The role of stem cell transplantation for chronic myelogenous leukemia in the 21st century

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The introduction of tyrosine kinase inhibitors (TKIs), a treatment of chronic myelogenous leukemia (CML), has largely replaced curative strategies based on allogeneic stem cell transplantation (SCT). Nevertheless, SCT still remains an option for accelerated/blast phase and selected chronic-phase CML. Transplant outcomes can be optimized by peritransplant TKIs, conditioning regimen, BCR-ABL monitoring, and relapse management. Controversies exist in transplant timing, pediatric SCT, alternative donors, and economics. SCT continues to serve as a platform of “operational cure” for CML with TKIs and immunotherapies. (Blood. 2015;125(21):3230-3235)

History of SCT in CML

Stem cell transplantation (SCT) to treat chronic myelogenous leukemia (CML) was pioneered by Buckner et al.1-2 and subsequently by Goldman et al.3 with the aim of treating accelerated-phase (AP) and blastic-phase (BP) CML with myeloablative radiation and an autologous chronic-phase (CP) bone marrow transplant to “set the clock back” to a more benign disease state.4,5 In most patients, this approach failed to control the leukemia but set the stage for allogeneic (allo)-SCT with syngeneic graft introduced by Fefer et al.6 and subsequently for bone marrow graft from HLA-matched siblings reported in 1982 by 3 groups.7-9 Outcomes in CP-CML patients were particularly promising, but it was soon realized that leukemia relapse was more frequent in T cell–depleted recipients and in those who did not develop graft-versus-host disease (GVHD).8-9 These experiences supported the evidence in humans that alloreactive T cells exerted a powerful graft-versus-leukemia (GVL) effect, which was directly confirmed by Kolb et al.10 who showed that donor lymphocyte infusions (DLIs) could achieve stable second remissions in CML patients relapsing after SCT.10-13 Outcomes for CP-CML patients continued to improve through the 1990s with general improvements in transplant management. The most recent reports indicate overall survival (OS) rates of over 85% for CP-CML patients receiving a matched-donor transplant.8 A European Group for Blood and Marrow Transplantation scoring system permitted the prediction of outcome based on disease status, donor status, and age.14

Current indications for allo-SCT in post–TKI-era CML

The decisive demonstration by Druker et al.15,16 that the tyrosine kinase inhibitor (TKI) imatinib was safe and highly effective at controlling CP-CML heralded a rapid decline in SCT for CP-CML, documented by the databases of both the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Group for Blood and Marrow Transplantation. Effective TKI therapy supplanted SCT because it represented a safer, low-technology alternative (no immediate drug-related mortality). Nevertheless, SCT is still preferred for patients in more advanced-phase CML and selected cases of CP-CML.8,17-19 Not all patients tolerate TKIs, some patients progress despite second- or third-line TKIs, and some develop TKI-resistant mutations. Although ponatinib and omacetaxine have some activities against the case with T351I mutation,20,21 SCT, which can achieve prolonged progression-free survival (PFS) in such mutations, may be preferable. Lastly, CML leukemia stem cells (LSCs) are not dependent on BCR-ABL signaling for survival,22 and the quiescent LSC population is not eliminated by TKIs.23 The generally accepted current indications for allo-SCT in CML are listed in Table 1.

Current best SCT practices in CML

The German CML Study Group24 reported 3-year respective OS rates after allo-SCT in selected high-risk CP, imatinib-failure CP, and AP/BP patients of 88%, 94%, and 59%, with only 8% transplant-related mortality (TRM), and concluded that allo-SCT is a favorable second-line option following first TKI failure. In a prospective study in AP-CML (not including BP), Jiang et al.25 demonstrated an advantage for allo-SCT over imatinib (6-year OS, 83.3% vs 51.4%; PFS, 71.8% vs 39.2%). In imatinib-resistant CML (including 40% BCR-ABL mutations), SCT had a response rate of 91%, a 2-year OS rate of 63%, and a PFS rate of 49%.26 Lastly, the latest CIBMTR analysis of allo-SCT for CML in the TKI era reported 3-year OS rates of 36% in second CP, 43% in AP, and 14% in BP.27 These data support a continuing role of allo-SCT as a salvage treatment of CML.

