Second-Generation Tyrosine Kinase Inhibitors Combined With Stem Cell Transplantation in Patients With Imatinib-Refractory Chronic Myeloid Leukemia

Yanmin Zhao, MD, Yi Luo, MD, Jimin Shi, MD, Zhen Cai, MD and He Huang, MD

Abstract: *Background:* Allogeneic stem cell transplantation (allo-SCT) remains a curative therapy for chronic myeloid leukemia with advanced diseases, but limited data exist on the efficacy of short-time 2nd-generation tyrosine kinase inhibitors (TKIs) used before and after allo-SCT for patients failing imatinib therapy. *Methods:* We present a single-center report of a series of 12 imatinib-refractory patients in advanced phases, 9 of whom harbored BCR-ABL1 mutations. All of them were treated with 2nd TKI, followed by allo-SCT. *Results:* Dasatinib or nilotinib reinduced complete hematologic responses in 11 patients and complete cytogenetic responses in 4 patients. All patients engrafted successfully. Five patients experienced acute graft-versus-host-disease (GVHD), including 4 with grade III-IV disease. Four patients experienced chronic GVHD, including 1 with extensive disease. Post-transplant prophylactic dasatinib or nilotinb was administrated in 9 patients and discontinued 1 year later, all of whom sustained complete molecular remission, even after a median follow-up of 13 months after withdrawal of the TKI. No hematologic relapse was observed. Four patients died: 1 of primary disease and 3 of transplant-related complications. After a median follow-up of 28 months (range, 12–37 months) after SCT, 8 (66.7%) of 12 patients are alive, including 7 with complete molecular remission. *Conclusions:* Allo-SCT has a satisfactory outcome when combined with 2nd-generation TKI, which could provide a good quality of remission before transplantation and prevent relapse after transplantation.

Key Indexing Terms: Second-generation tyrosine kinase inhibitors; Stem cell transplantation; Chronic myeloid leukemia; Kinase mutation; Accelerated phase; Blast crisis. **[Am J Med Sci 2014;347(6):439–445.]**

The tyrosine kinase inhibitor (TKI), imatinib mesylate, has become the 1st-line therapy for patients with chronic myeloid leukemia (CML); however, the emergence of imatinib resistance has become a matter of concern, especially for patients in the accelerated phase (AP) or blastic crisis (BC), when the rate of resistance to imatinib at 4 years increases to 70% to 90%.[1,2] The most common cause for imatinib resistance is point mutations in the kinase domain of BCR-ABL1. The administration of 2nd-generation TKIs might provide an effective approach for patients with BCR-ABL1 mutations.[3–6] Nilotinib (AMN107, Tasigna; Novartis Pharma, Basel, Switzerland) is a novel selective BCR-ABL1 inhibitor that was approved for use in patients with CML-chronic phase (CP) and accelerated phase (CML-AP) who are resistant to or intolerant of imatinib. Dasatinib (BMS354825, Sprycel; Bristol-Meyers-Squibb, New York, NY) is a potent, 2nd-generation, a dual SRC/ABL kinase inhibitor of BCR-ABL1 and is 325-fold more potent than imatinib, with an added advantage of being effective against all BCR-ABL1 mutations except T315I and F317L. Recent trials have shown that nilotinib induced a complete hematologic response (CHR) of 55% with a 32% major cytogenetic response (MCyR) rate in imatinib-resistant or intolerant AP-CML, whereas dasatinib induced a major hematologic response rate of 62%, with a 33% MCyR rate in imatinib-resistant or intolerant AP-CML, and a major hematologic response rate of 34%, with a 31% MCyR rate in BC-CML.[7–9] The excellent efficacy of 2nd-generation TKI has progressively justified its increased use in patients with imatinib-resistant patients, and even a minority of patients with excellent immediate and deep molecular response may benefit long-term and may be able to circumvent stem cell transplantation (SCT).

