



Donna Duke Morrison. *Emerald Eye*. Original watercolor on Yupo, 30" × 39", framed.

Allogeneic hematopoietic cell transplantation is now considered as second- or third-line therapy for chronic myeloid leukemia.

Tyrosine Kinase Inhibitors and Allogeneic Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia: Targeting Both Therapeutic Modalities

Hugo F. Fernandez, MD, and Mohamed A. Kharfan-Dabaja, MD

Background: Due to its curative potential, allogeneic hematopoietic transplantation (HCT) was a mainstay of treatment for chronic myeloid leukemia (CML), but the advent of tyrosine kinase inhibitors (TKIs) has markedly altered the use of allogeneic HCT.

Methods: The authors reviewed their experiences as well as the published data regarding the impact of TKIs on the natural history of CML and thus on the application and timing of TKIs in the management of CML.

Results: Most patients with CML respond well to TKIs given as up-front therapy. Available retrospective data suggest that allogeneic HCT is safe after TKI therapy. Work is ongoing regarding salvage of postallogeneic HCT failures using TKIs with and without donor lymphocyte infusion.

Conclusions: While allogeneic HCT therapy remains useful, the timing of its application in CML has changed, and it is now considered as second- or third-line therapy.

Introduction

Allogeneic hematopoietic cell transplant (HCT) remains the only established curative approach in the treatment

of chronic myeloid leukemia (CML). Prior to 2001, CML was among the most common indications for this procedure. With the introduction of targeted therapy to the BCR/ABL transcript, namely tyrosine kinase inhibitors (TKIs), the use of allogeneic HCT has been altered significantly. Moreover, the proportion of patients receiving transplant as first-line therapy for chronic-phase CML has decreased.^{1,2} In May 2001, imatinib mesylate (Gleevec®, Novartis Pharmaceutical Corp, East Hanover, New Jersey) became the first of these agents to be approved by the US Food and Drug Administration.³ The drug has shown clinical efficacy in interferon-resistant disease and subsequently proved superior to interferon plus cytarabine,⁴ the prior standard of care for initial therapy of CML.⁵ As the International Randomized Study of Interferon and STI571 (IRIS) trial has demonstrated, the excel-

From the Department of Blood and Marrow Transplantation at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, and the Department of Medicine, Division of Oncological Sciences at the University of South Florida, Tampa, Florida.

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Address correspondence to Hugo Fernandez, MD, Department of Blood and Marrow Transplantation, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612. E-mail: Hugo.Fernandez@moffitt.org

Abbreviations used in this paper: HCT = hematopoietic cell transplant, CML = chronic myeloid leukemia, TKI = tyrosine kinase inhibitor, MCyR = major cytogenetic response, CCyR = complete cytogenetic response, OS = overall survival, GVHD = graft-vs-host disease, DLI = donor lymphocyte infusion.

lent response and the prolonged benefit of this approach have made imatinib the new standard bearer in this disease.⁶ Since the approval of imatinib, two drugs — dasatinib (Sprycel®, Bristol-Myers Squibb Co, Princeton, New Jersey) and nilotinib (Tasigna®, Novartis Pharmaceutical Corp) — have been introduced as treatment for imatinib-resistant or -intolerant patients, with 38% to 40% of patients achieving a complete cytogenetic response (CCyR).^{7,9} Most of these responses are durable. These newer therapies have placed allogeneic HCT into a third-line status against CML.¹⁰

Approximately 15% to 25% of patients with CML are intolerant of the TKIs, develop resistance due to BCR/ABL domain mutations,¹¹ develop other gene mutations, Pgp expression and gene amplification,¹² or attain new cytogenetic abnormalities and progress to the accelerated or blastic phase of this disease. This manuscript reviews the timing and indications of allogeneic HCT in the treatment of CML and the outcomes of transplanted patients who have received prior therapy with the TKIs. The use of TKIs following allogeneic HCT for relapsed disease or as an adjunct to allogeneic HCT is also discussed.

Timing of Transplant

Prior to the availability of the TKIs, the European Group for Blood and Marrow Transplantation (EBMT) developed a scoring system that assisted in decision-making for allogeneic HCT based on histocompatibility, the stage of disease at the time of transplantation, the age and sex of the donor and recipient, and the time from diagnosis to transplantation. Patients with low scores had a 62% to 72% chance of a 5-year survival.¹³ After the introduction of imatinib mesylate, recommendations focused on the use of allogeneic HCT in patients with appropriate HLA histocompatible donors who were under 35 years of age or had a high Sokal score.¹⁴ Since the effects of long-term therapy with imatinib were unknown at the time, recommendations were to consider younger patients for transplantation. Treatment with allogeneic HCT was also recommended for patients with high Sokal scores¹⁵ who were at risk of progressing to accelerated phase or blast crisis.