Pretransplant TKI therapy

A CIBMTR analysis found that pretransplant TKI therapy also improved posttransplant survival in CP28 but not in advanced disease.27 In another study, major or complete cytogenetic response to TKI therapy before allo-SCT was associated with better posttransplant outcome.29 The choice of pretransplant TKI for advanced-phase disease is not well standardized, but dasatinib and nilotinib...
were at least safely administered before allo-SCT without increased TRM. Thus, it is appropriate to use TKIs to reduce the disease burden before allo-SCT for AP and BP-CML.

**Intensity of conditioning**

The powerful GVL effect in CML has prompted several studies to explore reduced-intensity conditioning (RIC) following the assumption that disease control in CP depends mainly on the rapid establishment of donor lymphoid engraftment. The limits of intensity reduction are now defined: we found that the entirely nonmyeloablative combination of fludarabine and cyclophosphamide followed by an HLA-matched sibling peripheral blood stem cell allograft achieved full, sustained molecular remission, but in only 2 patients. Although there was no treatment-related mortality, 4 other recipients required repeated DLIOrs or full-intensity conditioning SCT to achieve sustained molecular cure. In contrast, reduced-intensity SCT using combinations of fludarabine, anti-lymphocyte globulin, and busulfan were effective. The need to reduce conditioning regimens for older and debilitated patients has prompted a number of investigators to use RIC (usually by reducing doses of busulfan and fludarabine) to minimize regimen toxicity. It is unfortunate that these approaches show no superiority over full myeloablative transplants. Mortality in these patients can exceed 30% because of GVHD, failure of residual disease control, and older age of the recipient. In a study in which the outcomes of 28 patients receiving RIC conditioning were compared to those of 56 recipients of myeloablative SCT matched for disease severity and stage, the probabilities of 5- and 10-year leukemia-free survival and OS were similar. However, RIC recipients had higher rates of relapse, whereas myeloablative recipients had higher mortality. A multicenter CIBMTR analysis compared RIC regimens with even less intensive nonmyeloablative regimens (given largely to older recipients). Among other risk factors, when compared to nonmyeloablative regimens, RIC regimens were associated with a threefold higher risk of relapse and an almost twofold higher disease-free survival in a multivariate analysis. Thus, there is no advantage for nonmyeloablative regimens. RIC regimens may have a place for older recipients but, for other patients and those with advanced CML, an intensive conditioning offers the best chance to control disease.

**GVHD prophylaxis**

GVHD is strongly linked to the GVL effect in CML; thus, the choice of GVHD prophylaxis can play a critical role in transplant outcome. The role of T-cell depletion in favoring residual disease and leukemic recurrence has long been known in CML. Nevertheless, T-cell depletion has its advocates for CML SCT because it favors GVHD-free survival, and disease recurrence can be controlled with DLIOrs. Transplant regimens using the monoclonal antibody alemtuzumab are similarly associated with effective GVHD control, but also with prolonged immunosuppression. These regimens are associated with higher relapse rates but can be controlled with DLIOrs and TKIs, which can be useful adjuvants, even in patients previously resistant to these agents.

**Posttransplant BCR-ABL monitoring**

Because GVL is slow to develop, detection of BCR-ABL in the first few months after SCT has no adverse prognostic significance. However, the pattern of BCR-ABL (persistently negative, fluctuating, or persistently positive) after 6 months posttransplant predicts relapse risk. A recent study, however, showed that very low levels of persistent disease (ABL/BCR ratio <0.1%) occurring up to 10 years posttransplant had less implication for relapse: of 52 patients with occasional low levels of BCR/ABL detection posttransplant, 6 relapsed but 35 ultimately became polymerase chain reaction negative. In the RIC allo-SCT, BCR-ABL transcript may be detectable much longer, and preemptive DLIOrs may be needed to achieve sustained molecular remission without use of TKIs. Continued regular long-term monitoring of BCR-ABL posttransplant is needed to anticipate the occasional late relapsing patient; however, both the optimal frequency of monitoring and the threshold of BCR-ABL transcripts for preemptive therapy with TKIs or DLIOrs need to be established in the contexts of conditioning regimen and graft manipulation.

