**Title - Allogeneic Stem Cell Transplantation for Chronic Myeloid Leukaemia in the era of Tyrosine Kinase Inhibitors: striking the right balance**

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**Summary**

The management of chronic myeloid leukaemia has undergone extensive change in the past 15 years. Prior to the development of targeted therapies, themedian survival without allogeneic haematopoetic stem cell transplantation (HSCT) was 5-7 years and HSCT offered the only prospect of cure. HSCT was quickly established as the standard of care for eligible patients through the 1980s and 1990s, during which time considerable advances were made in the optimisation of conditioning regimens and supportive care. Exploiting a deeper understanding of the molecular basis of CML, the development of tyrosine kinase inhibitors (TKIs) in the late 1990s revolutionised the management of the disease. TKIs offer the prospect of long-term disease control with a simple oral therapy, and have established themselves as first line therapy in the 21st century. Interestingly, whilst the majority of patients treated with TKIs will achieve excellent responses with sustained therapies, some even continue to have undetectable or exceptionally low level disease upon TKI withdrawal, but for an almost equal number an adequate response cannot be achieved with any currently available TKI. For the later group HSCT offers the best prospect of long-term survival. This review will focus on the current role of HSCT in CML drawing on lessons learned from the extensive transplant experience over the last three decades.

**Background**

Chronic myeloid leukaemia (CML) is a clonal haematopoetic stem cell disorder characterised by the presence of the oncogenic BCR-ABL1 gene fusion. The reciprocal translocation of the long arms of chromosome 9 and 22 was named following its place of discovery in the early 1970s as the Philadelphia Chromosome[[1]](#endnote-1). The fused BCR-ABL1 oncogene is translated into the Bcr-abl1 protein, which depending on the exact breakpoint location, results in 185-210 kDa protein, with three clinically important variants (p190, p210 and p230). Bcr-abl1 is a dysregulated non-receptor tyrosine kinase that phosphorylates substrate proteins resulting in loss of cell cycle control with consequential increased proliferation, loss of stromal adhesion and resistance to apoptosis.

The disease course of CML is tri-phasic (WHO or ELN classification table 1[[2]](#endnote-2),[[3]](#endnote-3)), with the majority of patients presenting in the relatively stable chronic phase (CP), which if left untreated progresses through a period of increasing genomic instability to accelerated phase (AP) then on to invariably fatal blast crisis (BC). In contrast to the p190 Bcr-abl1 variant, which typically drives lymphoblastic lineage in acute lymphoblastic leukaemia (ALL)[[4]](#endnote-4), the p210 Bcr-abl1 variant, typical of CML[[5]](#endnote-5),[[6]](#endnote-6), drives a true stem cell disorder demonstrated by the fact the final transformation in CML can result in myeloblastic (50%) or lymphoblastic (25%) phenotypes, with 25% comprising biphenotypic or undifferentiated blast phenotypes.

The early treatment approaches in CP CML such as arsenic, busulfan, hydroxycarbamide or interferon were effective in symptom control but did little to alter the natural history of the disease. These therapies conferred little advantage in terms of survival, increasing median overall survival (OS) from 4-5 years to 6-7 years with even the best combination regimens that included α interferon and cytosine arabinosde[[7]](#endnote-7). During the 1980s allogeneic haematopoetic stem cell transplantation (HSCT) became the only treatment capable of curing CML. Despite transplant in the early days often being plagued by high transplant related mortality, it impacted considerably on median survival, and resulted in long-term cure for many. Registry follow-up data from transplants performed in the 1980s and early 1990s reports 20 year overall survival of 40%, 20% and 10% for CP, AP and BC respectively with transplant related mortality approaching 40%[[8]](#endnote-8),[[9]](#endnote-9). Subsequent improvements in conditioning regimens and supportive care over the late 1990s and into the 21st century have further improved outcomes, with most recent registry reports demonstrating 3 year overall survival for good risk patients in excess of 90% with 100 day transplant related mortality (TRM) of only 8% for those transplanted in CP[[10]](#endnote-10), figures which are closely mirrored by individual centres including our own[[11]](#endnote-11).

For several decades HSCT remained the gold standard treatment for eligible patients with a suitable donor until the development of TKIs in the late 1990s. These agents, of which imatinib was the first, block the ATP binding pocket of the Abl1 domain, inhibiting phosphorylation. The specificity of imatinib and the subsequent second (dasatinib, nilotinib and bosutinib) and third (ponatinib) generation drugs for the Abl1 tyrosine kinase results in preferential death of cells harbouring the BCR-ABL1 mutation. The introduction of these drugs dramatically altered CML care and offered the prospect of long-term disease control with an oral therapy. Long-term follow-up from the seminal studies continues to report excellent outcomes with estimated 8 year overall survival in the order of 85%[[12]](#endnote-12). Indeed results derived from patients entered into a series of first line studies of TKIs at a single centre suggest that the life expectancy of patients under the age of 65 years is now comparable to that of the normal US population[[13]](#endnote-13).

While the TKIs have undoubtedly revolutionised the management of CML, we must not forget that CML remains a fatal disease for those who do not respond to TKI. Equally HSCT is not without complications, and comes with its own long-term burden. The non-malignant long-term complications of HSCT range from those directly related to the conditioning such as cataracts, infertility and radiation induced tissue damage to those resulting from chronic graft versus host disease[[14]](#endnote-14), and can impact negatively on the quality of life[[15]](#endnote-15) and life expectancy[[16]](#endnote-16). Striking the balance between the poor survival associated with lack of response to treatment and the potential long-term complications of HSCT is therefore difficult. Here we aim to provide an update on the current literature and provide our own opinions as to guide this decision.

The European Leukaemia Network (ELN) has established criteria to guide the management of CML by defining both response categories and timescales by which optimal responses should be achieved allowing identification of optimal, warning and failing groups3,[[17]](#endnote-17). While early response guidelines employed complete haematological response (CHR), complete cytogenetic response (CCyR) and major molecular response (MMR) as milestones (table 2), the more recent recommendations incorporate the finding by several groups that an inability to achieve a ten-fold reduction in tumour load by 3 months, as indicated by a real-time, quantitative, reverse transcriptase polymerase (RTQ-PCR) result of greater than 10%, is associated with an inferior long-term survival[[18]](#endnote-18),[[19]](#endnote-19).

