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Chronic myelogenous leukemia: Role of stem cell transplant in the Imatinib era

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Historical role of allogeneic stem cell transplant (allo-SCT) in chronic myelogenous leukemia (CML) –pre-tyrosine kinase inhibitor (TKI)

The demonstration in the late 1970's that syngeneic (twin) donor transplant leads to the disappearance of Philadelphia chromosome established the paradigm of transplantation as curative therapy for CML.¹ Many studies in the early 1980's established the curative potential of allogeneic stem cell transplant (allo-SCT) for CML²⁻⁴, and allo-SCT became the treatment of choice for young patients with CML and a human leukocyte antigen (HLA)-identical donor. Up to the early 1990's, chronic phase (CP)-CML was the most common indication for allo-SCT worldwide.⁵ It was also the most effective treatment for patients with advanced stage CML, though the results in accelerated phase (AP)-CML and blast phase (BP)-CML were considerably worse than those in chronic phase because of increased rates of recurrence and of treatment-related mortality (TRM).^{6,7} Practically all transplants used bone marrow as the stem cell source and conditioning usually consisted of cyclophosphamide and total body irradiation (TBI). The initial studies used matched siblings (MSD); more recent ones also included unrelated donors (URD). Some of the most important studies are summarized in Table 1. Relapse rates were low for patients transplanted in chronic phase, but there was a considerable incidence of treatment-related complications and treatment-related deaths. Goldman et al. analyzed 450 patients with CP CML who received HLA-matched sibling (MSD) allo-SCT and reported 3-year TRM, relapse rate and overall survival (OS) from 29-53%, 9-14% and 45-67%, respectively, depending on the pretransplant treatment and interval from the diagnosis to the transplant.⁸ Robin et al. reported long-term outcomes of 102 CP patients who underwent myeloablative allo-SCT from an HLA-matched sibling using TBI/cyclophosphamide or busulfan/cyclophosphamide conditioning and cyclosporine based graft versus host disease (GVHD) prophylaxis.⁹ The 15-year relapse rate, TRM and OS was 8%, 46% and 53%, respectively. Hansen et al. reported outcomes on 196 patients with CP CML who received allo-SCT from unrelated donors (URDs) between 1985 and 1994 with the use of cyclophosphamide/TBI myeloablative conditioning. At 5 years, relapse rate was 10%, non-relapse mortality (NRM) 44% and OS 57%. Acute grade II-IV GVHD occurred in 77% patients and chronic extensive GVHD in 67% patients.¹⁰

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While most of the deaths after the allo-SCT occur within the first 5-years, some patients also succumbed to late sequelae. Goldman et al. analyzing Center for International Blood and Marrow Transplant Research (CIBMTR) data reported outcomes on 2444 patients who received myeloablative allo-SCT in CP1 and survived in continuous complete remission for ≥ 5 years.¹¹ OS for the entire patient population was 94% at 10 years and 87% at 15 years. Compared to the age-, sex-, race-matched general population, patients who had survived 5-years after allo-SCT still had a 2.5 times higher risk of death at 10-years, due to long-term complications of the allo-SCT. The most common cause of late deaths were organ failure (17%), infection (15%), GVHD (14%), disease relapse (7%) and secondary malignancies (7%). The mortality rates, however, for those surviving at 15-years post-allo-SCT approached that of the general population. The cumulative incidence of relapse for the entire cohort was 4% at 10 years and 7% at 15 years after allo-SCT.

In the pre-TKI era, there was a debate on appropriate age limits and timing of allo-SCT vs. non-curative treatments with moderate efficacy such as interferon (IFN) or IFN-cytarabine combination. The toxicity of myeloablative transplants was such that they were restricted to patients without significant comorbidities and mostly to those under 60 years of age. As the median age of diagnosis of CML is 65 years in the United States,¹² the majority of patients were not eligible for the myeloablative transplant.

Many different approaches were tested to circumvent this limitation, including T-cell depleted transplants, autologous transplants, and reduced-intensity conditioning (RIC). Experience with syngeneic transplants had shown that high-dose conditioning followed by the infusion of a tumor free graft can induce durable remission. Based on this concept several groups in the late '80's explored the use of in-vitro T-cell depletion to avoid both acute and chronic GVHD.^{13,14} These types of transplant were safer and effective in preventing GVHD. Unfortunately they were also associated with high rates of graft failure, opportunistic infections and increased rates of disease relapse, due to lack of induction of graft-versus-leukemia (GvL) effect. In one such series, reporting on the outcomes of 405 patients in CP CML reported to the IBMTR, patients with T-cell depleted allo-SCT had 3-year probability of relapse of 48% compared to 9% with non-T-cell depleted allo-SCT.¹³

An alternative approach utilized autologous transplants rather than allo-SCT. A number of studies evaluated induction of remission with chemotherapy followed by stem cell harvest in cytogenetic remission and autologous transplantation.¹⁵⁻¹⁹ These studies which used unmanipulated grafts, or a variety of *ex vivo* or *in vivo* purging methods to decrease the contamination by malignant clone are now merely of historical interest, but they did show that duration of remissions correlates with the extent of residual stem cell contamination which implies that autologous transplant with tumor free grafts might be a curative procedure.²⁰ McGlave et al. reported pooled data on 200 CML patients who underwent autologous transplant with most patients receiving unmanipulated grafts. Median survival for the entire group was 42 months (CP: not reached; AP: 35.9 months; BP: 4.1 months).¹⁸ Most surviving patients however had evidence of persistent disease by cytogenetic or hematological parameters.

