Blood Spotlight

Title: The Role of Stem Cell Transplantation for Chronic Myelogenous Leukemia in the 21st Century

Authors: A. John Barrett1* and Sawa Ito1

Affiliation: 1Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA.

*Correspondence author: A. John Barrett1, MD, Hematology Branch, NHLBI, NIH. Phone: 301-402-4170; Fax: 301-480-2664; Email: barrettj@nhlbi.nih.gov

Key words: stem cell transplantation, chronic myelogenous leukemia, immunotherapy
Abstract

The introduction of tyrosine kinase inhibitors (TKI) as a treatment for chronic myelogenous leukemia (CML) has largely replaced curative strategies based upon allogeneic stem cell transplantation (SCT). Nevertheless SCT still remains the option for accelerated/blastic-phase and selected chronic-phase CML. Transplant outcomes can be optimized by peri-transplant TKI, conditioning regimen, \textit{BCR-ABL} monitoring, and relapse management. Controversies exist in transplant timing, pediatric CML, alternative donors, and economics. SCT continues to serve as a platform of “operational cure” for CML with TKI and immunotherapies.
History of SCT in CML

Stem cell transplantation (SCT) to treat chronic myelogenous leukemia (CML) was pioneered by Buckner\(^1,2\) and subsequently by Goldman\(^3\) 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\(^1-3\). This approach failed in most patients to control the leukemia but set the stage for allogeneic SCT (allo-SCT) with syngeneic graft by Fefer\(^4\), and subsequently with bone marrow graft from HLA matched siblings reported in 1982 by three groups.\(^5-7\) Outcomes in CP were particularly promising but it was soon realized that leukemic relapse was more frequent in T cell-depleted recipients and those who did not develop graft-versus-host disease (GVHD).\(^8,9\) These experiences supported the evidence in humans that allo-reactive T-cells exerted a powerful graft-versus-leukemia (GVL) effect, which was directly confirmed by Kolb\(^10\) who showed that donor lymphocyte infusions (DLI) could achieve stable second remissions in CML patients relapsing after SCT.\(^10-13\) Outcome for CP-CML continued to improve through the 1990s with general improvements in transplant management. The most recent reports indicate overall survivals (OS) of over 85% for CP patients receiving a matched donor transplant.\(^8\) An EBMT 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 Drucker\(^15,16\) 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 both CIBMTR and EBMT databases. 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 and selected cases of CP.\(^8,17-19\) Not all patients tolerate TKI, some progress, despite second- or third-line TKI and some develop TKI resistant mutations. While 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. Finally, CML
leukemia stem cells (LSC) are not dependent upon BCR-ABL signaling for survival and the quiescent LSC population is not eliminated by TKIs. 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 group reported 3-year OS after allo-SCT in selected high risk CP, imatinib-failure CP, and AP/BP of 88%, 94% and 59% respectively with only 8% transplant related mortality (TRM) and concluded allo-SCT is a favorable second-line option following first TKI failure. In a prospective study in AP-CML (not including BP), Jiang 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-ABL1 mutations), SCT had a response rates of 91%, a 2-year OS of 63% and PFS of 49%. Lastly, latest CIBMTR analysis of allo-SCT of CML in the TKI era reported 3-year OS was 36% in CP2, 43% in AP, and 14% in BP. These data support a continuing role of allo-SCT as a salvage treatment for CML.

