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Allogeneic Stem Cell Transplantation for CML Resistant to Tyrosine Kinase Inhibitors

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is well established as a potentially curative treatment for patients with CML. The success of imatinib and other tyrosine kinase inhibitors (TKI) as initial therapy has changed the treatment paradigm in this disease. Allogeneic hematopoietic transplants are now reserved for patients failing to respond optimally to TKI treatment. Patients failing to have an optimal response to imatinib may respond to a second generation TKI, dasatinib or nilotinib, and many achieve major or complete molecular and cytogenetic responses. The indication for allogeneic HSCT vs. continued second line therapy is not well defined and is the subject of ongoing study. There has been continued progress in reducing the toxicity and risks of HSCT with development of reduced intensity regimens; transplants can be routinely performed in patients up to age 75 who are in fair general medical condition. Transplants from unrelated donors have improved, with survival similar that achieved with matched siblings. Results with haploidentical and cord blood transplants have markedly improved, and should be considered for patients lacking a matched donor. Allogeneic hematopoietic transplants have the best chance to be curative in patients with chronic phase that is under hematologic control with 80% disease free survival; patients progressing to accelerated phase or blast crisis have a much poorer prognosis. Thus, HSCT should be considered for patients with imatinib failure. Patients receiving second line TKI therapy need to be closely monitored, and referred for transplantation if a complete cytogenetic response and major molecular response is not achieved. HSCT should be performed if feasible in patients without a continued response to TKI treatment.

Allogeneic hematopoietic stem cell transplantation (ASCT) is a highly effective treatment for CML and was previously considered by many as the treatment of choice, able to induce durable molecular complete remissions in the majority of patients[1,2345,6]. Allogeneic HSCT carries substantial risks of treatment related morbidity and mortality due to drug toxicities, graft-vs.-host disease and infectious complications. Morbidity and mortality has been reduced by improvements in supportive care but 10–20% still succumb to treatment related mortality and chronic graft-vs.-host disease occurs to some extent in approximately half of patients. CML results from rearrangement and fusion of the bcr and abl genes, encoding a protein with enhanced tyrosine kinase activity. This molecular rearrangement is pivotal to development of the disease and continued proliferation of the malignant cells. The treatment of chronic myeloid leukemia (CML) has been revolutionized with the development of

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imatinib and subsequently other tyrosine kinase inhibitors as molecularly targeted therapy[7]. Initial imatinib treatment results approximately 83% event free survival and 93% freedom from progression to accelerated or blast phase at 6 years[8,9].

Given the safety and efficacy of treatment with TKIs, the role of hematopoietic transplantation as initial therapy has been reexamined[10–17]. An analysis by Hehlmann indicated superior survival in patients treated with interferon and imatinib compared to early treatment with stem cell transplantation[18], a conclusion confirmed by multiple reports. Imatinib is now recommended as the international standard of care for initial therapy of CML[19,2010]. However, approximately 15% fail to achieve a cytogenetic remission or progress during the first 5 years, and a small fraction of patients will develop blast crisis while responding to imatinib treatment[21]. In a recent follow-up of the IRIS study, approximately 30% of patients discontinued imatinib due to inadequate response or intolerance[8,22]. Baccarani et al summarized international consensus criteria for suboptimal response to imatinib; these criteria are utilized to select patients for studies of alternative therapies including hematopoietic transplantation[19,23]. The criteria for treatment failure include no hematologic response in 3 months of imatinib treatment, less than complete hematologic response or no cytogenetic response (Ph+ cells > 95%) at 6 months, Ph+ cells >35% at 12 months or less than complete cytogenetic response at 18 mo, loss of response or acquisition of mutation or intolerance to TKI based therapy.