Kolb et al. were the first to show that donor lymphocyte infusion (DLI) could reliably induce remission in those relapsing with CML after allo-SCT, an observation that has been extensively reproduced.²¹⁻²⁵ This, along with the observation that GvL effect plays an important role in disease control after allo-SCT²⁶⁻³⁰ and concerns over the potential toxicities of conventional myeloablation, led many groups in the last decade to use lower doses of the conditioning regimens (so called RIC or nonmyeloablative conditioning) with the aim of decreasing NRM and utilizing GvL effect to maintain the disease control (Table 2).^{7,26-29,31-42} Most of these studies were initiated in the pre-TKI era. After the introduction

of imatinib, many of these studies had difficulty accruing patients and few observations have been confirmed in large clinical trials.

Stem Cell Transplant in the era of TKIs

The Changing Paradigm

Given its superior efficacy, ease of administration and the lack of significant side effects, imatinib was rapidly adopted as the first-line medical therapy in CP CML patients. But clinicians across the globe also rapidly adopted the oral TKI therapy as a preferred alternative to transplant. Imatinib was approved by the United States Food and Drug Administration (FDA) in October 2001. The decline in the number of allo-SCT for CML started before FDA approval, and certainly before the availability of long-term follow-up data. Gratwohl et al. reported on behalf of EBMT (European Group for Blood and Marrow Transplantation) outcomes of all CML patients reported to EBMT between 1980 and 2004.⁴³ The number of allo-SCT in Europe peaked in 1999 with 1396 transplants with a subsequent decrease to 791 allo-SCT in 2003 and 434 allo-SCT in 2007, a 69% decrease.^{43,44} They also reported a significant increase in the proportion of URD transplants (7% in 1980-1990 to 36% in 2000-2003), increasing use of peripheral blood (PB) as a source of stem cells (53% in 2000-2003 vs. 21% in 1990-2000) and the use of RIC regimens.^{43,44} Bacher et al. reported 72% decrease in number of CML transplants from 1998 to 2004 in Germany with a larger percentage decrease in patients undergoing allo-SCT in CP1.⁴⁵ A similar pattern was reported by CIBMTR where the reported number of allo-SCT decreased from 617 in year 1998 to 223 in year 2003.⁴⁶ The majority of the decrease in the transplant numbers is for CP1 patients for which TKIs have become the frontline standard treatment. The number of patients transplanted in AP/BP has remained relatively stable.⁴⁶

Economic factors have an impact on the choice between allo-SCT and TKI therapy, especially in the developing countries. Ruiz-Argüelles et al. reported data on 24 patients transplanted in CP1 using matched sibling donor and RIC in four Latin American countries.⁴⁷ They mentioned the cost of allo-SCT in Mexico would be equal to approximately 200 days of imatinib 400mg daily, thus making the case for allo-SCT.⁴⁷ Similar observations were made by Gratwohl and colleagues when they analyzed the EBMT survey data.⁴⁸ They noticed that the rates of allo-SCT fell after the introduction of imatinib in high-income countries in Europe but they remained relatively stable for the lower income countries, indicating persistent reliance on the 'one-time' cost of allo-SCT as compared to expensive potentially 'life-long' TKI therapy.⁴⁸

Allo-SCT compared to imatinib as front-line therapy in CP

As imatinib was rapidly adopted as a standard frontline therapy for CP CML with excellent results, randomized clinical trials to prove the superiority of imatinib to allo-SCT were considered unjustifiable. As a result we only have indirect evidence to compare the two modalities. In a study by the German CML group, newly-diagnosed CP CML patients with a matched sibling were offered matched-related donor alloSCT; all others were given best available drug therapy (IFN plus hydroxyurea at the time of initiation of this study).⁴⁹ This type of treatment assignment based on donor availability is sometimes called genetic randomization. With median observation time of 8.9 years, the survival was superior for patients in the drug treatment arm ($p=0.049$), particularly in the low-risk patients. The survival difference was most pronounced at 3 years with the two curves merging only at approximately 8-years, given steady disease progression in the drug treatment arm. Of note, two thirds of the patients in the drug therapy arm were over time switched to imatinib because of failure of or intolerance to interferon/hydroxyurea. These data though debated at

the time, were the first study indicating superiority of drug treatment over allo-SCT in CP CML patients and provide a compelling argument for superiority of TKI therapy as frontline treatment for CP CML patients as compared to allo-SCT. In another retrospective analysis reported by Bittencourt et al. CP1 CML patients who failed or were intolerant to IFN either received imatinib as second line therapy (n=174) or allo-SCT (n=90) based on availability of donor and Sokal score.⁵⁰ The imatinib group had significantly improved event-free survival (EFS) and OS at 5-years compared to the allo-SCT group again indicating superiority of the imatinib in this setting.

A third more recent study from the German CML Study IV group took a slightly different approach. They reported interim outcomes on 1242 CML patients who underwent 5-arm treatment randomization (imatinib 400 mg versus imatinib plus IFN versus imatinib plus cytarabine versus imatinib post-IFN failure versus imatinib 800 mg).⁵¹ Based on predefined transplantation criteria (high Hasford score and/or low EBMT score, imatinib-failure or AP/BP), 84 of these 1242 patients underwent allo-SCT between 2003-2008 (23% in CP1 as an elective option, 44% after imatinib failure in CP1 and 33% in AP/BP). The median age at the time of transplantation was 37 years (range, 16-62 years). All except 3 patients received imatinib pre-transplantation. Seventy percent of CP patients and 42% of AP/BP patients had achieved cytogenetic remission at the time of transplantation. Three-year OS was 91% for patients in CP and 59% for patients in AP/BP. In the matched pair analysis, survival at 3-year was similar for the patients who underwent allo-SCT in CP1 vs. those who were treated with imatinib alone, though those assigned to transplant had a higher risk score. The authors draw attention to the very low TRM of 8% in this study. They attribute this to improvements in supportive care and also speculate that imatinib-induced reduction of tumor burden prior to transplant may have favorably influenced outcomes.