While the TKIs are capable of inducing and maintaining a deep remission in the majority of patients, we are now faced with new questions posed by the two most divergent groups: i.e. the best and poorest responders. Recent data suggests that remission may be maintained following treatment cessation in a relatively small group of patients with the deepest responses (those achieving RTQ-PCR negativity for at least two years)[[20]](#endnote-20),[[21]](#endnote-21). One of these studies speculated that up to one third of patients may be eligible for a trial of treatment withdrawal, and up to 40% of those may remain in remission following cessation21. This group of patients (between 10-15%) is equalled almost exactly by the number of patients who will fail to achieve an adequate response to multiple TKIs either because of resistance or intolerance (figure 1) and it is this group for whom HSCT offers a well established, feasible alternative.

For 30 years, HSCT for CML informed transplant practice for many haematological malignancies, and many of the lessons learned remain applicable in current practice. Following the success of the TKIs, HSCT has been increasingly reserved for high risk patients with resistant and/or advanced disease, resulting in a steep decline in the number for HSCT for CML over the past 20 years (figure 2). The tragedy of the reluctance to perform SCT is that frequently patients are only referred for HSCT after disease progression has occurred, by definition increasing the complexity and risks of the transplant. The overwhelming data that disease stage at time of transplant remains one of the strongest predictors of transplant outcome, coupled with the recent findings that very early assessment can strongly predict inferior long-term outcome with TKIs may return HSCT to an early time point in the disease course for some. Therefore the key issues for HSCT in CML are those of patient selection, risk stratification and outcome optimisation by means of regimen selection and improved supportive care.

**Key lessons learned from HSCT in CML (Box 1)**

Graft versus Leukaemia -Allogeneic transplantation for CML was first reported using syngeneic donors in 1979[[22]](#endnote-22), then quickly followed by reports of encouraging outcome with sibling donors[[23]](#endnote-23). The restricted availability of compatible sibling donors soon led to the use of HLA-matched volunteer unrelated donors (VUD)[[24]](#endnote-24) although early attempts at VUD HSCT were hampered by high rates of transplant related mortality[[25]](#endnote-25). The introduction of T-cell depletion partially circumvented the problem in the short term by reducing the incidence and severity of acute graft versus host disease (aGvHD) but it rapidly became apparent that this was at the expense of a higher risk of relapse[[26]](#endnote-26). This direct evidence for the role of the graft-versus-leukaemia effect, which unveiled the sensitivity of the disease to T-cell dependent disease immune control, led the pioneers to try manipulate the GvL with the use of infusions of lymphocytes from the original donors to restore durable remissions (donor lymphocyte infusions (DLI))[[27]](#endnote-27). The development of escalating dose regimens largely abrogated the risk of concomitant aGvHD[[28]](#endnote-28),[[29]](#endnote-29) and are deemed safe for sibling, VUD and even mismatched donor use[[30]](#endnote-30). These regimens remain the mainstay of post-HSCT relapse management in CML, as well as other GvL sensitive malignancies such as some of the lymphomas.

The clinical impact of induced GvL responses lead to the realisation that an alloimmune mechanism, rather than conditioning chemoradiotherapy, is in large part responsible for disease control in CML, at least in the case of chronic phase disease. CML therefore paved the way for the development of reduced intensity regimens (RIC) as a natural evolution in order to extend access to HSCT to those who would be deemed unfit for conventional conditioning[[31]](#endnote-31),[[32]](#endnote-32). Interestingly, while these regimens remain useful, particularly in combination with early pre-emptive DLI[[33]](#endnote-33), and for those in whom co-morbidity would otherwise preclude transplantation, myeloablative conditioning (MAC) remains the preferred approach in suitable patients. This observation probably reflects the fact that MAC remains extremely well tolerated in CML CP patients compared to those with other malignancies, and the reduced intensity approach risks higher rates of chronic GvHD, complicating the use of DLI which is commonly required for disease eradication in this context.

Transplant and Disease Risk Stratification - HSCT for CML provided the first model of risk assessment strategies within transplantation. The European Group for Bone and Marrow Transplantation (EBMT) developed a risk scoring system in the 1990s when CML was the commonest indication for allogeneic HSCT[[34]](#endnote-34) (table 3). This system, based on more than 3000 CML patients, was subsequently validated in a data set of more than 56,000 transplants by European Group for Blood and Marrow Transplantation (EBMT)[[35]](#endnote-35) and remains the most powerful predictor of transplant outcome across haematological malignancies.

A key observation in pre-transplant optimisation was that debulking of disease in CP, either by splenectomy or splenic irradiation prior to transplantation, confers neither a survival advantage nor a reduce risk of relapse[[36]](#endnote-36). Conversely, progression of disease beyond chronic phase has a profoundly detrimental effect on outcome, with transplantation in frank blast crisis being frequently futile. These findings were observed nearly 30 years ago, but their implications remain equally pertinent today, in the TKI era.

Minimal Residual Disease (MRD) - MRD monitoring was pioneered in transplant for CML. Detection of BCR-ABL1 transcripts in peripheral blood by polymerase chain reaction (PCR) assays was developed to detect disease relapse following HSCT. While early methodologies were qualitative, systems were quickly developed which allowed serial quantitative measurement[[37]](#endnote-37). The new exquisitely sensitive techniques are now the cornerstone of disease and response monitoring in CML, but it should be remembered that the initial use of these tests were to reliably define molecular relapse (MR) following HSCT37,[[38]](#endnote-38).

**Indications for HSCT in the TKI era**

The advisability and timing of transplant depends on disease phase. The most clear cut indication for HSCT is disease beyond CP and for this reason we start with blast crisis.

