Allogeneic haematopoietic stem cell transplant (alloSCT) is an effective therapeutic choice for chronic myeloid leukaemia and remained the only curative option for many years. However, the introduction of targeted drugs against the BCR-ABL1 tyrosine kinase has changed the therapeutic approach for this disease. In this article, the authors describe the current indications for alloSCT during the tyrosine kinase inhibitor era and explore the role of these drugs in multiple situations, including before and after transplant.

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Abstract
The introduction of tyrosine kinase inhibitors (TKI) has dramatically improved the prognosis of chronic myeloid leukaemia (CML) patients and, therefore, changed the therapeutic scenario of this disease. Before the advent of the first TKI imatinib, allogeneic haematopoietic stem cell transplantation (alloSCT) was the only curative approach for CML, and all patients deemed eligible for transplant were referred to a centre for transplant where possible. Nowadays, with the wide availability of five different TKI, indications to alloSCT have been reduced to only include patients in the advanced
INTRODUCTION

BCR-ABL1 tyrosine kinase inhibitor (TKI) therapy is the current standard of care for patients with chronic myeloid leukaemia (CML) in the chronic phase (CML-CP). Nowadays, these patients usually have near-normal life spans and survival has reached approximately 80–90%. The percentage of patients progressing to advanced-phase disease (particularly to blast crisis [BC]) is smaller when compared to the pre-TKI era. In CML-CP patients receiving upfront second-generation TKI (2G-TKI), this rate is even lower when compared to imatinib, a first-generation TKI. Prior to the era of targeted therapy with TKI, early treatment modalities for patients with CML-CP included arsenic, busulfan, hydroxyurea, and IFN-α with or without cytosine arabinoside, but, in general, none of these treatments can induce a long-term survival benefit. During the 1980s, allogeneic haematopoietic stem cell transplantation (alloSCT) became the only curative therapy for CML. However, not all patients could undergo alloSCT because there were (and still are) some challenges, including age and donor availability problems that physicians and patients face during and after alloSCT, and this procedure can be associated with significant early and late transplant-related morbidities and even mortality. After the year 2000, with the introduction of imatinib, the number of transplants performed for CML-CP substantially decreased and, although it remains an important therapeutic option for eligible patients, the place of alloSCT in the management of CML has become limited.

ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHRONIC MYELOID LEUKAEMIA PRIOR TO THE TYROSINE KINASE INHIBITOR ERA

The first documented disappearance of a Philadelphia chromosome-positive (Ph+) clone following alloSCT was performed in syngeneic twins, which was then followed by transplantation using human leukocyte antigen (HLA)-matched sibling donors and later unrelated donors. Eventually, in the 1990s, CML was the most frequent indication for alloSCT. CML was a testing ground for the use of alloSCT, and this disease provided the first example for risk assessment with the European Group for Blood and Marrow Transplantation (EBMT) risk score, showing that disease stage was more important than the bulk of the disease; this score is still the most powerful predictor of transplant outcome for haematological malignancies. Patients with the lowest risk score have been shown to have a transplant-related mortality of 20% and a 5-year overall survival (OS) of 72%, whereas those with the highest score have been shown to have a transplant-related mortality of 72% with a 5-year OS of 22%. CML was also the first disease for which a consistent graft-versus-leukaemia (GvL) effect was demonstrated. Relapse risk was very high after T cell depletion and, conversely, donor lymphocyte infusion (DLI) was proven to be very effective in CML, especially with the additional role of pre-emptive DLI use in patients receiving reduced-intensity conditioning regimens. Although myeloablative conditioning remains the preferred approach for the majority of transplant-eligible CML patients, the understanding of transplant immunology resulted in the development of reduced-intensity conditioning regimens to extend access to alloSCT to those who are unfit for the myeloablative conditioning regimens.

THE PLACE OF ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE ERA OF TYROSINE KINASE INHIBITORS

Indications for Allogeneic Haematopoietic Stem Cell Transplantation

The data derived from the Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis of the...
Worldwide Network for Blood and Marrow Transplantation (WBMT) policy clearly showed that the number of patients with CML undergoing alloSCT was extensively reduced, with only 1,059 allotransplants (only 3.3% of the total number of transplants) performed globally in 2012. In a study by Özen et al., prior to the introduction of imatinib in Turkey, the percentage of patients receiving alloSCT for CML was 40%, whereas this percentage was 11% and 5% between 2002 and 2006 and after 2007, respectively. Supporting this finding, at the EBMT 2018 meeting, there were only five abstracts regarding SCT in CML out of a total of 1,083.