Though the debate over the frontline therapy for adults with CP CML has been settled in favor of TKI therapy whether the same could be said for pediatric patients with CML is not entirely clear. Cwynarski et al. reported retrospective EBMT data on the outcomes of 314 children (median age 14 years) who underwent allo-SCT for CML in the preimatinib era (between 1985-2001).⁵² Donor was an HLA-matched sibling in 58% and 81% were in CP1 at the time of allo-SCT. The source of stem cells was bone marrow for all patients. For CP1 patients, 3-year OS, TRM and relapse rate for those receiving sibling donor vs. URD was 75%, 20%, 17% and 65%, 31%, 13%, respectively. Grade III/IV acute GVHD occurred significantly more in the URD group (52% vs. 37% for sibling donors). Suttorp et al. reported 10-year prospective follow-up data on 176 children who underwent allo-SCT for CML from year 1995 to 2004 (median age 12.4 years).⁵³ At the time of allo-SCT, 82% were in CP1 and 66% underwent matched sibling allo-SCT. For CP1 patients, OS was 64% with significantly better OS in the matched sibling group (OS 87% compared to 52% in matched URD transplant group, $p = 0.002$). Thus the outcomes in pediatric patients appear superior to those in the adults. Data with use of imatinib in children is limited and again as is true for adults, very long-term data on imatinib use is unavailable. However, as is the case with adults, the current consensus is to use imatinib as frontline therapy for CML in children.⁵⁴

Currently, three broad groups of patients are considered to benefit from allo-SCT:

1. Those in AP or BP
2. Those failing/intolerant to TKI therapy
3. Those with TKI-resistant mutations such as T315I mutation

Patients in AP/BP

Long-term outcomes of patients treated with single agent imatinib for advanced phase disease range from an OS of 37-47 months for AP, and of approximately 7 months for BP.⁵⁵⁻⁵⁷ Second generation TKIs are superior to imatinib, but not considered curative in advanced phase CML. Allo-SCT provides the only potential for long-term survival for these individuals. However, the outcomes after allo-SCT for this group of patients remain suboptimal, especially for BP disease. Gratwohl et al. reported 2-years OS, TRM and relapse rate for AP and BP disease as 47%, 37%, 28% and 16%, 50%, 38%, respectively.⁴³ Patients with advanced phase CML remain a challenging group of patients with poor outcomes with currently available therapies and every effort should be made to induce a second chronic phase prior to allo-SCT.

Patients who fail TKI therapy

As TKIs have become standard therapy for newly-diagnosed CML patients, almost all patients with CML will have received imatinib and/or second generation TKIs prior to proceeding with an allo-SCT. Even for patients with advanced disease, as the plans for allo-SCT are being formulated, patients will usually be initiated on a TKI. Patients who failed TKI represent the majority of those undergoing transplantation. So an important question is whether prior use of TKIs affects the transplant outcomes.

Effect of prior imatinib or second generation TKIs on transplant outcomes—

Deininger et al. reported retrospective data on 70 patients with CML who underwent allo-SCT after imatinib treatment and compared the outcomes with a historical control group from EBMT registry.⁵⁸ Eighty four percent of the patients were in AP/BP prior to imatinib and this was reduced to 44% prior to allo-SCT. Median duration of imatinib therapy was 97 days and the median interval from diagnosis to transplantation was 22.6 months. When compared to the historical controls, the authors found no influence of prior imatinib use on OS, progression-free survival (PFS) and NRM. Another study from CIBMTR evaluated 409 patients (185 patients CP1; rest advanced disease) who received imatinib prior to allo-SCT and compared to 900 patients who did not receive imatinib prior to allo-SCT.⁵⁹ In the multivariate model, exposure to imatinib prior to allo-SCT was associated with better overall survival. Leukemia-free survival (LFS) and rates of acute and chronic GVHD were similar in the 2 groups. For the patients beyond CP1, there was no difference in the OS, LFS, TRM or relapse rate. Other groups have also reported that pre-transplant use of imatinib is safe and not associated with increased TRM.⁶⁰⁻⁶²

In addition, response to imatinib prior to allo-SCT has been shown to improve clinical outcomes for CP patients. Oehler et al. reported allo-SCT outcomes of 69 patients who had received imatinib prior to allo-SCT.⁶² Those who had achieved major cytogenetic remission (MCyR) prior to allo-SCT had better outcome than those who didn't (or who lost their cytogenetic response). The latter group had a statistically significantly higher hazard of mortality (HR: 5.31, p=0.03).

In the initial few years of the TKI era, allo-SCT was recommended after imatinib failure/intolerance.⁶³ Currently, second-generation TKIs (dasatinib and nilotinib) have shown excellent results in imatinib failure/intolerant patients with major cytogenetic response (MCyR) in up to 40-45% patients and as such have been approved by FDA for this indication.^{64,65} In addition, both dasatinib and nilotinib have shown excellent results as frontline therapy for CML and nilotinib has been recently approved by FDA for frontline therapy.^{66,67} It is therefore not surprising that most patients now will have received a second-generation TKI at the time of consideration for an allo-SCT. Second generation TKIs (dasatinib and nilotinib) have also been reported to be safe when use prior to allo-SCT.^{68,69}

In accordance with the above data, the recent European LeukemiaNet guidelines advocate allo-SCT after failure of a second generation TKI (and not after only imatinib-failure).⁷⁰