**Posttransplant prophylactic TKI therapy**

Given the high proportion of high-risk CML patients now selected for SCT, the role of prophylactic TKI therapy to prevent relapse has been extensively explored. Several reports suggest that early posttransplant TKIs (including second-generation TKIs) are safe to administer effectively in CP-CML but are less effective in advanced CML. Furthermore, the administration of TKIs with DLIOrs appears to be safe and does not risk GVHD. In 2 retrospective analyses, posttransplant TKI therapy was associated with a lower incidence of extensive chronic GVHD (hypothesized as the effects of TKI on platelet-derived growth factor receptor pathways). Although the use of posttransplant TKI therapy is widespread, prospective studies are needed to explore the best TKI dose, treatment duration, and coadministration with DLIOrs.

**Posttransplant relapse**

Relapse of CML can occur as late as the second decade after allo-SCT. Relapsed CML has been treated with DLIOrs, TKIs, chemotherapy, and second allo-SCT. Molecular relapse is frequent after T cell–depleted transplantation but can be salvaged. We reported that combinations of TKI therapy and DLIOrs can achieve a 5-year postrelapse survival rate of 62%, and some patients became TKI-free, suggesting a persistent GVL effect.

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**Table 1. Indication for allo-SCT in CML**

<table>
<thead>
<tr>
<th>CML phase</th>
<th>Clinical situation</th>
<th>TKI and chemotherapy management</th>
<th>HLA typing and donor search</th>
<th>Immediate allo-SCT referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>First failure of imatinib, high risk</td>
<td>Second-line TKI</td>
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<td>No</td>
</tr>
<tr>
<td></td>
<td>First failure of nilotinib or dasatinib</td>
<td>Second-line TKI</td>
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<td>Yes</td>
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<td></td>
<td>Failure to 2 TKIs</td>
<td>Third-line TKI</td>
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<td>Yes</td>
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<td>T315I mutation</td>
<td>Ponatinib or omacetaxine</td>
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<td>Yes</td>
<td></td>
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<td>AP</td>
<td>TKI naïve</td>
<td>TKI ± chemotherapy</td>
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<td>Yes</td>
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<tr>
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<td>TKI naïve, without optimal response</td>
<td>Second-line TKI ± chemotherapy</td>
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<td>Yes</td>
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<td></td>
<td>TKI pretreated</td>
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<td>TKI naïve or pretreated</td>
<td>Induction chemotherapy, TKI</td>
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<td>Yes</td>
</tr>
</tbody>
</table>

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Areas of controversy

Transplant timing

Opinions differ as to whether patients failing second-line TKI should receive a third-line agent or be considered for SCT. The decision to transplant is favored by the presence of unfavorable BCR-ABL kinase-domain mutations. Data from the CIBMTR showed that diagnosis-to-transplant intervals >12 months were associated with worse OS and PFS in AP-CML patients, irrespective of pretransplant TKI therapy.27 AP-CML patients are a heterogeneous population, and further risk stratification is needed to identify the high-risk group suitable for early allo-SCT. Whatever the ultimate treatment choice, it is reasonable to perform HLA typing and a donor search after first-line TKI failure for AP-CML. For BP-CML, prompt referral to a transplant center is critical, along with the immediate initiation of TKI therapy and induction chemotherapy.

Treatment of children with CML

There is unease about consigning children developing CML to a lifetime of TKI therapy. Several groups report imatinib-induced growth delay, especially in prepubeeral children, due to altered bone metabolism and growth hormone suppression.54-56 The International BFM Study Group and other experts recommended that guidelines for children with CML should follow those for adults.57,58 However, there are still concerns for lifelong safety and quality of life when using TKIs in pediatric CML. Fatigue, limited physical activity, and emotional problems are the major limitations in TKI use in CP-CML, especially in young and female patients.59 The shortcomings of long-term TKI use must be balanced against the potential complications of chronic GVHD and long-term immunosuppression, which are major factors associated with reduced health-related quality of life.60,61 A recent French study62 reported that 37% of children fail to achieve <10% BCR-ABL transcripts at 3 months and have shorter PFS, suggesting less-favorable kinetics of disease or TKI efficacy in pediatric CML. This observation opens the question for the indication of allo-SCT, especially when an HLA-identical sibling is available, because outcome of SCT in children is generally more favorable than in adults. More prospective data are urgently needed to define the best treatment approach for pediatric CML. Meanwhile, treatment decisions must be made on a case-by-case basis.