Most patients presenting with CML-CP receive upfront treatment with imatinib and approximately 70% achieve complete cytogenetic response (CCyR) after 12 months of therapy; however, during long-term follow-up, about 40% of these patients switched to a second-line TKI therapy due to resistance and/or intolerance. Nearly half of patients who fail frontline imatinib may achieve durable responses with 2G-TKI (dasatinib, nilotinib, and bosutinib). Although it can be beneficial, after failing two lines of TKI treatment the chance of achieving optimal responses with third-line 2G-TKI is relatively low. In patients with CML-CP receiving upfront dasatinib or nilotinib, by 24 months of TKI therapy, only 77% and 76% of the cases were still on 2G-TKI treatment, respectively. Also, in CML-CP patients who harbour a Thr315Ile mutation, the third-generation TKI ponatinib can be a reasonable option, and can be used in patients with CML-CP who fail two lines of TKI treatment. A paper reporting data within the era of TKI showed that when alloSCT was performed among cases in first CP with a low EBMT risk score (0–2), using standard myeloablative conditioning with standard graft-versus-host disease (GvHD) prophylaxis and an optimal stem cell source (e.g., HLA-identical sibling), the low transplant-related mortality results were remarkable.

In the most recent European LeukemiaNet (ELN) recommendations, CML-CP patients and siblings should undergo HLA typing at diagnosis only in cases of baseline warning signs. In cases of first-line imatinib failure, it is also recommended to search for a sibling donor. In addition, in patients with CML-CP who failed upfront 2G-TKI (nilotinib and dasatinib), searching for an unrelated stem cell donor is recommended in case an HLA-identical sibling donor is unavailable. In patients harbouring a Thr315Ile mutation, the search for a sibling or unrelated stem cell donor is highly advised at any line of TKI therapy.

In a recently published paper, it was shown that patients with newly diagnosed high-risk CML and non-responders to first-line TKI can benefit from an early low-risk alloSCT with improved long-term survival, shorter time of treatment, a higher rate of molecular remissions, and lower healthcare costs, which were consistent with another previous study performed in the imatinib era. In that study, patients undergoing early low-risk alloSCT had no early additional mortality but a significantly higher rate of molecular remissions compared to those with imatinib.

While proceeding to alloSCT, one should balance the potential risks of the transplant against the risk of disease progression. The indications for alloSCT in patients with CML-CP include failing to achieve durable responses with two lines of TKI therapy and cases with a Thr315Ile mutation. Even eligible patients with a low transplant score who fail initial TKI therapy might be considered for an early alloSCT rather than salvage TKI therapy. In patients with CML-CP who have a Thr315Ile mutation, alloSCT can be curative; however, in cases with advanced disease phases (accelerated phase [AP] or BC), transplantation should be preserved for patients who return to second CP after anti-CML therapy.

In cases with AP or BC, eligible patients should undergo alloSCT, and among patients with BC harbouring a Thr315Ile mutation, the outcomes are better with alloSCT than those with ponatinib. The current evidence suggests that alloSCT may be the best chance of cure in BC patients. In these patients, alloSCT should be performed following a treatment with a suitable TKI selected according to mutation profile in combination with chemotherapy in order to achieve a second CP. Nowadays, more CML patients are transplanted in second CP or advanced phases than in first CP.

Although long-term TKI treatment effectively controls the disease in most patients, this has resulted in a significant economic impact for patients and healthcare systems worldwide,
especially for those in low-income countries. In the developing world, early alloSCT can be considered in the management of selected cases before disease transformation, and this treatment modality may be, sometimes unavoidably, due to economic issues, chosen over 2G-TKI. As generic imatinib becomes available, this would decrease the therapy-related expenses, thus increasing the accessibility of TKI therapy, which might further minimise the rate of CML progression and the need for alloSCT.

The Impact of Prior Tyrosine Kinase Inhibitor Use on Allogeneic Hematopoietic Stem Cell Transplantation Outcomes

Several previous studies have demonstrated that the use of TKI prior to transplant does not seem to have a negative impact on the outcome of alloSCT in CML. In a more recent study by Kondo et al., the authors included patients receiving one, two, or three TKI before alloSCT (153, 49, and 35 patients, respectively). They clearly showed that, in addition to conventional risk factors, using three TKI prior to transplantation was associated with an adverse outcome. Non-relapse mortality rate was higher in patients with three TKI than those in patients treated with one or two TKI, and the authors concluded that alloSCT could be considered for young patients with CML-CP who had resistance to second-line TKI therapy and who had an appropriate donor.