Patients with TKI-resistant mutations

Though many mutations have been identified in Abl kinase domain contributing to the resistance to TKIs, threonine-to-isoleucine substitution at position 315 of Bcr-Abl fusion protein (T315I mutation) leads to resistance to all first and second generation TKIs (imatinib, dasatinib and nilotinib). Given the lack of effectiveness of the TKIs, early allo-SCT is recommended for such patients.⁷⁰ Velev et al. reported outcomes of 8 patients with T315I mutation who underwent allo-SCT.⁷¹ At the time of allo-SCT, 2 patients were in CP1, 3 patients were in AP and 3 patients were in CP2. The best responses after allo-SCT were complete molecular remission (CMR) in 3 patients, complete cytogenetic response (CCyR) in 4 patients and complete hematologic response (CHR) in 1 patient. The 2 patients in CP1 at the time of allo-SCT had the best outcomes.⁷¹ There have been other anecdotal reports of patients undergoing allo-SCT for T315I mutation with good outcomes.^{72,73} Jabbour et al. reported allo-SCT outcomes of 10 patients [9 CML, 1 Ph+ acute lymphoblastic leukemia (ALL)] with mutation-related imatinib failure.⁷⁴ Nine different protein kinase domain mutations were identified. All patients engrafted and the majority achieved CCyR and CMR, indicating allo-SCT as a viable option for patients with Abl kinase mutations.⁷⁴ Nicolini et al reported on 33 patients (8 CP CML CP, 7 AP CML, 14 BP CML and 4 Ph+ ALL) who underwent allo-SCT.⁷⁵ The 3-yr OS rate was 69% (95% CI, 21-91%) for CML CP, 71% for CML AP, 0 for CML BP, and 0 for Ph+ ALL. The outcome of allo-SCT is therefore dependent on the disease phase at the time of SCT.

Methods of transplantation and patient selection

Prognostic scoring systems

Patients and physicians deciding on transplantation face an uncertain outcome and various attempts have been made to better quantify risks and survival after allogeneic transplant. The prognostic risk scoring system developed by EBMT is the most commonly used scoring system for patient undergoing allo-SCT for CML and its predictive value has been validated in two independent data sets. It is based on the sum of 5 variables: donor type (0 for HLA-identical sibling donor, 1 for a matched unrelated donor); disease stage (0 for CP1, 1 for AP, and 2 for BP or higher CP); age of recipient (0 for <20 years, 1 for 20–40 years, and 2 for >40 years); sex combination (0 for all, except 1 for male recipient/female donor); and time from diagnosis to transplantation (0 for <12 months, 1 for >12 months).⁷⁶ A higher score is associated with worse TRM, OS and relapse rate. Survival at 5 year ranges from 76% for those with EBMT score 0 to 19% for EBMT score 6.^{76,77} Recently Pavlu et al. use a combination of comorbidity index (HCT-CI) together with levels of C-reactive protein (CRP) to predict not just overall survival but also TRM at 100 days after transplant.^{78,79} In the multivariate analysis both HCT-CI score >0 and CRP levels >9 mg/L were independent predictors for inferior OS and increased day-100 NRM. The authors suggested that patients with HCT-CI score of zero with normal CRP level might be candidates for early allo-SCT after imatinib failure.⁷⁸

Source of stem cells: PB vs. BM

Over the past decade mobilized peripheral blood stem cells have gradually replaced bone marrow as the preferred graft source particularly for sibling transplants. Ease and convenience of donor collection play an important role in this shift, as do important physiological differences between mobilized peripheral blood and bone marrow. Peripheral blood allo-SCT is associated with more rapid platelet and neutrophil engraftment and lower risk of disease relapse but has a higher risk of acute and particularly chronic GVHD.⁸⁰⁻⁸²

This has major implications for the outcome of allo-SCT in CML. Elmaagacli et al. reported on the outcomes of CP1 CML patients who underwent HLA-matched sibling/ or partial HLA-matched family donor and compared the outcomes of BM (n=62) vs. PB (n=29) donor source.⁸⁰ They reported a higher rate of molecular and cytogenetic relapse with BM as a stem cell source, but did not compare OS rates. In a meta-analysis for HLA-matched sibling donor transplants, the use of PB was associated with lower relapse risk (OR = 0.34; 95% CI, 0.2 to 0.58) and higher acute and chronic GVHD.⁸¹ OS was improved with the use of PB as stem cell source in advanced phase CML (CP2, AP, BP) as compared to BM but OS was similar for CP1 CML patients.⁸¹ Schmitz et al. also reported long-term outcomes for PB vs. BM for HLA-matched sibling transplants for CIBMTR/EBMT dataset.^{83,84} Contrary to the meta-analysis results reported above, relapse risk was similar for PB vs. BM group and significantly higher TRM, and worse disease-free survival (DFS) and OS was seen in CP1 group who received PB as stem cell source.⁸⁴ OS was improved for advanced phase CML with the use of PB as stem cell source, similar to that of the meta-analysis results.

Oehler et al. analyzed 72 CML patients who were randomized to undergo either HLA-matched allo-SCT with either BM or PB as the source of donor cells.⁸⁵ There was no statistically significant difference in the OS, incidence of acute/chronic GVHD, or NRM between the 2 groups.

Though the data from various reports are not entirely consistent, it is reasonable to conclude that there is little advantage to the use of unmanipulated PBSC in CML CP1 and that there is an increased risk for chronic GVHD. The more rapid blood count recovery and more profound GVL effects after PBSC transplant may however constitute an advantage in CML AP or BP.

