CCyR to assess their response to a change. If it showed good results, this could be a way forward to minimise or eliminate the chronic low grade side effects with no adverse impact on the clinical responses.
I.8 MD Project

The main essence of my MD was to optimise treatment for chronic myeloid leukaemia. I have tried to achieve optimisation through various strategies. The first is to optimise early molecular monitoring approaches to identify poor responders. We have tried to identify early time points that can help to prognosticate patients better and identify poor responders earlier. This can help to intervene early to possibly alter the clinical course. The second strategy is to optimise adherence. We wish to devise simple and practical means to identify non adherence using self reported measures and correlate them with clinical responses. We also wish to identify reasons for non adherence and develop surrogate markers for non adherence using a questionnaire based study. The third strategy is to optimise intolerance. This involves a study trying to change TKI therapy to ameliorate chronic low grade side effects to improve intolerance.

MD title: Optimisation of CML therapy

1. Optimisation of early molecular monitoring, by identifying cut offs to predict poor responders

2. Optimisation of adherence, to correlate self reported adherence with outcomes and identify reasons for non adherence to TKI therapy

3. Optimisation of intolerance by changing TKI therapies to overcome chronic low grade side effects
Chapter II. Methods

II.1 Database

There were two databases used for the purposes of my thesis. One was a database that was maintained in the haematology department at the Hammersmith hospital with records of all patients treated at the centre and the second database was created newly for the questionnaire based study.

First database for CML patients was an access database comprising three tables. Table I contains the basic demographic data, details of diagnosis and of treatment and response before starting treatment with imatinib. Table II contains descriptive data applicable at the actual time of starting imatinib. Tables I and II both contain a register for each patient. Table III contains the imatinib data, where each patient is represented by an unlimited number of registers each showing the situation of the patient at a given time point (visit). All three tables are by the patient identifier number (N). The variables and codes included in the database are shown in Appendix I.

The second database was designed to capture the information from the questionnaire study. It was an access database that contained 2 tables. Table 1 contained all the patient entered data including their diagnosis, date, treatments and answers to questions regarding adherence and factors thought to influence adherence. The second table included information that the clinician entered information pertaining to the treatment, line of therapy, PCR results and the dates.
II.2 Hammersmith Study

II.2.1 Patients and methods

Patients

For our analyses, we included a total of 274 patients with Ph +ve, BCR-ABL1 +ve CML patients in chronic phase who were treated with first line imatinib at the Hammersmith Hospital. These patients included: patients enrolled in current clinical trials; patients who are on follow up from older trials; and newly diagnosed patients who started imatinib therapy within 6 months of diagnosis as imatinib became available within the NHS (non trial patients).

TKI administration

Imatinib:

Imatinib was prescribed to patients at a dose of 400 mg orally daily. The dose was adjusted according to tolerance and response: it was reduced in the presence of grades 3-4 toxicity and hematopoietic growth factors were administered with the aim of maintaining imatinib higher than 300 mg/d.

Dose escalation for patients on imatinib who failed to achieve a complete haematologic response at 3 months or at least a minor cytogenetic response (defined as between 36 to 65% Ph-positive metaphases) at 12 months were applied as in the phase II trial or the IRIS study, but as more evidence accumulated, the criteria evolved and resembled the subsequent recommendations from the European Leukaemia-Net and NCCN. The patients were switched to a second generation TKI (nilotinib, dasatinib or bosutinib) either due to resistance or intolerance.

Dasatinib & Nilotinib:
Dasatinib was administered at a dose of either 70mg every 12 hours (twice daily) or 100mg once daily. Nilotinib was given at a dose of 400mg twice daily in patients intolerant or resistant to a previous TKI and in a dose of 300mgBD for upfront management of newly diagnosed patients. Doses were adjusted according to tolerance.

*Bosutinib:*

Bosutinib was prescribed to some of our patients who are participating in phase III clinical trials and was also used outside them. Bosutinib was given in a dose of 500mg/day, which was also adjusted according to tolerance.

Definitions and monitoring of responses

Chronic phase (CP) and complete hematologic response (CHR) are defined by standard criteria. Bone marrow morphology and cytogenetics are assessed at diagnosis and then every 3 months, until patients achieve CCyR using Giemsa banding. Thereafter, patients are monitored by real-time quantitative polymerase chain reaction (RQ-PCR) and annual bone marrow examinations.

A complete cytogenetic response (CCyR) is defined by the failure to detect any Philadelphia chromosome (Ph)-positive metaphases in two consecutive bone marrow examinations with a minimum of 20 metaphases examined. A partial cytogenetic response (PCyR) is defined as a decrease in the proportion of Ph-positive metaphases to between 1 and 35%, while a major cytogenetic response (MCyR) is defined by combining the number of complete and partial cytogenetic responses (<35% Ph +ve metaphases), and a minor cytogenetic response (MiCyR) is defined as a decrease in the proportion of Ph +ve metaphases to between 35 and 95%.

Measurement of *BCR-ABL1* transcripts
BCR-ABL1 transcripts were quantitated by RQ-PCR using the TaqMan Real-time PCR apparatus (Perkin-Elmer, Wellesley MA, USA) in the Minimal Residual Disease (MRD) Laboratory of the Hammersmith Hospital. BCR-ABL1 transcripts and ABL1 transcripts selected as internal control were quantified separately. Results were expressed as percent ratios relative to an ABL1 internal control with original laboratory values converted to the international scale (Hughes, 2006 #117). Peripheral blood cellular RNA was reverse transcribed to cDNA using standard molecular biology techniques (Cross, 2008 #140). The cDNA was then subjected to 50 cycles of analysis using the ABI 7700 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) and TaqMan Universal Master Mix in accordance with the manufacturer’s instructions in a final reaction volume of 25 µl. Probes and primers were designed using the Primer Express software (Applied Biosystems) to detect e13a2 and e14a2 junctions in a single reaction by RQ-PCR.

Probes were designed for BCR-ABL1 (cccttcagggccagctagctga-TAMRA) and ABL1 (tgctttgtggaagctcgtctctc-TAMRA) and dual labelled with 6-carboxyfluorescein (FAM) and 6-carboxy-tetramethyl-rhodamine (TAMRA). The primers used in Q-PCR were: BCR-ABL1 forward primer: 5’-tccgctgaccatcaayaagga-3’; BCR-ABL1 reverse primer: 5’-cactcagacccctgaggctcaa-3’; ABL1 forward primer: 5’-gatacgaagggagggtgtacca-3’; ABL1 reverse primer: 5’ctcgccaggtgtttgaa-3’. The probe and primer concentrations for ABL1 mRNA quantification were 200 nM and 300 nM respectively and 3 µl of cDNA. The BCR-ABL1 mRNA levels were measured using 100 nM of probe and 300 nM of each primer with 5 µl of cDNA.

BCR-ABL1 and ABL1 copy numbers were calculated by comparison with the standard curve generated using serial dilutions of linearized pNC210/G plasmid, containing the BCR-ABL1 insert described previously. The sensitivity in our laboratory of quantitative RQ-PCR is equal
to that of conventional nested PCR, i.e. $1 \times 10^{-5}$, so the failure to detect any BCR-ABL1 transcripts using RQ-PCR represents a reduction of at least 5 logs.

**Detection of tyrosine kinase mutations**

**Direct Sequencing**

The BCR-ABL1 amplicon from each subject in the study was subjected to nested primer PCR using primers NTPB+ and NTPE- to generate an 863-bp fragment containing the entire BCR-ABL1 kinase domain.

An aliquot of the PCR products was electrophoresed through 2.0 % agarose gel; if a single amplicon was observed the remaining PCR products were purified using Magna-PCR clean up kit in accordance with the manufacturer’s instructions (DRI, UK). Otherwise the PCR fragment containing the Abl kinase domain was isolated using commercially available gel purification kit (Qiagen, UK) as recommended by the manufacturer. The purified amplicons were then subjected to Sanger’s dideoxy chain termination reaction using a Big-Dye ABI 310 sequencer (Applied Biosystems, Foster City, USA). In each case the sequence obtained was compared with the published ABL1 type 1a sequence, GenBank M14752, using BLAST 2 software. All observed base substitutions were confirmed by sequencing the complementary strand.

**Statistical analysis**

The data was analysed using the statistical package SPSS statistics 20.0 (August 2012, SPSS Inc., Chicago, Illinois). Data was obtained from a database maintained in our department comprising of all patients with CML seen at the Hammersmith hospital since 2002. Probabilities of OS, PFS and event-free survival (EFS) were calculated using the Kaplan-Meier method. Events were defined as loss of a CCyR or CHR, progression to
advanced phase, death or imatinib discontinuation. Univariate analyses to calculate the probabilities of cytogenetic and molecular responses were done using the cumulative incidence (CI) procedure. The probabilities were compared using the log rank test or a Cox regression model. Variables found to be significant at \( p < 0.1 \) level was entered in the multivariate analysis unless otherwise mentioned in relevant sections.

II.3 Questionnaire study

**Ethics and approval**

The study was approved by London wandsworth research ethics committee and also by the institutional review board. All participants provided written informed consent in accordance with the declaration of Helsinki.

**Patients**

Patients:

Two hundred and ninety six patients with CML in 1st chronic phase (CP) were recruited during out-patient appointments from six hospitals (Hammersmith Hospital, Nottingham University Hospital, Royal Liverpool Hospital, Gartnavel General Hospital, Monklands and Hairmyers Hospitals) across the UK between September 2011 and January 2013. Two patients refused to take part.

The patients were all approached by the one of the members of the healthcare team in their routine outpatient clinic appointments. The patients all had to be on a TKI therapy for chronic phase chronic myeloid leukaemia and had to have been on it for atleast 3 months. Patients were given an information leaflet and the nature of the study explained. Patients who agreed
to take part were then made to sign an informed consent. They were then handed a pack containing the questionnaire, a copy of their signed consent form and an opaque envelope. The completed questionnaires were to be returned in the opaque envelope. There were no patient identifying details either on the questionnaire or on the envelope (anonymously coded). All the completed questionnaires were then centrally entered into a database. A clinical info sheet was to be parallelly completed by the treating physician.

The patient’s characteristics are presented in table 3.

**Patient demographics:**

The median age of the patients who answered the questionnaire was 58 years (range 18-90 years). Majority of the patients had their CML discovered in between 2000 and 2010. Sixty six percent of patients received TKI therapy as their first line treatment with or without hydroxycarbamide whilst the remainder had prior interferon therapy. For a third of the patients their CML tablets were their only pills and nearly 28% of patients took an additional 5 tablets along with their CML medications. Eighty five percent of patients were British with another 5% being non British caucasians with the remainder of patients being either Asians or Afro Caribbeans. A third of the patients worked full time and another third was retired with students accounting for 3.1% of the study population. The median income of the patients was between 25,000 to 35,000£ with nearly 28% of them earning below 15,000£.

**II.4 Questionnaire**

The questionnaire based study had its origins from previous studies on adherence by Marin et al and Eliasson et al. The rationale for the questionnaire was to device simple measures to predict adherence. One way was to have self reported measures that have been used in other settings and the other to develop surrogate measures that correlate well with self reported adherence measures. The questionnaire was devised with significant input from
psychologists as self reported measures are highly subjective and a slight twist in the nature of the questioning could make it unsuitable for clinical applications. The other part of the questionnaire included questions pertaining to everyday life and routine of the patients to derive surrogates to predict adherence. The questionnaire is divided into 12 sections (described in detail below and also a copy of the questionnaire is included in the supplement section). The first section collects patient’s details on current and previous treatments, number of tablets and other medications. Section 2 to section

II.4.1 Patient related factors:

This questionnaire includes a range of questions related to factors that appear to be related to adherence in CML patients. The questionnaire is mainly based on findings from the two previous adherence studies (Marin 2010; Eliasson 2010). The questionnaire includes questions related to medication management strategies such as daily routines and the use of reminders, doctor patient communication, usage of internet and support services and patients’ understanding of the illness and treatment (included in the appendix, described below and table w). The questionnaire also tries to understand patient’s beliefs about their medications using a BMQ questionnaire. There are 2 sections devoted to understanding emotive issues such as anxiety and depression among patients using the validated HADS scale. Quality of life among CML patients on TKI therapy will be calculated using the FACT-G questionnaire which comprises of 27 questions.

Section 1: Patient information

This section collected information from patients and included their year of birth, date of diagnosis, TKI therapies, their date of commencement, dosage and other pills that they take.
Section 2: Daily routines

The section had 5 questions pertaining to daily routine (table 5 & supplement section). The 5 questions all had 5 possible answers (1-strongly agree, 2-agree, 3-unsure, 4-disagree and 5-strongly disagree).

Section 3: Communication with the physician:

Communication section included 7 questions (table 6) that looked into the communication between the patient and the treating physician. It aimed to analyse the level of communication and to see if it predicted for better adherence to TKI therapy and also to see if they predicted for clinical outcomes.

Section 4: Internet and support networks

This section had 5 questions (table 7) looking into whether patients used internet to research about their disease and if support services like CML forums or psychologists were used by the CML patients. Each question as before had 5 possible answers ranging from 1-strongly agree, 2-agree, 3-unsure, 4-disagree to 5-strongly disagree. This was to see if better access to information and accessory facilities had a bearing on adherence.

Section 5: taking the medicine

It included thirteen questions (table 8) that captured information relating to patients taking their medications. The questions ranged from how difficult was it to remove the tablets from its package to swallowing them. There were a few questions pertaining to adherence and if patients took their tablets regularly, missed them on occasions and if they were adequately guided on how to take their medicines appropriately. The answers as in the sections above ranged from strongly agree to strongly disagree.
Section 6: Nilotinib usage

The section included 6 questions exclusively pertaining to nilotinib usage. The questions were intended to see if fasting and twice daily dosing of nilotinib had a detrimental effect on adherence and to see if it affected outcomes.

Section 8: Beliefs about medicines (BMQ questionnaire)

Patients’ beliefs about the prescribed treatment have been shown to be associated with and predict intentional nonadherence in other chronic illness groups (Clifford 2008). Beliefs about medicines questionnaire (BMQ – section 8) was used to assess the patients’ treatment beliefs. The BMQ is a 10 item questionnaire assessing the cognitive representation of medication. The BMQ comprises two sub-scales: **Necessity scale** assesses patients' beliefs about their personal need for the medicine and how important the medicine is in maintaining their health now and in the future. **Concerns scale** assesses perceptions of the potential negative consequences of taking the medicine including concerns related to beliefs about long-term effects, dependence and other disruptive effects.

Each item of the BMQ scales is scored on a 5-point Likert-type scale ranging from 1 = strongly agree to 5 = strongly disagree. Specific-Necessity and Specific-Concerns scales have 5 items and scores range from 5 to 25.

Scores obtained for the individual items within each scale are summed to give a scale score (necessity scale and concerns scale). Higher Necessity scores represent stronger perceptions of personal need for the medication to maintain health now and in the future. Higher Concerns scores represent stronger concerns about the potential negative effects of the medication.
A necessity concerns differential is calculated subtracting the necessity scores from concerns and the range obtained could vary from -20 to 20. A negative score represents concerns and a positive score leans towards necessity. The necessity and concerns scores are analysed as a continuous variable to see if they predict for adherence (also type of non adherence), response, relationship to anxiety and depression. Similar analysis is repeated using the necessity concerns differential. Here the necessity concerns differential is coded as 1 or 0 representing concerns and necessity respectively [score from -20 to 0 coded as “1” (concerns) and 1 to 20 coded as “0” (necessity)]. This categorical variable is then used to predict for adherence, clinical response and relationship to anxiety and depression.

(Section 9) Measures of adherence

Adherence was measured by four self-report measures

1. The visual analogue scale (VAS)

The patients estimate their adherence levels by placing a cross on a line. The VAS has previously been validated in chronic conditions like HIV and has been used in CML research\(^97,\,101,\,102\). VAS is a single question asking patients to estimate their adherence to TKI to determine a numerical value of adherence on a visually coded scale. Patients were asked to mark what they thought was their average adherence to TKI during the last 7 days on a 12 cm scale. Each cm corresponds to an adherence of 10% (0 to 120%). We used a 12cm scale instead of the typical 10cm scale to be able to capture over-adherence. The adherence values obtained are a continuous variable. They would be analysed as such and also be categorised to enable its usage in logistic regression. The VAS adherence scores were categorised into 4 categories (<80%, 81-90%, 91-98% and >100%) as a categorical variable.
2. **Haynes et al question:**

It involved asking patients about the number of tablets or capsules they have missed in the last 7 days\textsuperscript{103, 104}. The answer is numerical estimate of the missed doses in total for the last 7 days. The aim is to try and correlate the number of missed doses with clinical outcomes. We also categorised the missed doses into 4 categories (No missed doses, 1 missed dose, 2 missed doses and ≥ 3 missed doses. We compared the missed doses both as a continuous variable and as a categorical variable to predict clinical outcomes.

3. **Lu’s adherence scale**

The scale originally included 3 questions\textsuperscript{105}. The first two questions were likert scales asking patients the frequency with which they took their CML medications in the last 7 days and their ability to take all CML medicines as prescribed in the last 7 days). The responses involved 6 possible options which were codified from 0\% to 100\% at intervals of 20\% (0, 20,40,60,80 and 100). The third question asked patients the % of time they have been adherent to their TKI in the last 7 days and this was to be given as a verbal estimate and answers ranged from 0 to 100\%. The mean of the 3 answers was calculated as the measure of adherence. We categorised Lu’s adherence measure into 4 categories (<80\%, 81 to 90\%, 91 to 98\% and >98\%) as a categorical variable. The adherence was analysed both as a continuous and categorical variable to predict clinical outcomes.

Previous research has shown respondents find it difficult to estimate percentages verbally using the original Lu question; hence this question was changed to the visual analogue scale described above whereby patients could answer on a visual scale. We have referred to this adapted Lu’s scale as Lu’s in our study.