Pregnancy in CML

Imatinib and other TKIs are known to be associated with a higher risk of fetal malformation in women with CML.63,64 and the interruption of TKI therapy during pregnancy was associated with poor outcomes in CML.65 However, infertility is a major late event after allo-SCT,66,67 and the best strategy for fertility preservation is still in development. Both RIC (especially avoiding total body irradiation) and cryopreservation of sperm, oocyte, or gonadal tissue resulted in successful pregnancy in posttransplant survivors with CML.68,69 Fertility preservation should be discussed before allo-SCT with both pediatric and adult recipients who desire to bear children.

Identical-twin donors

The first successful SCT in CML using a healthy donor was from an identical twin.4 A CIBMTR analysis demonstrated that although the relapse rate of 40% in CML patients receiving syngeneic SCT was higher than the 7% observed in HLA-matched sibling recipients (as predicted by the lack of an allogeneic GVL effect), the long-term PFS rate of 59% was equivalent to the 61% seen in HLA-identical sibling recipients.70 Furthermore, patients receiving a larger marrow-cell dose from their twin had a significantly lower relapse rate, suggesting protective effects of some graft component against relapse.71 Given the favorable outcome for SCT in syngeneic transplants and the absence of severe GVHD, the opportunity to use an identical-twin donor should not be overlooked.

Alternative donors

A recent study from China using unrelated cord blood transplantation in AP/BP-CML showed 5-year OS and PFS rates of 62.5% and 50%, respectively, equivalent to the outcomes of their HLA-matched sibling cohort despite a higher TRM.72 Preliminary data using haploidentical SCT with postgraft cyclophosphamide have demonstrated the safety (0% TRM) and efficacy (60% OS and PFS) of this approach.73 These results should encourage the use of alternative graft sources for CML patients requiring allo-SCT who lack a fully matched related or unrelated donor.

Health economics

The high cost of lifetime TKI therapy can be simply unaffordable.74 SCT can be a less-expensive alternative to TKIs in some countries. A prospective study from Mexico75 not only showed comparable PFS rates for TKI therapy and SCT but also demonstrated that transplants were less expensive. An analysis from Sweden76 comparing pre-TKI (SCT-predominant) and post-TKI periods estimated the incremental cost-effectiveness ratio as €52 700 per quality-adjusted life-year gained. The incremental cost-effectiveness ratio was predicted to fall to only €22 700 per quality-adjusted life-year after the patent expiry of imatinib with an 80% cost reduction. Cost-effectiveness data should be interpreted in the context of health care systems in each country, and treatment choices for CML may be modified according to the local imperatives of patient care.

Future prospects for SCT as a platform for targeted therapy and immunotherapy

In the concept of cure in CML, Goldman and others preferred the term “operational cure”: prolonged survival in molecular remission without therapy.77,78 The challenge is to find a strategy to avoid lifelong dependency on TKI therapy,79 which in addition to its cumulative expense, may have unrecognized adverse effects. CML persistence, despite control of the leukemia at the molecular level of detection, relates to the inability of current therapy to target quiescent LSCs.80 Although neither TKI nor transplant strategies always succeed to eradicate the quiescent LSCs, using allo-SCT after deep remission is induced by TKI could achieve operational cure. The third option for operational cure is immunotherapy evolving from GVL effects observed in SCT. Many immunotherapeutic approaches are under investigation; clinical trials of vaccination with leukemia-associated antigens (LAAs) such as BCR-ABL, WT1, and PR1 showed variable immunologic and clinical responses in CML patients.81-85 Adoptive T-cell immunotherapy using multi-LAA–specific T cells86,87 and chimeric antigen receptor–modified T cells88 demonstrated antileukemic activities either preclinically or clinically in a phase I study. Novel LAAs (aurora A kinase89 and BMI-190) or surface
molecules (IL-1RAP and CD26) specific to CML LSCs have recently been discovered and would be applicable for future immunotherapy. Given that the safety of SCT is continually evolving, it is important to maintain an open mind about the application of SCT as a platform for future targeted therapy and immunotherapy in CML.

Acknowledgments

The authors dedicate this article to the memory of John Michael Goldman who inspired us with his insightful observations on the definition and nature of cure of CML.

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Authorship

Contribution: A.J.B. and S.I. wrote the manuscript.

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