Despite the high efficacy of 2nd-generation TKI for patients with advanced CML, it is worthwhile that these drugs can neither eradicate advanced disease nor result in durable remissions. In particular, in patients in BC, progression-free survival on 2nd-generation TKI is short, with a median time of 6.7 months or less and a median overall survival (OS) of 5.3 to 11.8 months.[8] In contrast to drug therapy, allogeneic stem cell transplantation (allo-SCT) is capable of eradicating CML in the majority of patients and still plays an important role in advanced CML. However, the outcome of SCT in the advanced stage of CML is very disappointing. A retrospective multicenter study by the European Group for Blood and Marrow Transplantation demonstrated that the 2-year survival after transplantation was approximately 47% and 16%, respectively, for patients in AP and BC.[10] Poor survival is associated with a high rate of morbidity and relapse, which limits the success of SCT for advanced diseases. Thus, for imatinib-resistant patients in advanced stages, an alternative treatment strategy needs to be developed and aimed toward both overcoming imatinib resistance and providing a definitive cure.

To take advantage of both the curative potential of SCT and the high efficacy of target therapy, short-term treatment with 2nd-generation TKI followed by allo-SCT is recommended for patients in the advanced stages of CML. However, data on the effectiveness of prior treatment with 2nd-generation TKI on allo-SCT outcomes are limited, in particular, for those patients with BCR-ABL1 mutations. In addition to pretransplant 2nd-generation TKI, there are limited data available on the protective effect of post-transplant 2nd-generation TKI on relapse. It is also of interest to investigate the possible influence of these new agents on engraftment and treatment-related complications. Herein, we conducted a prospective study involving 12 patients in the advanced stages with imatinib-resistant CML, most of whom had BCR-ABL1 mutations. All the patients underwent an allo-SCT following treatment with short-time dasatinib or nilotinib and

From the Department of Hematology and Bone Marrow Transplantation Center, The First Affiliated Hospital of Zhejiang University, Hangzhou, China.

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Correspondence: He Huang, MD, 79 Qingchun Road, Department of Hematology and Bone Marrow Transplantation Center, The First Affiliated Hospital of Zhejiang University, Hangzhou 310003, China (E-mail: hehuang@medmail.com.cn).

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received post-transplant dasatinib or nilotinib therapy within 1 year to prevent relapse.

METHODS

Patients

Between January 2007 and January 2011, 12 patients in the advanced stages of CML, who were admitted to the First Affiliated Hospital of the Zhejiang University School of Medicine, entered this study. All eligible patients fulfilled the following criteria: aged 12 years or older; diagnosed with CML, as confirmed by the presence of the Philadelphia (Ph) chromosome or the BCR-ABL1 fusion gene; in AP or BC; imatinib treatment failure, defined as the absence of any hematologic response at 3 months, less than a CHR or absence of any cytogenetic response at 6 months, less than an MCyR at 12 months, less than a complete cytogenetic response (CCyR) at 18 months, or loss of CHR or CCyR at any time; gave informed consent. Exclusion criteria were as follows: pregnancy or lactation; development of grade ≥3 adverse events during TKI therapy; severe irreversible comorbidity, such as renal, hepatic, pulmonary, or cardiac disease; without suitable donors. All enrolled patients were given dasatinib or nilotinib for 1 to 3 months and were then referred for myeloablative allo-SCT. Post-transplant prophylactic dasatinib or nilotinb was administrated to prevent relapse and discontinued 1 year later. The prospective study protocol (Appendix 1) was approved by the Institutional Review Board and registered in the Chinese Clinical Trial Registry (registration number ChiCTR-ONC-12002856).

Response Assessment and Chimerism Studies

To assess treatment response, patients were followed up every 4 weeks during 2nd TKI treatment, and at 1, 3, 6, 9, 12, 18, and 24 months after transplantation, as well as once a year thereafter, using bone marrow cytology, cytogenetics and real-time quantitative polymerase chain reaction (RQ-PCR) analyses for BCR-ABL1 transcripts.