Blast Crisis – Blast crisis is considered the result of genomic instability resulting from DNA damage consequent upon persistent Bcr-abl1 activity, often characterised by the accumulation of additional karyotypic abnormalities. The impact of the TKIs has been least striking in this group of patients, with only a modest rise in median survival following their widespread use (3-4 months in the pre-TKI era to 7-11 months with their use[[39]](#endnote-39)), with usually short-lived benefit. HSCT offers the only prospect of long-term survival for this group. There are two key messages when considering HSCT for patients presenting in or progressing to blast crisis: firstly, the best outcomes are achieved by returning patients to chronic phase prior to HSCT, with the outcome for those transplanted in frank BC dismal (less than 10% long-term survival)[[40]](#endnote-40). A second or subsequent chronic phase can be achieved using TKI alone[[41]](#endnote-41), conventional AML-type combination chemotherapy alone[[42]](#endnote-42) or both approaches simultaneously[[43]](#endnote-43),[[44]](#endnote-44),[[45]](#endnote-45). The evidence base for better outcome using combined chemotherapy and a TKI is limited but the need to restore chronic phase is urgent so giving maximum therapy *ab initio* is not unreasonable. Secondly, an intriguing observation is that the most frequent cause of death post transplant is not in fact progressive disease but rather transplant related mortality. These patients suffer extremely high non-relapse mortality with ‘TKI era’ registry data reporting 46% 1 year mortality if transplanted in BP[[46]](#endnote-46), which improves to 33% if CP2 is achieved. The reasons for this are unclear: whilst the contribution of pre-transplant chemotherapy, drug toxicity or atypical/fungal infections resulting from prolonged immunosuppression may partially explain the high TRM when comparing to those transplanted in first chronic phase, these factors cannot explain the differences observed between HSCT for CML BP and the acute leukaemias, who have experienced equally intense conditioning and transplant regimens. Even high risk acute myeloid leukaemia patients transplanted in first complete remission (with frequently comparable demographs and induction regimen characteristics) have 3 year TRM in the region of 10-20%[[47]](#endnote-47),[[48]](#endnote-48). Despite the high TRM, HSCT should be offered to all eligible BC patients with a suitable donor, as the only realistic prospect of long-term survival.

Accelerated Phase Disease – The definition of accelerated phase has always been more subjective than those of chronic phase and blast crisis, resulting in the term ‘acceleration’ describing a heterogeneous population. While some are in the early stages of transformation, others have further progressed to the brink of BC. This is confounded by the fact that the definitions were established in the pre-TKI era, where lost of response to therapy would constitute acceleration, whereas now loss of cytogenetic or molecular response to imatinib would simply trigger a switch to a second generation agent, often with good effect. This heterogeneity makes the group difficult to consider a single entity. For those on the brink of transformation to BC, HSCT undoubtedly offers the best chance of long-term survival, however a TKI based regimen may suffice for those early in the transition from CP to AP. For these reasons, there has been a recent attempt to further risk stratify AP patients (table 4)[[49]](#endnote-49). Based on their experience, Jiang et al suggested that low risk patients, those with no risk factors, gain no advantage from HCST over imatinib alone (6 year OS 81% vs 100%). However, the outcome for high-risk patients (with 2 or 3 risk factors) who did not receive HSCT was extremely poor, yet eminently salvageable with HSCT (5 year OS 18% vs 100%). Others have reported 3 year OS of 87% and 95% for AP patients treated with imatinib or 2GTKI respectively[[50]](#endnote-50), however, this cohort would appear to represent those in the early stages of transformation. In practical terms most clinicians will initiate therapy with a TKI and carefully monitor the molecular response. Lower risk groups may be continued on TKI alone if an ‘optimal response’ has been achieved, but this comes with the caveat that the definition of ‘optimal response’ has been validated only in chronic phase disease. Few clinicians would withhold HSCT in those with higher risk AP disease.

Chronic Phase Disease – The decision to transplant or not in CP is undoubtedly the most controversial and complex. Frontline imatinib induces MMR in the region of 60% of CP patients12. Dasatinib and nilotinib in front line setting are even more effective, achieving MMR in the region of 75% at the 4 year follow-up reports[[51]](#endnote-51),[[52]](#endnote-52). However, the rates of treatment discontinuation either from loss/lack of control or intolerable side effects are high. 45% of patients have stopped imatinib after 8 years of treatment12 while 32% and 31-34% have stopped dasatinib51  and nilotinib52 respectively after 4 years. For those who switch to a 2GTKI following imatinib cessation, 70% have discontinued their first choice 2GTKI after 6 years[[53]](#endnote-53),[[54]](#endnote-54). Whilst clear and reproducible data for subsequent bosutinib and ponatinib are maturing, it would seem similar failure/discontinuation rates should be expected. Irrespective of the first line treatment choice, these data suggests that a sizable minority (some 10-15%) will be unable to obtain an optimal response on a tolerable treatment, and will require an alternative strategy of which HSCT is one (figure 1).

Currently there are no biomarkers from diagnosis that can reliably identify patients destined to fail TKI therapy. The recent data, suggesting that a group of poorer risk patients can be identified as early as 3 months after the start of any TKI, is beginning to change our approach to management, with changes in drug therapy occurring earlier in an effort to prevent early disease progression. With five licensed drugs the tendency is to try multiple lines of therapy before referring the patient for transplant. Unfortunately the delay imposed by such a strategy will inevitably result in disease progression in some patients who might otherwise have benefited from HSCT. It is worth considering the rationale behind such an approach in some detail.

Worldwide the majority of newly diagnosed patients commence therapy with imatinib. If the patient fails to respond, loses an established response or experiences unacceptable toxicity, it is entirely reasonable to try a one or other of the second generation drugs, bosutinb, dasatinib or nilotinib. In some cases the actual choice might be guided by the presence of a kinase domain mutation or certain co-morbidities, but in the majority any of these drugs may be used as their efficacy is equivalent. The dilemma emerges if they are resistant and/or intolerant to the second line therapy. The efficacy of a third-line second generation drug is limited: reports of local or regional series and most recently a systematic review suggest the achievement of a complete cytogenetic response in 20-30%; the durability of these responses is less clear[[55]](#endnote-55),[[56]](#endnote-56),[[57]](#endnote-57). Furthermore it is difficult to determine any features that might predict response to the third line agent, although at least two reports have shown an association of prior cytogenetic response on the first and/or second line therapy51, 52,[[58]](#endnote-58). Intuitively one feels that a patient who has demonstrated resistance to two lines of therapy without an obvious explanation such as non-compliance or a kinase domain mutation, is less likely to be responsive to a third line agent of similar efficacy. Unfortunately the situation of multiple intolerances, particularly with haematological toxicity, although perhaps sensitive to the third drug, is likely to result in further intolerance. Similar arguments against a further second generation agent can be made for a patient failing first line dasatinib or nilotinib.

The third generation drug, ponatinib, has shown impressive efficacy in second, third and fourth line therapy[[59]](#endnote-59) : once again those patients likely to respond well can be identified at 3 months. It is entirely reasonable to suggest that a patient eligible for transplant should ideally transition through imatinib to a second generation agent and then currently to ponatinib, or from first –line dasatinib or nilotinib to ponatinib, so as to arrive at transplant as early as possible in the disease course. In practice, this pathway will be influenced by drug availability, the presence of mutations, co-morbidities or the nature of intolerance but the overall aim should be to avoid the risk of progression. Patients failing first line therapy should be referred for donor identification to avoid any subsequent delay if transplant becomes necessary.