Options for patients with imatinib failure

There are 2 major options for patients failing to respond optimally to imatinib, treatment with a second generation TKI or allogeneic stem cell transplantation. Second generation more potent TKIs, dasatinib and nilotinib, have been developed with the goal of overcoming imatinib resistance and bcr-abl mutations[15,16,24]. There is considerable interest in use of second generation TKIs in patients failing to respond to imatinib with 60–90 PFS after 2 years.[25–27] Approximately half of patients failing to respond to imatinib have mutations in bcr-abl conferring resistance. Some mutations are sensitive to dasatinib or nilotinib[28–30], and mutations can be scored as high, intermediate or low sensitivity to the second generation TKIs[27]. Jabbour recently reported results of second line TKI treatment. For patients in chronic phase, hematologic and cytogenetic responses as well as event-free and overall survival correlated with mutation sensitivity score[27]. Patients with intermediate or low sensitivity mutations had a high risk of disease progression. Notably, the T315I mutation is resistant to all available TKIs.

Allogeneic Stem Cell Transplantation for CML

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the most effective “antileukemic” treatment in CML, with the majority of surviving patients achieving molecular complete remission with undetectable bcr-abl rearrangement by polymerase chain reaction analysis; this represents superior cytoreduction of the leukemia than can be achieved with TKIs. However, this benefit must be balanced by the risks of treatment related morbidity and mortality. The curative effect of HSCT in CML is largely derived from the immune graft-vs.- leukemia (GVL) effect mediated by alloreactive donor T cells reacting against residual host malignant cells[31,32333435]. Donor lymphocyte infusion (DLI) can produce durable molecular complete remissions in up to 70% of patients with molecular or cytogenetic relapse post transplant, demonstrating the potency of GVL effects[36,37]. This observation led us to explore the use of reduced intensity conditioning to reduce treatment related toxicities. This involves using lower dose, relatively nontoxic chemotherapy for partial cytoreduction and immune suppression to prevent graft rejection. Post-transplant, donor immunocompetent cells mediate the GVL effect [33,38–41].

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We and others have demonstrated that reduced intensity HSCT reduces treatment related mortality and allows allogeneic transplantation to be successfully performed in older and medically debilitated patients who could not tolerate myeloablative regimens[42–44]. This is important since the median age of patients with CML is over 60 years of age and many have coexisting medical problems.

Use of TKIs post stem cell transplant

Anderlini et al evaluated the use of imatinib within the first hundred days after stem cell transplantation for high risk patients with advanced CML or Ph+ ALL and demonstrated that imatinib can be safely administered to patients early following stem cell transplantation[45]. Reversible myelosuppression was the limiting toxicity and that tacrolimus serum levels increased 25–33%. Close monitoring for hematologic toxicity was required. Kantarjian et al demonstrated that imatinib was effective treatment for CML relapsing post transplant, achieving complete molecular remission in many patients[46]. Prophylactic administration of imatinib or other TKIs post transplant is being evaluated with promising results for Philadelphia-chromosome positive leukemias[47,48]. The optimal dose and duration of tyrosine kinase inhibitor treatment, and its use in relation to donor lymphocyte infusion for persistent or recurrent disease must be determined[49].

Allogeneic stem cell transplantation after treatment with tyrosine kinase inhibitors

A study by the Center for International Blood and Marrow Transplantation Research (CIBMTR) found that prior imatinib treatment does not compromise the results of allogeneic HSCT while in chronic phase[50,51], but patients with hematologic progression and transformed disease have poor results.

We recently evaluated novel strategy to provide a safe, nontoxic approach for allogeneic stem cell transplantation in patients with chronic phase CML who have not responded optimally to imatinib[52]. This involved sequential therapy using a reduced intensity preparative regimen, designed to reduce the risks of the preparative regimen designed to minimize toxicity, GVHD and treatment related mortality. Patients received a reduced intensity preparative regimen involving fludarabine 40 mg/m2 × 4 days, busulfan 130 mg/m2 × 2 days, and antithymocyte globulin (ATG,Thymoglobulin) 2.5 mg/kg daily × 3 days followed by allogeneic stem cell transplant from an HLA identical or one antigen mismatched related or unrelated donor. Those with residual disease received post-transplant treatment with a TKI, and those who did not achieve a molecular remission received donor lymphocyte infusion. Results are summarized in Figures 1 and 2.