**Pre transplant TKI:** A CIBMTR analysis, found that pre-transplant TKI also improved post-transplant survival in CP but not in advanced disease. In another study, major or complete cytogenetic response to TKI before allo-SCT was associated with better post-transplant outcome. The choice of pre-transplant 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 TKI 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 exploring 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 non-myeloablative combination of fludarabine and cyclophosphamide followed by an HLA matched sibling peripheral blood stem cell allograft achieved full sustained molecular remission but only in two patients. While there was no treatment related mortality, four other
recipients required repeated DLI or full intensity conditioning SCT to achieve sustained molecular cure.\textsuperscript{31} In contrast, reduced intensity SCT using combinations of fludarabine, antilymphocyte globulin and busulfan were effective.\textsuperscript{32} The need to reduce conditioning regimens for older and debilitated patients has prompted a number of investigators to use reduced intensity conditioning (usually by reducing doses of busulfan and fludarabine) to minimize regimen toxicity. Unfortunately these approaches show no superiority over full myeloablative transplants.\textsuperscript{33,34} Mortality in these patients can exceed 30\% because of GVHD, failure of residual disease control and older age of the recipient.\textsuperscript{34} In a study where the outcome of 28 patients receiving RIC conditioning were compared with 56 recipients of myeloablative SCT matched for disease severity and stage\textsuperscript{35}, the probability of 5- and 10-year leukemia-free- and overall survival were similar. However RIC recipients relapsed more, while myeloablative recipients had higher mortality. A multicenter CIBMTR analysis compared RIC regimens with even less intensive non-myeloablative regimens (given largely to older recipients). Amongst other risk factors, when compared with nonmyeloablative regimens, RIC regimens were associated with a three-fold lower risk of relapse and almost two-fold higher disease free survival in multivariate analysis\textsuperscript{36} Thus there is no advantage for non-myeloablative regimens. RIC regimens may have a place for older recipient but for other patients and those with advanced CML an intensive conditioning offers the best chance to control disease.

\textit{GVHD prophylaxis:} GVHD is strongly linked to the GVL effect in CML\textsuperscript{37} thus the choice of GVHD prophylaxis can play a critical role in transplant outcome. The role of T cell depletion (TCD) in favoring residual disease and leukemic recurrence has long been known in CML. Nevertheless TCD has its advocates for CML SCT because it favors GVHD free survival and disease recurrence can be controlled with DLI.\textsuperscript{38} Similarly transplant regimens using the monoclonal antibody alemtuzumab are associated with effective GVHD control but prolonged immunosuppression.\textsuperscript{39} These regimens are associated with higher relapse rates but can be controlled with DLI and TKI which can be useful adjuvants even in patients previously resistant to these agents.
Post-transplant 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 post-transplant 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 post-transplant had less implication for relapse: of 52 patients with occasional low levels of BCR/ABL detection post-transplant 6 relapsed but 35 ultimately became PCR negative. In the reduced intensity conditioning allo-SCT, BCR-ABL transcript may be detectable much longer and pre-emptive DLIs may be needed to achieve sustained molecular remission without use of TKIs. Continued regular long term monitoring of BCR-ABL post-transplant is needed to anticipate the occasional late relapsing patient, however the optimal frequency of monitoring and threshold of BCR-ABL transcripts for pre-emptive therapy with TKIs or DLI needs to be established in the context of conditioning regimen and graft manipulation.

Post-transplant prophylactic TKI: Given the high proportion of high risk CML patients now selected for SCT, the role of prophylactic TKI to prevent relapse has been extensively explored. Several reports suggest that early post-transplant TKI (including second-generation TKI) are safe to administer effective in CP CML but less effective in advanced CML. Furthermore the administration of TKI with DLI appears to be safe and does not risk GVHD. In two retrospective analyses, post-transplant TKI was associated with a lower incidence of extensive chronic GVHD, (hypothesized as the effects of TKI on PDGFR pathways). While the use of post-transplant TKI is widespread prospective studies exploring the best dose, treatment duration, and co-administration of DLI are needed.

