

Second Generation Tyrosine Kinase Inhibitors Combined With Allogeneic Hematopoietic Stem Cell Transplantation Improve the Prognosis of Patients with Chronic Myelogenous Leukemia in Blast Crisis

Zhengping Yu¹, Jia-hua Ding^{1*}, Aining Sun², Zheng Ge¹, Baoan Chen¹ and Wenduo He¹

¹Department of Hematology, Key Department of Jiangsu Medicine, Zhongda Hospital, Medical School, Southeast University, Nanjing, China

²Hematology Division, Suzhou Medical University, Suzhou, China

Abstract

The prognosis for patients with Chronic Myelogenous Leukemia (CML) in Blastic Crisis (BC) is poor, with a median survival of only 3-6 months. Blast crisis (BC) is highly refractory to therapy and has a poor prognosis. To determine the efficacy of TKIs-II combined with allogeneic hematopoietic stem cell transplantation (allo-HSCT) in CML BC, we present four consecutive, recent cases of CML BC in which TKIs-II were used before or after allo-HSCT. Patient 1, a 28-year-old male received a HSCT from a half-matched-donor. Patient 2, 3 received an HLA-identical unrelated-donor HSCT. To date, patients 1,2,3 and 4 have survived postprocedure for 22, 23, 21 and 25 months, respectively. We conclude that compared with imatinib, TKIs-II may reduce tumor burden more rapidly and thoroughly when administered before or after allo-HSCT and enhance the graft versus leukemia effect, prolonging the long-term survival of patients. We speculate that GVL and tumor burden are negatively correlated.

Keywords: Second generation tyrosine kinase inhibitors; Allogeneic hematopoietic stem cell transplantation; Chronic myelogenous leukemia; Blast crisis

Introduction

Chronic Myelogenous Leukemia (CML) typically progresses through 3 phases: the Chronic Phase (CP), the Accelerated Phase (AP), and the Blast Crisis (BC). The therapy of blast crisis in patients with CML is a major challenge, with limited chances of success. Historically, therapy for BC has used combination chemotherapy regimens. This treatment is frequently associated with significant toxicity and mortality, and with short remission durations, and low long-term survival rate. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) induces durable remission in less than 10% of CML patients with BC [1]. Even the achievement of complete hematologic remission (CHR) with imatinib before transplantation does not improve the prognosis of CML in BC, probably due to the frequent development of imatinib resistance in BC [2]. Second-generation tyrosine kinase inhibitors (TKIs-II) alone induce CCyR in 20–40% of patients [3,4]. However, the majority of these patients relapse within 1 year, and the median survival is only 8 months [4]. Thus, although TKIs-II is an effective agent in this setting, it is necessary to improve these results. Few reports [5] are available about the efficacy of TKIs-II combined with allo-HSCT in CML BC. In the current study, we analyzed the effect of treatment with TKIs-II before or after allo-HSCT in four CML patients in BC and discussed the possible mechanisms.

Materials and Methods

Patients

Patient 1: A 28-year-old man presented with priapism in 2009. A complete blood count showed that his White Blood Cell (WBC) count was $444 \times 10^9/L$. A bone marrow aspirate examination revealed 0.01% myeloid blasts. Fluorescence in situ hybridization (FISH) showed that 90% of the cells tested were positive for the BCR/ABL fusion gene, and the BCR-ABL: ABL ratio detected by reverse transcription polymerase chain reaction (RT-PCR) was 42%. A diagnosis of Chronic-Phase (CP) CML was made. The patient commenced treatment with 400 mg/day imatinib (Novartis US). After 3 months, the Philadelphia (Ph)