According to standard criteria,[11] the cytogenetic response was categorized as follows: complete (CCyR, Ph+ 0), partial (PCyR, Ph+ 1%–34%), major (MCyR, Ph+ 0%–34%), minor (mCyR, Ph+ 35%–65%), minimal (minCyR, Ph+ 66%–95%) and none (Ph+ 96%–100%). Molecular responses were defined by the ratio of BCR-ABL1 gene transcripts to ABL1 gene transcripts on RQ-PCR analyses on bone marrow aspirate or peripheral blood. A complete molecular response was defined as the absence of BCR-ABL1 transcripts. A major molecular response was defined as BCR-ABL1/ABL1 ratio <0.05%. RQ-PCR analysis was performed as previously described,[12] and the sensitivity of RQ-PCR is at least 0.01%. Chimerism status was analyzed using amplification of short tandem repeats. Mutation analysis was performed using nested PCR-based sequencing of the entire BCR-ABL1 kinase domain.[13]

Second-Generation TKI Therapy

Patients were treated with 70 mg of dasatinib twice daily or 400 mg of nilotinib twice daily for 1 to 3 months before transplant. After transplantation, prophylactic administration of dasatinib or nilotinib was commenced on day +90 in engrafted patients to prevent relapse and discontinued at 15 months after transplantation. TKI-related toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0). Criteria for response and treatment failure were defined according to recommendations of the European LeukemiaNet.[11]

Conditioning Regimen and Graft-Versus-Host-Disease Prophylaxis

For HLA-matched and 1-locus mismatched transplantation, the conditioning regimen was intravenous busulfan (BU) (3.2 mg/kg/d; days −7 to −4) and cyclophosphamide (CY) (60 mg/kg/d; days −3 to −2). For HLA-haploidentical transplantation, the conditioning regimen was a modification of BU/CY and antithymocyte globulin (ATG) and consisted of the following: cytosine arabinoside (4 g/m^2/d; days −10 to −9); intravenous BU (3.2 mg/kg; days −8 to −6); CY (1.8 g/m^2/day; days −5 to −4); oral semustine (250 mg/m^2; day −3); rabbit ATG (Fresenius, Bad Homburg, Germany) (2.5 mg/kg/d; days −4 to −1). Cyclosporin A (CsA), mycophenolate mofetil (MMF) and short-term methotrexate (MTX) were used for the prevention of acute graft-versus-host-disease (aGVHD). CsA was scheduled to be given at 2.5 mg/kg/d intravenously from day −7, with a target blood level of 200 to 300 ng/mL. CsA was tapered from day +45 according to chimeric status and evidence of GVHD, and discontinued by 6 months. MMF was started orally at 500 mg/d on day +1 and withdrawn on day +28 for HLA-matched sibling transplants; while for unrelated donor transplants, MMF was tapered from day +45 and discontinued on day +100. In haploidentical transplants, MMF was started on day −9, tapered from day +60 and discontinued until day +100. MTX was given at 10 mg/d on days +1, +3 and +6. An additional dose of MTX was administered on day +9 in haploidentical transplants. Patients who survived 100 days or longer were monitored for chronic GVHD (cGVHD). Acute GVHD and chronic GVHD were graded according to the consensus criteria.[14] Primary treatment of GVHD consisted of systemic corticosteroids.

Statistical Analysis

Descriptive statistics were used in this study. OS was calculated using Kaplan-Meier analysis from the time of transplantation to the date of death or the last contact for living patients. Transplant-related death was defined as death that occurred after transplantation because of any complication other than relapse or progression of the primary disease. Data analysis was performed using SPSS version 11 for Windows (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

The main clinical features of the 12 patients from the study are summarized in Table 1. Four patients were in AP and 8 patients were in BC. Seven patients were males and 5 were females. The median age at transplant was 36 years (range, 12–48 years). Eleven patients had a history of CP, and 1 patient had a history of AP, with a median interval period of 48 months (range, 6–163) from diagnosis to disease progression. All patients received imatinib (2 as initial therapy, 10 after interferon or other treatment failure) and had become resistant. Briefly, 7 patients lost the cytogenetic response and progressed to the advanced phase on imatinib. The other 5 patients (patients 5, 6, 8, 7 and 11) did not receive TKIs during the CP, and while progressing to BC imatinib was administered but showed either no response or a short-term response. The median duration of imatinib therapy was 15 months (range, 3–81 months).

BCR-ABL1 Mutations in CML Patients

Among the 12 patients with resistance to imatinib, BCR-ABL1 mutations were detected in 9 patients. The most frequent mutant site was Y253, which occurred in 4 patients (Y253H in patients 5, 6 and 7, Y253F in patient 8). The other mutations

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