Post-transplant relapse: Relapse of CML can occur as late as the second decade after allo-SCT. Relapsed CML has been treated with DLI, TKI, chemotherapy or second allo-SCT. Molecular relapse is frequent after T cell depleted transplantation but can be salvaged. We reported combinations of TKI and DLI achieve 5-year post-relapse survival of 62% and some patients became TKI-free, suggesting a persistent GVL effect.
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. Decision to transplant is favored by the presence of unfavorable BCR-ABL kinase-domain mutations. Data from CIBMTR showed that diagnosis to transplant intervals >12 months were associated with worse OS and PFS in AP-CML, irrespective of pre-transplant TKI.27 AP-CML is 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 following first-line TKI failure or AP-CML. For BP-CML, prompt referral to a transplant center is critical along with the immediate initiation of TKIs 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 pre-pubertal children due to altered bone metabolism and growth hormone suppression.54-56 An International BFM Study Group and expert opinions recommended that guidelines for children with CML should follow those for adults.57,58 However, there are still concerns of life-long safety and quality of life (QOL) of 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 QOL.60,61 A recent French study62 reported that 37% of children fail to achieve <10% BCR-ABL1 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 since outcome of SCT in children is generally more favorable than for adults. More prospective data is 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 females with CML\textsuperscript{63,64} and the interruption of TKI during the pregnancy was associated with poor outcomes in CML.\textsuperscript{65} On the other hands, infertility is a major late event after allo-SCT\textsuperscript{66,67} and the best strategy for fertility preservation is still in development. Both reduced intensity conditioning (especially avoiding total body irradiation) and cryopreservation of sperm, oocyte or gonadal tissue resulted in successful pregnancy in post-transplant survivors with CML.\textsuperscript{68,69} Fertility preservation should be discussed before allo-SCT for 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.\textsuperscript{4} A CIBMTR analysis demonstrated that while the relapse rate of 40\% in CML receiving syngeneic SCT was higher than the 7\% observed in HLA matched sibling donors (as predicted by the lack of an allogeneic GVL-effect) but long term PFS of 59\% was equivalent to the 61\% in HLA-identical sibling recipients.\textsuperscript{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.\textsuperscript{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 62.5\% and PFS 50\% respectively, equivalent to the outcomes of their HLA matched sibling cohort despite a higher TRM.\textsuperscript{72} Preliminary data using haplo-identical SCT with post-graft cyclophosphamide have demonstrated the safety (0\% TRM) and efficacy (OS and PFS 60\%) of this approach.\textsuperscript{73} These results should encourage the use of alternative graft source for CML patient 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.\textsuperscript{74} SCT can be a cheaper alternative to TKI in some countries. A prospective study from Mexico\textsuperscript{75} showed not only comparable PFS between TKI therapy and SCT but also showed transplant were less expensive. An analysis from Sweden\textsuperscript{76} comparing pre-TKI (SCT-predominant) and post-TKI periods estimated the
incremental cost-effectiveness ratio (ICER) as €52,700 per quality adjusted life year (QALY) gained. The ICER was predicted to fall to only €22,700 per QALY 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.\textsuperscript{77,78} The challenge is to find a strategy to avoid lifelong dependency on TKI\textsuperscript{79}, which beside 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 LSC.\textsuperscript{80} While neither TKI nor transplant strategies always succeed to eradicate the quiescent LSC, 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, PR1 showed variable immunological and clinical responses in CML patients.\textsuperscript{81-85} Adoptive T cell immunotherapy using multi-LAA specific T cells\textsuperscript{86,87} and chimeric antigen receptor modified T cells (CART\textsuperscript{123,88}) demonstrated anti-leukemic activities either pre-clinically or clinically in a phase I study. Novel LAAs (aurora A kinase\textsuperscript{89} and BMI-1\textsuperscript{90}) or surface molecules (IL-1RAP\textsuperscript{91} and CD26\textsuperscript{92}) specific to CML LSC have been recently discovered and would be applicable for future immunotherapy. Given that the safety of SCT is continually evolving\textsuperscript{93}, it is important to maintain an open mind about future application of SCT as a platform for future targeted therapy and immunotherapy in CML.
Acknowledgments:

This paper is dedicated to the memory of John Michael Goldman who inspired us with his insightful observations on the definition and nature of cure of CML.

Funding:

This manuscript preparation was supported by the Intramural Research Program of the National Institutes of Health, at the National Heart, Lung, and Blood Institute.

Authorship:

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

Competing interests:

Both authors declare no conflict of interest.
References


<table>
<thead>
<tr>
<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>Chronic Phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st failure of imatinib, high risk</td>
<td>second-line TKI</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>1st failure of nilotinib or dasatinib</td>
<td>second-line TKI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>failure to 2 TKIs</td>
<td>third-line TKI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T315I mutation</td>
<td>ponatinib or omacetaxine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Accelerated Phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TKI naïve</td>
<td>TKI +/- chemotherapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>TKI naïve, without optimal response</td>
<td>second-line TKI +/- chemotherapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>TKI pre-treated</td>
<td>second-line TKI +/- chemotherapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blast phase</td>
<td>induction chemotherapy, TKI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: Allo-SCT, allogeneic stem cell transplantation; CML, chronic myelogeneous leukemia; HLA, human leukocyte antigen; TKI, tyrosine kinase inhibitor.
The role of stem cell transplantation for chronic myelogenous leukemia in the 21st century

A. John Barrett and Sawa Ito