With the results of the IRIS trial^{4,6} and the continued excellent long-term outcomes with imatinib, those recommendations have become obsolete.^{16,17} The current consensus as based on the National Comprehensive Cancer Network (NCCN) guidelines¹⁸ (Table 1) is to consider allogeneic HCT in cases where responses to imatinib or other TKIs have not been optimal. Patients who fail to achieve a complete hematologic response within 6 months, in the salvage setting, should be considered for allotransplant. The same applies to patients who do not achieve a major cytogenetic response (MCyR), defined as < 35% BCR/ABL by conventional cytogenetics by 12 months, or a CCyR, defined as zero

BCR/ABL by fluorescence in situ hybridization (FISH) or cytogenetics by 18 months. Patients who attain these response landmarks but later lose such responses should also be considered for allogeneic HCT.

Similar consideration should be given to patients who present with accelerated-phase or blast-crisis CML, especially when considering that response rates and the durability of responses to TKIs are limited.^{19,21} Patients who are in accelerated phase or blast crisis should be treated with an aggressive approach, which may include the TKIs to attain a second chronic phase. Allogeneic HCT in this setting has reasonable outcomes.²² Allo-transplants should not be offered to patients in active blast crisis because outcomes are dismal.

Many of these patients may be treated successfully with dasatinib²³ or nilotinib,⁸ but the initial consideration and evaluation for allogeneic HCT should be performed for those who are appropriate candidates for the procedure. Transplant should also be considered for patients who develop the mutation of the TK domain, particularly the T315I,²⁴ which is resistant to the currently available TKIs. Patients who develop additional cytogenetic abnormalities in the Philadelphia chromosome clone should also be considered for allogeneic HCT since these patients often proceed to accelerated or blastic phase and become resistant to the TKIs.²⁵ Clinical trials with newer agents may also be an alternative, particularly for patients without an available donor.

Concerns regarding the long-term cost of imatinib treatment compared with that of an allogeneic HCT may affect treatment decisions. In countries with limited resources and in those that provide care through their national health care system, utilizing allogeneic HCT may be more cost-effective than administering TKIs. In two medical centers in Mexico, patients were offered transplants due to the high cost of treatment with ima-

Table 1. — Considerations for Allogeneic Hematopoietic Cell Transplant

At Presentation
Pediatric patients
Patients in accelerated phase
Patients in blast crisis
TKI is unavailable or cost-prohibitive
TKI may be used as bridge to allogeneic HCT
After Prior Treatment With Imatinib
Patients who have failed to achieve an HR after 3 months
Patients with no cytogenetic response by 6 months
Patients who have failed to achieve an MCyR by 12 months
Patients who have failed to achieve a CCyR by 18 months
Patients who achieved an HR, MCyR, or CCyR and have lost the response
Patients who have developed a T315I ABL kinase domain mutation
Patients with clonal evolution in Ph+ clone
Patients who develop accelerated phase
Patients who develop blast crisis
HR = hematologic response.

Table 2. — Allogeneic Hematopoietic Cell Transplant (HCT) After Treatment With Tyrosine Kinase Inhibitors (TKIs)

Author	No. of Patients	Median Age at Allogeneic HCT (yrs)	Median Duration of TKI Prior to HCT (mos)	Response Rate Prior to HCT (%)	Median Follow-Up After HCT (mos)	Chronic Phase (%)	NRM/TRM (%)	Event-Free Survival Rate (%)	Overall Survival Rate (%)
Deininger et al ³¹	70	43.1	3	80	24	55.7	31	28.8	33.7
Oehler et al ³²	145	40.1	10	50	36	81	NR	NR	78
Weisser et al ³³	30	51	7	NR	12	100	30	72	81
Zaucha et al ³⁴	26	32	7	NR	20	38	17	NR	NR
Jabbour et al ²⁴	12	46.5	4	50	10	10	NR	60	70

NRM/TRM = nonrelapse mortality/treatment-related mortality, NR = not reported.

tinib, while a second group received subsidized imatinib for long-term therapy.²⁶ There was no difference in overall survival (OS) between the two groups. The cost of a reduced-intensity transplant was equivalent to only 6 months of imatinib therapy. Pediatric patients may be considered for allotransplant since the issue of life-long therapy with the TKIs may be too costly when compared to an up-front allogeneic HCT.²⁷

