Maintenance Therapy With Tyrosine Kinase Inhibitors After Transplant in Patients With Chronic Myeloid Leukemia

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Abstract

Because of their outstanding efficacy and low toxicity, tyrosine kinase inhibitors (TKIs) have replaced allogeneic hematopoietic cell transplant (HCT) as the standard frontline therapy for patients with newly diagnosed chronic myeloid leukemia (CML). Until a decade ago, HCT was the preferred treatment for CML, with 5-year overall survival rates of approximately 80%, 40%, and 20% for patients in chronic, accelerated, and blast crisis phases, respectively. Relapse after transplant is a problem for patients who undergo transplant in advanced phase disease and those undergoing a T-depleted transplant. Until the introduction of TKIs, therapy for relapsed CML after transplant relied on interferon and/or donor leukocyte infusion (DLI). Although effective in inducing remission, DLI is associated with clinically significant graft-versus-host disease or myelosuppression, with an accompanying treatment-related mortality of 5% to 20%. TKIs have emerged as an attractive alternative therapy for persistent or relapsing CML after HCT. Similar to DLI, the effectiveness of TKI posttransplant is largely determined by the phase of disease at relapse, showing very good response in patients experiencing relapse in the chronic phase, with high rates (>60%) of hematologic and cytogenetic remissions, but less favorable outcomes in patients with advanced disease, with only a minority experiencing durable cytogenetic or molecular remissions. Molecular monitoring of the BCR-ABL chimeric mRNA posttransplant is important for early detection of patients at high risk of relapse. (JNCCN 2013;11:308–315)

Tyrosine Kinase Inhibitor Therapy for Chronic Myeloid Leukemia, 2012

Before the introduction of the tyrosine kinase inhibitors (TKIs), allogeneic hematopoietic cell transplantation (HCT) was the only “curative” approach for chronic myeloid leukemia (CML). Survival rates were greater than 80% for chronic phase (CP), 40% for accelerated phase (AP), and 20% for blast crisis phase (BP) CML. In most major transplant settings, survival rates for matched related and unrelated transplants are similar.

In 2012, TKIs are unquestionably the standard frontline therapy for patients with newly diagnosed CML. The International Randomized Study of Interferon Versus STI571 (IRIS) trial showed that for patients treated with imatinib, the cumulative complete cytogenetic response rate was 87% and the overall survival rate was greater than 85%.1 Cytogenetic, molecular, and progression all indicate the superiority of second-generation TKI over imatinib, although so far overall survival rates are similar.2,3

Therefore, which patients with CML should be considered for allogeneic transplant? Not many. With imatinib, approximately 40% of patients will eventually discontinue therapy, either because of initial failure to achieve milestones, intolerance, or relapse. For dasatinib and nilotinib, these numbers are somewhat less. Patients in all of these clinical categories can generally be considered candidates to move to another TKI, and a significant proportion will be effectively treated using this strategy. However, in patients with imatinib resistance, only approximately 40% will experience a complete cytogenetic response (CCyR) after switching to a second-generation TKI. Patients who become resistant should undergo ABL mutation testing, because the results may guide the choice of the next TKI. Each TKI has a unique sensitivity profile to each type of ABL point mutation. Moreover, mutation testing can discov-
er the T315I mutation, which is important because currently none of the FDA-approved agents are effective in these patients.

Given the successful induction of durable responses with imatinib in most patients and the recent results showing superior early efficacy of nilotinib and dasatinib in newly diagnosed patients, allogeneic HCT is no longer recommended as a first-line treatment option for patients with CP-CML by expert committees such as NCCN or European LeukemiaNet. Rather, allogeneic HCT is considered for patients who are intolerant to all TKIs (rare); whose disease failed to respond to salvage TKI; who have a T315I mutation (if a clinical trial of an agent active in patients with the T315I mutation is not available); or who present with or progress to AP or BP.

Transplantation for CML, 2012

The widespread application of allogeneic HCT is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility to many centers to younger than 65 years. Ongoing advances in alternative donor sources (eg, unrelated donors and cord blood), more accurate HLA typing of unrelated donors, and less-toxic regimens are broadening the use of allogeneic HCT. Transplants from unrelated matched donors can now be used for many patients with CML, and the results with unrelated, fully matched donors are comparable to those of related matched donors. Nonmyeloablative reduced-intensity conditioning has been promoted to impart a graft-versus-leukemia (GVL) effect without exposing the patient to the toxicity associated with the myeloablative preparative regimen, and these investigational approaches suggest that molecular remissions may be achieved with nonmyeloablative reduced-intensity conditioning in patients with CML.

