Multiple tyrosine kinase inhibitors before allogeneic stem cell transplantation for chronic myeloid leukemia: toxicity and efficacy in a single-center experience

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm associated with a unique cytogenetic abnormality characterized by a reciprocal translocation between chromosomes 9 and 22. This defective chromosome, known as the Philadelphia chromosome, contains the BCR-ABL1 fusion gene, which encodes a protein with uncontrolled tyrosine kinase activity. According to the current international guidelines, therapy with tyrosine kinase inhibitors (TKIs) remains the mainstay of treatment in patients with newly diagnosed CML.1 The introduction of TKIs resulted in a significant reduction of the number of allogeneic stem cell transplants (allo-SCTs) for CML. Nowadays, the decision on when to perform the transplant and who should undergo this procedure depends on the disease phase and the patient’s response to targeted therapy.2 Considering the toxicity profile of TKIs and potential selection of more aggressive clones during treatment, one may anticipate their detrimental effect on the post-transplant outcome; however, such negative impact has not been demonstrated so far.3

In this study, we present our data on the impact of the pretransplant TKI use on post-transplant outcomes in heavily pretreated patients with CML.

Patients and methods

The diagnosis of CML, response criteria, and monitoring were based on the European Leukemia Net recommendations.4 Post-transplant maintenance with TKIs was unavailable for the Polish patients. Molecular monitoring of the BCR-ABL transcripts was performed using the reverse transcriptase–quantitative polymerase chain reaction method, as described elsewhere.5 Informed consent was obtained from all participants included in the study. The ethics committee approval was not required as a transplant for CML is the standard of care.

Statistical analysis

Differences in median values between the study groups were determined using the Mann–Whitney test. Nonrelapse mortality (NRM) was defined as all deaths before disease recurrence. The distribution for overall survival (OS) was estimated using the Kaplan–Meier method and compared with the log-rank test. A P value less than 0.05 was considered significant. The time to event was assessed from the day of transplant. All calculations were performed with the Statistica software, version 12.0 (StatSoft Poland, Kraków, Poland).

Results

Patient characteristics

Thirty-nine patients (11 women and 28 men) with CML at the median (range) age of 42 (19–63) years underwent allo-SCT between the years 2009 and 2019. Twenty-six patients with CML were diagnosed in the chronic phase (CP), 6 in the accelerated phase (AP), and 7 in the blast crisis (BC).

Thirty-two patients with CML received imatinib mesylate as the first-line TKI after the median (range) time of 24 (0–2405) days from the diagnosis. The reasons for imatinib mesylate discontinuation included: lack of efficacy (n = 26), intolerance (n = 5), and the patient’s decision to stop taking the drug (n = 1). A second-generation TKI, nilotinib, was given to 18 patients and stopped after the median (range) time of 269 (14–1069) days owing to lack of efficacy (n = 13), intolerance (n = 4), and an unknown reason (n = 1). Thirty-one patients were receiving dasatinib for the median (range) time of 203 (13–1235) days, and it was...
Patients’ hematological status at transplant was as follows: CP1 in 13 patients, beyond CP1 (>CP1) in 22, and active AP / BC in 4. Twelve patients in the phase >CP1 had been in the AP / BC phase before, but remained in remission at transplant. Thirty patients achieved a less than major molecular response before transplant, 8 patients at least a major molecular response, and data were not available for 1 patient. The median (range) time from diagnosis to transplant was 1.9 (0.2–9.2) years.

Transplant data  Baseline characteristics of transplant recipients  Thirteen patients received transplants from a human leukocyte antigen (HLA)-matched sibling, and 26 from either a 10/10 HLA-matched unrelated donor (n = 14) or 9/10 HLA-mismatched grafts (n = 12). Peripheral blood was a source of stem cells in 36 patients (93%). In total, myeloablative conditioning was used in 25 patients, and reduced-intensity conditioning in 14. Graft-versus-host disease (GVHD) prophylaxis included cyclosporine and methotrexate.

Outcomes of transplant recipients  All patients except 1 individual were engrafted after the median (range) time of 16 (11–39) days. A platelet count greater than 20 × 10^9/l was achieved after the median (range) time of 13 (8–36) days. Acute GVHD developed in 32 patients (82%), and acute grade 3–4 GVHD was present in 14 (35%). Chronic GVHD developed in 6 patients (18%). Infectious complications were seen early after transplant in 19 patients and most commonly included grade 3/4 mucositis (n = 10), pneumonia (n = 5), BK polyomavirus–related hematuria (n = 4), Klebsiella pneumoniae bacteremia (n = 4), and Clostridium difficile infection (n = 1). The co-occurrence of acute GVHD and infections was demonstrated in 15 patients.