Another issue is whether treatment with a TKI is better than allotransplant after failure of other front-line therapy. Transplant centers in Brazil evaluated 174 patients after interferon failure: 90 patients received allografts (matched sibling = 83, matched-unrelated = 7) compared to 84 treated with imatinib.²⁸ The imatinib group had better event-free survival (62% vs 52%, $P = .0002$) and OS (93% vs 59%, $P < .0001$) than the allogeneic HCT group. A genetic-based randomization in Germany compared up-front transplantation to drug therapy.²⁹ Patients received interferon-based therapy and upon failure were treated with imatinib. With a median follow-up of 11 years, patients who received drug therapy had superior survival compared with patients treated with allogeneic HCT as front-line therapy, particularly in low-risk patients. This benefit remained for 8 years.

Responses Following Treatment With Imatinib

Prior to the availability of imatinib, common practice and consensus recommendations were to offer allogeneic HCT within the first year of diagnosis.³⁰ Patients taken early to allogeneic HCT had significantly better OS. The use of imatinib and other TKIs has now significantly delayed the procedure for most patients. However, outcomes do not seem to be affected by this delay, and initial responses are similar to those seen in patients previously transplanted in similar phases of the disease.

Several groups have published their experience of allogeneic HCT after prior imatinib therapy (Table 2). The general consensus is that its use prior to transplant does not appear to adversely impact engraftment, toxicity of the conditioning regimen, acute or chronic graft-vs-host disease (GVHD), or survival.^{24,31-34}

The EBMT evaluated allogeneic HCT after imatinib therapy in 70 patients with CML and compared this group to historical controls in the transplant registry; 55.7% were in a chronic phase.³¹ No new or unusual organ toxicities were seen in the cohort treated with imatinib. There was no difference in engraftment, acute GVHD or treatment-related mortality (TRM) at 2 years and was not statistically different than those patients not treated with imatinib. There was a trend for higher relapse mortality, probably due to an increased number of patients with more advanced disease. There was also a trend for less chronic GVHD.

An analysis from the Fred Hutchinson Cancer Research Center evaluated 145 patients who received imatinib for a minimum of 3 months prior to transplant and compared this group to 231 patients who did not.³² There was no difference in hepatotoxicity or engraftment, relapse-free survival (RFS), OS, or nonrelapse mortality between the two groups. Response to imatinib prior to transplant was predictive of the post-transplant outcome, particularly for those patients who attained a CCyR or MCyR prior to allografting.

A retrospective analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) compared 409 patients who received imatinib prior to transplant to 900 patients who did not. Patients in chronic phase who received imatinib prior to transplant had a superior OS but a similar TRM, RFS, and leukemia-free survival (LFS) than those who did not receive the drug prior. Acute GVHD rates were similar in both groups.³⁵

One particular challenge that arises when interpreting these data is that more patients are now undergoing transplants in the accelerated or blastic phase of the disease, which leads to poorer outcomes overall with allogeneic HCT. In the CIBMTR analysis, patients with advanced CML who received transplants and were given imatinib prior to allogeneic HCT did not have an improved TRM, RFS, LFS, or OS compared with those who were not treated with imatinib.³⁵ Interestingly, a response to imatinib prior to transplant portends a better transplant outcome.³³ At the M. D. Anderson Cancer

Center, 12 patients in the BMT program underwent transplant after failure of imatinib therapy.²⁴ Of these 12 patients, 8 received an ablative regimen and 4 a nonablative approach. The majority of patients had accelerated-phase or blastic-phase CML. Three had disease progression 30 days after transplantation. Nine achieved a molecular response. Follow-up was short (10 months), but 7 of 12 were alive in molecular response.

Imatinib Therapy Following Transplant

NCCN guidelines recommend molecular monitoring by polymerase chain reaction (PCR) every 3 months for 2 years posttransplant and every 6 months for 3 years thereafter.¹⁸ Despite allotransplant, evidence of molecular, cytogenetic, or overt morphologic relapse of the disease may be present in some patients, particularly in the accelerated or blast phase of the disease. With the emergence of imatinib mesylate, patients who relapsed after transplant can be salvaged with this agent either alone or in combination with donor lymphocyte infusion (DLI).