Type of donor: sibling vs. unrelated

Only about 25% of patients have HLA-identical siblings and unrelated donor transplantation is a necessary alternative. In an early report from the NMDP reporting on AP/BP CML patients, 5-year OS for MSD was 31%, significantly better than 20% for URD (p=0.002).⁸⁶ As typing technology and supportive care for transplant improved, so did outcomes of unrelated donor transplantation. In a 1998 study, the Seattle group reported a 74% five-year survival for patients with CP1 under the age of 50 undergoing URD.¹⁰ A recent report from the CIBMTR compared the outcomes of URD transplants (n=1052) to MSD transplants (n=3514) in patients receiving BM transplants for CML in CP1.⁸⁷ OS at 5-year was approximately 8% better after MSD group (63%) vs. 8/8 matched URD group (55%). Survival was progressively worse with greater degrees of HLA-mismatch in the URD group. Thus, a MSD remains the preferred donor type, though the results for URD in early phase CML are currently quite similar to those of MSD. For those lacking either MSD or URD many centers currently recommend umbilical cord stem cell transplantation (UCB). Sanz et al recently reported the outcome of 27 patients with CML who underwent UCB SCT.⁸⁸ At the time of transplantation, 7 patients were in CP1, 11 were in CP2, 2 were in AP, and 6 were in BP. TRM was 41% for patients undergoing UCB SCT in CP1 or CP2 and 100% for patients in AP or BP. After a median follow-up of 8 years, none of the patients relapsed, giving an overall DFS at 8 years of 41%. The DFS for patients undergoing UCBT while in any CP was 59%. A Japanese registry study reported outcomes in 86 patients with CML (median age 39 years) who underwent UCB SCT. OS and LFS were 53% and 38% respectively.⁸⁹

Conditioning regimen

Classic myeloablative transplantation combining TBI with high-dose cyclophosphamide was long considered the standard conditioning regimen for allo-SCT in CML. The high-dose

busulfan/cyclophosphamide regimen was developed as an alternative conditioning regimen and in randomized studies was found to result in equivalent long-term outcomes, though the toxicity profile was slightly different.⁹⁰ Subsequently attempts were made to 'target' the busulfan dose to achieve optimal results.^{91,92} More recently, the majority of groups have focused on non-myeloablative or RIC regimens. Low-dose TBI (200 cGy) alone as a conditioning regimen was associated with an increased graft rejection in CML patients, prompting the combination with fludarabine. In the study by the Seattle group, the 2-year survival estimates for patients in CP1 (n=14) and beyond CP1 (n=10) were 70 and 56%, respectively.³⁵ Kebriaei et al, for the MD Anderson group, reported long term outcomes of 64 patients, most of whom received a reduced intensity fludarabine melphalan combination. Thirteen patients were in CP1, 17 were in CP2, 29 were in AP and 5 were in BP. With median follow-up of 7 years, OS and PFS were 33% and 20%, respectively, at 5 years. Incidence of TRM was 33% at 100 days and 48% at 5 years after HSCT. In multivariate analysis, only disease stage at time of allo-SCT was significantly predictive for both OS and PFS. For CP1/2 patients PFS and TRM were 31% and 42% at 5 years, respectively. These data confirm the curative potential of RIC conditioning in CML, but the authors also acknowledge considerable failure rates and TRM. In order to avoid some of the complications associated with fludarabine/melphalan based conditioning, we and others have combined it with in-vivo T-cell depletion using alemtuzumab. The main concern with this approach is increased risk of disease relapse which could be countered by use of prophylactic imatinib and/or DLI post-transplant which is discussed below.⁹³⁻⁹⁵

Treosulfan, a busulfan analog, may have a more favorable toxicity profile and a fludarabine-treosulfan combination has extensively been tested in Europe. Holowiecki reported on 40 patients with CML CP who underwent allo-SCT.⁹⁶ The 2-year probability of OS, LFS and TRM were 85%, 82% and 15%, respectively. The cumulative incidence of hematologic relapse was only 2.5%, but 15 patients received further therapy for declining chimerism and cytogenetic recurrence. The combined cumulative incidence of hematologic and cytogenetic recurrence reached 46%. This regimen, though well tolerated, may therefore not be sufficiently antileukemic by itself to provide durable remissions and warrants post transplant therapy in many cases.

Monitoring after Allo-SCT

Relapse after allo-SCT remains an important clinical problem and though most cases occur within the first few years after the allo-SCT, relapses 10-15 years post-allo-SCT have been reported.¹¹ Detection of peripheral blood/ bone marrow Bcr-Abl transcript level has been shown by many groups to be predictive for disease relapse.⁹⁷⁻¹⁰¹ Kaeda et al. reported on 243 CML patients who underwent conventional myeloablative allo-SCT and had serial monitoring by Bcr-Abl real-time polymerase chain reaction (RT-PCR) of the peripheral blood.¹⁰⁰ Patients were characterized as "persistently negative" (n=36, single low-level positive result), "fluctuating positive, low level" (n=51, >1 positive result but never >2 consecutive positive results), "persistently positive, low level" (n=27, persistent low levels but never >3 consecutive positive results) or "relapsed" (n=129). The risk of relapse significantly correlated with the risk category (persistent negative: 2.7%; fluctuating positive: 20.8%; persistent positive: 30.0%) with most relapses occurring within the first 5 years after transplant.¹⁰⁰ The same group had previously reported the importance of quantitative RT-PCR done early (3-5 months) after allo-SCT.¹⁰¹ Three-year relapse rates were reported as 16.7%, 42.9%, and 86.4% for those with negative, low-positive and high-positive transcripts levels, respectively.¹⁰¹ Therefore, serial Bcr-Abl RT-PCR monitoring is considered by many a standard clinical practice after allo-SCT and can be used to guide therapeutic interventions. The detection of low levels of BCR-ABL early after transplant is expected and treatment decisions are based on serial measurements of high or increasing

levels of BCRABL.¹⁰⁰ International efforts are ongoing to implement standardization of RT PCR levels.¹⁰²

Prevention or early treatment of disease recurrence with TKI's or cellular therapy post-transplant

DLI routinely induces remissions in patients with disease recurrence after allo-SCT and was long considered the standard treatment for patients with early disease recurrence. But DLI carries a risk of myelosuppression and GVHD, which in turn is associated with DLI related mortality. The risk for GVHD can be modulated (but not abolished) by decreasing the dose of T-cells contained in the DLI and by delaying DLI as much as possible.^{24,103-105} Because of its associated risks, DLI is rarely given prophylactically, but rather for treatment of molecular relapse as defined by an increasing level of BCRABL. The routine induction of remission by DLI has given rise to the concept of "current leukemia free survival" defined as the probability that a patient is alive and in remission at a given time after transplantation.¹⁰⁶