42 pts, median age 42 (range 14–69) years were entered into this study. All were previously treated with imatinib, and had detectable disease. 20 had early disease (chronic phase or isolated clonal evolution) and 22 had advanced CML (prior accelerated or blast phase). 4 early and 9 advanced pts had a cytogenetic complete remission (CyCR) at the time of transplant. The regimen was well tolerated without life-threatening toxicity. Two patients had graft failure; one required a second transplant and the other had autologous recovery with Ph- hematopoiesis; both are alive in molecular CR (mCR). Only one pt died within 100 days post transplant. At 3 months, all of the patients in first chronic phase or with clonal evolution and 21 of the 18 more advanced patients (2nd chronic phase or accelerated) achieved cytogenetic CR and 7 early and 5 advanced pts achieved a mCR. None of the patients with minimal residual disease by quantitative polymerase chain reaction analysis for bcr-abl rearrangement achieved a molecular CR without intervention. 22 pts received treatment with TKIs post transplant; mCR was achieved in 7 of the 9 early pts and 2 of 13

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advanced pts. 16 pts subsequently received DLI; 2 of 2 pts with early disease achieved mCR with one other pt too early to evaluate; 2 of 13 advanced pts have a mCR. 31 pts are alive. This includes 18 of 20 (90%) transplanted with early disease, (all in cCyR 13 in cMR) and 13 of the 22 (59%) with advanced disease (7 in cCyR and 9 in cMR). In conclusion, sequential therapy including reduced intensity HSCT, post transplant treatment with TKI, and donor lymphocyte infusion was well tolerated and capable of prolonged cytogenetic remissions and survival.

There has been substantial improvement in the results of HSCT. Reduced intensity preparative regimens, and improved control of graft-vs.-host disease and supportive care has reduced treatment related morbidity and mortality. Transplants from unrelated donors have improved, with survival similar that achieved with matched siblings. Results with haploidentical and cord blood transplants have markedly improved, and should be considered for patients lacking a matched donor.

Transplants after second line TKIs

Patients undergoing allogeneic hematopoietic stem cell transplantation for CML are increasingly likely to have received a second generation tyrosine kinase inhibitor (dasatinib and nilotinib) after failing imatinib. It is unknown whether the use of these agents effect the outcome of stem cell transplantation. Clearly patients with overt hematologic relapse or transformation to accelerated phase or blast crisis have a poor prognosis. Jabbour et al. analyzed outcome of 12 patients, most with advanced CML (1 in chronic phase, 6 accelerated phase, and 5 blastic phase) who had received dasatinib, nilotinib, or both before allogeneic stem cell transplantation. Nine patients achieved a molecular response: 4 complete and 5 major (quantitative reverse transcriptase-polymerase chain reaction <0.05%). After a median follow-up of 10 months, 7 patients were alive with molecular response and 5 patients had died, 4 from disease progression. We concluded that previous treatment with a TKI did not increase transplant-related toxicity and outcomes were similar to historical patients with advanced CML prior to the imatinib era[53].

Allogeneic HSCT for CML patients with bcr-abl kinase mutations

We assessed the impact of these mutations on the outcome of allogeneic stem cell transplantation. Ten imatinib-resistant patients with bcr-abl kinase mutations received a transplant: 9 had CML (3 in chronic phase, 4 in accelerated phase, and 2 in blast phase) and 1 had Philadelphia-positive acute lymphocytic leukemia (ALL). Patients harbored 9 different protein kinase mutations, including the T315I mutation (which results in resistance to all available TKIs) in two. Preparative regimens were ablative (n = 7) and nonablative (n = 3). All patients engrafted; there were no treatment-related deaths. Disease response was complete molecular (CMR; n = 7), major molecular (n = 2), and no response (n = 1). Three patients (mutations Q252H, E255K, and T315I) died of relapse after ASCT. Seven patients are alive (6 in CMR) for a median of 19 months. We conclude that allogeneic transplantation remains an important salvage option for patients who develop imatinib resistance through bcr-abl mutations. Further study in larger numbers of patients is required[54].