The outcome of allogeneic HCT is influenced by disease phase, HLA matching, age, sex, and time from diagnosis to transplant. Low HCT comorbidity index and low C-reactive protein level were identified as prognostic indicators of a lower nonrelapsed mortality rate and somewhat improved survival rate. The disease phase at time of transplant remains an important prognostic factor; outcomes after transplant are clearly better for patients in CP than those with advanced disease; 5-year survival rates after matched related transplants are approximately 80%, 40%, and 20% for patients in CR, AP, and BP, respectively. Patients who undergo allogeneic HCT for CML in first CP and remain in remission for at least 5 years have a favorable subsequent long-term survival. Survival remains poor for patients transplanted in AP or BP compared with those transplanted in CP.

In the German CML IV study, the 84 patients who underwent allogeneic HCT because of either a high disease risk score at diagnosis, imatinib failure, or disease progression, the 3-year survival rates were 91% for those in CP and 59% for those in advanced phase, with a treatment-related mortality rate of 8%.

In the past, therapy with busulfan or interferon before transplantation had a negative impact on survival. Several studies have shown that the use of imatinib before allogeneic HCT is not associated with a significant increase in relapse or nonrelapse mortality. The International Bone Marrow Transplant Registry data on patients who underwent transplant in CP showed that prior use of imatinib was associated with improved survival, although this was limited to patients who pursued transplant because of intolerance rather than failure.

Use of TKIs Posttransplant

The response to disease recurrence after transplant depends partly on the amount of disease burden. Before the 1990s, cytogenetic monitoring posttransplant was routine. It should be noted that molecular monitoring of the BCR-ABL chimeric mRNA, now such an important part of CML therapy with TKIs, was developed first as a way to predict early relapse in CML after transplant. Before the development of quantitative polymerase chain reaction, the mere qualitative (yes vs. no) detection of BCR-ABL transcripts after transplant was routine. 6 to 12 months posttransplant. Quantitative testing has “fine-tuned” risk assessment, with higher molecular burdens associated with higher relapse rates. Two important caveats have emerged—the risk associated with BCR-ABL positivity is very high in T-cell–depleted transplant, and the prognostic significance of BCR-ABL positivity is less after a longer period after transplantation. The potential of early detection of BCR-ABL transcripts after trans-
plant to identify patients at high risk of relapse has set the stage for the use of TKIs in this setting to avoid relapse.

Management of Posttransplant Relapse and the Role of TKIs

Until the introduction of TKIs, first-line therapy for relapsed CML after HCT often consisted of administration of donor leukocyte infusion (DLI), harnessing the well-documented GVL effect that has been observed in CML. DLI is effective in inducing durable molecular remission in most patients with relapsed CML after allogeneic HCT, and it is more effective in patients with CP relapse than AP relapse. One-third of patients may experience clinically significant graft-versus-host disease (GVHD) or myelosuppression after DLI, with an accompanying treatment-related mortality of 5% to 20%.

TKIs have emerged as an alternative to DLI for patients with persistent or relapsing CML after HCT. Several studies have evaluated the use of TKIs, especially imatinib, in relapsed CML after HCT.

The data suggest that the effectiveness of TKI therapy posttransplant is largely determined by the phase of disease at relapse. In general, responses have been very good in patients experiencing relapse in CP, with high rates (>60%) of both hematologic and cytogenetic remissions. Fewer studies have evaluated the effect of TKI therapy in patients with advanced disease after HCT; however, the available literature suggests a less favorable outcome, with only a minority of patients with advanced CML after HCT experiencing durable cytogenetic or molecular remissions with TKIs. Posttransplant imatinib treatment is generally well tolerated, with pancytopenia the main toxicity. This toxicity is resolved with dose adjustments and/or temporary drug discontinuations. In all studies, imatinib discontinuation because of toxicity was rare and generally temporary. Table 1 summarizes major clinical trials evaluating the use of TKIs for CML after allogeneic HCT.