The Type of Transplant: Myeloablative Versus Reduced-Intensity Conditioning

Transplantation should be performed with an HLA-identical sibling or HLA-matched unrelated donor; if unavailable, a haploidentical donor can be used, bearing in mind that haploidentical transplants in CML are rare. Although the number of patients undergoing haploidentical alloSCT continues to increase, in a recent activity survey report of EBMT, it was demonstrated that 398 transplants were performed for CML and, of these, only 26 were haploidentical. For years, myeloablative conditioning regimens were used in CML and are still in use among fit patients. It remains the standard of care for those who tolerate the regimen and includes total body irradiation and cyclophosphamide or busulfan and cyclophosphamide. For GvHD prevention, the combination of cyclosporine and short-term methotrexate is commonly used. Since long-term remission is usually dependent on the GvL effect, reducing the intensity of the conditioning and reinforcing the GvL effect with pre-emptive DLI enables transplantation of elderly patients and those with comorbidities. Although T cell depletion is associated with reduced severity and frequency of GvHD, the risks of relapse and infection are both increased.

Source of Haematopoietic Stem Cells

Generally, over the last decades there has been a shift from bone marrow to peripheral blood as a source for stem cells. However, the use of peripheral blood stem cells for CML-CP has been associated with an increased risk of non-relapse mortality and chronic GvHD. The issue of increased GvHD risk is of particular interest in CML due to the frequent need for DLI to treat molecular relapse after transplant. If the eventual goal is to limit the risks on GvHD, as may be the case in CML-CP, a prudent approach would favour the use of bone marrow-derived haematopoietic stem cells.

Prevention of Relapse after Allogeneic Haematopoietic Stem Cell Transplantation

Relapse after alloSCT still represents an important cause of failure of transplant procedures, mainly in high-risk disease cases which make up the majority of CML patients undergoing alloSCT. Though the real value of the use of TKI after a successful alloSCT is still unknown, mainly because most CML patients receive transplant after failure of multiple TKI, the possible role of prophylactic TKI therapy to prevent disease relapse remains attractive.

In the last 10 years, various investigations have tested the safety and efficacy of imatinib and, later, 2G-TKI after alloSCT. Carpenter et al. reported on 22 patients with Ph+ leukaemias (15 with acute lymphoblastic leukaemia [ALL] and 7 with CML) prospectively treated with imatinib 400 mg from engraftment to Day 365, proving the overall safety of imatinib administration despite a high incidence of nausea, vomiting, and transaminase increase. A Japanese group compared 20 patients (18 with Ph+ ALL and 2 with CML) receiving
Imatinib for the prevention of disease relapse for at least 3 months after alloSCT with 76 patients (33 with Ph+ ALL and 43 with CML) who did not receive imatinib. Imatinib, started at 400 mg and administered within 100 days of alloSCT, was associated with a reduced incidence and severity of chronic GvHD in most patients, but this study failed to assess the prophylactic impact of TKI therapy on the incidences of leukaemia relapse due to a small number of patients and its retrospective nature. In 2015, Shimoni at al. reported on a Phase I/II study of nilotinib prophylactic maintenance in 16 patients with advanced CML or Ph+ ALL undergoing alloSCT, started after engraftment and continued until progression or toxicity. Nilotinib’s maximal tolerated dose was determined to be 200 mg twice a day. The median duration of therapy was 20 months and 6 patients stopped nilotinib due to toxicities (hepatic in 3, haematological in 1, allergic in 1, and late cerebrovascular in 1). Among the 11 patients who achieved a complete molecular response with alloSCT with or without nilotinib, only 1 progressed on nilotinib maintenance, with an overall 2-year survival rate of 55% and a 2-year relapse risk of 23%, lower than what is expected in such a high-risk population. The same group subsequently studied the immune function of 12 patients receiving nilotinib for at least 90 days after transplant, demonstrating a rapid reconstitution of NK cells and CD8+ T cells; moreover, T cell response was not inhibited by nilotinib administration. DeFilipp et al. published a monocentric experience of 26 patients (17 Ph+ ALL and 9 AP/BC CML) receiving maintenance post-alloSCT therapy with different TKI, including dasatinib (n=14), nilotinib (n=1), and ponatinib (n=1). The TKI was chosen according to pre-alloSCT response, tolerability, and ABL mutation; imatinib was started at 400 mg daily and other TKI at 50% of the pretransplant dose. The 9 CML patients were transplanted in second or third CP and started TKI (7 with dasatinib) while in molecular remission. The 5-year OS for CML and Ph+ ALL in second complete remission (reported together) was 79%. Recently, a multicentric study enrolled 40 patients who received nilotinib (n=11) or imatinib followed by nilotinib by Day 81 (n=29) after myeloablative alloSCT for Ph+ leukaemias; 17 patients who consented to enter the study before alloSCT were not eligible to start TKI prophylaxis at engraftment. Despite various causes of discontinuation of treatment that produced a failure rate of 77% (44 out of 57) of the starting intention-to-treat population, all 13 patients who completed nilotinib therapy were alive and in remission.