The M. D. Anderson group used imatinib doses ranging from 400 mg to 1,000 mg daily to treat 28 adults with CML who had relapsed after allogeneic HCT.³⁶ Patients had relapsed a median of 9 months (range: 1 to 137 months) posttransplant. Thirteen patients had undergone prior salvage with DLI. The overall response rate was 79% (22 of 28 patients) with a complete hematologic response rate of 74% and a cytogenetic response rate of 58%, with 35% being CCyR. At a median follow-up of 15 months, 19 patients were alive, and 9 had no evidence of disease. The 1-year estimated survival rate was 74%. Five patients had recurrence of GVHD. Myelosuppression was a side effect, with neutropenia and thrombocytopenia in 43% and 27% of patients, respectively. Both effects were reversed with dose adjustments of imatinib.

Hess et al³⁷ monitored patients with PCR following transplantation. Upon documentation of relapse, 44 patients (18 molecular, 19 cytogenetic) were given imatinib 400 mg daily. Grade III/IV leukopenia developed in 13.5% of patients and grade I/II GVHD in 1 patient. Imatinib was discontinued or increased based on molecular responses. Seventy percent of patients attained complete molecular responses (CMRs), most of which have remained durable for greater than 1 year even after discontinuation of imatinib. DLIs were given to 7 patients who did not attain a CMR despite imatinib. Four of the 7 patients attained CMRs, 2 had major molecular responses, and 1 was not evaluable after DLI.

Investigators from the University of Munich retrospectively evaluated imatinib as a single modality in comparison to DLI.³⁸ Ten patients treated with imatinib following relapse from allogeneic HCT were compared with 21 receiving DLI. Demographics were similar in both groups. CMRs were attained in 90% of the DLI group and in 70% of the imatinib-treated group, albeit

not statistically significant. Relapses occurred in 14% of the DLI patients and in 60% of the imatinib patients ($P = .006$). However, 52% of patients in the DLI group developed grade II-IV GVHD compared with none in the imatinib group. Leukemia-free survival was better in the DLI group ($P = .016$); however, OS in the two groups was similar ($P = .183$), with all of the patients receiving imatinib alive at 5 years.

Finally, investigators in the Stem Cell Allogeneic Transplantation Section at the National Institutes of Health evaluated a combined modality of DLI plus imatinib.³⁹ Thirty-seven patients with relapsed CML (10 molecular, 14 hematologic, and 13 advanced-phase relapse) were treated. Nine received imatinib only, 13 received DLI, and 15 received combination of the two (four not concurrently). The overall response rate was 81%. Ten of the 11 who received the combination attained a molecular remission and remained in remission. However, only 2 of 22 patients treated with the single modality attained remission at 3 months. Eight patients developed grade I GVHD, and none died of complications. Because the toxicity of the combined approach does not appear to be worse than either modality alone, current recommendations support using the two modalities together (imatinib plus low-dose DLI) to attain the maximum efficacy with reasonable toxicity.

Conclusions

TKIs are now considered the standard of care for up-front treatment of all adult patients with CML. High-risk patients need close follow-up with cytogenetic or molecular monitoring, but the recommendation for initiating TKIs remains the same. Second-line therapies such as dasatinib and nilotinib have been used with excellent results. Patients who do not tolerate TKIs or develop resistance to the TKIs should be considered for treatment with allogeneic HCT. Other patients who might be considered for transplant include those with advanced forms of CML and those with cytogenetically or molecularly unfavorable disease. Data from retrospective analysis show that TKIs are safe to offer prior to transplant and may favorably impact outcome, particularly if the patient attains a complete cytogenetic or molecular response. Transplant toxicity is not affected by the use of TKIs. Treatment-related nonrelapse mortality and leukemia-free and overall survival are not affected by their use.

Imatinib or DLI can be used to achieve remission in patients who relapse after allogeneic HCT. Combining DLI with imatinib may augment efficacy and may allow a reduction in the dose of T cells, which may result in reduced risk of the life-threatening complications from DLI. Prospective, randomized studies are needed to determine if TKIs should be used in high-risk or advanced-phase patients to prevent relapse after transplant. Anecdotal cases of cytopenias have been described, mostly at relapse.

With the availability of various therapies, the future for CML patients is bright. The introduction of TKIs to the therapeutic armamentarium against CML has improved OS. Moreover, their use has shifted the need for transplantation to later in the course of therapy. Some patients, although not cured with these inhibitors, may never require the more intensive transplant therapy. Finally, allogeneic HCT can be safely offered to those patients for whom a more aggressive approach is required.

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