A small retrospective study compared DLI (n=21) versus imatinib (n=10) as first-line treatment for relapsed CML after allogeneic HCT. Transplantation was performed in CP-CML in 17 patients in the DLI group and 7 patients in the imatinib group. No data were provided regarding history of TKI treatment before HCT. Most patients from the 2 groups were experiencing cytogenetic relapse at the time of treatment with DLI or imatinib after transplant (14 in the DLI group, 9 in the imatinib group), whereas 8 patients (7 in the DLI group, 1 in the imatinib group) were experiencing hematologic relapse. Molecular remission was achieved among 95% of patients who were treated with DLI, compared with 75% in the imatinib group, and relapse occurred in only 3 patients (14%) after DLI compared with 6 patients (60%) after imatinib. The rate of treatment-related mortality was 10% in the DLI group and 0% in the imatinib group. The probability of overall survival at 5 years was 100% in the imatinib group and 76% in the DLI group, but this difference was not statistically significant (P=1.83).

Limited data are available on the use of second-generation TKIs (dasatinib and nilotinib) for the treatment of relapsed CML after HCT. Data are based mainly on case reports and small retrospective studies. Most patients in these reports had received imatinib pre-HCT. Klyuchnikov et al reported on 9 patients with advanced phases of CML who were treated with dasatinib after HCT. All patients had received TKIs pre-HCT (3 patients received imatinib only; 4 patients received imatinib and dasatinib; 1 patient received imatinib, dasatinib, and nilotinib; and 1 patient received dasatinib and bosutinib). Discontinuation of dasatinib was necessary in 1 patient (13%) because of thrombocytopenia-related gastrointestinal bleeding. Stable response was seen in 4 of 9 patients with CML who all had a history of AP/BP or extramedullary disease. Atallah et al analyzed outcomes in 11 patients with relapsed CML (n=9) or Ph+ acute lymphocytic leukemia (ALL; n=2) after HCT who received treatment with dasatinib post-HCT. Ten of the patients were treated with imatinib pre-HCT. High rates of gastrointestinal bleeding (27%), pulmonary complications (18%), and liver toxicity (9%) were seen, and side effects were well managed in most cases through dose reduction and interruption of treatment. Major molecular complete response was achieved in 3 patients (relapsed ALL, CML in AP, and CML in BP).