Separately, we analyzed results in 8 patients with the T315I mutation resistant to available TKIs[55]. At the time of SCT, 2 patients were in chronic phase, 3 accelerated phase and 3 in second chronic phase. After a median follow-up of 13 months from SCT, 5 patients remained alive, including 3 patients in CMR, 1 patient in CCyR, and 1 patient in CHR. Thus HSCT is potentially effective treatment for this group of very high risk patients.

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Conclusion

HSCT remains an important, potentially curative treatment for patients with CML should be considered for patients with failure to imatinib treatment[56,57]. Preliminary analysis indicates that prior imatinib treatment does not compromise the results of HSCT for patients in chronic phase, but patients with overt transformed disease have poor results[51]. The factors related to the risk of allogeneic transplantation should also be considered in patient selection for allogeneic transplantation. Patients with major comorbidities and elevated C-reactive protein levels have a higher risk of treatment related mortality[58,59].

Patients with imatinib failure have a high rate of response to second generation TKIs, but only short term follow up is available[26,60]. It is unclear whether patients with imatinib failure should receive HSCT immediately or receive a trial of treatment with a second generation TKI; this issue is being addressed in ongoing clinical trials. Patients receiving definitive treatment with second line TKI treatment need to be closely monitored with plans for HSCT at the first signs of treatment failure. Patients failing treatment with two TKIs should receive HSCT if feasible. Reduced intensity preparative regimens reduce the toxicity and treatment related mortality associated with the transplant procedure and allow transplants to be performed in older and medically infirm patients. This approach, including post transplant immunomodulatory therapy and donor lymphocyte infusion produces a high fraction of durable molecular complete remissions in patients failing to respond optimally to TKIs.

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Results

	Response to Prep Regimen @ 3 months	Molecular CR to Imatinib	Molecular CR to DLI	Alive/cCR mCR/ Relapse
N=42				
20 Early	Cyto CR 20-- mCR 7	7 of 9 --	2 of 2	18/18/13/0
22 Advanced	Cyto CR 21-- mCR 4	2 of 13 --	2 of 6	13/ 10/ 7/9

Figure 1.

The initial response after the reduced intensity preparative regimen is assessed at three months. Patients with molecular evidence of residual disease receive imatinib treatment and are assessed after 3 months. Patients with residual disease after imatinib treatment receive donor lymphocyte infusion. The final column summarizes the current status of patients, number alive, complete cytogenetic remission cCR, molecular complete remission mCR, and number with hematologic relapse and progression of disease.

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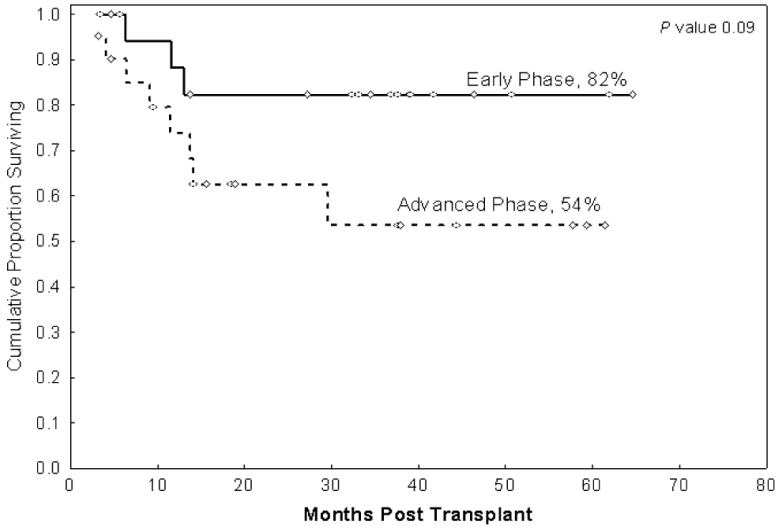

Figure 2.

Survival for Busulfan-Fludarabine-ATG reduced intensity HSCT with Post Transplant Imatinib and Donor Lymphocyte Infusion for Chronic Myeloid Leukemia. Early phase includes first chronic phase or clonal evolution. Advanced phase includes accelerated disease or second chronic phase.