There were 4 deaths until day +30 after transplant. The causes of death were as follows: pneumonia with septic shock (n = 2), cerebral hemorrhage (n = 1), and steroid-resistant acute GVHD (n = 1). Two patients died of steroid-resistant acute GVHD between days +30 and +100 after the procedure. The median (range) age of the deceased patients was 47 (27–60) years. All except 1 received at least 2 TKIs before transplant. Three patients underwent a transplant in the phase >CP1.

At the last follow-up, 15 patients (38%) were reported as deceased. The main causes of death included disease relapse and/or progression (n = 4), infectious complications (n = 2), and steroid-resistant GVHD (n = 9). Nine out of 15 deceased patients were in the phase >CP1 at transplant, 4 in CP1, and 2 in BC. In total, there were 13 deaths (86%) within the first 2 years after transplant. Nonrelapse mortality was 28% at 2 years.

Twenty four patients (62%) were alive at the last contact and 23 remained in the hematologic and molecular complete remission. The median (range) follow-up from diagnosis and from the transplant was 4.1 (0.5–16.4) years and 18.8 (0.46–105.2) months, respectively. The median (range) follow-up in survivors was 38.2 (2.5–105.2) months.

The estimated 2-year OS for the entire study cohort was 65%, and the median OS was not reached. There was no difference in the 2-year OS between patients undergoing a transplant in the CP1, >CP1, and AP / BC phases: 69%, 60%, and 37%, respectively (P = 0.92). No difference was also demonstrated when patients with active AP / BC and AP / BC in remission were grouped together (68% for CP1, 66% for >CP1, and 61% for AP / BC). Detailed patients’ characteristics and transplant data are shown in Table 1.

Discussion  Owing to the introduction of TKIs, allo-SCT for TKI-naive patients with CML is no longer justified, and this procedure is currently reserved for a small number of patients who are refractory or intolerant to TKIs. In this study, a total of 39 patients underwent a transplant for CML in our center and all 3 available TKIs were given to 18 individuals (50%). Most patients discontinued TKIs because of lack of efficacy. Of note, approximately 40% of the study patients received TKIs combined with conventional chemotherapy used in the advanced phases of CML. Finally, more than half of the patients underwent a transplant beyond CP1. Although TKIs for CML were found to be generally safe, a proportion of patients discontinues the treatment due to unacceptable adverse effects leading to a switch to an alternative therapy. Some previous studies showed no increased toxicity of imatinib administered prior to the transplant. Furthermore, no negative effect of the second-generation TKIs in patients with CML before allo-SCT was demonstrated; however, the number of pretransplant TKIs may play a role. Based on the safety profile of TKIs, one may expect an increased risk of post-transplant complications affecting the cardiac or hepatic function in particular. Therefore, we focused on the safety aspects of transplants in the era of TKIs. Six patients (15%) from our study cohort died within the first 100 days after the transplant, mainly of immunosuppressive therapy-resistant severe acute GVHD (n = 3) or pneumonia followed by septic shock (n = 2). Briefly, 82% of our study population had acute GVHD, and approximately 50% developed infectious complications.

Surprisingly, we did not observe any case of veno-occlusive disease (VOD). Our findings are in contrast to a study by Piekarska et al., in which VOD was observed in 25% of the patients undergoing a transplant, reaching up to 67% in those with BC at transplant. Of note, VOD following allo-SCT for CML has not been recently reported by other authors.

Another issue is related to the high incidence of post-transplant grade 3 to 4 acute GVHD, which
In our study, NRM was 28% at 2 years after transplant and similar results were reported by other authors. However, NRM frequently depends on the CML phase and the number of TKIs administered prior to the procedure. 6.9

The estimated 2-year OS was 65% for the entire study cohort and our results were in line with those presented by the Japanese authors, who reported a 2-year OS of 64%. 6.9 By contrast, much better results were provided by some European teams, with OS exceeding 90% in patients undergoing a transplant in the CP1 phase. 6 The factors found to be associated with better outcomes include a less advanced disease phase, the achievement of complete molecular remission after the procedure, and the use of less than 3 TKIs before transplant. 6,10

The quiescent leukemic stem cells in CML may persist despite the achievement of a deep molecular response after TKI use, and, therefore, allo-SCT still remains a treatment method offering long-term benefits. 11 One should bear in mind that the adequate and early identification of a transplant candidate is a key step in reducing the peritransplant toxicity. In accordance with current recommendations, allo-SCT should be performed in patients with chronic-phase CML who are resistant or intolerant to multiple TKIs or in those with an insufficient recovery of hematopoiesis after TKI use. All patients presenting in the AP / BC phase or progressing to the AP / BC phase during TKI therapy should be considered for urgent allo-SCT. However, the achievement of the second or subsequent CP phase before transplant has a favorable impact on the post-transplant outcome. 12

Despite the relatively small number of patients included, our report indicated that allo-SCT may be a promising approach in some patients with CML in whom TKIs failed. However, one should be aware of post-transplant complications including the high risk of severe and fatal acute GVHD in particular.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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