In December 2012, the FDA granted accelerated approval to ponatinib for the treatment of adult patients with CP-, AP-, or BP-CML, or Ph+ ALL who are resistant or intolerant to prior TKI therapy. The approval was based on the results of the PACE trial, a multicenter, international, single-arm clinical trial of 449 patients with disease that was resistant or intolerant to prior TKI therapy. The primary
## Table 1 Posttransplant Use of Tyrosine Kinase Inhibitors in Patients With Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Indication for Treatment</th>
<th>TKI</th>
<th>Median Daily Dose</th>
<th>Median Interval From HCT to Treatment (mo)</th>
<th>Median Treatment Duration (mo)</th>
<th>Most Significant Toxicity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantarjian et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>28 (no indication whether patients received TKI pre-HCT)</td>
<td>Relapse</td>
<td>Imatinib</td>
<td>600 mg</td>
<td>30</td>
<td>N/A</td>
<td>Treatment was continued until: Disease was considered unresponsive</td>
<td>CHR: 74% (CP: 100%; AP: 82%; BP: 43%); CgR: 58% (CP: 63%; AP: 63%; BP: 43%); CCgR: 35%</td>
</tr>
<tr>
<td>Olavarria et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>128 (no indication whether patients received TKI pre-HCT)</td>
<td>Relapse</td>
<td>Imatinib</td>
<td>400 mg (CP) 600 mg (AP/BP)</td>
<td>14</td>
<td>N/A</td>
<td>Median follow-up, 9 mo</td>
<td>N/A</td>
</tr>
<tr>
<td>DeAngelo et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>15 (no patients received TKI pre-HCT)</td>
<td>Relapse</td>
<td>Imatinib</td>
<td>600 mg</td>
<td>52 (CP) 111 (AP/BP)</td>
<td>N/A</td>
<td>Median follow-up, 25 mo</td>
<td>Grade 3/4 liver toxicity</td>
</tr>
<tr>
<td>Hess et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>44 enrolled 37 evaluated (no indication whether patients received TKI pre-HCT)</td>
<td>Relapse</td>
<td>Imatinib</td>
<td>400 mg</td>
<td>64</td>
<td>8</td>
<td>Grade 3/4 hematologic toxicity</td>
<td>CCgR: 44% (CP: 58%; AP: 48%; BP: 22%); CMR: 26% (CP: 37%; AP: 33%; BP: 11%); CP 2-y OS: 100%; AP 2-y OS: 86%; BP 2-y OS: 12%</td>
</tr>
<tr>
<td>Atallah et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>11 (9 CML, 2 ALL) (10 patients received imatinib pre-HCT)</td>
<td>Relapse</td>
<td>Dasatinib</td>
<td>70 mg bid</td>
<td>9</td>
<td>N/A</td>
<td>Gastrointestinal bleeding, thromboctopenia, pulmonary complications, liver toxicity</td>
<td>CMR: 22% (CML) Median OS: 12 mo</td>
</tr>
<tr>
<td>Carpenter et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>22 (15 ALL, 7 CML) (7 CML patients and 14 ALL patients received imatinib pre-HCT)</td>
<td>Prophylaxis</td>
<td>Imatinib</td>
<td>400 mg</td>
<td>1</td>
<td>12</td>
<td>Grade 1–3 nausea, emesis, liver toxicity</td>
<td>CCgR: 57%; CMR: 57%</td>
</tr>
<tr>
<td>Olavarria et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>22 (11 patients received imatinib pre-HCT)</td>
<td>Prophylaxis</td>
<td>Imatinib</td>
<td>400 mg</td>
<td>1</td>
<td>12</td>
<td>?</td>
<td>68% relapse at median of 17 mo after HCT</td>
</tr>
<tr>
<td>Palandri et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>16 (no indication whether patients received TKI pre-HCT)</td>
<td>Relapse</td>
<td>Imatinib</td>
<td>400 mg</td>
<td>34</td>
<td>30</td>
<td>Grade 3/4 hematologic toxicity</td>
<td>CCgR: 88%; CMR: 75%</td>
</tr>
<tr>
<td>Klyuchnikov et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>11 (9 CML, 2 ALL) (all patients received TKI pre-HCT)</td>
<td>Relapse</td>
<td>Dasatinib</td>
<td>50 mg bid</td>
<td>12</td>
<td>8</td>
<td>Thromboctopenia related gastrointestinal bleeding stable response in 4 patients (2 with extramedullary relapse)</td>
<td>CMR: 86% (AP/BP); CCgR: 77% (AP/BP); CMR: 64% (AP/BP); 57%</td>
</tr>
<tr>
<td>Wright et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>22 (6 patients received imatinib pre-HCT)</td>
<td>Relapse</td>
<td>Imatinib (n=20) dasatinib (n=6)</td>
<td>39.5</td>
<td>N/A</td>
<td>Grade 3/4 hematologic toxicity</td>
<td>CHR: 86% (AP/BP); CCgR: 77% (AP/BP); CMR: 64% (AP/BP); 57%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphocytic leukemia; AP, accelerated phase; BP, blast crisis phase; CCgR, complete cytogenetic molecular response; CgR, cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CMR, complete molecular response; CP, chronic phase; HCT, hematopoietic stem cell transplants; MR, molecular response; N/A, not applicable; OS, overall survival; TKI, tyrosine kinase inhibitor.<br/>

<sup>a</sup>Patients treated with TKI pre-HCT.
end points were major cytogenetic response (MCyR) for patients with CP-CML, and major hematologic response (MaHR) for patients with AP-CML, BP-CML, or Ph+ ALL. The efficacy results showed a 54% MCyR rate in patients with CP-CML. Seventy percent of patients with CP-CML with T315I mutation experienced a MCyR. The median duration of MCyR had not yet been reached at the time of analysis. For patients with AP-CML, BP-CML, and Ph+ ALL, the MaHR rates were 52%, 31%, and 41%, respectively. The median duration of MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 9.5, 4.7, and 3.2 months, respectively. The most common side effects reported in the clinical trial include hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, fever, joint pain, and nausea. Arterial thrombosis and liver toxicity were also reported. Data regarding the use of ponatinib after HCT are very limited.46