5. **Diagnostic adherence to medicines scale (DAMS):**
DAMS scale comprises of a set of 4 questions\textsuperscript{106}. They not only detect non-adherence, but also aim to distinguish between intentional and unintentional nonadherence. The first question is essentially a modification of the question by Haynes et al. The question asks patients to provide a numerical value of the tablets or capsules missed in the last 7 days. The actual tablets taken in the last 7 days is then derived by subtracting the missed doses from the prescribed dose. Question 2 seeks to identify the type of non-adherence (intentionally versus unintentionally missing doses) by asking patients to mention a reason for missing tablets or capsules in the last 7 days. Question three involves asking patients to estimate the number of extra tablets or capsules of the medication they have taken in addition to their usual dose in the last 7 days and this is meant to assess overuse of medication. Question 4 seeks to identify whether this overuse of medication was intentional or unintentional by again asking patients to specify a reason.

\textbf{Section 10: FACT-G (Functional Assessment of Cancer Therapy-General) : QOL}

Quality of life will be collected using the FACT-G (Supplement section), a validated quality of life questionnaire\textsuperscript{107, 108}. FACT-G comprises of 27 questions divided into four primary Quality of life domains: Physical Well-Being (PWB) (7 questions), Social/Family Well-Being (SWB) (7 questions), Emotional Well-Being (EWB) (6 questions), and Functional Well-Being (FWB) (7 questions). All four domains are to be scored simultaneously. There are 5 possible answers to all the 27 questions, scored on a 5-point Likert-type scale from 0 (not at all), 1(a little bit), 2 (some what), 3 (quite a bit) and 4(very much). The responses to all the 27 questions are summed up (the negatively worded questions are coded in the reverse). In cases where individual questions are skipped, scores are prorated using the average of the other answers in the scale. The total FACT-G score is obtained by summing individual
subscale scores (PWB + EWB + SWB + FWB). The higher the FACT-G score better is the quality of life.

**Section 11: Hospital Anxiety and Depression Scale**

The patients’ level of anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale (HADS)\(^{109}\) (supplement section). The HADS is a validated and widely used scale for assessing anxiety and depression in patients. HADS comprises of fourteen items of which 7 of the items relate to anxiety and seven relate to depression. All the 14 questions have 4 possible answers, scored using a likert type scale. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety or depression. A cut off point of 8 identifies anxiety or depression. The anxiety and depression scores are also categorised as 0 and 1. The anxiety and depression scores as both a continuous variable and categorical variable is then analysed to look for relationships with adherence and clinical outcomes.

**Section 12: Patient demographics**

Various patient demographic data were captured in this section ranging from their educational background, employment status, socioeconomic status and affordability to take their medicines if it was not provided free of charge.

**II.5 Statistical methods:**

The data was analysed using the statistical package SPSS statistics 20.0 (August 2012, SPSS Inc., Chicago, Illinois). The data collected from the questionnaire study was used in the analysis. The statistical methodology used for the individual analysis has been described in detail in the chapters (4, 5 and 6). P values were 2 sided and 95% confidence interval was used in the statistical analysis.
Chapter III. Importance of early molecular responses

III.1 Introduction

Various clinical trials have shown that second generation tyrosine kinase inhibitors (2G-TKIs) such as nilotinib and dasatinib induce higher rates of early complete cytogenetic response (CCyR) and deeper molecular responses than imatinib\textsuperscript{110, 111}. On the other hand imatinib has clear advantages over the 2G-TKIs such as the facts that we have more than thirteen years of experience using this drug and that its side effect profile is well understood\textsuperscript{112}. Moreover imatinib is likely to become much cheaper when the patent expires as it does soon in most countries. For these reasons there is an increasing interest in developing strategies that allow one to identify as early as possible those patients who are not going to respond optimally to imatinib, so that they can be offered 2G-TKI. These strategies are often referred to as ‘early intervention’ strategies. Strategies for early intervention may also be applied to patients treated with upfront 2G-TKI, but then the best alternative therapy is far from clear.

Several groups have shown that that the BCR-ABL1 transcript level measured at 3 or 6 months after starting TKI therapy strongly predicts for achievement of cytogenetic and molecular responses as well as for progression-free survival (PFS) and overall survival (OS)\textsuperscript{78, 91, 92, 113-115}. Marin et al has shown that CML patients treated with imatinib who at 3 months have a transcript level lower than 9.8% on the international scale or at 6 months lower than 1.67% have a better OS, PFS and higher CI of attainment of cytogenetic and molecular milestones compared to patients who fail to attain them\textsuperscript{91}. Hanfstein et al has showed that patients with Bcr-Abl transcripts <10% at 3 months have a better OS compared to patients >10% and similarly patients with transcripts less than 1% at 6 months fare better than patients who fail to attain them\textsuperscript{92}. We have also shown that similar results are evident in
2G-TKI dasatinib treated patients with a transcript level lower than 10% at 3 months fare significantly better than those with higher levels\textsuperscript{78}. Similarly Branford et al showed that patients with transcripts $\leq 10\%$ at 3 months on nilotinib had higher cumulative incidence of CCyR by 24 months than patients with transcripts of $> 10\%$ (53\% vs 16\%, $p<0.001$)\textsuperscript{116}. We have also shown that the molecular assessment made at 3 months on imatinib therapy is a better predictor of prognosis than transcript numbers assessed at 6 months or 12 months\textsuperscript{91}. Here we investigated whether it is possible to improve the prognostic accuracy of early measurement of the transcript level by combining the 3- and 6-month results.

### III.2 Methods

#### III.2.1 Patients

For this analysis we used 3 populations of newly diagnosed CML in CP patients. The first sets of 274 patients were seen at our institution as described in the methods section (chapter 2). They were all CP CML patients treated with imatinib 400 mg daily first line. The median follow-up was 69 months (range 17–131). During follow-up 118 patients discontinued imatinib and received nilotinib (n=37), dasatinib (n=72) or an allogeneic stem cell transplant (n=9).

The second patient cohort was a validation sample of 95 patients also treated with imatinib first line at the Royal Liverpool University Hospital. The third patient group was 142 patients treated with dasatinib 100 mg daily as first line therapy in the SPIRIT 2 study between August 2008 and September 2011 (ClinicalTrials.gov Identifier: NCT01460693). SPIRIT 2 trial is a phase 3 study in which newly diagnosed CML patients in chronic phase are randomly allocated to receive either imatinib 400 mg daily or dasatinib 100 mg daily. The median follow-up was 18.2 months (range, 12-35 months). Patients in all three cohorts gave written informed consent for their data to be used in this analysis.
Methods:

This is a retrospective analysis of the data. We have tried to combine the BCR-PCR values from the patients at various time points (3 and 6 months) to see if they combine to give a better predictor of poor responders. We have tried to identify patients who achieved both milestones of 9.84% at 3 months and 1.67% at 6 months and patients who failed to achieve both. The other 2 subgroups consisted of patients who attained the 3 month milestone of 9.84% but failed the 6 month cut off of 1.67% and also patients who failed the 3 month but attained the 6 month milestone. In this way we had 4 groups of patients and we tried to analyse overall survival (OS), cumulative incidence of CCyR and attainment of Complete molecular responses as described below.

Statistical analysis:

The data was analysed using the statistical package SPSS statistics 20.0 (August 2012, SPSS Inc., Chicago, Illinois). Probability of OS was calculated using the Kaplan meier method. We used standard definitions of CCyR and complete molecular response (CMR). Univariate analyses to calculate the probabilities of cytogenetic and molecular responses were done using the cumulative incidence (CI) procedure. P values were 2 sided.

III.3 Results:

We classified 274 patients, treated at Hammersmith Hospital according to their transcript levels. We used as a cut off the previously identified and validated transcript levels that optimally predict for OS at 3-months (lower or higher than 9.8%) and 6-months (lower or higher than 1.67%).
### III.3.1 Overall survival at 8 years:

One hundred and eighty one patients (66%) had low transcripts both at 3 (<9.8%) and 6 (<1.67%) months; these patients had an excellent overall survival of 93.5% at 8 years (Figure 5). Fifty seven patients (21%) who had high transcript levels on both occasions (3 and 6 months); these patients had an outcome significantly worse than those with lower transcripts at both time points, with an OS of 55.6% (p<0.0001 when comparing the survival outcomes for the two groups).

![Figure 5- Overall survival at 8 years](image)

8 year probability of OS. The 181 (66%) imatinib-treated patients with low transcript numbers both at 3 (<9.8%) and at 6 months (<1.67%) had an OS of 93.5% and constitute the reference category for this analysis (group A). The 57 (21%) patients who had high transcript levels on both occasions (group B) had an OS of 55.6% (p<0.001). The 30 (11%) patients with low transcript levels at 3 months but high transcript levels at 6 months (group C) had a OS of 92.4% (p=0.78). The 6 patients (2%) who had high transcript levels at 3 months but low levels at 6 months (group D) had OS= 83.3% (p=0.23). The p value for the comparisons between groups B and C was p=0.004 and between groups B and D was p=0.39.

Thirty (11%) patients had low transcript levels at 3-months but high transcript levels at 6-months; these patients had a prognosis similar to the patients with low transcripts at both
time points with an OS of 92.4% (p=0.78 when compared with patients who attained both cut offs, p=0.004 when compared to patients who failed both time paints). Only 6 patients (2%) had high transcript levels at 3-months but low levels at 6-months; these patients had an outcome similar to the patients with high transcript levels at both two time points with an OS of 83.3% (p=0.39).

III.3.2 Cumulative incidence of CCyR at 8 years

The patients who attained a transcript cut off of 9.8% at 3 months and 1.67% at 6 months (66%, 181 patients) had a 100% CI of attainment of CCyR, whereas the CI of CCyR was 14.9% in the patients (21%, 57 patients) who failed to attain both the cut offs at 3 and 6 months (p<0.001) (figure 6).

Figure 6- CI of attainment of CCyR at 8 years

8 years CI of CCyR for patients who attained both cut offs, failed both time points, attained 3 and failed 6 and failed 3 but attained 6 was 100%, 14.9% (p<0.001), 99.5% (p=0.001) and 33.3% (p<0.001).
In the patients who achieved the cut off at 3 months, but failed the 6 month cut off (11%, 30 patients), the CI of attainment of CCyR was 99.5% (p<0.001 when compared to the patients who failed both milestones). However the kinetics of attainment of CCyR was slower in the group that failed 6 month cut off after attaining the 3 month milestone as compared to the group that attained both. The median time to attainment of CCyR between the two groups was 6 months for the group that attained both milestones as compared to 16 months for the group that failed the 6 month milestone (p<0.001).

Finally the patients who failed the 3 month cut off but attained the 6 month milestone (2%, 6 patients), the CI of attainment of CCyR was 33.3% (p<0.001). The difference in attainment of CCyR between patients who attained 6 month milestone and failed the 3 month was no different to the patients who failed both milestones (p=0.09).

**III.3.3 Complete molecular response:**

We have previously identified cut offs in the 3- and 6-month transcript levels that predict with maximal sensitivity and specificity for the achievement of CMR, namely 0.61% and 0.21% respectively. We therefore wanted to investigate whether it was possible to improve the predictive value of the 3-month assessment by combining the 3- and 6-month results in patients who started treatment with imatinib (Figure 7).
8 year CI of CMR: Thirty four (13%) patients had low transcripts both at 3 and 6 months the 8-year CI of CMR was 75.5%. The CI of CMR for the six (2%) patients who had low transcript levels at 3 month but high levels at 6 months was CI=100%, p=0.8. The 193 (70.5%) patients who had high transcript levels on both occasions had a CI of CMR of 1.25 (p<0.001) and the 40 (14.5%) patients who had high transcript level at 3 months but low a 6 months had a CI of CMR of 3.6% (p<0.001).

We classified the patients using these cut-offs. Thirty four (13%) patients had low transcripts both at 3 and 6-months; these had a very high probability of achieving CMR (75.5%). Six patients (2%) with low transcript levels at 3 months but high at 6 months also had a high probability of achieving CMR (100%, p=0.8). On the other hand both the 193 patients (70.5%) who had high transcript levels on both occasions and the 14.5% patients who had high transcript level at 3 months but low levels 6 months had a very low probability of achieving a CMR at 1.25% (p<0.001) and 3.6% (p<0.001) respectively.

**Validation cohort 1:**

We validated our results by classifying the 95 patients treated with imatinib at the Royal Liverpool University Hospital according to their transcript levels at 3 and 6 months. As with our study patients, patients who met the 3-months landmark but who failed the 6-month landmark (n=9) had OS, PFS and CI of CCyR and CMR similar to those of patients who met
both landmarks (n=45), and patients who failed the 3-month landmark but who met the 6-month one (n=6) had OS, PFS and CI of CCyR and CMR similar to patients who failed both landmarks (n=34).

**Second validation cohort using 2G-TKI dasatinib**

We also investigated whether it was possible to improve the prognostic accuracy of early transcript measurements for patients who started treatment with dasatinib. We classified the patients according to transcript level at 3 months (lower or higher than 10%) and six months (lower and higher than 1%). As with imatinib, the 6-month transcript level did not improve the predictive power of the 3-month measurement (Table 1). Patients with a low transcript level on both occasions (86.3%) had a very high CI of CCyR. Patients with a high transcript level at both occasions (7%) fared poorly. As with imatinib the patients (10.9%) who had low transcript at 3 months and high transcripts at 6 also fared well but the kinetic of the response was significantly slower. Only one patient had high transcript levels at 3 months and low levels at 6 months.

<table>
<thead>
<tr>
<th>Transcript ratio</th>
<th>n (%)</th>
<th>CI of CCyR</th>
<th>CI of MR4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>6 months&lt;10%</td>
<td>&lt;1%</td>
<td>104 (81.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>&gt;1%</td>
<td>14 (10.6)</td>
<td>86.9</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>&lt;1%</td>
<td>1 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>&gt;1%</td>
<td>9 (7%)</td>
<td>55.0</td>
</tr>
</tbody>
</table>

Table 1: 2-year CI of CCyR and MR 4.5 in dasatinib treated patients

III.4 Discussion:

In summary the measurement of the transcript levels at 6 months adds very little prognostic discrimination to the measurement already taken at 3 months for patients who started...
treatment with either imatinib or dasatinib. With both drugs the patients who met the 3-month landmark but failed the 6-month landmark had outcomes similar to the patients who achieved both milestones. On the other hand the patients who failed the first landmark at 3 months do not seem to be “rescued” by the fact that they achieved the 6-month landmark, although this group is too small to be sure of this conclusion and clinical decisions in this group of patients should be made with caution. It is possible that the prognosis for patients starting TKI can be established accurately by assessing the transcript level just at 3 months. This means that strategies for early intervention can be based with confidence on decisions taken at this time point.

One of the possible discussion points using the early molecular monitoring is whether changing therapy on the basis of a 3 month failure will alter the outcome. To argue against the merits and demerits of changing TKI on the basis of a 3 month transcripts level, one has to take into account if the patients who fail the 3 month cut off represent an inherently poor risk CML patient cohort who may do badly irrespective of a change in TKI therapy. It remains to be validated in prospective randomised control trials if changing to a next generation TKI in the face of a failure to attain the 3 month milestone will improve the eventual clinical outcome. The ideal trial would have two arms where TKI therapy needs to be changed at 3 or 6 months to refute or accept the ideal time point to alter therapy.
Chapter IV. Self reported adherence measures predict poor responses and correlate well with each other

IV.1 Introduction

Adherence - Definition

WHO in 2001 had defined adherence as "the extent to which the patient follows medical instructions"\textsuperscript{117}. This definition limits the role of the patient to being passive without much involvement. A more practical definition of adherence incorporates the behaviour of the patient "the extent to which a person's behaviour - taking medication, corresponds with agreed recommendations from a health care provider"\textsuperscript{118, 119}. This not only adds weightage to the role a patient has in complying with the medical recommendations but also reiterates the fact that it is voluntary and depends on the patient's willingness to comply with advice.

Initially the problems related to non adherence was thought to be confined only to the chronic medical conditions like diabetes and hypertension. One of the best examples of a change in mentality about adherence involved HIV. Adherence was considered very critical in HIV as it involved taking 3-4 drugs in a perfect sequence to avoid resistance. Poor adherence rates leading to less than ideal outcomes in HIV patients were an eye opener for clinicians. This was validated in a number of studies looking at adherence in HIV patients\textsuperscript{13, 105, 120-122}.

It was not plausible at the beginning to think that people taking oral anti-cancer medications could also be non-adherent to therapy. Emerging evidence over the years have shown adherence to oral medications to vary from 20 to 100\%\textsuperscript{102}. Adherence studies with TKI therapies have shown startling results as well. Noens et al showed that only 14\% of all patients took the medications exactly as prescribed and only two thirds of the patients took
90% of their medications. Efficacie et al showed that only 53% of patients were adherent to TKI therapy in their observational study using questionnaires. Marin et al has showed that only 60% of patients took their medications all the time as prescribed and 26% of patients were found to taking only 90% of the medications from a study done using MEMS (micro electronic monitoring system). Ganesan et al showed non adherence rates of 30% in an observational study of over 500 patients with CP CML on TKI therapy.

Adherence has been shown to be critical in achieving deeper molecular responses. Marin et al showed that the 6 year probability of MMR was 94.5% with an adherence of >90% as compared to 28.4% probability with an adherence of <90% (p<0.001). Similarly the 6 year probability of complete molecular remission was 43.8% with an adherence of >90% as compared to 0% with a lower adherence (p=0.002). Ibrahim et al showed that poor adherence contributed to the loss of CCyR and imatinib failure in CP CML patients on imatinib therapy. The cumulative incidence of loss of CCyR was 26.8% with an adherence <85% as compared to 1.5% with an adherence of >85%. Given the significance of adherence to improved clinical outcomes, it became extremely important to find ways to monitor them.