In summary, there is no definitive evidence that prophylactic use of TKI after alloSCT may significantly reduce the risk of CML recurrence. On the other hand, there are no concerns of TKI safety in the post-alloSCT setting and the National Comprehensive Cancer Network (NCCN) 2018 guidelines recommend considering 1 year of standard TKI therapy after a successful transplant.

Treatment of Relapse

In patients relapsing after alloSCT, CML recurrence can occur quickly or many years after transplant, and is generally preceded, at least in patients receiving alloSCT in CP, by a molecularly detectable BCR-ABL1 transcript. As previously stated, prior to the era of TKI, treatment of CML relapse relied on DLI, exploiting the well-known GvL effect observed in CML. However, due to the potential complications of DLI use in terms of GvHD or myelosuppression, TKI have emerged as an alternative. The MD Anderson Cancer Center (MDACC) group reported in 2002 its experience of 28 CML patients (5 in CP and 23 in AP/BC) receiving imatinib 400–1,000 mg daily for relapse occurring at a median of 9 months after alloSCT. Though it was not reported if patients had received imatinib prior to alloSCT, responses were promising, particularly in CP or AP, with a CCyR rate of 63%. One year later, a larger study of 128 CML patients relapsing after alloSCT was published by the EBMT group. The study included patients in all phases of the disease (51 at CP, 31 at AP, and 46 at BC) and, among CP cases, there were few cytogenetic or molecular relapses; 50 patients had failed DLI before imatinib treatment. Beyond confirming the MDACC experience (CCyR was 58% for CP, 48% for AP, and 22% for BC, and 2-year survival for CP and AP patients was 100% and 86%, respectively), it was found that imatinib therapy was able to restore full donor chimerism in 57% patients. Other subsequent studies also confirmed the efficacy of imatinib in inducing durable cytogenetic and molecular responses...
and in restoring complete donor chimerism,\textsuperscript{63,64} as well as the possible synergic activity of imatinib and DLI, which, when used in combination, induced rapid and sustained molecular responses in patients relapsing in advanced-phase CML and that some patients maintained response even after imatinib was stopped.\textsuperscript{65} In all these studies, post-transplant imatinib was generally well tolerated and haematological toxicity was manageable with dose adjustments and brief discontinuations.

Fewer data are available on the efficacy and safety of 2G-TKI for the treatment of CML relapse after alloSCT, since most of the published experiences are single cases or very small series of patients. The MDACC group reported at the 2006 American Society of Hematology (ASH) meeting on 11 patients (9 with CML and 2 with ALL) treated with dasatinib as salvage therapy after alloSCT; all patients had failed high-dose imatinib before transplant. Nine patients (82\%) responded, including three with molecular remission, one with CCyR, and two with a partial cytogenetic response. Dasatinib was well-tolerated at a dose of 100 mg daily, while higher doses led invariably to drug discontinuation.\textsuperscript{66} Another study of nine patients with advanced CML receiving dasatinib 100–140 mg daily in the post-alloSCT period reported a lower response rate (four out of nine) and negligible toxicity, with only one patient interrupting dasatinib because of thrombocytopenia-related gastrointestinal bleeding.\textsuperscript{67} Overall, the data on 2G-TKI for the post-transplant relapse are too scarce to draw any firm conclusions.

A main limit to TKI use in the post-alloSCT relapse scenario is that most CML patients receiving transplant have often received multiple lines of treatment before alloSCT, experiencing either resistance or intolerance that had led to the ultimate transplant decision. Three studies compared DLI with TKI therapy (mainly imatinib) at first CML relapse after alloSCT.\textsuperscript{68-70} Despite the small numbers (31, 46, and 40 patients, respectively), all studies found TKI to be at least not inferior to DLI in terms of efficacy and superior in terms of safety, even if outcomes were poor in advanced-phase relapse, confirming a possible role of combination therapy. However, future trials are needed to compare different TKI, with and without DLI, to determine the most effective and safe treatment modality.\textsuperscript{71}

**CONCLUSION**

With the development of TKI, alloSCT has become a salvage therapy for a minority of CML patients, mostly those in CP. The current indication of alloSCT in CP is limited to cases failing ≥2 lines of TKI therapy. Also, for patients with advanced disease and cases harbouring a Thr315Ile mutation, alloSCT is a reasonable treatment option. Transplantation should be performed with an HLA-identical sibling or HLA-matched unrelated donor, or alternatively a haploidentical donor. Myeloablative conditioning is generally used in fit patients, while reduced-intensity conditioning and DLI enable transplantation in elderly patients and those with comorbidities. As a result, alloSCT remains the only proven curative approach in CML and, though limited, its use must be considered by physicians treating CML patients.

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