Given the effectiveness of imatinib in the frontline setting, and its attractive safety profile, many groups have explored the use of imatinib as a prophylactic measure post-allo-SCT to prevent relapse. Carpenter et al. treated 22 patients (7 CML patients beyond CP1 and 15 Ph+ ALL) with imatinib post-allo-SCT at the standard dose of 400mg daily.¹⁰⁷ Imatinib was started at a median of 29 days post-allo-SCT and continued for 1 year. Imatinib was safe without significant cytopenias, and did not affect the calcineurin inhibitor levels.¹⁰⁷ The results were encouraging with 17 of the 22 patients in CMR after 1.3 years follow-up. Olavarria et al. evaluated the role of imatinib after the allo-SCT in 22 patients with an alemtuzumab based RIC regimen in CP1 with HLA-matched sibling donors.⁹³ Imatinib was given from day 35 to 1 year post-allo-SCT and was well tolerated. All patients achieved major molecular remission (MMR) with imatinib administration and none had a cytogenetic relapse during the duration of imatinib use. After the planned imatinib discontinuation at 1 year, 75% of patients relapsed and all these patients underwent DLI. With DLI, the majority regained a molecular response. Whether or not all patients should be offered imatinib as a maintenance therapy post-transplant and for what duration or with which remission goal (such as MMR or CMR) remains unclear at this point. In the study by Olavarria and colleagues (as above)⁹³, the majority of the patients relapsed after imatinib discontinuation, indicating that imatinib may have to be continued for longer durations and that perhaps life-long treatment may be needed. It is likely that increasingly patients will be referred who have failed all available TKIs. Occasional observation of restoration of sensitivity to TKI after transplant justifies their reintroduction in that setting.⁴⁰ Still, whenever possible a TKI should be chosen with documented activity and mutation analysis of Bcr-Abl is essential in all cases. While post-transplant imatinib seems safe, this may not be the case for all TKIs. Dasatinib in particular can cause life-threatening fluid retention and may also be quite immunosuppressive.¹⁰⁸

One could also consider a synergistic combination of DLI with TKI as suggested by Savani et al.¹⁰⁹ Given the rapid development of novel TKIs and other drugs, it is likely that in the near future the patients referred to allo-SCT will be those that have exhausted a plethora of medical strategies. Post transplant management is likely to change, but it is safe to predict that post-transplant cellular therapy will assume a larger role again with their use guided by serial BCR-ABL RT PCR monitoring and its dosing optimized to avoid GVHD.¹⁰³

Management of hematologic relapse after Allo-SCT

In the pre-imatinib era, DLI was the cornerstone of treatment for patients who relapse after allo-SCT.^{21,25} Other therapies used commonly at that time included IFN and a second allo-SCT. With the clinical efficacy of the TKIs in the pre-transplant setting, there was an

increasing interest in using TKIs at the time of disease relapse after the transplant. Kantarjian et al. reported on 28 such patients who relapsed at a median of 9 months post-transplant.¹¹⁰ Of these, 13 patients had already received DLI as salvage. Overall, imatinib led to CHR in 74% and CCyR in 35% patients with better responses seen in CP patients. The majority of patients who had received DLI as salvage responded to imatinib. Olavarria et al. used imatinib in 128 patients with CML relapsed after allo-SCT.¹¹¹ Fifty of the patients had failed prior DLI. The overall CHR was 84%. The CCyR ranged from 58% for patients in CP to 22% for patients in BP. Imatinib was well tolerated with 10% patients with worsening of underlying GVHD and no episode of new-onset GVHD after the initiation of imatinib.¹¹¹ Hess et al. reported outcomes of a prospective phase II trial in which patients in CP1 undergoing allo-SCT were treated with imatinib at the time of disease relapse [n=37; molecular relapse (n=18), cytogenetic relapse (n=19)].¹¹² Imatinib was well tolerated with only 1 patient (2.3%) with grade 1-2 reactivation of GVHD. Within the first 9 months, CMR was achieved in 62.2% patients (77.8% in those with molecular relapse and 47.4% in those with cytogenetic relapse), which improved to 70.3% during the entire study period. Overall molecular response (CMR and MMR) was achieved in 97.3% patients (36/37 patients). These excellent molecular results, much better than the ones achieved by use of imatinib frontline in CP CML patients, likely represent the combined effects of GVL and imatinib usage. They also report that of the patients who stopped imatinib in CMR, 2/3 lost CMR, all of whom regained CMR with the reintroduction of imatinib or use of DLI.¹¹² There was a trend towards longer duration of imatinib treatment in patients with sustained CMR after imatinib discontinuation (269 days) vs. those who lost CMR (151 days).

No prospective data is comparing DLI vs. imatinib in the relapse setting. In a retrospective review, Weissner et al. analyzed outcomes of 31 patients (24 CP, 7 AP) who received DLI (n=21) or imatinib (n=10).¹¹³ They reported higher relapse rate with imatinib compared to DLI (60% vs. 14%, $p = 0.006$). However, there was a better OS trend in the imatinib arm likely due to development of grade II-IV GVHD in 52% and chronic extensive GVHD in 33% of patients in the DLI arm.

Synergism of the combination therapy of DLI and imatinib has also been suggested in a study by Savani et al. in which patients relapsing after allo-SCT were retrospectively analyzed into 4 groups depending on post-allo-SCT therapy received: imatinib alone, DLI alone, concurrent combination therapy and sequential therapy.¹⁰⁹ They reported faster molecular responses with the concurrent therapy. In addition, most patients on the imatinib only arm relapsed after imatinib discontinuation, unlike the combination arm where the majority of patients maintained the molecular response even after imatinib discontinuation. Prospective evaluation of this approach is needed.