Adherence can be monitored by a number of methods. The best would be continuous and directly observed monitoring, similar to DOPS (directly observed pill swallowing) used in multi drug resistant tuberculosis in some highly endemic countries. This method requires a lot of resources both financially and man power wise and hence unlikely to be a solution for rapid and effective monitoring tool in out-patient clinics. The next best solution is MEMS, which records the opening and closing of containers with the help of a micro chip embedded in the cap of the pill containers. We have shown that MEMS is superior to conventional methods in detecting non-adherence as the conventional methods sometimes tend to often
underestimate non-adherence\textsuperscript{93}. The downside of MEMS is the financial constraints involved and is not practically feasible in most instances. Pill counting involves counting pills at the end of each visit to determine the number of pills left over to assess the medications that has been taken in the intervening period of time. Unfortunately pill counting does not reflect the period of adherence over time as patients may have taken additional pills leading up to the clinic visit as has been shown in the MEMS study by Marin et al which compared MEMS with self reporting and pill counting. Monitoring of blood levels can capture a measure of adherence leading to the clinic visit, but the downside is that it does not reflect adherence over a period of time (similar to HbA1c). Pharmacy and insurance databases have been the basis for a number of adherence studies, but they too have their downsides in that they do not reflect actual pill taking by patients, rather only the fact that the patients come for a refill on time or not. The last but not the least method of adherence monitoring involves self reported measures. Self reported measures have historically been used in a number of chronic conditions like diabetes, hypertension and HIV. More and more studies are being done using self reported measures of adherence in oral anti cancer therapy. The advantage of self reported measures is that they are simple, easy to use and do not involve financial burden\textsuperscript{97}. The turnover can be rapid and they can be repeated used for monitoring adherence particularly useful in an out-patient setting. The downside of the self reported measures is that they often tend to under estimate non adherence as shown by Marin et al. The conditions under which the self report measures are recorded are also important as patients may feel they may be judged on the basis of their responses and hence likely to overestimate their level of adherence in the fear of not wanting to jeopardise the relationship with their healthcare professional.

We used four self-reported adherence measures (described in the methods section below) to predict clinical responses. The visual adherence scale (VAS), Haynes et al question, Lu’s
adherence scale and diagnostic adherence to medicines scale (DAMS). The VAS has previously been shown to be useful in not only chronic conditions like diabetes, hypertension and HIV, but also TKI therapy\textsuperscript{94, 97, 101, 120}. Haynes et al is recommended for predicting adherence to oral therapies using a simple question\textsuperscript{103}. DAMS scale was designed to try and extract information pertaining to the rates and type of non-adherence (intentional and non-intentional). It has been shown to be useful in identifying non adherence\textsuperscript{106}. Lu’s adherence scale was developed to detect non adherence in chronic conditions requiring oral therapies\textsuperscript{105}. Using a questionnaire based study we tried to correlate adherence with clinical outcomes and also wished to see if the adherence measures correlated with one another.

IV.2 Methods

Patients:

Two hundred and ninety six patients with CML in 1\textsuperscript{st} chronic phase (CP) were recruited during out-patient appointments from six hospitals (Hammersmith Hospital, Nottingham University Hospital, Royal Liverpool Hospital, Gartnavel General Hospital, Monklands and Hairmyers Hospitals) across the UK between September 2011 and January 2013. They were all asked to complete the questionnaires. The patient characteristics are presented in table 3. One hundred and fifty two patients (51.4\%) were on first line therapy, of whom 110 were on imatinib, 22 were on nilotinib and 20 on dasatinib. Of the remaining 144 patients (48.6\%) who had switched over to a second line therapy and beyond, 8 were on imatinib, 82 on nilotinib, 40 patients on dasatinib, 8 on bosutinib and 6 were on ponatinib. The median age was 58 years (range 18 to 92 years) and the median duration on tki therapy was 37 months (range from 3 to 156 months)
Adherence measures

VAS \(^{14}\) used a single item to determine a numerical value of adherence based on a visually coded scale. Patients were asked to mark what they thought was their average adherence to TKI during the last 7 days on a 12 cm scale. Each cm corresponds to an adherence of 10% (0 to 120%). We used a 12cm scale instead of the typical 10cm scale to be able to capture over-adherence.

Haynes et al\(^{103}\) was a single item asking patients to report the number of tablets/capsules they have missed in the last 7 days. DAMS\(^{106}\) was derived from the Haynes et al question. DAMS measured adherence as a percentage of the medications taken over 7 days (Calculated by subtracting the missed doses from the total prescribed dose and expressing the result as a percentage). The scale also comprised of 3 other items from which it was possible to calculate rates of intentional and non intentional adherence in the last 7 days (we have not used the three other items in this study).

Lu’s adherence scale\(^{105}\) included three questions. (The first two questions were likert scales asking patients the frequency with which they took their CML medications in the last 7 days and their ability to take all CML medicines as prescribed in the last 7 days). The responses to the two questions ranged from 0% to 100% at intervals of 20%. In the original Lu scale, the third question asked patients the % of time they have been adherent by oral questioning. As previous research \(^{11}\) has shown respondents find it difficult to estimate percentages using the original Lu question, we used the VAS scale where patients estimated their measure of adherence on a visual scale. The three questions provided 3 answers and the average of the three was taken as the measure of adherence.

Clinical responses
We compared the four adherence measures with responses based on the current European leukaemia network (ELN-2009) guidelines. The patients were classified as having optimal, suboptimal and poor responses based on BCR-ABL PCR values and dates of measurement of responses. For the purposes of this study optimal and suboptimal responses were pooled together. The analysis was done to see if low adherence could predict poor responders.

**Statistical methods**

The relationship between adherence as a continuous variable and responses (optimal and poor responses) were explored by Logistic regression. Adherences were categorised into cut offs of <95%, <90%, <85% and <80% and compared with responses using the Fisher's exact test and chi square tests. Spearman’s correlation index was used to correlate the four adherence scales. Logistic regression was used to predict the best adherence cut off in a multivariate model. P vaues were 2 sided and 95% confidence intervals were used. Data was analysed using SPSS V.20.

**IV.3 Results**

**IV.3.1 Visual adherence scale predicts for poor responses**

The median visual adherence scores for the 296 patients was 100% (range 50-120%). 11.5% of patients had an adherence of <95% and 6.4% of patients had an adherence of <90%. The adherence scores from VAS predicted poor responses (Relative risk- 1.03, p=0.003). We have previously shown that adherence <90% correlates with poor clinical outcomes. Nineteen patients with adherence <90% had significantly higher probability of having a poor response than the 274 patients with adherence levels >90% (36.8% vs. 15%,
p= 0.022). We tried to investigate the predictive value of other adherence cut offs (table 2) and thirty four patients with an adherence of <95% had a higher proportion of poor responders as compared to 259 patients with an adherence of >95% (29.4% vs. 14.7%, p=0.029). Similarly 18 patients with an adherence of <85% had a higher proportion of poor responders compared to 275 patients with an adherence of >85% (38.9% vs. 14.9%, p=0.015). Eleven patients with an adherence of <80% had a higher proportion of poor responders as compared to 282 patients with an adherence of >80% (54.5% vs. 14.9%, p=0.003).

Using a multivariate model, we tried to predict the best adherence cut off for predicting poor responders using the VAS. The adherence cut off of 80% (p=0.003) was found to have the best predictive value.

IV.3.2 Haynes et al question correlated with poor responses and increasing missed doses correlated with poorer levels of responses

Haynes et al question measured the number of tablets or capsules missed in the last 7 days. The median missed doses amongst the 296 patients was 0 (range 0-8). The missed doses estimated by Haynes et al was predictive of poor responses (OR 1.45, p<0.0001). Twenty two people who missed atleast 1 tablet (Haynes >1) in the last seven days had higher proportion of poor responses as compared to 271 people with no missed doses (36.4% vs. 14.8%, p=0.015). Although Haynes et al was developed to reflect predictive value of atleast 1 missed dose, we found increasing numbers of missed doses was predictive of poorer responses (table 2). Eleven patients who missed atleast 2 doses had a higher proportion of poor responders when compared to 282 patients with less than 2 missed doses (63.6% vs. 14.5%, p<0.001). Ten people who had missed more than 3 doses had a higher proportion of
poor responders as compared to 283 people who had missed fewer than 3 doses (70% vs. 14.5%, p<0.0001). Similarly 8 people with more than 4 missed doses had increased proportion of poor responders compared to people with fewer missed doses (75% vs. 14.7%, p<0.0001).

We tried to analyse different cut offs (different numbers of missed doses) that had the best predictive value in identifying poor responders. When analysed in a multivariate model, the most significant cut off was Haynes et al >3 (p<0.0001) in predicting poor responders.

**IV.3.3 Lu’s adherence scale was predictive of poor responses**

The median adherence by Lu’s measurement was 100% (range 33% to 107%). The adherence score from the scale was predictive of poor responders (Relative Risk- 1.03, p=0.021). Sixty nine patients with an adherence of <95% had a higher proportion of poor responders compared to 217 patients with an adherence of >95% (23.2% vs. 12.9%, p=0.039). Forty nine patients with an adherence <90% had higher proportion of poor responders as compared to 237 patients with an adherence >90% (26.5% vs. 13.1%, p=0.018). Similarly, patients with adherence cut offs of 85% and 80% had higher proportions of poor responders but did not reach statistical significance (table2).

All adherence cut offs were analysed in a multivariate model and the cut off <90% (p=0.018) was the best predictor of poor responses.

**IV.3.4 Diagnostic adherence to medicines scale predicts poor responders**

The median adherence reported on the DAMS was 100% (range 50 to 100%) and adherence scores predicted poor responses (Relative Risk- 1.06, p=0.005). Thirty eight patients with an adherence of <95% had a higher proportion of poor responders compared
to 255 patients with an adherence of >95% (28.5% vs. 14.9%, p= 0.025). Twenty eight patients with an adherence <90% had a higher proportion of poor responders compared to 265 patients with an adherence of >90% (39.3% vs. 14%, p= 0.002). Fourteen patients with an adherence of <85% had a higher proportion of poor responders compared to 279 patients with an adherence of >85% (57.1% vs. 14.3%, p<0.001). Similarly 13 patients with an adherence <80% had a higher proportion of poor responders compared to 280 patients with an adherence of >80% (53.8% vs. 14.6%, p=0.002).

Using a multivariate model, the best independent predictor of poor response was cutoff<85% (p<0.001).

**Haynes et al Qn predicts for the best responses and Self-reported adherence measures correlate with each other**

The four adherence scales were introduced into a multivariate model to see which one predicted the best for poor clinical responses. Haynes et al was found to be the best predictor of poor responses (OR- 1.5, p<0.0001). When we tried to combine the other adherence scales with Haynes et al, it did not improve the predictive ability of the scale.

Haynes et al correlated well with VAS (Pearson’s -0.85, p<0.0001), adapted Lu’s scale (Pearson’s -0.662, p<0.0001) and DAMS (Pearson’s -0.943, p<0.0001). Similarly DAMS correlated with adapted Lu (Pearson’s 0.65, p<0.0001) and VAS (Pearson’s, p<0.0001). There appears to be a positive correlation between some and a negative correlation between others. Haynes shares a negative correlation with the other scales because of the fact that lower numbers (less missed doses) by Haynes scale correlates with higher numbers of the other scales (adherence). The other scales VAS, Lu’s and DAMS all share a positive correlation between them (Table 1 below).
Table 2- Bivariate correlations between the 4 adherence measures

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Correlation</th>
<th>VAS</th>
<th>Haynes et al</th>
<th>Lu’s</th>
<th>DAMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>Pearson</td>
<td>1</td>
<td>-0.804</td>
<td>0.735</td>
<td>0.814</td>
</tr>
<tr>
<td>Haynes et al</td>
<td>Pearson</td>
<td>-0.804</td>
<td>1</td>
<td>-0.662</td>
<td>-0.943</td>
</tr>
<tr>
<td>Lu’s</td>
<td>Pearson</td>
<td>0.735</td>
<td>-0.662</td>
<td>1</td>
<td>0.656</td>
</tr>
<tr>
<td>DAMS</td>
<td>Pearson</td>
<td>0.814</td>
<td>-0.943</td>
<td>0.656</td>
<td>1</td>
</tr>
</tbody>
</table>

VAS- visual adherence scale, DAMS- diagnostic adherence to medicines scale, correlations > 0.7 are considered good, p <0.0001 for all correlations.

IV.4 Discussion:

We have showed that the four self reported adherence measures (VAS, Haynes et al, Lu’s and DAMS) correlate with poor responders as defined by ELN guidelines. In the case of VAS, adherence cut offs of 95%, 90%, 85% and 80% proved to have predictive value in identifying poor responses. However the best cut off on a multivariate model was the cut off of 80%. In the case of Lu’s adherence scale, only cut offs of 95% and 90% were found to be significant. DAMS however could predict poor responders with all four cut offs (95%, 90%, 85% and 80%). The best predictor on Lu’s and DAMS scales were 90% and 85% respectively. We have previously shown both these cut offs (90% adherence cut off identifying patients with increased 6 year probability of MMR\textsuperscript{93} and 85% cut off in predicting loss of CCyR\textsuperscript{124}) to be significant in predicting clinical outcomes in our MEMS study. Haynes et al looked at adherence as a measure of the number of missed doses in a 7 day period and increasing numbers of missed doses was found to be highly predictive of poor responses and the best predictor on a multivariate model was more than 3 missed doses.
There appeared to be a correlation between the four adherence measures. The best correlations were seen between the Haynes et al and the DAMS scale. This should be interpreted in the fact that DAMS is a modification of the Haynes et al scale and hence the strength of the correlation. There appears to be a slightly weaker correlation between the Lu’s scale and the rest, indicating that the group identified as being non adherent by Lu’s appears different to those identified by the other scales, further strengthening the independent predictive value of the four scales. With some weak correlations, the significance of all of them appears to be extremely good due to the large number of patients in the analysis.

The four self reported measures appeared to all identify a slightly different section of non adherent patients. We tried to predict the best out of the four and analysed them in a multivariate model, Haynes et al scale (predicting missed doses) was found to be the best predictor of poor responses. The other scales could not add sufficient value when they were combined with Haynes scale.

We have shown that self report measures have good predictive value in identifying poor responses and also correlate with each other. They appear to have varying best cut offs, but the underlying fact that they all are able to predict clinically useful non-adherence is important. One possible explanation for the different cut offs could be because of different adherence patterns being picked up by the four scales. For example, Lu’s is a product of 3 three questions, two of them not asking patients directly to indicate a numerical measure of adherence hence it may pick up more non-adherent patients (hence a higher cut off of 90%) as compared to VAS or DAMS which involve a more direct questioning and hence patients less likely to be forthcoming (deeper cut offs of 80% with VAS and 85% with DAMS). We
propose these self-report measures are easy to use and can be used repeatedly to identify a pattern of non-adherence which would help in addressing issues related to non-adherence
**Table 3: Patient characteristics**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current TKI therapy</td>
<td>Imatinib-118 (40%)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib-104 (35%)</td>
</tr>
<tr>
<td></td>
<td>Dasatinib-60 (20%)</td>
</tr>
<tr>
<td></td>
<td>Bosutinib-8 (2.7%)</td>
</tr>
<tr>
<td></td>
<td>Ponatinib-6 (2%)</td>
</tr>
<tr>
<td></td>
<td>Imatinib-400mg (72.8%)</td>
</tr>
<tr>
<td></td>
<td>300mg (11%)</td>
</tr>
<tr>
<td></td>
<td>600mg (7.6%)</td>
</tr>
<tr>
<td></td>
<td>800mg (3.3%)</td>
</tr>
<tr>
<td></td>
<td>Other doses (5.3%)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib-800mg (35.5%)</td>
</tr>
<tr>
<td></td>
<td>600mg (26.9%)</td>
</tr>
<tr>
<td></td>
<td>400mg (28.8%)</td>
</tr>
<tr>
<td></td>
<td>200mg (5.7%)</td>
</tr>
<tr>
<td></td>
<td>Other doses (3.1%)</td>
</tr>
<tr>
<td></td>
<td>Dasatinib-100mg (61.6%)</td>
</tr>
<tr>
<td></td>
<td>80mg (8.3%)</td>
</tr>
<tr>
<td></td>
<td>70mg (11.6%)</td>
</tr>
<tr>
<td></td>
<td>50mg (6.6%)</td>
</tr>
<tr>
<td></td>
<td>Other doses (11.9%)</td>
</tr>
<tr>
<td></td>
<td>Bosutinib-500mg (25%)</td>
</tr>
<tr>
<td></td>
<td>400mg (25%)</td>
</tr>
<tr>
<td></td>
<td>300mg (25%)</td>
</tr>
<tr>
<td></td>
<td>Other doses (25%)</td>
</tr>
</tbody>
</table>

| Age                                   | Median- 58 years                               |
|                                       | (range 18 to 92 years)                        |
| Duration of treatment                 | Median- 37 months                              |
|                                       | (range 3 to 156 months)                       |
| Medication frequency                  | Once a day- 202 (68%)                         |
|                                       | Twice a day- 94 (32%)                         |
| Current Treatment                     | First line TKI - 152 (51.4%)                  |
|                                       | Second line TKI - 74 (25 %)                   |
|                                       | Third line and beyond- 70 (23.6 %)            |
| Current TKI doses                     | Imatinib (n=118)                               |
|                                       | 400mg (72.8%)                                  |
|                                       | 300mg (11%)                                    |
|                                       | 600mg (7.6%)                                   |
|                                       | 800mg (3.3%)                                   |
|                                       | Other doses (5.3%)                             |
|                                       | Nilotinib (n=104)                              |
|                                       | 800mg (35.5%)                                  |
|                                       | 600mg (26.9%)                                  |
|                                       | 400mg (28.8%)                                  |
|                                       | 200mg (5.7%)                                   |
|                                       | Other doses (3.1%)                             |
|                                       | Dasatinib (n=60)                               |
|                                       | 100mg (61.6%)                                  |
|                                       | 80mg (8.3%)                                    |
|                                       | 70mg (11.6%)                                   |
|                                       | 50mg (6.6%)                                    |
|                                       | Other doses (11.9%)                            |
|                                       | Bosutinib (n=8)                                |
|                                       | 500mg (25%)                                    |
|                                       | 400mg (25%)                                    |
|                                       | 300mg (25%)                                    |
|                                       | Other doses (25%)                              |

(TKI- tyrosine kinase inhibitor)
Table 4- Probability of poor clinical responses related to adherence cut offs

VAS- visual adherence scale, DAMS- diagnostic adherence scale, p values are 2 sided. Various non adherence cut offs were explored to identify poor responders.