When considering HSCT as an alternative to TKI because of toxicity or intolerance, every attempt must have been made to manage the side effects of the responsible drug. While many of the toxicities seen early after treatment initiation such as rash, fluid retention, nausea, diarrhoea, and other gastrointestinal upset respond well to temporary treatment interruption or dose reduction, some do not and treatment cessation is necessary. Recurrent haematological toxicity, even after dose reduction, can render continued TKI treatment problematic. Recently more serious and life-threatening toxicities have been described after treatment with both second and third generation drugs59,[[60]](#endnote-60),[[61]](#endnote-61), also requiring cessation of the causative drug. In these cases a strong argument can be made for recommending HSCT.

Just as adherence to treatment is a critical factor in achieving molecular response in CML[[62]](#endnote-62), so too is adherence to post transplant regimens in order to minimise the complications of HSCT such as GvHD, infection and viral reactivation. While it may seem logical to assume that those who came to transplant because of known or unknown poor compliance with TKI therapy will be poorly compliant with post-transplant prophylaxis, this cannot necessarily be assumed. Compliance behaviour is complex62,[[63]](#endnote-63) and often poor compliance is driven by side effects or treatment fatigue induced by prolonged treatment durations. Therefore while poor compliance with TKI therapy should alert the transplant physician to the possibility of poor compliance post-HSCT, it should not preclude it use *per se*.

In order to inform patient choice regarding the risks and benefit of HSCT, we need to be confident that existing data, accumulated in the pre-TKI data remains valid in current practice. Several early studies seeking to validate existing data support the notion that TKI use does not negatively impact on subsequent transplant outcome[[64]](#endnote-64),[[65]](#endnote-65),[[66]](#endnote-66), however these were often small, and confounded by the fact that the control group (non-TKI treated) were historical comparators, not contemporaneously transplanted patients. Several authors have subsequently tried to address the question of HSCT in the TKI era, and Table 6[[67]](#endnote-67),[[68]](#endnote-68),[[69]](#endnote-69),[[70]](#endnote-70),[[71]](#endnote-71),[[72]](#endnote-72),[[73]](#endnote-73),[[74]](#endnote-74),[[75]](#endnote-75),[[76]](#endnote-76) summarises the most recent literature. Perhaps the most systematic approach however comes from, a recent reanalysis of EBMT data. Milojkovic *et al.* addressed the validity of the original EBMT risk score by reviewing the outcome of more than 5500 patients transplanted for CML between 2000 and 2011[[77]](#endnote-77), the period of transition to TKI use. Similar 5 year overall and progression free survivals (PFS) were seen in TKI treated compared to TKI naive transplant recipients (OS 59% vs 61% and PFS 42% vs 46%). Interestingly whilst time from diagnosis to transplantation of more than 12 months from diagnosis remained an independent predictor of poorer outcome in the TKI naive group, this was no longer of predictive value in those treated with TKI. Whilst this is difficult to fully understand, it may be speculated that even in those ‘resistant’ and particularly in those intolerant to TKIs, some may have benefited from a limited degree of disease control

For many young healthy patients, despite the excellent long-term results with the TKIs, the prospect of lifelong medication with frequent monitoring and clinical review may compare less favourably to an intense period of treatment undergoing an HSCT*.* Moreover while access to TKIs is relatively easy in countries of high economic status, this is not the case in many developing countries. Even in developed countries, a case can be made for the cost effectiveness of HSCT compared to lifelong TKI therapy particularly in children, adolescence and young adults[[78]](#endnote-78). One relatively small study from 2006 compared the cost of HSCT to imatinib, concluding that treatment with imatinib was 25% more expensive than RIC HSCT over the first 2 years of treatment. The contrasting influences of falling costs of TKI as patents expire and the normalisation of lifespan on these treatments make predictions about relative cost-effectiveness difficult.

Few studies directly compare HSCT to TKI, however the German CML VI study reported 56 patients transplanted in CP either because of patient choice or imatinib failure. In a matched paired analysis 106 patients not undergoing HSCT were compared to those who underwent HSCT and similar overall survivals were demonstrated (96% vs. 92% respectively)[[79]](#endnote-79). Perhaps more importantly, reinforcing the idea that prolonged prior use of imatinib does not negatively impact on transplant outcome, patients electing to undergo HSCT following brief initial imatinib treatment (n=19) had survival similar to those who proceeded to transplantation following imatinib failure (n=37) (3 year OS of 88% and 94% respectively). Predictably, the 3 year overall survival for those transplanted in accelerated phase disease was significantly lower at 59%.

Ultimately, when considering the indications for HSCT, two key facts must be considered (box 2): Firstly, progression of CML beyond chronic phase negatively impacts on transplant outcome, therefore patients should be referred for HSCT prior to progression. Secondly, the mechanism of disease control exerted by HSCT is dependent on GvL and therefore different to that of the TKIs. Thus, resistance to one or more TKI, whether in the presence of an identifiable tyrosine kinase domain mutation or not, does not, *per se*, impact on transplant outcome.

**Intricacies of HSCT in the TKI era**

Conditioning Regimens – Early regimens of chemoradiotherapy given to condition the marrow for the stem cell transplant were fully myeloablative. Typically these regimens consisted of total body irradiation (TBI) with additional chemotherapy, frequently cyclophosphamide. Realisation that long-term remission is dependent upon GvL led to the suggestion that transplantation regimens may be made safer, by reducing the intensity of the conditioning and reinforcing the GvL with pre-emptive DLI[[80]](#endnote-80),[[81]](#endnote-81),[[82]](#endnote-82). Although there are no prospectively randomised trials of myeloablative vs reduced intensity conditioning (RIC), case series reports and registry data suggests that RIC are feasible strategies to increase accessibility to transplant for otherwise ineligible patients (table 7[[83]](#endnote-83),[[84]](#endnote-84),[[85]](#endnote-85),[[86]](#endnote-86),[[87]](#endnote-87),[[88]](#endnote-88),[[89]](#endnote-89),[[90]](#endnote-90),[[91]](#endnote-91)). In particular, they extent the age to which HSCT may safely be undertaken thereby limiting the degree to which HSCT is restricted to young patients. Their previously discussed higher relapse rate however, deem them unsuitable for high risk patients. Therefore, MAC remains the standard of care for those capable of tolerating it, with the majority of centres frequently continuing to employing TBI and cyclophosphamide based protocols.