Role of stem cell harvesting and autologous stem cell transplant

There has been some interest in stem cell collection at the time of CCyR on a TKI therapy for potential use at a later time if there is evidence of disease progression. The United Kingdom CML Working Party reported on 58 patients in CCyR using recombinant human granulocyte colony-stimulating factor (G-CSF) while continuing imatinib therapy.¹¹⁴ Collection goal ($\geq 2 \times 10^6$ CD34+ cells/kg body weight) was achieved in 40% patients, all of whom had CML duration less than 50 months. The median number of apheresis procedures was two. Apheresis product was negative for Ph chromosome by cytogenetics and FISH in 84% cases, though the majority had positive Bcr-Abl transcripts levels.¹¹⁴ Hui et al. reported that short-term interruption (5–7 days prior to stem cell collection and until the completion of apheresis) of imatinib improved the CD34+ collection with 71% achieving the target cell dose (median number of apheresis cycle needed -1) compared to 50% in the group where imatinib was uninterrupted (median number of apheresis cycle needed were 3).¹¹⁵ Kreuzer et al. performed G-CSF induced stem cell mobilization during

imatinib therapy in 18 patients in CCyR.¹¹⁶ Apheresis was successful in 72% patients with no significant change in peripheral blood Bcr-Abl transcript levels after mobilization. Perseghin et al. attempted *in vivo* purging by increasing the imatinib dose to 800mg daily for 15 days prior to starting G-CSF in 18 patients who had achieved CCyR on imatinib.¹¹⁷ Of these, 50% failed to mobilize after first apheresis collection. Myelosuppression from high-dose imatinib (as indicated by significantly lower pre-mobilization and day 5 WBC count) could have contributed to the poor collection. For the second collection, imatinib was withheld and 2/3 were able to be collected. At our own institution, Gordon et al. reported on 19 patients who had achieved CCyR on imatinib.¹¹⁸ Eighty-nine % achieved target yields without imatinib discontinuation with the remaining 11% achieving target yield with a brief imatinib discontinuation giving 100% success rate. The majority of patients in this study were being treated with imatinib as frontline therapy which might have contributed to improved mobilization success rate as compared to other reported studies. This study also reported safety of this approach with all patients remaining in CCyR after a median follow-up of 18 months and none requiring autologous transplant.¹¹⁸ Bashir et al. reported on G-CSF mobilization on 24 patients in CP1 who had achieved CCyR on imatinib. Seventy-three % achieved the target cell dose (majority were bone marrow harvest).¹¹⁹ Stopping imatinib prior to mobilization was associated with significantly higher CD34+ cell yield in this study.¹¹⁹ In contrast to a relative abundance of data on stem cell collection, there have been only anecdotal reports of patients undergoing autologous transplants in the TKI era.^{39,116,119} Current European LeukemiaNet guidelines do not mention autologous transplants or stem cell mobilization/collection.⁷⁰ This is in line with the clinical practice that most centers do not advocate stem cell mobilization/collection for CML patients.

Conclusions and Current Recommendations—In the pre TKI era, allo-SCT was the frontline treatment of choice for young patients with CML with good performance status. During the initial few years after the introduction of imatinib, there was a debate whether TKI therapy should replace allo-SCT as frontline treatment for all patients given lack of randomized data. Now a decade after introduction of imatinib, this debate is largely over with imatinib being well established frontline therapy with excellent long-term outcomes. For patients with high-risk CML by Sokal / Hasford criteria,^{120,121} a case for early transplantation in CP1 could be made, especially if they have low EBMT score or HCT-CI. However, in practical terms, this is a small population of individuals and given the effectiveness of TKIs, unless there are other mitigating factors (such as economic considerations),^{47,48} almost all newly diagnosed CML patients are offered TKIs upfront.

Current indications for allo-SCT include patients in AP/BP CML, failure of a second generation TKIs and development of TKI resistant mutation such as T315I. For those with blast phase or accelerated phase, every effort should be made to induce second chronic phase prior to transplant (Box 1). The outcomes of URD and MSD transplant are nearly equivalent, but advanced disease continues to negatively affect treatment outcomes. Since many patients are older and heavily pretreated, many centers routinely use RIC regimens, sometimes combined with *in vivo*-T cell depletion. Some of the best long-term rates of disease control have been achieved with the combination of such regimens and post-transplant treatment of cytogenetic or molecular relapse using TKI, low dose DLI or combinations of the two.

Allo-SCT has a completely different mechanism of action than the TKI's. Its effects are to a large extent immunologically mediated and in contrast to the TKI's, allo-SCT can induce eradication of the leukemic stem cells and cure. Its role in the management of CML will require continual reappraisal.¹²²

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Table 1
Myeloablative conditioning allogeneic stem cell transplant in chronic myelogenous leukemia

Reference	No. of patients	Disease phase	Donor source	Conditioning regimen	TRM	Relapse rate	GVHD	OS
Thomas et al ⁶	167	CP1- 67, CP2- 12, AP- 46, BP- 42	MSD	TBI/CY	43% for CP1	18% for CP1	51% chronic GVHD among long-term survivors	At 3 years: CP – 58%, AP- 14%,
Goldman et al ⁸	450	CP	MSD	TBI/CY or Bu/CY	29-53%	9-14%		45-67% at 3 years
Hansen et al ⁹	196	CP	URD	TBI/CY	43%	10% at 5 years	Acute grade II-IV GVHD: 77%, extensive chronic GVHD: 67%	57% at 5 years
Radich et al ¹⁰	131	CP	HLA-matched relative	Targeted Bu/CY	14%	8% at 3 years	Acute grade II-IV GVHD: 65%, extensive chronic GVHD: 60%	86% at 3 years
Robin et al ¹¹	102	CP	MSD	TBI/CY or Bu/CY	46% at 15 years	8% at 15 years	Chronic extensive GVHD 49%	53% at 15 years