<table>
<thead>
<tr>
<th>Scales</th>
<th>Adherence cut offs</th>
<th>Number</th>
<th>Poor responses (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>&lt;95%</td>
<td>yes-34</td>
<td>29.4% vs. 14.7%</td>
<td>p= 0.029</td>
</tr>
<tr>
<td></td>
<td>No- 259</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;90%</td>
<td>yes-19</td>
<td>36.8% vs. 15%</td>
<td>p= 0.022</td>
</tr>
<tr>
<td></td>
<td>No- 274</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;85%</td>
<td>yes-18</td>
<td>38.9% vs. 14.9%</td>
<td>p= 0.016</td>
</tr>
<tr>
<td></td>
<td>No- 275</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;80%</td>
<td>yes-11</td>
<td>54.5% vs. 14.9%</td>
<td>p= 0.003</td>
</tr>
<tr>
<td></td>
<td>No- 282</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haynes et al</td>
<td>≥1 missed dose</td>
<td>yes-22</td>
<td>36.4% vs. 14.8%</td>
<td>p= 0.015</td>
</tr>
<tr>
<td></td>
<td>No- 271</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥2 missed dose</td>
<td>yes-11</td>
<td>63.6% vs. 14.5%</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No- 282</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3 missed dose</td>
<td>yes-10</td>
<td>70% vs. 14.5%</td>
<td>p &lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>No- 283</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥4 missed dose</td>
<td>yes-8</td>
<td>75% vs. 14.7%</td>
<td>p &lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>No- 285</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu’s adherence scale</td>
<td>&lt;95%</td>
<td>yes-69</td>
<td>23.2% vs. 12.9%</td>
<td>p= 0.039</td>
</tr>
<tr>
<td></td>
<td>No- 217</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;90%</td>
<td>yes-49</td>
<td>26.5% vs. 13.1%</td>
<td>p= 0.021</td>
</tr>
<tr>
<td></td>
<td>No- 237</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;85%</td>
<td>yes-37</td>
<td>24.3% vs. 14.1%</td>
<td>p= 0.106</td>
</tr>
<tr>
<td></td>
<td>No- 249</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;80%</td>
<td>yes-29</td>
<td>24.1% vs. 14.4%</td>
<td>p= 0.177</td>
</tr>
<tr>
<td></td>
<td>No- 257</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAMS</td>
<td>&lt;95%</td>
<td>yes-38</td>
<td>28.5% vs. 14.9%</td>
<td>p= 0.025</td>
</tr>
<tr>
<td></td>
<td>No- 255</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;90%</td>
<td>yes-28</td>
<td>39.3% vs. 14%</td>
<td>P=0.002</td>
</tr>
<tr>
<td></td>
<td>No- 265</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;85%</td>
<td>yes-14</td>
<td>57.1% vs. 14.3%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No- 279</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;80%</td>
<td>yes-13</td>
<td>53.8% vs. 14.6%</td>
<td>p=0.002</td>
</tr>
<tr>
<td></td>
<td>No- 280</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter V. Relationship between self reported adherence and patient related factors

V.1 Introduction

WHO estimates that nearly half the patients in the developed countries fail to take their long term medications regularly. Adherence to TKI therapies has been identified to be a key determinant of improved outcomes amongst CML patients. The potential problems that can arise in patients on long term medications could arise either at initiation or compliance or early discontinuation. A number of factors are thought to influence adherence to taking long term TKI therapy. The factors could be patient related (intentional or non intentional non adherence) or physician related (patient education or adequate management of side effects). Poor adherence to prescribed treatments are usually thought to be due to a combination of various factors like side effects, access to medications, patient education, routines and patient behaviours. It has been postulated that a therapy that requires a higher degree of change in one’s routine or behaviour decreases compliance. We have tried to study the influence of such patient related factors in a cohort of 296 patients with CML in CP to see if they influence adherence to TKI therapy using a questionnaire based study.

V.2 Methods

5.2.1 Patients

Two hundred and ninety six patients with chronic myeloid leukaemia in 1st chronic phase from 6 hospitals across the UK completed questionnaires on adherence measures and patient related factors. The patient cohort is the same one that has been used in the analysis for chapter 4 and their characteristics have been described in detail in the previous
chapter (chapter 4, tabular column 3). Briefly, the median age of the patients is 58 years (range 18 to 92 years). The median duration of TKI therapy was 37 months (range 3 to 156 months).

5.2.2 Questionnaire:

We have used the questionnaire described in detail in the methods chapter (also included in the supplement section). From the questionnaire we have used questions (outlined in tables 5-8) pertaining to daily routine (n=5), communication (n=7), internet support (n=5) and taking the medications (n=13) (sections 5, 6, 7 and 8 respectively). There were a total of 30 questions that we have used in this analysis. All the questions had 5 possible answers marked from 1 to 5 (1- strongly agree, 2- agree, 3-unsure, 4- disagree, 5- strongly disagree). The positively worded questions were marked from 1 to 5 and the negatively worded questions were marked from 5 to 1 for the purposes of this analysis.

In order to study the relationship between adherence and patient related factors we have done 2 types of analysis. In the first we have analysed the questions individually (n=30) to see if they predicted for adherence. Second, as a group (i.e. like Daily routine (5 questions) was analysed as one to see if they predicted for adherence. The sections were considered to be a single blocks. The blocks were meant to convey the mood or sense of the 5 questions it includes, for example the first block includes 5 questions on daily routine and the block referrers to routines remaining the same in spite of the cml treatment. An agreement in the form of answers 1 or 2 would mean that patients feel their routines have not changed. We tried to see if the answers in agreement to the questions predicted high or low adherence.

5.2.3 Statistical methods:
Briefly, the questionnaire consists of 8 sections in which we have used sections 5, 6, 7 and 8 for the purposes of this analysis. The questions (outlined in table 5, 6, 7 & 8) were considered both independently and as a block (each section) to see if they predicted for adherence. The block refers to the mean of the questions in each section, for example the first section on daily routines has 5 questions. The questions were coded to ensure they reflected the fact that the routines had not changed despite CML treatment. We then tried to see if this predicted for adherence categories.

The average of the answers for each block was used in the analysis when being considered together. The answers ranged from 1 to 5 and these were used as a continuous variable for the purposes of analysis. The four adherence measures (Visual adherence scale, Haynes et al question, Lu's and DAMS) have been described in detail in the previous chapter. The four adherence measures were categorised into 4 categories (table 9) and these were used as a categorical variable. We tried to predict adherence (dependent variable) using the answers from the questions (independent variable) using ordinal logistic regression. P values were 2 sided and were corrected accordingly.

V.3 Results:

V.3.1 Section 5: Daily routines: description of answers

Daily routines of patients do not seem to be affected by their CML treatment. Majority of patients (70%) felt that their routines remained the same and even when it changed, they (80%) were able to adapt easily to it. The questions involving daily routine and the median value of the answers are given in the table below (table 5).

Eighty two percent of patients felt their mealtimes had not changed much since they started taking their TKI therapy. An interesting point to note is that majority of the patients did not have support at home; with 79% saying they did not have someone helping them with
managing their treatment at home. Most of the patients (65%) did not travel long to get to their hospital for treatment.

**Table 5 - Daily routine questions & Answers**
The answers were codified as classified as 1: strongly agree, 2: agree, 3: unsure, 4: disagree and 5: strongly disagree. The first column reflects the percentage of patients who agree or strongly agree with the question. The second column reflects the percentage of patients who disagree or strongly disagree with the question and the third column represents the median of the answers to the question.

<table>
<thead>
<tr>
<th>Questions</th>
<th>(Agree/strongly agree) %</th>
<th>(Disagree/strongly disagree) %</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My mealtimes have NOT changed much since I started taking my current medicine</td>
<td>82%</td>
<td>15.2%</td>
<td>2</td>
</tr>
<tr>
<td>2. Someone helps me with managing my treatment at home</td>
<td>18%</td>
<td>77.4%</td>
<td>4</td>
</tr>
<tr>
<td>3. My daily routine changed a lot when I started my current CML medicine</td>
<td>27.8%</td>
<td>65%</td>
<td>4</td>
</tr>
<tr>
<td>4. I found it easy to adapt to the routine of taking my current medicine</td>
<td>80.4%</td>
<td>12.4%</td>
<td>2</td>
</tr>
<tr>
<td>5. I travel for a long time to get to my CML appointments at the hospital</td>
<td>33.3%</td>
<td>60%</td>
<td>4</td>
</tr>
</tbody>
</table>

(Questions 3 and 5 are worded negatively, hence a median value in excess of three for these mean a disagreement to the questions, which would in fact mean agreeing with a positively worded question)

**V.3.2 Section 6: Communication with the physician: description of answers**
The section of the study deals with communication between the patient and the treating physician. The median and the percentage of the answers to the communication questions are tabulated below (table 6).

The questions were intended to see if there was good communication between physicians’ and the patients and if that influenced adherence. Ninety two percent of patients were told how to take their medicines as per advice and 78% of patients agreed that their doctor had spoken to them about how to manage side effects from their treatment.

The patients agreed with statements where they were asked if their physician had advised them appropriately about their medicines, cml management and dealing with side effects. Eighty percent of patients concurred their doctor has asked them about how they are getting
on with taking their medicine. Eighty seven percent of them felt their doctor has explained how to manage their CML treatment. Ninety two percent agreed that their doctor has advised them to take their medicine as prescribed.

Patients seemed to understand what their physicians told them (89%) and even when they did not, majority (90%) asked for clarifications and explanations. Ninety five percent of patients think their doctor listens to what they have to say.

**Table 6- Communication questions & answers**

The answers were codified as classified as 1: strongly agree, 2: agree, 3: unsure, 4: disagree and 5: strongly disagree. The first columns reflect the percentage of patients who agree or strongly agree with the question. The second column reflects the percentage of patients who disagree or strongly disagree with the question and the third column represents the median of the answers to the question.

<table>
<thead>
<tr>
<th>Questions</th>
<th>(Agree/strongly agree) %</th>
<th>(Disagree/strongly disagree) %</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. My doctor has spoken to me about how to manage side effects from my current CML medicine</td>
<td>78%</td>
<td>13%</td>
<td>2</td>
</tr>
<tr>
<td>7. My doctor does NOT generally ask me about how I am getting on with taking my medicine</td>
<td>17.2%</td>
<td>80.4%</td>
<td>4</td>
</tr>
<tr>
<td>8. My doctor has explained to me how to manage my current CML treatment</td>
<td>87.6%</td>
<td>8.6%</td>
<td>2</td>
</tr>
<tr>
<td>9. My doctor has told me to take my medicine exactly as prescribed</td>
<td>92%</td>
<td>4%</td>
<td>1</td>
</tr>
<tr>
<td>10. I generally do NOT understand what my doctor says about my CML treatment</td>
<td>6.2%</td>
<td>89%</td>
<td>5</td>
</tr>
<tr>
<td>11. If I do NOT understand what my doctor says I generally ask the doctor to explain</td>
<td>87.3%</td>
<td>11.6%</td>
<td>2</td>
</tr>
<tr>
<td>12. My doctor does NOT listen to what I have to say</td>
<td>3.1%</td>
<td>95%</td>
<td>5</td>
</tr>
</tbody>
</table>

(Questions 7, 10 and 12 are worded negatively; hence a median value in excess of three means a disagreement to the questions, which would in fact mean agreeing with a positively worded question)

**V.3.3 Section 7: Internet usage and patient support groups**

In our study, we included this section to understand how much the patients used internet to learn about their CML treatment and to see if they utilised the services of the support groups. The median values of the answers given by the patients to the questions pertaining to internet are provided in the table below (table 7).
The overwhelming message seems to be that the patients did not use the internet much nor did they utilise the support service networks, in fact nearly 52% of patients do not search the internet to find out information about their CML.

Seventy three percent do not use the CML internet forums or networks. Eighty three percent are not in contact with CML patient advocacy groups. Eighty six percent of patients who answered the questionnaire have not used the CML patient support services in the form of a councillor or a psychologist and an equal number have never been in contact with a support person who is also a CML patient.

Table 7- Internet support questions & answers

The answers were codified as classified as 1: strongly agree, 2: agree, 3: unsure, 4: disagree and 5: strongly disagree. The first columns reflect the percentage of patients who agree or strongly agree with the question. The second column reflects the percentage of patients who disagree or strongly disagree with the question and the third column represents the median of the answers to the question.

<table>
<thead>
<tr>
<th>Questions</th>
<th>(Agree/strongly agree) %</th>
<th>(Disagree/strongly disagree) %</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. I search the internet to find information about my CML</td>
<td>43.3%</td>
<td>52.2%</td>
<td>3</td>
</tr>
<tr>
<td>17. I use online CML internet forums / networks</td>
<td>18.5%</td>
<td>76%</td>
<td>4</td>
</tr>
<tr>
<td>18. I am in contact with CML patient advocacy groups</td>
<td>8.8%</td>
<td>86%</td>
<td>4</td>
</tr>
<tr>
<td>19. I have used CML patient support services (e.g. councillor/psychologist)</td>
<td>7.4%</td>
<td>89.5%</td>
<td>4</td>
</tr>
<tr>
<td>20. I have been in contact with support person who is also a CML patient</td>
<td>8.8%</td>
<td>87.4%</td>
<td>4</td>
</tr>
</tbody>
</table>

(Values higher than 3 indicate a strong disagreement with the question)

V.3.4 Section 8: Taking the medications: description of the answers

Thirteen questions (detailed in table 8 below) on taking the medications represented patients’ views on problems faced when having to take their medications. Over 90% of patients did not have problems whilst physically taking the medications in terms of swallowing, packaging or having reminders to help them. In fact nearly three fourths of the patients do not keep their medicines in little compartments with timings and days of the week and also not use an alarm to help them take their CML medications.
In our study, we identified that generally patients are not forgetful in taking their medications and appear to have strong perceptions when it comes to it. When asked about missing doses, 78% of the patients interviewed do not forget to take their CML medicine. Ninety percent of patients do not stop taking their medications for some reason without consulting their doctor. Thirty two percent of patients were told by their doctors that it did not matter if they missed an occasional dose.

We tried to find out about patients’ perceptions on the effect of missed doses with their clinical outcomes. Only 64% disagreed with the fact that their response will not be affected if they miss an occasional dose of their CML medicine. When asked if the patients did miss an occasional dose, 25% said yes. On direct questioning, 90% felt they would not skip their CML medicine and two thirds of patients (60%) agreed that they would be worried if they missed a dose.

To understand the physicians role in patients perceptions, 30% of patients felt that they have been told that they needed to take every single dose of their cml medications or they might not work. The median values of the answers to the questions in this section are outlined below (table 8).

Table 8- Taking the medicines questions & answers

The answers were codified as classified as 1: strongly agree, 2: agree, 3: unsure, 4: disagree and 5: strongly disagree. The first columns reflect the percentage of patients who agree or strongly agree with the question. The second column reflects the percentage of patients who disagree or strongly disagree with the question and the third column represents the median of the answers to the question.

<table>
<thead>
<tr>
<th>Questions</th>
<th>(Agree/strongly agree) %</th>
<th>(Disagree/strongly disagree) %</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. I find it difficult to swallow my CML medicine</td>
<td>5.5%</td>
<td>93.2%</td>
<td>5</td>
</tr>
<tr>
<td>22. I sometimes forget to take my medicine</td>
<td>19.3%</td>
<td>88%</td>
<td>4</td>
</tr>
<tr>
<td>23. The doctors have said that it does NOT matter if I miss the occasional dose</td>
<td>18.7%</td>
<td>68.4%</td>
<td>4</td>
</tr>
<tr>
<td>24. I find it difficult to take the medicine out of the packaging</td>
<td>6.4%</td>
<td>92.2%</td>
<td>5</td>
</tr>
<tr>
<td>25. Sometimes I stop taking my CML medicine for some reason for a few days without consulting my doctor</td>
<td>6.8%</td>
<td>92.2%</td>
<td>5</td>
</tr>
<tr>
<td>26. It will NOT affect my response if I miss the occasional dose of</td>
<td>17%</td>
<td>65%</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>medicine</td>
<td>22.8%</td>
<td>75%</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------------------------------</td>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>27</td>
<td>I keep my medicine in a box with little compartments for timings and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>days of the week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>I was off my medicine for some time and it did NOT affect my CML much</td>
<td>26.3%</td>
<td>61.7%</td>
</tr>
<tr>
<td>29</td>
<td>I think it is ok to miss a few doses now and again</td>
<td>13.4%</td>
<td>79.4%</td>
</tr>
<tr>
<td>30</td>
<td>I sometimes decide to skip doses of my current CML medicine</td>
<td>6.5%</td>
<td>91.4%</td>
</tr>
<tr>
<td>31</td>
<td>I use an alarm to help me remember to take my CML medicine</td>
<td>19.7%</td>
<td>88.3%</td>
</tr>
<tr>
<td>32</td>
<td>I would feel worried if I missed a dose</td>
<td>61.6%</td>
<td>28.4%</td>
</tr>
<tr>
<td>33</td>
<td>I have been told that I need to take every single dose or my treatment</td>
<td>30.3%</td>
<td>46.9%</td>
</tr>
<tr>
<td></td>
<td>might NOT work</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**V.3.5 Adherence measures**

The four adherence measures (VAS, Lu’s adherence, DAMS and Haynes et al) were calculated as described in detail in the methods chapter and chapter 4.

Visual adherence scale (VAS) was based a single question and the self reported adherence ranged from 50% to 120% with a median of 100%. 49 patients (16.5%) had a self reported adherence of less than 100%. VAS was divided into 4 categories (<80%, 81-90%, 91-98% and >98%) to facilitate this analysis. Similarly self reported Lu’s adherence had a median value of 100% (range 33% to 107%). DAMS adherence values had a median of 100% (range 50 to 100%). Both Lu’s and DAMS were categorised into the same 4 categories as VAS. Haynes et al question measured the number of missed doses through a single question. It was also divided into 4 categories based on the number of missed doses (no missed doses, 1 missed dose, 2 missed doses and greater than 3 missed doses) for the purposes of this analysis. The median missed dose was 0 and the range was 0 to 8. The adherence measures categorised to 4 categories (0 to 3) and the number of patients in each category has been summarised below (table 9).
Table 9- Adherence categories with patients according to the 4 adherence measures

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>Adherence categories</th>
<th>Number of patients</th>
<th>Categorical variables</th>
<th>(missed doses)</th>
<th>patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAS</td>
<td>Lu’s</td>
<td>DAMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt;80%</td>
<td>16</td>
<td>28</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>80-90%</td>
<td>17</td>
<td>21</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>91-98%</td>
<td>14</td>
<td>26</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;98%</td>
<td>239</td>
<td>203</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&gt;=3 doses</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 doses</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 doses</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 dose</td>
<td>250</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These 4 categories of adherence measures were used as a categorical variable to compare against the answers to the questions both individually and as a group of questions in each category.