T-Cell Depletion (TCD) – Depletion of T-cells, either by *in vitro* treatment of the graft typically by negative selection of donor T-cells, or *in vivo* treatment of the recipient with either monoclonal antibodies (alemtuzumab) or anti-thymocyte globulin, is well established to ameliorate the risk of GvHD but at the expense of the GVL. Socié and colleagues[[92]](#endnote-92) demonstrated some dissociation of the risk of relapse from the risk of aGvHD using rabbit ATG to achieve T-cell depletion in recipients of unrelated transplant following myeloablation. While these data are encouraging, at present the decision to use TCD is based on an assessment of the risk of aGVHD vs the risk of relapse. Whilst there may be an advantage in employing T-cell depletion in a mismatched recipient undergoing HSCT in chronic phase, there is little or no benefit in sibling HSCT in CP2. Based on a lack of evidence, these decisions will be institute and physician dependent.

Bone Marrow vs Peripheral Blood Stem Cells – Historically stem cells derived from bone marrow (BM) have been used, but the advent of clinical grade growth factors now allows collection of stem cells from peripheral blood. For reasons of faster engraftment and donor preference, peripheral blood stem cells (PBMC) have now largely replaced bone marrow (BM) as the favoured stem cell source. However, the use of PBSC for those in CP1 is associated with higher rates of non-relapse mortality and, consequently, lower rates of survival[[93]](#endnote-93). A more recent randomised controlled trial comparing PBSC to BM, which included but was not limited to CML patients, showed higher rates of chronic graft versus host disease with PBSC (53% vs 41%)[[94]](#endnote-94). Although there was no impact on OS or PFS in this study, the findings are particularly pertinent to CML patients; Up to 50% of patients transplanted for CP CML will subsequently develop molecular relapse necessitating DLI to restore remission, particularly if RIC regimens are used[[95]](#endnote-95). Active chronic graft-verus-host disease precludes the use of DLI, thereby hampering the management of relapse. Therefore every effort should be made to reduce the risk of cGvHD to enable subsequent use of DLI if required, not to mention to reduce the burden of morbidity associated with cGvHD. Although a cautious approach would therefore favour the use of BM in CP patients, however more often than not the final choice lies with the donor.

Relapse Strategies - For those transplanted in CP, if relapse occurs it will most likely be at low level and initially detectable only by BCR-ABL1 RTQ-PCR. Long standing criteria exist to define relapse following HSCT, which are highly predictive of progressive disease[[96]](#endnote-96),[[97]](#endnote-97). Following relapse, immune modulation with cessation of ongoing immunosupression followed by DLI if necessary, is the most powerful strategy for restoring remission in the majority of patients with molecular relapse24,25,[[98]](#endnote-98). Adherence to escalating dose regimens (starting with 1x106 T-cells per kg in VUD and 1x107T-cells per kg in sibling recipients, rising in a step wise fashion, until response is achieved) minimises the risk of GvHD making them a safe first choice strategy for the majority of patients, providing 6-9 months has elapsed from HSCT28,29. Interestingly, while DLI is capable of restoring remission in the majority of patients undergoing treatment for molecular relapse by achieving undetectable BCR-ABL1, many of these patients subsequently develop intermittently detectable BCR-ABL1 transcripts by sensitive PCR techniques but rarely develop progressive disease96. This might reinforce the idea that rather than eliminating the BCR-ABL1 clone, HSCT exerts a T-cell dependent immune control of the disease.

Although TKIs have been used in the setting of post HSCT relapse it is likely that significant resistance or intolerance to TKI will have developed prior to HSCT given that most HSCT recipients have cycled through multiple TKIs, making their use less likely to be effective. In the case of relapse in TKI naive or TKI responsive patients a trial or re-introduction of these agents may offer benefit. For those relapsing early or with aggressive disease, rapid withdrawal of existing immunosuppression, immune therapy with DLI and TKIs unlikely to restore remission, and experimental agents offer the only prospect of survival.

**Conclusions**

TKIs are undoubtedly a huge step forward in the management of CML, but not all patients will respond or can tolerate these drugs. New tools of early assessment should help identify poor responders quickly, allowing them to rapidly cycle through TKIs and be considered for HSCT early if necessary. When considering HSCT it is important to remember that a poor response to TKI does not *per se* predict a poor response to transplant because of the independent mechanism of disease control. HSCT should not be seen as a ‘last ditch’ or ‘salvage’ option but rather a feasible treatment strategy to be considered early in the management plan of those with less than optimal responses. Poor TKI responders should be identified early and given the opportunity to undergo HSCT, particularly given the excellent outcome in the most recent studies. A goal of CML physicians is now to normalise the life span for CML patients and HSCT offers one route to achieve this. Several unanswered questions remain however, particularly regarding regimen choice, use of T-cell depletion and pre-transplant optimisation, but with the reduced number of patient undergoing HSCT, it seems unlikely that studies with sufficient power will exist to answer them. A vast wealth of existing data does provide a firm base for HSCT in CML moving forward, and the key message remains that transplantation is viable treatment avenue that should not be delayed or overlooked.

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|  | WHO criteria2 | ELN criteria 3 |
| **Blast Crisis** |  |  |
| Peripheral blood or bone marrow blasts | ≥ 20% | ≥ 30% |
| Additional defining characteristics | Extramedullary blast proliferation (Except spleen), Large foci of blasts in spleen or bone marrow | Extramedullary blast involvement (except spleen) |
| **Accelerated Phase** |  |  |
| Peripheral blood or bone marrow blasts | 10-19% | 15-29% blasts;  or blasts plus promyelocytes > 30%, with blasts alone <30% |
| Peripheral blood basophils | ≥ 20% | ≥ 20% |
| Platelets | <100 x 109/L not attributable to treatment, or platelets >1000 uncontrolled on treatment | <100 x 109/L not attributable to treatment |
| Evidence of clonal evolution | Appearance of additional genetic abnormalities on treatment | Appearance of additional genetic abnormalities on treatment |
| White cell count and spleen size | Increasing and uncontrolled on treatment | Not included |

**Table 1** - Current defining characteristics of blast crisis and accelerated phase (by present classification systems: WHO World health organization, ELN European Leukaemia Network)

|  |  |
| --- | --- |
| **Definitions** | |
| Complete Haematological Response (CHR) | WCC < 10 x 109/L  Basophils <5%  No Myelocytes, promyelocytes or myeloblasts in the differential count  Platelet count < 450 x 109/L  Non-palpable spleen |
| Complete Cytogenetic Response (CCyR) | No detectable Ph+ cells measured by conventional cytogenetic testing (examination of a minimum of 20 metaphase by G-banding) or FISH analysis (examination of a minimum of 200 nuclei). |
| Partial Cytogenetic Response (PCyR) | 1-35% Ph+ cells measured by conventional cytogenetic testing (G-banding) or FISH analysis |
| Major Molecular Remission (MMR) | BCR-ABL1 ≤ 0.1% (3 log reduction in tumour load, measured ) |