Despite the abundant data indicating that imatinib may reduce the disease bulk in CML, it is likely that the leukemia progenitor cells remain, because recurrent disease is often observed after discontinuation of imatinib. In contrast, DLI provides an immune-mediated GVL effect, which can potentially permanently eliminate residual disease. Thus, combining TKIs and DLI is a logical, although poorly studied, approach to treating relapse. In a study by Kantarjian et al,26 DLI were given to 13 of 28 patients experiencing relapse of advanced phase CML. The median interval between DLI and imatinib was 4 months (range, 3–29 months). The combination of imatinib and DLI was well tolerated; however, no differences were seen in complete response rates compared with the cohort of 15 patients who received imatinib alone. DeAngelo et al44 administered DLI more than 12 months before the start of post-transplant imatinib in 4 of 15 patients with different phases of CML. No signs of increased toxicity were seen with the combined approach, and 2 patients experienced a transient cytogenetic complete response. Savani et al37 performed a retrospective comparison of 37 patients experiencing a hematologic or molecular relapse of CML who received imatinib, DLI, or a combination of both in concurrent or sequential regimens. A beneficial effect of the DLI/imatinib combination was seen compared with the use of either agent alone: with the combination, patients were able to stop imatinib without recurrence of molecular disease and had superior overall survival rates (100%, 89%, and 54% for imatinib/DLI, imatinib alone, and DLI alone, respectively) and disease-free survival rates after treatment (100%, 54%, and 43% for imatinib/DLI, imatinib alone, and DLI alone, respectively). It was also remarkable that a molecular complete response was achieved sooner in patients receiving the DLI/imatinib combination compared with those treated with DLI or imatinib alone (90%, 7.7%, and 11%, respectively, at 3 months from start of treatment). Considering AP-CML, all 4 patients achieved molecular remission and were disease-free after follow-ups of 8 to 42 months.

The optimal time of initiation after transplant, dose, and duration of TKI therapy for relapsed CML after HCT are unclear. The intervals between HCT and initiation of TKI therapy have been variable in prior reports. In most posttransplant studies, imatinib at doses of 400 to 800 mg daily were continued for periods ranging from 9 to 14 months. In most posttransplant studies, imatinib at doses of 400 to 800 mg daily were continued for periods ranging from 9 to 14 months.3,26,27,34,35 Palandrini et al47 continued imatinib for longer periods, with a median treatment duration of 31 months. In total, 12 of 16 (75%) patients with hematologic, cytogenetic, or molecular relapse of CP or AP/BP achieved molecular complete response. This suggests that prolonged treatment with imatinib is effective and feasible in the posttransplant period and can be safely administered over longer periods. However, close monitoring of peripheral blood counts is strongly recommended for patients receiving TKIs in the posttransplant period so that dose reductions can occur when necessary. Clinical research should continue to evaluate the effect of TKIs on GVL and GVHD when given with or without DLI.

Ongoing Issues and Questions

- What is the time and disease burden “trigger point” for starting TKIs? No one would argue that cytogenetic relapse should be treated with some sort of therapy (see later discussion), but molecular monitoring should be performed in this day and age. Data from the non-TKI era suggest that molecular relapse early (at <3 months) is not as significant as in the 6- to 12-month range, and that any level of disease burden puts patients at increased risk, with the higher the level, the greater the risk of subsequent relapse. In the context of T-cell depletion, molecular re-
lapse at any time should be treated; no data are available for nonmyeloablative transplants, but adopting standard transplant rules seems logical.

• Should all patients be treated prophylactically, or only when molecular relapse occurs? Should different phases be treated differently (eg, only treat molecular relapse in CP, administer prophylaxis for advanced phase disease)?

• Should different drugs be used for different situations? For example, imatinib for low molecular burden in CP disease, second-generation TKIs for higher burden and/or advanced phase disease, and combination therapy (eg, TKI and DLI) for advanced phase disease and/or cytogenetic relapse.

• What will be the efficacy/toxicity of second-generation TKIs after HCT? Imatinib seems to be remarkably benign, apparently having a modest effect on normal hematopoiesis. The hematologic toxicity of second-line agents seems higher than imatinib; will these data from diseases of the hematopoietic system (ie, CML) also be seen when the predominant hematopoiesis is from a normal donor?

• Should pretransplant treatment with TKIs affect the decision whether to use TKIs after transplant? Early studies have used TKIs primarily in TKI-naive patients; however, currently many patients will not proceed to stem cell transplantation unless they did not respond to 2 or more TKIs. Thus, the patient population has changed, and the question remains whether and what TKIs should be used posttransplant in patients whose disease did not respond to TKIs pretransplant.

• Does pretransplant mutation status matter? Studies have shown that resistant mutations such as T315I only have the advantage in the case of TKI selective pressure; that is, in the context of TKI absence, they grow slower than wild-type. If that is true, what clone recurs after transplantation? Is it wise to allow pretransplant mutational profile to dictate posttransplant TKI choice?

• How long does TKI therapy need to be given after HCT? Indefinitely? Until molecular remission? If so, how long a molecular remission?

However, there is a “good news, bad news” twist: TKIs are so effective that increasingly fewer patients will need transplantation, and thus these questions, interesting or not, will likely never be fully answered.

References


45. Bar and Radich