V.3.6 Predictive value of patient related factors on self reported measures of adherence.

**Block: (description)**

Briefly, as described in the methods, when the entire section was analysed as one, it is referred to as the block. The block is meant to convey the meaning of all the questions as one, for example in the section on daily routines, there are 5 questions. When being analysed as a block, it refers to “the routines have not changed much since cml therapy was commenced”. The median of all the 5 answers are used and the average is taken to be the number representative of the block and it can range from 1 (strongly agree) to 5 (strongly disagree). A value closer to 1 would mean the people agree with the statement that their routines have not changed and closer to 5 would mean they disagree.

V.3.6.1 Daily routine (5 questions)

The answers were first compared as a block and secondly analysed individually to see if they predicted for the 4 categories of adherence. The questions were re-coded to reflect the
fact that the routines have not changed or have been affected despite cml therapy. The median of these 5 questions reflected the mood of the block.

V.3.6.1a Questions when analysed as a block: (No change in routines predicted for higher adherence)

The median value of the block is 2 (agreement). The block refers to the routines being unchanged by CML treatment. The daily routine questions and their answers did not predict for adherence by VAS (Odds Ratio (OR) -0.21, p = 0.209). The daily routine block was predictive of the missed doses (Haynes et al) (OR +0.43, p=0.053). Patients whose daily routines were unchanged since the commencement of cml therapy predicted for higher adherence using Lu’s scale (OR -1.05, p<0.0001). When the routines were unchanged, the answers were not predictive of the adherence measurements by DAMS (OR -.39, p=0.085). The high negative factor (OR) estimate implies that for every 0.2 reduction in the answer score, the adherence increases by 5%. The factor is positive for the Haynes scale; here it implies a positive correlation as a reduction of missed doses is considered significant.

V.3.6.1b Questions when analysed individually using the 4 adherence measures:

The questions (n=5) were individually analysed using logistic regression to see if they predicted for the adherence categories by the four measures.

Using VAS

Questions 2 (Someone helps me with managing my treatment at home); p=0.046 and 3 (My daily routine changed a lot when I started my current CML medicine); p=0.05 were independently predictive of adherence by VAS. The answers to the other 3 questions could not predict adherence using VAS.
Using Haynes et al:

Question 2 (Someone helps me with managing my treatment at home); p=0.01 was independently predictive of the missed doses by Haynes et al. The answers to the other 4 questions could not predict for adherence using Haynes scale.

Using Lu’s adherence scale:

Question 2 (Someone helps me with managing my treatment at home); p=0.019 was independently predictive of adherence by Lu’s. The answers to questions 3 (My daily routine changed a lot when I started my current CML medicine); p= 0.02 and 4 (I found it easy to adapt to the routine of taking my current medicine); p= 0.002 were found to have independent predictive values. The answers to the other 2 questions could not predict adherence using Lu’s.

DAMS:

Question 2 (Someone helps me with managing my treatment at home); p=0.03 was independently predictive of the DAMS. The answers to the other 4 questions could not predict adherence using DAMS adherence measures.

V.3.6.2 Communication with the doctors (7 questions)

V.3.6.2a Questions when analysed as a block (Good communication between patients and doctors predicted for adherence)

The median value of the block was 2, refers to good communication between the patients and doctors. This did not predict for adherence by VAS (OR -.38, p=0.24) or by Haynes et al (OR +.3, p=0.132). The answers to the communication questions, referring to good communication between patients and doctors predicted for high adherence by Lu’s (OR -.5,
p=0.038) and not by the DAMS scale (OR -.31, p=0.108). The negative factor estimate (OR) in the case of Lu’s adherence implies that for every 0.2 reduction in the value of the answer, there is an increase in adherence by 2.5%.

V.3.6.2b Questions when analysed individually to look for predictive value:

The questions (n=7) were individually analysed using logistic regression to see if they predicted for the adherence categories by the four measures.

The communication questions did not have any independent predictive in predicting adherence by any of the four scales.

V.3.6.3 Internet and support services network usage: (5 questions)

V.3.6.3a Questions when analysed as a block using the adherence measures (usage of internet and support services did not predict for higher adherence)

The median value of the block was 4 implying poor patient’s usage of the internet and support services. The usage of internet and support services did not predict adherence by VAS (OR -.22, p=0.27). Patients usage of internet and the services of the support groups was not predictive adherence by Haynes et al (OR +.19, p=0.3) or Lu’s adherence categories (OR -.02, p=0.288). Similarly, the 5 answers as a block was not predictive of DAMS adherence categories either (OR -.17, p=0.289). There is a change in adherence by 2.5% for 0.2 reduction in the value of OR.

V.3.6.3b Questions when analysed individually to look for predictive value:

The questions (n=5) were individually analysed using logistic regression to see if they predicted for the adherence categories by the four measures.
Using VAS:

Answers to question 3 (I am in contact with CML patient advocacy groups) could independently predict for adherence (p=0.034). The other 4 questions and their answers could not predict for adherence.

Haynes et al question:

None of the 5 questions had any significant independent predictive value in predicting for adherence using Haynes et al.

Lu’s adherence categories

Answers to question 3 (I am in contact with CML patient advocacy groups) could independent predict for adherence using Lu’s (p=0.032). The other 4 questions and their answers could not predict for adherence.

DAMS:

None of the 5 questions had any significant independent predictive value in predicting for adherence using DAMS.

V.3.6.4 Taking the medications (13 questions)

V.3.6.4a Questions when analysed as a block using the adherence measures (Patients views on taking the medications, i.e. patients who had less problems taking their medications had higher adherence)

The median value of the block is 2; implying patients are not having problems whilst taking their medications. This correlated with high adherence as measured by the four categories
of VAS (OR -1.31, p<0.001). Similarly, the block was highly predictive of high adherence by Haynes et al (OR +1.59, p<0.0001), i.e. patients who did not have problems missed fewer doses of their TKI. The block was also highly predictive of higher categories of adherence by Lu’s (OR -1.23, p=0.001) and the DAMS categories (OR -1.45, p<0.0001). The high factor estimates (OR) establishes the significance of the block in predicting adherence. The negative values in the case of VAS, Lu’s and DAMS indicates an increase of >10% in adherence for every 0.2 reduction in the value of the answers. Similarly a positive estimate for Haynes correlates with a decrease in missed dose by 1.6 for every 0.2 reduction in the value of the answer.

V.3.6.4b Questions when analysed individually to look for predictive value:

The questions (n=13) were individually analysed using logistic regression to see if they predicted for the adherence categories by the four measures.

VAS:

There were three questions that had independent predictive value. Answers to question 26 (It will NOT affect my response if I miss the occasional dose of medicine) was predictive of VAS; p=0.01. Similarly answers to question 30 (I sometimes decide to skip doses of my current CML medicine); p=0.022 and question 31 (I use an alarm to help me remember to take my CML medicine); p=0.01 were predictive of adherence by VAS independently. The other 10 questions were not found to have independent predictive value.

Haynes et al

There were four questions that had independent predictive value. Question 22 (I sometimes forget to take my medicine) was found to be predictive of adherence by Haynes et al; p=0.05. Answers to question 26 (It will NOT affect my response if I miss the occasional
dose of medicine) was predictive; p=0.003. Similarly answers to question 30 (I sometimes decide to skip doses of my current CML medicine); p=0.002 and question 31 (I use an alarm to help me remember to take my CML medicine); p=0.02 were predictive of missed doses by Haynes et al independently. The other 9 questions were not found to have independent predictive value.

Lu’s adherence categories

There were four questions that had independent predictive value. Question 22 (I sometimes forget to take my medicine) was found to be predictive of adherence by Lu’s categories; p=0.04. Answers to question 26 (It will NOT affect my response if I miss the occasional dose of medicine) was predictive; p=0.02. Similarly answers to question 30 (I sometimes decide to skip doses of my current CML medicine); p=0.05 and question 31 (I use an alarm to help me remember to take my CML medicine); p=0.05 were predictive of adherence by Lu’s independently. The other 9 questions were not found to have independent predictive value.

DAMS

There were four questions that had independent predictive value. Question 22 (I sometimes forget to take my medicine) was found to be predictive of adherence by DAMS categories; p=0.022. Answers to question 26 (It will NOT affect my response if I miss the occasional dose of medicine) was predictive; p=0.004. Similarly answers to question 30 (I sometimes decide to skip doses of my current CML medicine); p=0.005 and question 31 (I use an alarm to help me remember to take my CML medicine); p=0.02 were predictive of adherence by
DAMS independently. The other 10 questions were not found to have independent predictive value.

V.3.7 Questions that were found to have independent prognostic value in predicting adherence categories are combined together

There were a total of 30 questions of which 8 were found to be significant in predicting poor adherences using the 4 scales. Of the 8, two questions (Question 22 and 30) were found to directly reflect adherence, hence they were excluded.

Using the remaining six questions [Someone helps me with managing my treatment at home (Q2), My daily routine changed a lot when I started my current CML medicine (Q3), I found it easy to adapt to the routine of taking my current medicine (Q4), I am in contact with CML patient advocacy groups (Q18), It will NOT affect my response if I miss the occasional dose of medicine (Q26) and I use an alarm to help me remember to take my CML medicine (Q31)], we tried to create a block of questions to test their ability to predict adherence both as a group and individually.

On multivariate analysis, 4 questions were found to predict adherence independently. Question 2 (p=0.04), 3(p=0.005), 4(p=0.001) and 26(p=0.009).

These 4 questions as a block were found to be highly significant in their ability to predict adherence (VAS, p=0.001; Haynes et al, p=0.001 and Lu’s, p<0.0001 and DAMS. P=0.001).

V.4 Discussion

In our study we identified that Patient related factors like daily routines, communication with physician and more importantly factors related to the patient experience in taking the medications were found to influence adherence as we had speculated.
Patients’ day to day routines, when they remain unaltered with their CML therapy was associated with higher adherence as measured by Lu’s adherence scale and was also predictive of lower number of missed TKI doses. However when the routines remain the same, they were not found to be significantly predictive of adherence by the other 2 measures (VAS and DAMS). This could be explained by the higher numbers of people being found non adherent by the Lu’s method and hence shows a better relationship compared to other methods. Individual answers indicate that majority of the patients felt their routines had not changed following their CML therapy, but patients found it easy to adapt change in routine when it happened. Most of the patients surveyed did not have support at home to help them manage their CML treatment. It appears that when routines remain the same or when patients are able to adjust to the routines without a great deal of change to their lifestyle, it results in better adherences. It may be speculated that that people who are able to adjust their lifestyle are more likely to cope with issues arising out of their CML management and hence appear to be better at adhering to the therapy as prescribed.

Good communication between the patient and their treating physician predicted for higher adherence categories by Lu’s adherence scale (p=0.038) and not by the other three adherence measures. One possible explanation for the predictive value using Lu’s and not the others could be because of the nature of the adherence estimation between the four measures. Lu’s adherence scale includes more patients as being not adherent (25% not having 100% adherence as compared to between 15 to 16.5% for the other 3) as compared to the other adherence measures, prompting a speculation that it captures more people with borderline non adherence than may have otherwise been estimated by the other three measures. Moreover Lu’s scale includes questions that detect non adherence through indirect means whereas the other three adherence measurements appear to involve direct
questioning. This may potentially have an effect in under reporting of adherence due to the fear of repercussion from the healthcare professionals by the patient.

Individually, none of the questions addressing communication between patients and doctors could predict adherence on its own. Majority of the people were happy with the communication to and fro from their doctor and felt they received enough information pertaining to the CML medication and their management. The patients understood what their doctor said and majority did ask for an explanation when they did not understand.

Patients admit to reduced usage of the internet with just over half of them admitting to find out information about their CML online. Usage of the internet and patient support groups was found to be not predictive of adherence by any of the 4 adherence measures. Interestingly the use of internet was not associated with age; 25% of the patients younger than 60 years use the internet as compared to 29% of patients older than 60 years (p=0.6). A significant majority of the patients (90%) also appeared to not use the services of the support networks both online and in person to help them deal with issues arising out of their CML management. Patients who use the services of the patient advocacy groups were 2 times more likely to be adherent as compared to people who did not. It is not very clear as to the possible reason behind this but could be speculated that association with the patient advocacy groups probably made the patients more aware of the current issues in CML and the importance of adherence in attaining better clinical outcomes.

This could potentially be an area to target as these support services could not only be very helpful for the patients to deal with issues arising out of management of their CML but also potentially educational messages can be sent across through such forums. On the other hand, the message from the study could mean efforts to promote more online educational
activities and information may not be useful in reaching the intended audience and other forms of information dissipation needs to be looked at.

In our study, we found that the majority of patients are not troubled by issues related to taking medications like packaging, swallowing, forgetting to take and the use of reminders to help them take it regularly. The answers to this effect were highly predictive of adherence by all the 4 adherence measures (VAS, \(p<0.001\); Haynes et al, \(p<0.0001\); Lu's, \(p=0.001\); DAMS, \(p<0.0001\)). When patients were questioned as to what they thought of missing a dose occasionally or would they be worried if they missed one, the answers were indeed startling that only a third would actually be worried. Such views are likely to influence adherence significantly.

Majority of the patients still seemed to follow the advice given in that they would not stop taking the medications without consulting their doctor. Only three out of 10 patients admitted that they had been told by their doctor to take every single medication or their treatment might not work. These two statements convey a very important message for the clinicians in that a proper advice regarding compliance to therapy would go a long way in influencing patient behaviour. Even if nothing else is discussed in the clinic, it seems just perhaps reminding the patients to take every tablet as prescribed could go a long way to improving adherence.

We tried to combine the questions that had an independent prognostic value in predicting adherence. After excluding the 2 questions that seemed to directly reflect adherence, there were 4 questions which were found to be independent predictors in the multivariate analysis, namely someone helps me with managing my treatment at home (Q2), \((RR=2.87, \ p=0.02\)), My daily routine changed a lot when I started my current CML medicine (Q3), \((RR=4.54, \ p=0.005\)) I found it easy to adapt to the routine of taking my current medicine (Q4),
(RR=5.23, p=0.001) and it will NOT affect my response if I miss the occasional dose of medicine (Q26) (RR= 4.3, p=0.009). As ours was a retrospective observational study, these questions and their relationship to adherence needs prospective validation in the setting of clinical trial. We propose that these potentially could be incorporated into clinical practice to obtain surrogate markers for adherence to TKI therapy and also could help gain an insight into patient related factors influencing adherence.

**Value of surrogate markers to deal with issues of anonymity**

The perceived downside to self reported adherence could be to do with anonymous responses and the way the results could be incorporated into practice without compromising the confidentiality. This day and age where time is of essence, a shorter questionnaire that does not involve direct questioning about non adherence could be of value in day to day clinical practice as a surrogate for self reported measures. Moreover it can help to build a pattern of adherence over a period of time which could help clinicians address issues related to compliance if they see a downward trend rather than a one off value.

This short questionnaire could in fact be coupled with an adherence measure to both objectively determine adherence and also study factors that could be influencing adherence as surrogate markers.
Chapter VI. Relationship between self reported adherence and patient related factors II

VI.1 Introduction:

Oral anticancer therapies have revolutionised the way cancers are managed these days and the most classic example is the use of tyrosine kinase inhibitors to treat CP CML. Tyrosine kinase inhibitors have changed outlook of CML from being a fatal condition to more of a chronic condition\(^\text{127}\). The onus of treatment has definitely moved away from the treating physician or the healthcare professional towards the patient with the improvements in oral therapies. Such changes have brought into focus numerous factors that could potentially be influencing patient’s behaviours and state of mind thereby indirectly having an effect on adherence to therapy and subsequently clinical outcomes.

We and others have previously shown that adherence to therapy is critical to achieving optimal outcomes in CP CML patients on TKI therapy\(^\text{91, 96, 124}\). Research on factors influencing adherence behaviour has gained increasing importance of late. This is to identify, understand and implement strategies to overcome the possible influence of the factors on adherence to oral therapies. In this study we try to understand the relationship between patient’s views about medicines and its effect on adherence and outcomes through a BMQ (Beliefs about medicines) questionnaire (explained in methods section)\(^\text{128}\). We have also tried to study the influence of anxiety and depression on adherence and clinical outcomes through a validated HADS (Hospital anxiety and depression) scale (methods section)\(^\text{109}\). Finally we tried to predict if quality of life [FACT-G (Functional Assessment of Cancer Therapy-General) scale, explained below]\(^\text{108}\) was dependent upon adherence or
outcomes and whether it was related to anxiety, depression or concerns patients had with regards to their medicines. Our study was a questionnaire based one involving 296 CP CML patients in outpatient clinics.

VI.2 Methods

Patients:
Two hundred and ninety six patients with chronic myeloid leukaemia in 1st chronic phase from 6 hospitals across the UK completed questionnaires on adherence measures and patient related factors. The patient cohort is the same one that has been used in the analysis for chapter 4 and their characteristics have been described in detail in the previous chapter (chapter 4, tabular column 3). Briefly, the median age of the patients is 58 years (range 18 to 92 years). The median duration of TKI therapy was 37 months (range 3 to 156 months).

Questionnaires:
There are a total of twelve sections in the questionnaire (described in detail in methods chapter and also included in supplement section) out of which we have used three sections of the questionnaire (BMQ, HADS scale and the FACT-G scale) in this study. Briefly, the BMQ (beliefs about medicines) questionnaire was to determine patient’s beliefs about medicines\textsuperscript{128}, HADS (Hospital anxiety and depression scale) was a 14 question scale to identify anxiety and depression amongst hospital patients\textsuperscript{109} and FACT-G (Functional Assessment of Cancer Therapy-General) is a validated quality of life questionnaire\textsuperscript{108}. The questions that make up these scales are included in the supplement section 1.
Beliefs about medicines (BMQ) questionnaire:

The BMQ\textsuperscript{128} is a 10 item questionnaire assessing the cognitive representation of medication (Questions included as supplement y and described in the methods section). The BMQ comprises two sub-scales: Necessity scale assesses patients’ beliefs about their personal need for the medicine and how important the medicine is in maintaining their health now and in the future. Concerns scale assesses perceptions of the potential negative consequences of taking the medicine including concerns related to beliefs about long-term effects, dependence and other disruptive effects.