TRM: transplant-related mortality, GVHD: graft versus host disease, OS: overall survival, CP: chronic phase, AP: accelerated phase, BP: blast phase, MSD: HL-A-matched sibling donor, TBI: total body irradiation, CY: cyclophosphamide, Bu: busulfan, URD: unrelated donors

Table 2

Reduced-intensity conditioning allogeneic stem cell transplant in chronic myelogenous leukemia

Reference	No. of patients	Median age	Time period	Disease phase	Donor type	Donor source	Median follow-up (mo.)	Conditioning regimen	Use of prior imatinib	TRM	Relapse rate	GVHD	OS
Or R et al ³⁴	24	35	1996-2001	CP1	MSD (n=18), father (n=1), URD (n=5)	PB	37	Flu/Bu (n=19), Flu/Bu/ATG (n=5)	No	0% at 100 days, 4% at 1-year	0%	Acute (grade II-IV) – 71%, Chronic – 54%	85%
Das M et al ³³	17	34	1998-2000	CP1 (n=16), AP (n=1)	MSD	BM (n=3), PB (n=14)	30	Flu/Bu/ATG (n=11), Flu/Bu/TBI (n=6)	No	12% at 100 days		Acute (grade II-IV) – 41%, Chronic – 65%	47% (1-year)
Bornhauser et al ⁴³	44	52	NR	CP (n=26), AP (n=11), BP (n=7)	MSD (n=19), URD (n=15)	BM (n=15), PB (n=29)		Flu/Bu (ATG in 34 patients)	No	NR	NR	Acute (grade II-IV) – 43%, Chronic – Not reported	14.8 months
Weisser M et al ³⁵	35	51 (included patients only ≥45 years)		CP1 (n=26), CP2/AP (n=9)	MSD (n=19), URD (n=16)	BM (n=31), PB (n=4)	30	TBI 8 Gy/Flu/CX/ATG	No	11% at 100 days, 28.5% at 1-year	8% CP1, 33% for CP2/AP	Acute (grade II-IV) – 48%, Chronic extensive – 23%	69% at 2 year
Crawley C et al ⁷	186	50	1994-2002	CP1 (63%), CP2 (14%), AP/BP (23%)	MSD (60%), URD (25%)	BM (28.5%), PB (71.5%)	35	Variety of regimens; Flu/Bu/ATG in 40%	8%	3.8% (100 days); 13.3% (1 year); 18.9% (2-year)	47% at 3-years	Acute (grade II-IV) – 30%, Chronic – 42%	54% at 3 years
Kerbauy FR et al ³⁶	24	57.5	1998-2003	CP (n=14), CP2 (n=4), AP (n=6)	Matched related donors	PB	36	TBI 2Gy alone (n=8); TBI/Flu (n=16)	Yes (n=7)	4% at 100 days	For CP1 – 22% at 2 years	Acute (grade II-IV) – 46%, Chronic – 57%	For CP1 – 70% at 2 years
Kebriaei P et al ³⁷	64	52	1996-2005	CP1 – 20%, CP2 – 27%, AP/BP – 53%	Matched related – 47%, URD – 47%	BM – 59%, PB – 41%	84	All regimens Flu-based; Flu/Mel 47%	14%	TRM at 100 days 33%, 1-year – 38%	34%	Acute (grade II-IV) – 31%, Chronic – 31%	For CP – OS at 2 and 5 years was 66% and 48%.
Luo Y et al ⁴⁰	28	26	2005-2007	CP1	HLA identical donors	BM (n=7); PB (n=21)	23	Flu/Bu/ATG; prophylactic imatinib from day 100 till 1 year	Yes, all patients	3.6% at 100 days, 14.3% at 1 year	32%	Acute (grade II-IV) – 8% (no grade II-IV), Chronic – 48%	81% at 3 year
Olavarria et al ⁹³	22	49	NR	CP1	HLA-identical sibling	PBSC	36	Flu/Bu/Alectuzumab patients received post-transplant imatinib	Yes (50% patients)	0% at 100 days, 4% at 1 year	68% (all after post-transplant	Acute (grade II-IV) – 5%,	87% at 3-years

Reference	No. of patients	Median age	Time period	Disease phase	Donor type	Donor source	Median follow-up (mo.)	Conditioning regimen	Use of prior imatinib	TRM	Relapse rate	GVHD	OS
											imatinib discontinuation	Chronic – none	
Champlin R et al ³⁸	33	41		CP1 (n=16), CP2/AP (n=17)			29	Flu/Bu/ATG Patients with residual disease received planned imatinib and DLI	Yes, all patients	0% at 100 days,	41% for AP/BP, none in CP	Acute (grade II-IV) – 21%	76%
Poire X et al ⁴¹	9	61	2002-2007	CP1 (n=3), CP2 (n=2), AP (n=1), BP (n=3)	MSD (n=7), URD 8/8 match (n=1), URD 7/8 match (n=1)	PB		Flu/Bu/Alemtuzumab (n=4), Flu/Mel/Alemtuzumab (n=4), Bu/CY/Alemtuzumab (n=1)	Yes, all patients prior dasatinib also	0% at 100 days, 33% at 1 year		Grade II-IV acute GVHD (45%) (none grade III-IV)	

TRM: transplant-related mortality, GVHD: graft versus host disease, OS: overall survival, CP: chronic phase, MSD: HLA-matched sibling donor, URD: unrelated donor, PB: peripheral blood, BM: bone marrow, Flu: fludarabine, BU: busulphan, ATG: anti-thymocyte globulin, TBI: total body irradiation, AP: accelerated phase, BP: blast phase, CY: cyclophosphamide, Mel: melphalan, DLI: donor lymphocyte infusion