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Optimal** | **Warning** | **Failure** |
| **Baseline** | NA | High risk or Clonal chromosomal abnormalities in Ph + cells | NA |
| **3 Months** | BCR-ABL1 ≤ 10% and/or  PCyR (Ph+ ≤ 35%) | BCR-ABL1 ≥ 10% and/or  Ph+ 36-95% | Non-CHR and/or  Ph+ ≥ 95% |
| **6 months** | BCR-ABL1 ≤ 1% and/or  CCyR (Ph+ 0%) | BCR-ABL1 1-10% and/or  Ph+ 1-35% | BCR-ABL1 ≥ 10% and/or  Ph+ ≥35% |
| **12 Months** | BCR-ABL ≤ 0.1% | BCR-ABL ˃0.1-1% | BCR-ABL ˃1% |
| **Then, and at any time** | BCR-ABL ≤ 0.1% | Clonal chromosomal abnormalities in Ph- cells (monosomy 7 or 7q-) | Loss of CHR  Loss of CCyR  Confirmed loss of MMR  Mutations  Clonal chromosomal abnormalities in Ph + cells |

**Table 2** – Definitions and response categories adapted from the current ELN guideline17. NA not applicable, Ph + Philadelphia positive, Ph – Philadelphia negative.

|  |  |  |
| --- | --- | --- |
| **Risk factor** | **Category** | **Score** |
| Donor type | HLA-identical sibling | 0 |
| Matched unrelated donor | 1 |
| Disease stage | 1st Chronic phase | 0 |
| Accelerated phase | 1 |
| Blast crisis | 2 |
| Age of recipient | <20 years | 0 |
| 20-40 years | 1 |
| > 40 years | 2 |
| Sex combination | All except: | 0 |
| Male recipient/female donor | 1 |
| Time from diagnosis to transplant | <12 months | 0 |
| >12 months | 1 |

|  |  |  |  |
| --- | --- | --- | --- |
| Risk Score | Probability of outcome at 5 years (%) | | |
| LFS | OS | TRM |
| 0 | 60 | 72 | 20 |
| 1 | 60 | 70 | 23 |
| 2 | 47 | 62 | 31 |
| 3 | 37 | 48 | 46 |
| 4 | 35 | 40 | 51 |
| 5 | 19 | 18 | 71 |
| 6 | 16 | 22 | 73 |

**Table 3-**  EBMT risk stratification score, developed in CML, but broadly applicable across haematological malignancies34.

|  |  |
| --- | --- |
| **Proposed Accelerated Phase Risk Stratification** | |
| **Risk Factors** | **Risk Category** |
| CML duration ≥ 12 months | High Risk – At least 2 risk factors |
| hemoglobin < 100 g/L | Intermediate Risk – Any risk factor |
| peripheral blood blasts ≥ 5% | Low – No risk factors |

**Table 4** – Proposed risk stratification of accelerated phase disease49. Note that this is derived from a single study.

|  |  |
| --- | --- |
| **Indications for HSCT in CML** | |
| Blast Crisis | **∙** All eligible patients in BC should be considered for HSCT  ∙ Every effort should be made to achieve CP2 prior to transplantation |
| Accelerated Phase | ∙ All eligible AP patients should be considered for HSCT  ∙ Every effort should be made to achieve CP2 prior to transplantation  ∙ TKI use in AP should be within the context of a clinical trial, with particular attention paid to rigorous PCR monitoring. |
| Chronic Phase | ∙ All eligible patients with a T315I mutation should be referred to a transplant centre for early discussion: ponatinib should be initiated  ∙ All eligible patients failing 2 x 2GTKI should be referred for HSCT  ∙ All eligible patients failing 1x 2GTKI should be referred to a transplant centre for risk/benefit discussion  ∙ Consideration should be given undertaking a donor search following failure of first line therapy (see text) |