Each item of the BMQ scale is scored on a 5-point Likert-type scale ranging from 1 = strongly agree, 2 = agree, 3 = uncertain, 4 = disagree and 5 = strongly disagree. Specific-Necessity and Specific-Concerns scales have 5 items and scores range from 5 to 25.

Scores obtained for the individual items within each scale are summed to give a scale score (necessity scale and concerns scale). Higher Necessity scores represent stronger perceptions of personal need for the medication to maintain health now and in the future. Higher Concerns scores represent stronger concerns about the potential negative effects of the medication.

A necessity concerns differential is calculated by subtracting the necessity scores from concerns and the range obtained could vary from -20 to 20. A negative score represents preponderance of concerns over necessity and a positive score preponderance of necessity over concerns. The necessity and concerns scores are analysed as a continuous variable to see if they predict for adherence (also to see if they predicted for intentional or non intentional non adherence, as described in the results section), response, relationship to anxiety and depression. Similar analysis is repeated using the necessity concerns
differential. Here the necessity concerns differential is coded as 1 or 0 representing concerns and necessity respectively [score from -20 to 0 coded as “1” (concerns) and 1 to 20 coded as “0” (necessity)]. This categorical variable is then used to predict for adherence, its type, clinical response and relationship to anxiety and depression.

**HADS scale (Hospital anxiety and depression scale)**

HADS\textsuperscript{109} is a well validated fourteen item scale of which 7 of the items relate to anxiety and seven relate to depression (Questions included as supplement z and described in the methods section). All the 14 questions have 4 possible answers, scored using a likert type scale. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety or depression. A cut off point of 8 identifies anxiety or depression. The anxiety and depression scores are also categorised as 0 and 1. The anxiety and depression scores as both a continuous variable and categorical variable is then analysed to look for relationships with adherence and clinical outcomes.

**FACT-G (Functional Assessment of Cancer Therapy-General)**:

FACT-G\textsuperscript{108} comprises of 27 questions divided into four primary Quality of life domains: Physical Well-Being (PWB) (7 questions), Social/Family Well-Being (SWB) (7 questions), Emotional Well-Being (EWB) (6 questions), and Functional Well-Being (FWB) (7 questions) (Questions included as supplement w and described in the methods section). All four domains are to be scored simultaneously. There are 5 possible answers to all the 27 questions, scored on a 5-point Likert-type scale from 0 (not at all), 1 (a little bit), 2 (some what), 3 (quite a bit) and 4 (very much). The responses to all the 27 questions are summed up (the negatively worded questions are coded in the reverse). In cases where individual questions are skipped, scores are prorated using the average of the other answers in the
scale. The total FACT-G score is obtained by summing individual subscale scores (PWB + EWB + SWB + FWB). The higher the FACT-G score better is the quality of life.

**Type of non-adherence**

Non adherence can either be intentional or non intentional. Using the DAMS (diagnostic adherence to medicines scale- described in detail in methods chapter and also chapter 4), we were able to determine the type of non adherence depending on the answers provided by the patients for the possible reasons for missing doses. The patients could choose between 4 options and also had a blank space to provide reasons for missing tablets/capsules of TKI in the last 7 days. The answers were codified as per the recommendations of the DAMS scale as intentional or non intentional non adherence. For example option 1 was forgot to take, would be classified as non intentional non adherence, and whereas option 2- too tired and so missed a dose was intentional non adherence. We tried to see if the BMQ scale, especially concerns about medicines could predict for intentional non adherence.

**Statistical methods:**

Patient related factors including patients beliefs on medications (BMQ questionnaire), anxiety, depression and Quality of life has been analysed to see if they predicted for better adherence using the 4 adherence measures described in detail in chapter 4. Briefly the four adherence measures were visual adherence scale (VAS), Haynes et al question, Lu’s adherence scale and the diagnostic adherence to medicines scale (DAMS). The self reported adherence as measured by the 4 scales were divided into 4 categories as
described in detail in the previous chapter. Briefly the adherence from VAS, Lu’s and the DAMS were categorised as <80%, 81 to 90%, 91% to 98% and >98%. The missed doses reported by Haynes et al scale was categorised as no missed doses, >1 missed dose, >2 missed doses and >3 missed doses. The adherence categories were the dependent variable and patient related factors were the independent variable in ordinal logistic regression. Patient related factors were analysed as both a continuous and a categorical variable.

We also performed a second analysis where the predictive value of patient related factors on responses as defined by ELN was calculated using binary logistic regression. The responses and their results are described in detail in chapter 4. Briefly, the responses were categorised into optimal, suboptimal and poor responses (failure). For the purposes of this study, the optimal and the suboptimal responses have been grouped together. In binary logistic regression, the responses were the dependent variable (failure vs. Optimal and suboptimal and the patient related factors were the independent variables). Again the patient related factors were analysed as both a continuous and a categorical variable.

We also tried to see if concerns (derived from the BMQ scale, necessity concerns differential coded as 1) could predict for intentional non adherence using binary logistic regression.

**VI.3 Results:**

**VI.3.1 Description of Necessity and concerns of the patients**

Two hundred and eighty six patients (97%) completed the 10 point BMQ questionnaire. The median scores for the necessity scale was 21 (range 9-25). The median score for the concerns scale was 9 (range 5 to 23). The necessity concerns differential median score was 10 (range -3 to 20). Two hundred and sixty seven (93%) patients felt their medicines were...
necessary and it was important to them whereas 19 patients (7%) of the patients felt concerned about their medicines.

**Increasing concerns scores predicts adherence:**

The concerns scale was analysed as a continuous variable to look for a relationship with adherence measured by all 4 scales (VAS, Haynes scale, Lu’s Scale and DAMS).

Higher concerns scores were not predictive of adherence by VAS (OR- 0.95, p=0.51). Similarly the scores were not predictive of missed doses by Haynes et al (OR- 0.25, p=0.348). Increasing concerns were predictive of increasing adherence by the Lu’s scale (OR-1.3, p<0.0001). The concerns score was not found to be predictive of adherence by DAMS (OR-0.944, p=0.63). Higher concerns scores were not predictive of poor clinical responses by the ELN guidelines (OR- 0.98, p=0.77)

**Necessity scores did not predict for adherence or clinical outcomes:**

Higher necessity scores were not predictive of adherence by VAS (OR- 0.92, p=0.48) or Lu’s scale (OR-0.94, p=0.35). Similarly increasing scores in the necessity scale was not predictive of adherence by Haynes (OR-1.06, p=0.59) or DAMS (OR- 0.88, p=0.11). Higher scores were not predictive of poor clinical responses either (OR-1.01, p=0.71).

**Relationship between necessity concerns scores with anxiety and depression**

Necessity scores were not predictive of anxiety (OR-0.95, p= 0.4), however higher scores were predictive of depression (OR- 1.07, p=0.05). On the other hand people with higher
scores for concerns were highly likely to be anxious (OR-1.37, p<0.0001) and depressed (OR-1.07, p=0.026).

**Necessity-concerns differential (N-C diff):**

N-C Diff, a continuous variable, was analysed for its predictive value in being able to predict adherence and clinical responses, also for its relationship to anxiety and depression.

N-C diff was unable to predict responses by VAS (OR- 0.62, p=0.27), Haynes et al (OR-0.02, p=0.98) or DAMS scales (OR-0.11, p=0.874). However, a positive N-C diff (increasing concerns) was predictive of higher adherence by Lu’s adherence scale (OR- 1.08, p=0.025). N-C diff was not predictive of poor responses by ELN criteria (OR-0.97, p=0.95). N-C diff had an inverse relationship with anxiety (i.e. higher N-C diff correlated inversely with anxiety). There was no relationship between N-C diff and depression.

**N-C differential was not predictive of intentional non adherence:**

A total of 51 patients (17%) answered the question meant to categorise the non adherent patients into intentional or non intentional non adherence. Of this 33 patients (65%) indicated a reason that was classified as intentional non adherence and 18 patients (35%) indicated that their reason for non adherence was non-intentional. This was then compared with the 19 patients (N-C diff) who expressed concerns to their medications. There was no association between intentional non adherence and concerns to medicines as determined by the BMQ scale (p=0.6). Necessity (OR-0.8, p=0.5) and concerns scores (OR-0.92, p=0.6) separately did not predict for intentional non adherence either.
VI.3.2 Anxiety and depression:

A total of 284 (96%) patients answered the questions regarding anxiety and depression. The median anxiety score was 12 (range 4 to 17) and depression score was 9 (range 3 to 15). Applying the recommended cut off of 8 for both the scales, a total of 256 patients (90%) were found to be anxious about their CML treatment and 143 (50%) patients appeared to be depressed. Forty eight percent of patients who were anxious were not found to be depressed whereas 95% of patients who were depressed were found to also be anxious (p=0.016).

Relationship between anxiety and depression with adherence:

Anxiety and depression scores were analysed as a continuous variable to predict for adherence as well as a categorical variable (using a cut of 8 for both). Odds ratios with their significance for all four adherence measures are outlined in Table 1 below. Anxious patients appeared to have lower adherence as estimated by Lu’s adherence scale and not by others, whereas depression was unrelated to adherence.

Higher anxiety scores (i.e. anxious patients) as a continuous variable was unable to predict for adherence using VAS (OR- 0.32, p=0.559), nor as a categorical variable (using cut off 8 for indicating anxiety), (OR-0.47, p=0.43). Similarly, higher scores in depression was unable to predict for adherence using VAS as a continuous variable (OR-0.12, p=0.26) or as a categorical variable using a cut off of 8 (OR- 0.35, p=0.27), [table 1].
Increased anxiety levels among patients could not predict for missed doses (Haynes et al) either as a continuous scale (OR- 0.11, p=0.86) or as a categorical variable (OR-0.85, p=0.2). Depression does not appear to be related to patients missing doses of their TKI therapy (OR- 0.23, p=0.9) nor was the depression scores predictive of adherence by Haynes scale (OR- 0.1, p=0.92), [table 1].

Anxious patients appeared to have lower adherence levels by Lu’s scale (OR- 0.911, p=0.034) and also increasing anxiety scores correlated with decreasing adherence (OR-1.04, p=0.009). Depression appeared to be unrelated to adherence by Lu’s categories (OR-0.29, p=0.8), [table 1].

Anxiety (OR- 0.83, p=0.21) and depression (OR- 0.6, p=0.95) neither appeared to correlate with levels of adherence as determined by DAMS scale as a categorical variable nor as a continuous variable (table 1)

Table 10- Relationship between anxiety and depression with the 4 adherence measures- showing p-values and odds ratios

The second column shows comparison with the four adherence measures as a categorical and continuous variable with significance and odds ratios in third and fourth columns.

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Adherence measures</th>
<th>P values</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>Continuous</td>
<td>0.62</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Categorical</td>
<td>0.43</td>
<td>0.47</td>
</tr>
<tr>
<td>Haynes et al</td>
<td>Continuous</td>
<td>0.86</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Categorical</td>
<td>0.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Lu’s adherence</td>
<td>Continuous</td>
<td>0.009</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td>Categorical</td>
<td>0.034</td>
<td>0.29</td>
</tr>
<tr>
<td>DAMS</td>
<td>Continuous</td>
<td>0.94</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Categorical</td>
<td>0.21</td>
<td>0.83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression</th>
<th>Adherence measures</th>
<th>P values</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>Continuous</td>
<td>0.26</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Categorical</td>
<td>Continuous</td>
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<td>----------------</td>
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<td></td>
</tr>
<tr>
<td>Haynes et al</td>
<td>0.27</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.35</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Lu’s adherence</td>
<td>0.94</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.23</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>DAMS</td>
<td>0.27</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

(VAS- visual adherence scale, DAMS- diagnostic adherence to medicines scale, P values 2 sided, 95% confidence interval, the highlighted values shows significant results)

**Anxiety and depression does not appear to be related to clinical responses**

Anxious patients did not appear to have any relationship with poor clinical response (OR-0.90, p=0.84). Similarly patients with higher depression scores also did not appear to predict poor clinical responses (OR- 1.3, p=0.4).

**VI.3.3 Quality of life (FACT-G): Description of answers**

Quality of life is based on 28 questions over 4 different sections. The total number is taken as the representative of the quality of life. Higher the number better is the quality of life.

The median value for the FACT-G questionnaire is 88 (range 32 to 108). We divided the FACT-G values into 4 categories. The categories were 0 (1 to 27), 1 (28 to 54), 2 (55 to 81) and 3 (82 to 108). We analysed the relationship between quality of life with adherence, responses, anxiety, depression, necessity and concerns as both a continuous and categorical variable.

**Better quality of life predicts for higher adherence to TKI:**

When analysed as a continuous variable, QOL was predictive of adherence by VAS (OR-1.1, p=0.031) and missed doses by Haynes et al (OR = 1.5, p=0.033). Higher scores in QOL
was highly predictive of higher adherence by Lu’s scale (OR- 2.9, p<0.0001), however, QOL was not predictive of adherence by DAMS (OR- 0.20, p=0.065)

When QOL is analysed as a categorical variable, the higher categories were highly predictive of better adherence by Lu’s adherence scale (OR- 2.8, p<0.0001). However the categorical divisions of QOL was not predictive of adherence by VAS (OR- 0.92, p=0.11), Haynes et al (OR- 0.8, p=0.22) or by DAMS (OR- 0.5, p=0.37).

**Better quality of life did not predict for poor responses:**

QOL when analysed as a continuous variable did not predict for responses as defined by the ELN criteria (OR- 0.2, p=0.22). Similarly, the categorical divisions of QOL was not predictive of responses either (OR- 0.45, p=0.18).

**Relationship between QOL and other patient related factors:**

Anxiety levels appeared to negative correlate with QOL with high significance (OR- 2.07, p<0.0001). This was true whether anxiety scores were analysed as a continuous or a categorical variable. On the other hand, there appeared to be no relationship between depression and QOL. Patients with concerns appeared to have an extremely poor QOL (OR- 6.9, p<0.0001) whereas patients who had higher necessity scores did not have bearing on their QOL (OR- 0.69, p=0.59). N-C differential did not appear to predict or have a relationship to patients QOL.

**VI.4 Discussion:**
Necessity scores were found to be higher when compared to the concerns voiced by the patients regarding their medicines. When analysed in totality, nearly all patients felt their TKI therapy was necessary and very few patients had concerns regarding it (7%). When patients were concerned about their medicines, it appeared to have an effect on their adherence to TKI as well. An increase in concerns score by 1 predicted for a 2.5% increase in adherence levels as determined by Lu’s scale, this finding was particularly surprising, considering one would have expected to find an opposite result of decreasing adherence when patients are concerned about their medicines. The necessity scores on the other hand were unable to predict for adherence to therapy or clinical outcomes. The BMQ scale was developed to reflect the fact that when patients are concerned about their medicines, they are likely to have an intentional non adherence towards taking their TKI therapy. In our study, we found that necessity concerns differential, was unable to predict for intentional non adherence, however the N-C diff was able to predict for adherence by Lu’s scale. The self reported adherence by Lu’s appeared to correlate well with anxiety as compared to the other 3 adherence measures. A possible explanation could be the number of patients deemed non adherent by Lu’s scale, which is much higher than those by the others. Also Lu’s questioning involved indirect means of determining self reported adherence as compared to the other three which included more direct questions relating to taking medications or missing them, hence possibly capturing more non adherent patients. Also it is worth noting that only 18 patients were deemed to have concerns as per the BMQ scale, hence correlating this small number to the group of non adherent patients which were also small did not appear to be significant in the case of the three other adherence measures (VAS, Haynes et al and DAMS).

We found in our study that when patients found their medicines to be necessary, they were likely to be depressed, but not anxious. Similarly, when patients had concerns about their
medications, they were both likely to be depressed and anxious about their life and
treatment. The relationship between concerns with anxiety and depression appears to be
logical one as patients who are worried about their medicines are likely to be anxious about
their therapy and feel low in mood. Similarly, when patients think their medicines are
extremely imperative and necessary to a good life, it could make them feel depressed that
they are have to depend on it for ever and they are likely to be less anxious compared to
patients who are worried about the possible consequences of their medications.

Majority of the patients who participated in the study (90%) appeared to be anxious about
their CML treatment whereas half the patients questioned appeared depressed. Majority of
the depressed patients appeared to be anxious (p=0.01). These numbers appear to be in
keeping with similar such studies involving patients with cancer and on long term therapies.

What is striking to note is that even with advancements in TKI therapies and clinical
outcomes with excellent overall survival in patients with CP CML, they still appeared anxious
about their therapies. Perhaps communicating the current survival trends to patients may put
their mind at ease and could possibly decrease their anxiety levels. Half the patients appear
to be depressed, but this may not necessarily mean clinically evident depression,
nonetheless, is a useful statistic for the treating physicians to consider recommending
appropriate interventions if clinically obvious.

Anxiety levels appear to be related to adherence to TKI therapy as measured by Lu’s
adherence scale and not by other means. One would expect anxious patients to be more
likely to be adherent to therapy, but anxiety levels may not always mean anxiety about the
disease, but could also mean anxiety about the medications and its long term effects and
potential implications. This may lead to the speculation that anxious patients may potentially
miss doses leading to a form of intentional non adherence, however when analysed, there
appeared to be no basis for such a conclusion. It is also possible that small sample size of
patient’s reasons for non-adherence could potentially hide a true relationship between the two. A study with larger numbers could strengthen or refute this theory. Depression did not appear to have any relationship with adherence. Both anxiety and depression were not predictive of poor clinical outcomes.

Patients in general appeared to have a good quality of life. The median value of the FACT-G questionnaire for 296 patients was 88 (range 32 to 108), with higher numbers predicting a better QOL. Better QOL was related to better adherence as measured by VAS and missed doses (Haynes et al). The most significant association of better QOL with higher levels of adherence was by Lu’s adherence scale. QOL however did not appear to predict for clinical outcomes.

Patients’ QOL seemed to be influenced by other patient-related factors like anxiety and feeling concerned about their medication. The most significant association was between patients who had concerns about their medications and poor QOL (OR- 6.9). There was also a very strong relationship between anxious patients and poor quality of life. QOL however did not appear to be influenced by patients feeling depressed or by increased necessity to take their medications.
Chapter VII. Optimising intolerance by changing TKI therapy to minimise low grade side effects

VII.1 Introduction

Imatinib induces durable responses in the majority of the patients who receive this drug as first line therapy while in chronic phase, however a substantial proportion of patients have persistent low grade side effects that impair their quality of life\(^{112}\). We and others have shown that poor adherence to TKI therapy correlates with inferior clinical outcomes and side effects to therapy have been identified as one of the possible reasons for poor adherence to medication\(^{93, 99}\). Our group has also shown that the loss of complete cytogenetic responses occur due to poor adherence and intolerance is thought to play a significant role in it\(^{124}\). Cortes et al has shown that patients on nilotinib and imatinib had very little cross intolerance amongst them in a study of patients in a phase 2 clinical trial\(^{73}\). Although not formally shown outside this study it is generally acknowledged that TKI therapies have low cross intolerance amongst them and this thought was the reason behind our current study. We tried to use this strategy to minimize side effects by taking advantage of the low cross intolerance between different tyrosine kinase inhibitors (TKIs) and to change therapy in the presence of insidious low grade side effects. However, what was unclear was whether such a change in therapy can adversely affect response, or induce resistance and whether indeed eliminate the side effect. Here we retrospectively report our experience in 57 patients who began treatment on imatinib and achieved complete cytogenetic response (CCyR) on imatinib as first line therapy. The patients then had their TKI changed solely on account of minor persistent side effects to second and third generation TKIs namely (nilotinib, dasatinib and bosutinib). We have tried to analyse the effect of changing TKI solely on the basis of side effects on clinical outcomes, mutations and subsequent development of side effects.
VII.2 METHODS

Two hundred and seventy four patients with chronic phase CML who were treated at the Hammersmith hospital with first line imatinib therapy as described in chapter 2 formed the basis of this cohort. Fifty-seven patients of the 274 (20.8%) patients on imatinib attained CCyR and subsequently had their TKI therapy changed due to minor chronic (>6 months) low grade (Grade 1 to 2) side effects in the absence of any sign of resistance. The median age was 54 years (range 36-69) and 35 (62%) were male. Five (9%) patients had additional chromosomal abnormalities at diagnosis. The Sokal risk group distribution was 24 (42%) low, 20 (35%) intermediate and 13 (23%) high. Thirty-seven patients received dasatinib second line, 19 nilotinib and 1 bosutinib. Seventeen of these patients subsequently changed to a third line TKI (14 patients to nilotinib and 3 to dasatinib) again due further intolerance and finally two of these 17 patients changed to a fourth line TKI (one patient to nilotinib and one to bosutinib). Dasatinib, nilotinib and bosutinib were administered as described by others. Patients gave informed consent for their clinical data to be reported. Minor side effects were defined as any side effect caused by the TKI therapy that persisted at grade I despite optimal care. Common toxicity criteria (CTC) were used to grade the side effects on the basis of guidance provided by NCCN129.

BCR-ABL1 transcripts were measured in the blood at 6 to 12 week intervals using RTq-PCR as described previously in chapter 2130. Molecular responses (MR) were expressed according to the log reduction in the transcript level below the conventionally defined starting point of 100%.131, 132. MR3 (equivalent to major molecular response) was defined as a transcript level ≤0.1% on the international scale. MR4.5 was defined as BCR-ABL1 ratio of 0.0032% on the international scale provided copies numbers of the control was at least
40,000. Complete molecular response (CMR) was defined by the presence of two consecutive samples with no detectable transcripts and an ABL1 control >40,000 copies. Samples with an ABL1 control <10,000 were discarded. Samples obtained for RTq-PCR were also analyzed for KD mutations at the moment of changing therapy using direct sequencing as described in the methods chapter and when resistance therapy was suspected\textsuperscript{133}.

Statistics:

The data was analysed using the statistical package SPSS statistics 20.0 (August 2012, SPSS Inc., Chicago, Illinois). Probability of remaining on therapy was calculated using the Kaplan-Meier method. The probabilities of molecular responses were calculated using the cumulative incidence (CI) procedure, whereby molecular responses were the events of interest and death and therapy discontinuation were the competitors. P values were 2 sided and 95% confidence interval was used.

VII.3 RESULTS

Patients received imatinib for a median of 44 months (range 16-135) before discontinuation. The median duration on 2nd line TKI therapy was 48 months (range 10 to 50). The median duration on third line therapy was 30 months (range 7-42). Two patients eventually changed to a fourth TKI (bosutinib n=1, nilotinib n=1) due to side effects. At the time of starting second line TKI, 2 patients were in CMR, 3 in MR4.5, 25 in MR3 and 27 in CCyR (but not in MR3 or better). During the follow up there was no loss of response, progression to advanced phase or CML related deaths. Two patients died from non-CML related causes.
VII.3.1 Second line TKI is generally well tolerated and there is minimal cross-intolerance following change of TKI

Table 1 shows the dominant grade I side effects on imatinib that motivated the initial change of therapy; the commonest were arthralgia (16%), dermatologic events such as rash and pruritus (16%), and headache (14%).

Table 11- Grade I side effects on imatinib therapy that led to treatment change in the 57 patients

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (14.0)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Elevated LFTs*</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3 (5.3)</td>
</tr>
</tbody>
</table>

* LFTs: Liver function tests

Twenty-five (44%) patients developed side effects on the second line drug. The commonest side effects were pleural effusion (n=9, 36%) and headache (n=2, 8%). The side effects were grade II-IV in 5 of these patients (pleural effusion n=4 and retinal hemorrhage n=1) and necessitated change of therapy. In the remaining 20 patients the side effects were grade I and 12 of these patients changed TKI (Table 2). Eight of these patients who had grade I
side effects on second line TKI elected not to changed therapy as the side effects were very mild and the patients perceived them as insignificant and therefore requiring no action. These side effects were skin rash (n=2), muscle cramps (n=1), asthenia (n=3) and arthralgia (n=2). Only four patients developed the same side effect on second line TKI that they had experienced on imatinib (muscle cramps and arthralgia).

As explained above 17 patients changed to third line therapy (5 patients with grade II-IV side effects and 2 patients with grade I). On third line TKI, 12 (71%) patients become totally free of side effects. Two of the remaining five patients changed to a fourth line drug (recurrent pleural effusion and peripheral occlusive arterial disease), and are now asymptomatic. The remaining three patients elected not to change treatment as again the side effects were very minor and perceived by the patients as negligible (rash, pruritus and headache). Table 2 details side effects that warranted change of therapy and their outcome.

*Table 12- Management and outcome of the side effects that occurred on the different TKIs*

<table>
<thead>
<tr>
<th>SIDE EFFECTS ON IMATINIB (n)</th>
<th>TKI CHANGE (n)</th>
<th>OUTCOME (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia (9)</td>
<td>Dasatinib (4)</td>
<td>No recurrence (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly reduced (1)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (5)</td>
<td>No recurrence (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly reduced (2)</td>
</tr>
<tr>
<td>Skin Rash (9)</td>
<td>Dasatinib (6)</td>
<td>No recurrence (6)</td>
</tr>
<tr>
<td>Effect</td>
<td>Treatment 1</td>
<td>No recurrence</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Nausea (6)</td>
<td>Dasatinib (4)</td>
<td>No recurrence (4)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (2)</td>
<td>No recurrence (2)</td>
</tr>
<tr>
<td>Diarrhoea (5)</td>
<td>Dasatinib (2),</td>
<td>No recurrence (2)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (3)</td>
<td>No recurrence (3)</td>
</tr>
<tr>
<td>Asthenia (6)</td>
<td>Dasatinib (6)</td>
<td>No recurrence (6)</td>
</tr>
<tr>
<td>Headache (8)</td>
<td>Dasatinib (5)</td>
<td>No recurrence (5)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (3)</td>
<td>No recurrence (5)</td>
</tr>
<tr>
<td>Muscle cramps (7)</td>
<td>Dasatinib (5)</td>
<td>No recurrence (5)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (2)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence (1)</td>
</tr>
<tr>
<td>Elevated LFTs* (4)</td>
<td>Dasatinib (4)</td>
<td>No recurrence (4)</td>
</tr>
<tr>
<td>Peripheral edema (3)</td>
<td>Dasatinib (1)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (2)</td>
<td>No recurrence (2)</td>
</tr>
</tbody>
</table>
### Table 3 continued

<table>
<thead>
<tr>
<th>SIDE EFFECTS ON DASATINIB (n)</th>
<th>TKI CHANGE (n)</th>
<th>OUTCOME (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion (9)</td>
<td>Nilotinib (8)</td>
<td>No recurrence (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence (1)</td>
</tr>
<tr>
<td></td>
<td>Bosutinib (1)</td>
<td>Recurrence (1)</td>
</tr>
<tr>
<td>Diarrhoea (1)</td>
<td>Nilotinib (1)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td>Asthenia (1)</td>
<td>Nilotinib (1)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td>Headache (1)</td>
<td>Nilotinib (1)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td>Muscle Cramps (1)</td>
<td>Imatinib (1)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td>Peripheral oedema (1)</td>
<td>Nilotinib (1)</td>
<td>No recurrence (1)</td>
</tr>
<tr>
<td>Retinal haemorrhage (1)</td>
<td>Nilotinib (1)</td>
<td>No recurrence (1)</td>
</tr>
</tbody>
</table>

#### SIDE EFFECTS ON NILOTINIB (n)

| Muscle cramps (1)               | Imatinib (1)   | No recurrence (1) |
| PAOD** (n=1)                    | Bosutinib (1)  | No recurrence (1) |

#### SIDE EFFECTS ON BOSUTINIB (n)

| Pleural effusion (1)            | Nilotinib (1)  | No recurrence (1) |

LFTs: Liver function tests;
VII.3.2 Patients who change TKI therapy on account of persistent minor side effects sustain or improve their previously attained response

All 57 patients had further reduction in BCR-ABL1 transcript levels following change of therapy. The median transcript level at the time of changing was 0.29% (range 0.09% to 3.5%) and the median reduction in 12-month BCR-ABL1 transcript level after change in TKI was half log (range 0.2-1.5). Two patients were in complete molecular response (CMR) prior to change and maintained CMR thereafter. On second line therapy, 14 patients achieved CMR, 13 MR4.5 and 15 MR3. The 1- and 4-year cumulative incidence (CI) of MR3 for the 38 who had not achieved MR3 at the point of change was 78% and 94% respectively. Similarly the 1-and 4-year CI of MR4.5 was 30% and 48% respectively and the 1 and 4 year CI of CMR was 8% and 24% respectively. The probability of remaining on second line therapy at 48 months after switching TKI was 72.4%.

The 17 patients who changed to a third line TKI also attained further reduction in their BCR-ABL1 transcript numbers. The median reduction in the BCR-ABL1 transcript level obtained 12 months after change to third line therapy was 1 log (range 0.1-2). Two patients were subsequently changed to a fourth TKI due to side effects (bosutinib n=1, nilotinib n=1) and also continued to have further reduction in their transcript levels. When considering the global outcome of all 57 patients that changed therapy, the 4-year probability of being in MR3, MR4.5 and CMR were 98.2%, 52.1% and 26.6% respectively.
VII.3.3 Repeated change of TKI therapy does not seem to increase the frequency of kinase domain mutations

Patient samples were tested for the presence of BCR-ABL1 kinase domain mutations. Our institutional practice has changed with time but samples were tested at least at the moment of changing TKI therapy and in case of doubling of BCR-ABL1 ratio (provided that there were more than 10 BCR-ABL1 transcripts). In the analysis performed at the moment of changing therapy we unexpectedly identify one kinase domain mutation (D276G) in a patient receiving first line imatinib. The patient had not had any prior increase in the transcript level and the mutation disappeared with the change of therapy. We performed an additional 143 mutation analyses during second or subsequent lines on account of increasing transcript levels. In all these cases the mutation analysis was negative and the transcript level subsequently declined without intervention.

VII.4 DISCUSSION

Low grade side effects induced by TKI are often dismissed by clinicians used to dealing with much more toxic regimens. Patients may also often fail to bring the persistence of minor side effects to the attention of their treating physicians as some times patients feel that the side effects are a very small price to pay for not succumbing to their leukaemia. However these side effects can have a significant impact on the quality of life of patients, particularly as most patients are likely to require lifelong therapy. However, minor persistent side effects may have clinical consequences other than poor quality of life. We and others have shown that side effects are often the reason for poor adherence and poor adherence may lead to loss of response. For example in a study performed at the Hammersmith Hospital the 2-year
CI of loss of CCyR for adherent and not adherent patients was 1% vs 36% (p<0.0001). For these reasons it is important to develop strategies that are aimed at minimizing the side effects suffered by patients.

In this work we have shown that by proactively changing TKI therapy, we were able to free the majority of the patients from low grade chronic side effects (Figure 1). Forty-six (81%) patients become totally asymptomatic and an additional 11 patients (19%) had their side effects reduced to a point where the patients themselves considered that no further intervention was necessary. Thus all patients were liberated from minor persistent side effects. Most of the patients’ side effects resolved with the first change of medication, but 17 (30%) required one or two additional changes. In the majority of the cases the second or subsequent changes of therapy were motivated by the occurrence of a different side effect rather than by the persistence of the original one. These new side effects, although sometimes more severe, were reversible or easy to manage in all cases.
Negligible side effect indicates a grade I side effect, perceived as insignificant by the patient and not requiring intervention.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>1st line</th>
<th>2nd line</th>
<th>3rd line</th>
<th>4th line</th>
<th>1st line</th>
<th>2nd line</th>
<th>3rd line</th>
<th>4th line</th>
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<tbody>
<tr>
<td>no</td>
<td></td>
<td>57</td>
<td></td>
<td>32</td>
<td></td>
<td>17</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>present</td>
<td>17</td>
<td></td>
<td>3</td>
<td>8</td>
<td>57</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>negligible</td>
<td></td>
<td>17</td>
<td>3</td>
<td>2</td>
<td></td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effects</th>
<th>1st line</th>
<th>2nd line</th>
<th>3rd line</th>
<th>4th line</th>
</tr>
</thead>
<tbody>
<tr>
<td>81%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Furthermore, all patients improved their molecular response as noted by a further decrease in BCR-ABL1 transcript levels. In fact, the probability of being in MR3 or MR4.5 4 years after discontinuing imatinib was very high, namely 98.2% and 52.1% respectively. It is possible that this improved response was due to the greater efficacy of the 2G-TKI in comparison to imatinib, but we also showed improvement in those patients who changed from one second generation drug to another. We speculate that by reducing the side effects we were able to improve adherence to medication which also may have impacted on the response.

It is theoretically possible that repeated changes of therapy may lead to the development of resistance. We did not observe this; during the follow up no patient developed resistance.
fact all the patients improved their responses. We also carefully monitored patients for the
development of BCR-ABL1 kinase domain mutations and none that could be attributed to a
change of therapy was detected. We conclude that changing therapy on account of
persistent minor side effects is an effective and safe therapeutic option.

The impact of carrying on with imatinib in the long run may have produced similar clinical
responses as the change in TKI therapy, but with the cost of patients putting up with chronic
low grade side effects. This can only be known if a prospective study was done with 2 arms;
one changing on account of side effects and the other remaining on the same TKI therapy.
To truly validate the finding that there would have been no long term repercussions following
change due to intolerance, one would have to conduct a larger study. The fact that if
subsequently the patient needed a change in therapy for resistance, there may not be an
option left because of an earlier change. But the argument in favour of an earlier change is
that you have already changed over to a stronger TKI and hence the chance of a resistance
in the future becomes extremely low and as per our findings although with a small cohort
had a follow up for close to 8 years and we did not find any degree of resistance or new
mutations.
Chapter VIII. Conclusion

TKI therapy has revolutionised the management of CP CML patients. Beginning with imatinib, the subsequent second and third generation TKI’s have begun to improve the already excellent responses achieved with imatinib therapy. The landmark IRIS trial at the latest update showed the OS considering only CML related deaths to be well in excess of 90%. With improving survival rates, strategies for pursuing newer therapeutic options were beginning to climb down the ladder of importance whereas research into methods to improve outcomes using existing therapies were beginning to gain momentum. A number of areas which could potentially be tapped to improve outcomes have been explored in the last few years.

The importance of early molecular milestones in determining long term outcomes has been shown by us and a number of groups in patients on imatinib, dasatinib and nilotinib. Marin et al showed that patients who attain Bcr-Abl transcripts of less than 9.84% at 3 months and 1.67% at 6 months have a better OS, PFS and higher CI of attainment of cytogenetic and molecular milestones compared to patients who fail to attain them. In this study we tried to combine the 3 and 6 month cut offs to identify poor risk patients. We showed that patients who attained the 3 and 6 month milestones as well as patients who attained the 3, but failed the 6 month milestone did equally well and had similar outcomes in terms of OS, CI of CCyR and CMT rates at 8 years. We also showed that the patients who failed to attain the 3 month milestone of 9.84%, but attained the 6 month cut off of 1.67% did equally badly as the group of patients who failed to achieve both milestones. In this way, we have added to the importance of early molecular monitoring by showing that patients who attain the 3 and 6 month cut offs are the ones who are likely to have the best outcomes and that patients do
not improve their outcomes even if they attain the 6 month milestone after failing the 3 month cut off. We propose that a single measurement of Bcr-ABL transcripts at 3 months is good enough to identify patients who are likely to do badly.

Another key area of interest is adherence to TKI therapies and we along with others have shown that adherence is important to achieving molecular milestones and that lack of adherence contributes to loss of existing cytogenetic responses. The main drawbacks of the existing methodologies are either a prohibitive cost or lack of standardisation to being extremely labour intensive. We have showed that self reported measures are effective in identifying non-adherence and correlates with clinical outcomes.