**Table 5** – Indications for HSCT in CML; HSCT, haematopoetic stem cell transplantation, CML, chronic myeloid leukaemia, CP2, second chronic phase, AP, accelerated phase, TKI, tyrosine kinase inhibitor, PCR, polymerase chain reaction, 2GTKI, second generation tyrosine kinase inhibitor.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1. **Authors** | **Number of patients / Transplant period** | **Disease stage** | **TKI use** | **Donor** | **Stem cell source** | **Regimen** | **DFS/PFS** | **OS** | **TRM** | **Study type** |
| **Chronic phase** | | | | | | | | | | |
| Luo *et al* 200967 | 28 /  2005 - 2007 | CP1 100% | Imatinib 100% | Sib 46%  URD 54% | BM 25%, PB 75% | RIC 100% | 67% (DFS at 3 years) | 81%  (3 years) | 4% | Retrospective single centre study |
| Pavlů *et al* 200911 | 173 /  2000 - 2010 | CP1 100% | NR | NR | NR | NR | NR | 89%  (If EBMT score 0 or 1)  (3 year) | NR | Retrospective single centre study |
| Liu *et al* 201168 | 91 /  1997 - 2009 | CP1 100% | Imatinib resistance 4% | Sib 53%  Related, other 14%,  URD 33% | BM 34%,  PB 66% | MAC 100% | 75% (DFS at 5 years) | 81.8  (5 year) | 15.9  (5 year TRM) | Retrospective single centre study |
| **Advanced phase (AP and BC)** | | | | | | | | | | |
| Jiang *et al* 201149 | 132 /  2001 - 2008 | AP 100% | Imatinib only 66%  Imatinib + HSCT 34% | Sib 42%,  Other 58% | NR | 100% MAC (of those transplanted) | Low Risk:  Imatinib 85%  HSCT 95%  (PFS at 6 years)  High Risk:  Imatinib 19%  HSCT100%  (PFS at 5 years) | Low Risk:  Imatininb 100%  HSCT 81%  (OS at 6 years)  High Risk: Imatinib 18%  HSCT100%  (OS at 5 years) | NR | Prospective single centre study (Imatinib vs HSCT) |
| Khoury *et al* 201246 | 449 /  1999 - 2004 | CP2 41%,  AP 41%,  BC 18% | Imatinib 50% | Sib 27%,  URD 70%,  Other=3% | BM 52%,  PB 48% | MAC 78%,  RIC 22% | CP2 27%,  AP 37%,  BC 10%  (LFS at 3 years) | CP2 36%,  AP 43%,  BC 14%  (OS at 3 years) | CP2 33%,  AP 34%,  BC 46%  (TRM 1 year) | Retrospective multicentre study (CIBMTR) |
| Zheng *et al* 201369 | 32 /  2002 - 2011 | AP 59%,  BC 41% | Prior imatinib 53% | Sib 50%,  Cord 50% | BM 3%,  PB 18%,  BM+PB 28%  Cord 50% | MAC 94%,  RIC 6% | Cord 50%  Sib 40%  (LFS at 5 years) | Cord 62%,  Sib 49%  (OS at 5 years) | Cord 38%,  Sib=12%  (180d CI) | Retrospective single centre study  (Cord vs sib) |
| **Mixed Phase Disease** | | | | | | | | | | |
| Shimoni *et al* 200970 | 21 /  NR | CP1 24%,  AP 29%,  BC 38%,  ALL 10% | \*Dasatinib 62%,  \*Nilotonib 38% | Sib 33,  URD 62%,  Haplo 5% | BM 10%,  PB 90% | MAC 67%,  RIC 33% | 46%  (DFS at 2 years) | 64%  (OS at 2 years) | 7% | Retrospective single centre study |
| Saussele *et al* 2009 79 | 84 /  2003 - 2008 | CP1 (elective) 23%,  CP1 (TKI failure) 44%,  AP 4%,  BC 30% | All imatinib | Sib 36%,  URD 64%, | BM 24%  PB 76% | MAC 68%,  RIC 13%,  Other 19% | CMR at last PCR 88% | CP1(elective) 88%,  CP1(imatinib failure) 94%,  AP 59%  (OS at 3 years) | Early TRM  8% | Prospective multicentre study  (CML IV study) |
| Sanz *et al*  201071 | 26 /  1997 - 2009 | CP1 27%,  CP2 47%,  AP 8%,  BC 23% | None reported | Cord 100% | Cord 100% | MAC 100% | 41% (DFS at 8 years)  (CP 59% vs non-CP 0%) | NR | NR | Retrospective single centre study |
| Jabbour *et al* 201172 | 47 /  2004 - 2007 | CP1 34%,  CP2 21%,  AP 25%,  BC 19% | Imatinib failure 100%  + Second Generation TKI 62% | Sib 49%  Other 51% | NR | MAC 32%,  RIC 68% | 49%  (EFS at 2 years)  (Mutation 36% vs no mutation 58%) | 63%  (OS at 2 years)  (Mutation 44% vs no mutation 76%) | 13%  (2 years) | Retrospective single centre study |
| Warlick *et al* 201273 | 306 /  2001 - 2007 | CP1 52%,  CP2/AP 41%,  BC 8% | Imatinib 72%,  No TKI 26%,  Unkonwn 2% | Sib 47%,  URD 53% | BM 19%,  PB 81% | RIC 100% | 40-49yrs 35%,  50-59yrs 32%,  >60yrs 16%  (DFS at 3 years) | 40-49yrs 54%,  50-59yrs 52%,  >60yrs 41%  (OS at 2 years) | 40-49yrs 13%,  50-59yrs 7%,  >60yrs 9%  (100d) | Retrospective multicentre study (CIBMTR) |
| Topcuoglu *et al* 201274 | 84 /  1989 - 2007 | CP1 79%,  CP2 6%,  AP 15% | NR | Sib 100% | BM 10,  PB 90 | MAC 67%,  RIC 33% | 48%  (LFS at 5 years)  No difference RIC vs MAC | 56%  (OS at 5 years)  No difference RIC vs MAC | 7% RIC  14% MAC | Retrospective single centre study (RIC vs MAC) |
| Zuckerman *et al* 201275 | 38 /  1999 – 2005 | CP1 89%,  AP 11% | Imatinib 11%,  No TKI 89% | Sib 97%,  URD 3% | PB 100 | MAC 100% | 79%  (LFS at 5 years) | 84%  (OS at 5 years) | 13%  (CI at 10 years) | Single institution long term follow up |
| Oyekunle *et al* 201376 | 68 /  2002 – 2009 | CP1 40%,  >CP1 60% | Pre-HSCT TKI 71%,  Post-HSCT TKI 29% | Matched 87%,  Mismatched 13% | BM 15%,  PB 85% | MAC 66%,  RIC 33% | 54%  (LFS at 2 years) | 63%  (OS at 2 years) | NR | Single institute HSCT in TKI era |
| Milojkovic *et al* 201377 | 5732 /  2000-2011 | Prior-TKI:  CP 51%,  CP>1 25%,  AP 14%,  BC 10%,  Non-TKI:NR | Prior TKI 22%,  No TKI 78% | NR | NR | NR | Non-TKI 46%  Prior TKI 42%  (PFS at 5 years) | Non-TKI 61%  PriorTKI 59%  (OS at 5 years) | NR | Retrospective multicentre study (EBMT) |

CP1 first chronic phase, CP2 second chronic phase, AP accelerated phase, BC blast crisis, TKI tyrosine kinase inhibitor, Sib sibling, URD unrelated donor, HSCT haematopoetic stem cell transplantation, NR not reported, BM bone marrow, PB peripheral blood, DFS disease free survival, EFS event free survival, LFS leukaemia free survival, TRM transplant related mortality, MAC myeloablative conditioning, RIC reduced intensity conditioning, CI cumulative incidence