The four self reported adherence measures (Visual adherence scale, Haynes scale, Lu’s modified adherence scale and the diagnostic adherence to medicines scale) correlate well with each other and are able to predict poor responders. Adherence cut offs <95%, <90%, 85% and <80% all correlated with poor clinical responses and the cut off < 80% was identified to be the best predictor. Similarly with the Haynes scales, increasing numbers of missed doses from 1 to >3 all showed good correlation with poor responders with the missed doses >3, the best predictor. In the Lu’s scale cut offs <95% and <90% were only significant and <90% being the best predictor of poor responses. In the DAMS scale all the four adherence cut offs (<95%, <90%, <85% and <80%) were significant with the 85% cut off being the best predictor.

The best adherence cut offs for identifying poor responders varied between the different scales. This could be down to the varying methods used to identify adherence in the four methods. Haynes scale which is based on the number of tablets missed in the last 7 days was found to be the best of all the four self reported measures in identifying poor responders.
Patients whose day to day routines remained unaffected by CML and its treatment were found to have the best adherence to TKI therapy. Patients in general felt their communications with their physician was good. However nearly a third of the patients felt it was ok to miss an occasional dose and a similar number mentioned that they have never been told by their HCP that they need to take all their tablets and they may not do as well if they did not. Majority of the patients in the study did not use the internet to know about CML or engage with the patient support groups and this was uniform across age groups. The patients had no problems in terms of swallowing or physically taking the pills.

On analysis of the individual questions, 4 out of a total of 30 were found to have independent predictive value in multivariate analysis, Someone helps me with managing my treatment at home, My daily routine changed a lot when I started my current CML medicine, I found it easy to adapt to the routine of taking my current medicine and it will NOT affect my response if I miss the occasional dose of medicine. These 4 questions were found to correlate very well with non adherence and hence can be used as surrogate markers in an out-patient setting without directly having to ask patients if they missed taking their pills. To apply these into clinical practice requires further validation in prospective trials.

Majority of the patients felt their CML medications were necessary and very few felt they had concerns regarding their treatment. The small number of patients with concerns had decreased adherence as compared to patients with increased necessity. The BMQ scale did not predict for intentional non adherence as had been suggested by previous reports. Nearly all patients (90%) appeared to be anxious and half of them depressed. The anxious patients appeared to have a lower adherence as determined by Lu’s scale and it is possible this could be due to patients being anxious about the effects of long term effects of treatment.
with TKI. Patients with higher QOL appeared to have better adherence to therapy and poor QOL correlated with patients being anxious and concerned about their CML treatment. Intolerance to therapy has been shown to contribute to poor adherence to therapy and subsequently inferior outcomes. Low grade chronic side effects are present in a number of patients on TKI therapy and it interferes with their QOL. We have shown that it is possible to change TKI therapy when patients are in cytogenetic remission with low grade side effects and it leads to a near complete resolution in most patients. All the patients improved upon their previously attained molecular responses and none developed resistance or mutations. In this way it is possible to ameliorate chronic low grade side effects to improve tolerability and ultimately compliance to therapy.

VIII.1 Future Directions:

The main areas where future work could be undertaken based on the findings of this study would be a prospective randomised trial to see if switching or altering therapy at 3 or six months leads to improved outcomes. A number of trials are looking to switch therapy at these early time points to improve outcomes but it remains to be seen if the failure to meet the 3 month milestone is in fact a poor risk group of patients who may do badly anyway. There is a school of thought that the patients who fail the 3 month milestone might represent a biologically poor risk group and hence identifying them early could help in rationalising appropriate therapies for them.

Adherence can be tricky to measure in day to day clinics, hence the use of self reported measures assume significance as they are cheap and effective methods to identify non adherence and also they can be used repeatedly over a period of time to build a patterns of non adherence that be addressed. Tailored and patient specific interventions to tackle intentional and non-intentional non adherence needs to be developed. More needs to be
done to educate patients and other healthcare professionals involved in the care of CML patients on the impact of poor adherence. The simple questionnaire can be used in a variety of settings to determine non adherence. With the cancer treatment going towards targeted oral therapies, such tools can be invaluable in addressing the problems arising due to non compliance in a number of malignancies. Also such tools can be tried in non malignant settings such as oral anticoagulants where compliance can be vital in short acting drugs.
References:


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86. Sung-Hyun Kim HMea. Efficacy and Safety of Radotinib in Chronic Phase Chronic Myeloid Leukemia Patients with Resistance or Intolerance to BCR-ABL Tyrosine Kinase Inhibitors: Radotinib Phase 2 Clinical Trial. ASH Oral and Poster Abstracts 2012.


126. Melissa K. Accordino DLH. Disparities and Challenges in Adherence to Oral Antineoplastic Agents. ASCO Educational Book 2013


Appendix 1: Questionnaire study (Questionnaire)

<table>
<thead>
<tr>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study no.</td>
</tr>
<tr>
<td>Date</td>
</tr>
<tr>
<td>Hospital</td>
</tr>
</tbody>
</table>

- Please think about the medicine that you have been prescribed for your chronic myeloid leukaemia (CML), when answering the following questions.
- The questions all are examples of what other patients with CML have told us they experience and how they manage their treatment.
- There are no right and wrong answers; we are interested in your personal views and experiences.
- Remember your answers are anonymous, meaning that no one will link your name to your answers.
- **Please seal in your answers in the envelope provided. This is to ensure or doctors and nurses will not read your responses. All your answers are completely confidential.**

Thank you for taking time to answer these questions!

**TREATMENT INFORMATION**

1) What medicine have you been prescribed for your chronic myeloid leukaemia (CML), please indicate by ticking the right box:

- ☐ Imatinib (Glivec)
- ☐ Nilotinib (Tasigna)
- ☐ Dasatinib (Sprycel)
- ☐ Bosutinib
- ☐ Other, please specify________________________________________

2) How much medicine have you been prescribed?

   a) How many tablets/capsules have you been asked to take per day?
b) How much is your dose in milligrams (mg) per day?

_______________mg

3) How many times per day do you take your medicine?

☐ Once / day ☐ Twice / day ☐ Three times / day

☐ Other, please specify__________________________
4) When you were first prescribed your CML medicine, did you take a different dose to what you do now?

☐ YES    ☐ NO

   a) If YES, how many tablets/capsules were you initially asked to take per day?

   _____________________________________

   b) If YES, how much were your previous dose in milligrams (mg) per day?

   _____________________ mg

5) What MONTH and YEAR were you born?

   _____________________________________

6) What MONTH and YEAR where you diagnosed with CML?

   _____________________________________

7) What MONTH and YEAR did you start your current CML treatment?

   _____________________________________
8) Did you receive any treatment for your CML before starting on your current therapy?

☐ YES  ☐ NO

a. If YES, please name the treatment you received previously.

____________________________________________________________________________________

____________________________________________________________________________________

9) Are you prescribed any other medicines at this point in time in addition to your CML treatment?

☐ YES  ☐ NO

a. If YES, how many other medicines are you prescribed (you only need to say the number of different medicines you take, NOT the names).

____________________________________________________________________________________

b. If YES, how many times per day do you take your medicines?

____________________________________________________________________________________
Please indicate the extent to which you agree or disagree with each statement below by circling the appropriate answer.

<table>
<thead>
<tr>
<th>Daily Routine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>My mealtimes have NOT changed much since I started taking my current medicine...</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Someone helps me with managing my treatment at</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>
My daily routine changed a lot when I
started my current CML medicine.............

I found it easy to adapt to the routine
of taking my current medicine..................

I travel for a long time to get to my
CML appointments at the hospital..............

COMMUNICATION
My doctor has spoken to me about how to manage side effects from my current CML medicine.

My doctor does NOT generally ask me about how I am getting on with taking my medicine.

My doctor has explained to me how to manage my current CML treatment.

My doctor has told me to take my medicine exactly as prescribed.

I generally do NOT understand what my doctor says about my CML treatment.

If I do NOT understand what my doctor says I generally ask the doctor to explain.
My doctor does NOT listen to what I have to say.

It is generally the nurse who gives me advice on how to manage my CML treatment.

It is generally the pharmacist who...
gives me advice on how to manage my CML treatment...........................

It is generally my doctor who gives me advice on how to manage my CML treatment...........................

INTERNET AND SUPPORT NETWORKS

I search the internet to find information about my CML.............................

I use online CML internet forums / networks
............................................................................................

I am in contact with CML patient advocacy groups..............................

I have used CML patient support services (e.g. councillor /...
psychologist) .....................

I have been in contact with support person who is also a CML patient .........................

**TAKING THE MEDICINE**

I find it difficult to swallow my CML medicine .............................................. 1 2 3 4 5

........

I sometimes forget to take my 1 2 3 4 5
medicine......

The doctors have said that it does NOT matter if I miss the occasional dose............

I find it difficult to take the medicine out of the packaging...........................................
...

Sometimes I stop taking my CML medicine for some reason for a few days without consulting my doctor........................

It will NOT affect my response if I miss the occasional dose of medicine........................

I keep my medicine in a box with little compartments for timings and days of the week..............................................

........

I was off my medicine for some time and it did NOT affect my CML much......................

☐ please tick if you have never been
I think it is ok to miss a few doses now and again..........................

I sometimes decide to skip doses of my current CML medicine..................

I use an alarm to help me remember to take my CML medicine..........................

I would feel worried if I missed a dose........

I have been told that I need to take every single dose or my treatment might NOT work..........................

NOTE: Please only answer N1-N6 if you take NILOTINIB (TASIGNA)
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I find it difficult to fast.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I sometimes forget to fast.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

If I have NOT managed to fast I skip my dose.

[ ] please tick if you always manage to fast.

I think it is better to eat when I am hungry than to always fast exactly as they tell me...
I take my Nilotinib even if I have NOT been fasting…………………………………

........... 1 2 3 4 5

☐ please tick if you always manage to fast

I use a ‘dosing wheel’ to help me decide when it is time to take my Nilotinib and when to fast………………………………...
1) Do you have any other comments about what makes it MORE DIFFICULT for you to take your CML medicine?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

2) Do you have any other comments about what makes it EASIER for you to take your CML medicine?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Please turn page
• We would now like to ask you about your personal views about your medicine.
• These are statements other people have made about their medicine.
• Please indicate the extent to which you agree or disagree with them by circling the appropriate number.
• There are no right or wrong answers. We are interested in your personal views.

My health, at present, depends on my CML medicine...................................................
Having to take my CML medicine worries me...  

My life would be impossible without my CML medicine...  

Without my CML medicine I would be very ill...  

I sometimes worry about long-term effects of my CML medicine...  

My CML medicine is a mystery to me...  

My health in the future will depend on my CML medicine...  

My CML medicine disrupts my life...  

I sometimes worry about becoming dependent on my CML medicine...
My CML medicine protects me from becoming worse ...............................................................

1 2 3 4 5

.................

Please turn page

• These questions ask about how you are getting on with taking your medicines. We know that many patients at times miss or change doses of their medicines. Some forget, others have various problems taking their medicine, and yet other patients adapt their treatment so it better fits in with their life. Please answer the following questions the best you can. The information will help us to understand how we can better adjust individual patients’ treatments to suit their life.

• Although there is some repetition in the following questions, please answer all of the questions best you can.

1) People often miss taking doses of their CML medicine, for a whole range of reasons.

Thinking of the last 7 days:

HOW MANY tablets/capsules of your CML medicine have you MISSED taking in the last 7 DAYS?

_____________________________________________________________________________

If you HAVE MISSED tablets/capsules, GO TO question 2. If not, please GO TO question 3

Page 151 of 171
2) Here are examples of reasons other people have given for missing doses of their CML medicine. THINKING OF THE DOSES YOU MISSED IN THE LAST 7 DAYS, which of the following statements best describe what happened (you can choose more than one option)?

- □ I decided not to take it
- □ I forgot to take it
- □ I was unable to take it
- □ The doctor told me not to take it
- □ Other (please specify) __________________________________________

3) People often take more of their medicine than has been prescribed.

Thinking of the last 7 days:

How many EXTRA tablets/capsules did you take in the last 7 DAYS?

____________________________________________________________________

*If you HAVE taken extra capsules GO TO question 4. If not, please go to question 5.*

Please turn page
4) Here are examples of reasons other people have given for taking extra CML medicine. THINKING OF THE EXTRA DOSES YOU HAVE TAKEN IN THE LAST 7 DAYS, which of the following statements best describe what happened (you can choose more than one option)?

- [ ] I decided to take more
- [ ] I accidentally took more
- [ ] The doctor told me to take more
- [ ] Other (please specify) ____________________________

5) In the last 7 days did you take all your CML medicine?

- [ ] None of the time
- [ ] A little of the time
- [ ] Some of the time
- [ ] A good bit of the time
- [ ] Most of the time
- [ ] All of the time
6) Rate your ability to take all your CML medicine as prescribed in the last 7 days?

☐ Very poor

☐ Poor

☐ Fair

☐ Good

☐ Very good

☐ Excellent
7) Put a cross on the line below at the point showing your best guess about how much of your CML medicine you have taken in the last 7 days.

For example, 0% means you haven't taken any medicine, 50% means you have taken half of your medicine and 100% means you have taken every single dose of medicine. If you have taken more medicine than you have been prescribed it means you have taken more than 100%.
Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea</td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain</td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment</td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill</td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
I am forced to spend time in bed........................................ ( 1 2 3 4)

**SOCIAL/FAMILY WELL-BEING**

I feel close to my friends........................................ ( 1 2 3 4)

I get emotional support from my family ......................... ( 1 2 3 4)

I get support from my friends ....................................... ( 1 2 3 4)

My family has accepted my illness................................ ( 1 2 3 4)

I am satisfied with family communication about my illness ........................................................................ ( 1 2 3 4)

I feel close to my partner (or the person who is my main support) ............................................................. ( 1 2 3 4)

*Regardless of your current level of sexual activity,*

please answer the following question. If you prefer not to answer it, please mark this box and go on.

I am satisfied with my sex life ........................................ ( 1 2 3 4)
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>EMOTIONAL WELL-BEING</th>
<th>1</th>
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<th>4</th>
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<tr>
<td>I feel sad........................................................................</td>
<td>0</td>
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<tr>
<td>I am satisfied with how I am coping with my illness.............</td>
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<td>3</td>
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<tr>
<td>I am losing hope in the fight against my illness..............</td>
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<td>3</td>
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<tr>
<td>I feel nervous....................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>I worry about dying.........................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>I worry that my condition will get worse............................</td>
<td>0</td>
<td>1</td>
<td>2</td>
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</table>
## FUNCTIONAL WELL-BEING

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</table>

I am able to work (include work at home)..........................  

My work (include work at home) is fulfilling..........................

I am able to enjoy life......................................................

I have accepted my illness..............................................

I am sleeping well..........................................................
I am enjoying the things I usually do for fun...................

I am content with the quality of my life right now............
Emotions play an important part in most illnesses. These questions are designed to help the researchers know how you feel. Read each item and underline the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

**I feel tense or 'wound up':**

Most of the time

A lot of the time

From time to time, occasionally

Not at all

**I still enjoy the things I used to enjoy:**

Definitely as much

Not quite so much

Only a little

Hardly at all

**I get a sort of frightened feeling as if something awful is about to happen:**
Very definitely and quite badly

Yes, but not too badly

A little, but it doesn't worry me

Not at all

I can laugh and see the funny side of things:

As much as I always could

Not quite so much now

Definitely not so much now

Not at all

Worrying thoughts go through my mind:

A great deal of the time

A lot of the time

From time to time, but not too often

Only occasionally

I feel cheerful:
Not at all

Not often

Sometimes

Most of the time

I can sit at ease and feel relaxed:

Definitely

Usually

Not Often

Not at all

I feel as if I am slowed down:

Nearly all the time

Very often

Sometimes

Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all

Occasionally
Quite Often

Very Often

I have lost interest in my appearance:

Definitely

I don't take as much care as I should

I may not take quite as much care

I take just as much care as ever

I feel restless as I have to be on the move:

Very much indeed

Quite a lot

Not very much

Not at all

I look forward with enjoyment to things:

As much as I ever did
Rather less than I used to

Definitely less than I used to

Hardly at all

I get sudden feelings of panic:

Very often indeed

Quite often

Not very often

Not at all

I can enjoy a good book or radio or TV program:

Often

Sometimes

Not often

Very seldom

Please turn page
The following questions ask a few personal details about you in order for us to get a better understanding of the background of the patients included in this study.

1. Who else lives in your household? Please tick the appropriate boxes (as many that apply).

□ I live alone  □ Partner/spouse  □ children under age of 18

□ Children over age of 18

□ my parents  □ my spouse’s/partner’s parents  □ my/my spouse’s/partner’s grandparents

□ flatmate/lodger  □ Other, please specify ________________________________

2. What is your ethnic group?

A White  B Mixed / multiple ethnic groups

□ British  □ White and Black Caribbean
□ Any other white background, write below □ White and Black African

____________________________________ □ White and Asian

□ Any other mixed / multiple ethnic background,

write below

____________________________________

C Asian

Black European

□ Indian □ African

□ Pakistani □ Caribbean

□ Bangladeshi □ Any other Black / African /

Caribbean background

□ Chinese write below
Any other Asian background, write below

________________________________

________________________________

E Other ethnic group

□ Arab

□ Any other ethnic group, write below

__________________________________

3. Do you sometimes worry that you will not have enough money to pay for your CML treatment?

□ Yes □ No □ I don’t have to pay for my treatment

4. What category best described your occupation, please tick ALL boxes that apply:
☐ I work fulltime  ☐ I work part-time  ☐ I look after a household

☐ I am retired  ☐ I am actively looking for work  ☐ I am unemployed

☐ I am a student

5. What category best describes your HOUSEHOLD’s annual income received from salary or wages, or pensions, benefits and allowances, before deducting tax?

☐ £10 000 or less  ☐ £10 000 – £14 999  ☐ £15 000 – £19 999

☐ £20 000 – £24 999  ☐ £25 000 – £34 999  ☐ £35 000 – £49 999

☐ £50 000 – £69 999  ☐ £70 000 or more

6. Which of these qualifications do you have?
€ None
€ Secondary education or sixth form college
€ Trade apprenticeship
€ College or University
€ Graduate school
€ Other

END OF QUESTIONNAIRE


**Publications from the MD project:**


   Ash Oral presentation: Atlanta 2012 and an award for the abstract