**Table 6** - Transplant outcome data for HSCT reported since 2009, restricted to studies conducted at least in part following the introduction of the tyrosine kinase inhibitors.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Number of patients / Median age** | **Disease stage** | **Regimen** | **Progression free survival (PFS)** | **Overall survival (OS)** | **Transplant related mortality (TRM)** | **% developing acute GVHD (II-IV)** | **% developing chronic GVHD (Extensive)**  **(CI where reported)** |
| Kelemen *et al* 199883 | 19 | CP 74%,  AP 26% | DBM/AraC/cyclo 100% | 82% at median follow-up 4 years | 89% at median follow-up 4 years | NR | 11% | 67% |
| Barta *el al* 200184 | 36  15-59 years (no median) | CP 72%,  AP 28% | DBM/AraC/cyclo 100% | 72% at follow-up 45-113 months | 83% at follow-up 45-113 months | 17% | 25% | 56% (22%) |
| Or *et al* 200380 | 24  35 years [3-63] | CP1 100% | Flu/Bu ± ATG | 85% at 6 years | 85% at 6 years | 0% at 100d | ≥Grade I 75%, ≥ Grade III 29% | 54% (severe 17%) |
| Weisser *et al* 200485 | 35  51 years [45-62] | CP1 74%,  CP2/AP 26% | 8Gy TBI/Flu/Cyclo/ATG | LFS 49% at 30 months | 69% at 2 years, 59% at 5 years | 11% at 100d, 28% at 1 year | 48% | 23% extensive |
| Crawley *et al* 200581 | 186 /  50 years [17-64] | CP1 64%,  CP2 12%,  AP 17%,  BC 6% | Mixed reduced intensity | 37% at 3 years | 58% at 3 years | 11.6% at 1 year, 23.3% at 2 years | 32% | 43% (24%) |
| Kerbauy *et al* 200586 | 24 /  58 years [27-71] | CP1 58%,  CP2 17%,  AP 25% | 2Gy TBI 33%,  2Gy TBI/Flu 67% | 68% 2 year for TBI/Flu | 70% at 2 years for CP1  56% at 2 years for >CP1 | 15% NRM at 2 years for CP1  12% NRM at 2 years for >CP1 | 50% | 38% (29%)  2 year estimated CI of chronic extensive 32% |
| Ruiz-Argüelles *et al* 200587 | 24  41 years [10-71] | CP 100% | Flu/Bu/Cyclo | NR | 92% at 830d | 4% at 100d | 25% | 30% |
| Krejci *et al* 200688 | 20 /  47 years [15-59] | CP1 95%,  AP 5% | Flu/Bu/ATG | NR | 90% at 2 years | 0% at 100d | 45% | 75% (40%) |
| Faber *et a*l 200789 | 29  48 years [19-57] | CP1 83%,  CP2 10%,  AP3%,  BC3% | Flu/Bu/ATG 97%,  Flu/cyclo 3% | NR | Approx 70% at 3 years | NR | 31% | 41% |
| Kebriaei *et al* 200790 | 64 /  52 years [17-72] | CP1 20%,  CP2 27%,  AP 45%,  BC 8% | Flu/AraC/Ida 19%  Flu/Melph 70%  Flu/Melph/AraC 11% | 29% at 2 years, 20% at 5 years, | 48% at 2 years, 33% at 5 years, | 33% at 100d, 39% at 2 years, 48% at 5 years | 31% | 31% (20%) |
| Olavarria *et al* 200791 | 22 /  49 years [25-57] | CP1 100% | Flu/Bu/alemtuzumab | NR | 87% at 3 years | 0% at 100d, 4% at 1 year | 4% | 0% |
| Luo *et al* 200967 | 28 /  26 years [17-49] | CP1 100% | Flu/Bu/ATG | 67% at 3 years | 81% at 3 years | ‘”early” TRM 4%,  15% at 32 years | 7% | 1 yr CI 48% |
| Topcuoglu et al 201274 | 28  40 years (21–57) | CP1 71%,  CP2 7%,  AP 21% | Flu/Bu/ATG 36%,  Flu/Bu 39%,  Flu/AraC/ATG 14%,  Flu/Cyclo 4%` | 48% at 5 years\* | 56% at 5 year\* | Early TRM 7% | 31% | 72% |
| Warlick et al 201273 | 306  117 40-49 years (44)  119 50-59 years (55)  70 ≥ 60 years (70) | CP1 52%,  CP2/AP 41%,  BC 7% | Mixed | 40-49 yrs 35%, 50-59 yrs 32%, ≥ 60 yrs 16% at 2 years (DFS) | 40-49 yrs 54%, 50-59 yrs 52%, ≥ 60 yrs 41% at 3 years | 40-49 yrs 13%, 50-59 yrs 7%, ≥ 60 yrs 9% at 100d | 40-49 yrs 26%, 50-59 yrs 32%, ≥ 60 yrs 32% | 40-49 yrs 58%, 50-59 yrs 51%, ≥ 60 yrs 43% at 3 years |

\* reported for combined MAC and RIC groups, with no significant difference between MAC and RIC

PFS progression free survival, OS overall survival, TRM transplant related mortality, GVHD graft versus host disease, CP1 first chronic phase, CP2 second chronic phase, AP accelerated phase, BC blast crisis, Flu fludarabine, AraC Cytarabine, Ida idarubicin, Melph melphalan, Gy Gray, TBI total body irradiation, Bu busulphan, ATG anti-thymocyte globulin, Cyclo cyclophosphamide, DBM dibromomannitol, MAC myeloablative conditioning, DFS disease free survival, RR relative risk, HR hazard ratio, DLI donor lymphocyte infusions, HSCT haematopoetic stem cell transplantation., NR not reported.

**Table 7** – Outcome of reduced intensity transplant regimens in chronic myeloid leukaemia.

Lessons Learned from HSCT in CML

\* Graft versus leukaemic (GvL) effect is responsible for disease control following HSCT for CML

\* T-Cell depletion ameliorates some of the risks GVHD but at the expense of higher risk of relapse

\* The GvL can be reinforced/restored with infused donor lymphocytes

\*Non-myeloablative regimens allow delivery of a graft to exert a GvL in GvL sensitive malignancies

\* EBMT risk stratification system was developed for CML, prior to validation and acceptance across the scope of haematological malignancies

\* Disease stage, but not disease bulk *per se* impact on HSCT outcome in CML

\* The predictive power of detection of minimal residual disease (MRD) was pioneered using detection of BCR-ABL1 following HSCT

**Box 1** – Lessons learned from HSCT in CML. HSCT, haematopoetic stem cell transplantation, CML, chronic myeloid leukaemia, GvL, graft versus leukaemia, GVHD graft versus host disease, EBMT European Society for Blood and Marrow Transplantation, MRD, minimal residual disease.

|  |
| --- |
| Key considerations in HSCT for chronic phase |
| 1. Progression beyond CP prior to HSCT negatively impacts on outcome  - Every effort must be made to identify suitable patients early, and not wait for progression  2. HSCT exerts disease control with graft vesus leukaemia effect, independent of TK inhibition  - Resistance to TKI does not therefore impact *per se* on HSCT outcome |

**Box 2** – Key consideration in HSCT for chronic phase CML, CP, chronic phase, HSCT haematopoetic stem cell transplantation, TK tyrosine kinase, TKI tyrosine kinase inhibitors







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