chromosome was detected on cytogenetic studies of bone marrow specimens, and the BCR-ABL: ABL ratio detected by RT-PCR was 0.53%. In December 2010, the BCR/ABL fusion gene was detectable on FISH 0/500, and the patient was deemed to have achieved a CCyR. However, 19 months after commencing treatment, he showed a significant increase in the BCR-ABL mRNA level (BCR-ABL:ABL ratio, 55%) and was diagnosed with a cytogenetic relapse. Imatinib was discontinued, and he started therapy with nilotinib at a dose of 400 mg twice daily (Novartis US). However, 2 months later, progression to the blast phase (BP; hematologic and cytogenetic relapse) occurred, with detection of the kinase domain mutations M244V and Y253H. His peripheral blood WBC count increased to $69.45 \times 10^9/L$ with 58% blasts, and bone marrow cytogenetics revealed Ph-positive cells in all metaphases analyzed. The patient was then administered a course of daunorubicin (60 mg i.v. on days 1 to 3, Pfizer US) and cytarabine (200 mg on days 1 to 7, Pharmacia Italy) together with imatinib 600 mg daily. However, the effects were unsatisfactory, and the percentage of blasts in the peripheral blood increased to 79%. In November 2011, he commenced treatment with 140 mg/day dasatinib (Bristol-Myers Squibb Company, US). After only 1 week of this treatment, his peripheral blood WBC count decreased to $1.14 \times 10^9/L$, and a major Cytogenetic Response (MCyR) was achieved after 5 months of treatment (BCR/ABL fusion gene detected in 1.3% of cells on FISH, and 500 white blood cells were obtained). He then underwent a half-matched, related-donor, Stem Cell Transplantation (SCT) in May 2012;

***Corresponding author:** Jia-Hua Ding, MD, PhD, Department of Hematology, Affiliated Zhongda Hospital Medical College of Southeast University, Ding Jia Qiao, Number 76, Nanjing, 210009, China, Tel: 86 25 83262460; Fax: 86 25 83262461; E-mail: zll313628@sina.com

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the 4.63×10^6 /kg CD34+ cells from his mother and transplanted, and the BuCy (the dose of busulfan 0.8 mg/kg was administered every 6 h for a total of 12 doses, Otsuka Pharmaceutical, Japan. Cyclophosphamide 60 mg/kg/day were administered intravenously for 2 days following the completion of the busulfan treatment, Shanghai Institute of Health Industry. simustine (MeCCNU, 250 mg/m², a single dose oral. Swiss Pharmaceutical, Zhejiang). Conditioning regimen was used when cells were transplanted.

Patient 2: A 52-year-old man was diagnosed with CP CML in 2000. He was initially treated with hydroxyurea, and in April 2002, underwent HLA-identical, sibling, HSCT; the donor was his younger brother. However, he continued to have pancytopenia after the transplantation, and FISH revealed the BCR/ABL fusion gene in 5% of cells. Chimerism analysis showed mixed chimerism. He underwent splenectomy [6], and 6 months later, his complete blood count gradually returned to normal. Moreover, the BCR/ABL fusion gene was now undetectable on FISH. Chromosome analysis of a bone marrow aspirate showed complete donor conversion. Thus, the patient achieved a CCyR. However, in June 2011, his WBC and platelet counts increased to 17.48×10^9 /L and 1801×10^9 /L, respectively, with a bone marrow aspirate showing 11.6% myeloid blasts. He also had cytogenetic evidence of the t (9;22) (q34;q11) translocation and progressed to the accelerated phase (AP). He was treated with interferon- α at a dose of 3,000,000 IU twice weekly, but without satisfactory effects. In July 2011, he received 600 mg/day imatinib but progressed to BC, and FISH showed that the BCR/ABL fusion gene was present in 45.6% cells, while chimerism analysis showed that the percentage of donor genes was 19%. In December 2011, treatment with nilotinib was commenced at a dose of 400 mg twice daily, and an MCyR was achieved after only 3 months of treatment (BCR/ABL fusion gene detected in 5.3% cells on FISH). Fortunately, the patient had a second opportunity to undergo to a matched, unrelated-donor SCT in March 2012. the number of CD34+ cells 5.38×10^6 /kg were transplanted, and the patient was discharged after hematopoietic recovery.

Patient 3: A 36-year-old man was diagnosed with CP CML in 2000. He was initially treated with interferon- α and imatinib for 2 years, and achieved a partial cytogenetic response (PCyR). However, in 2005, he progressed to the AP. Later that year, he underwent an 8-of-10 HLA-matched, unrelated-donor, HSCT. The 5.96×10^6 /kg CD34+ and 29.87×10^9 /L white blood cells were obtained and transplanted. Graft versus host disease (GVHD) prophylaxis consisting of cyclosporine and dexamethasone was administered. Nevertheless, he developed a grade 4, acute GVHD of the skin, and finally recovered after treatment with cyclosporine, dexamethasone and immunoglobulin. He also developed chronic GVHD of the liver, kidney and eyes. In April 2012, his WBC and platelet counts increased to 19.14×10^9 /L and 939×10^9 /L respectively, with a bone marrow aspirate showing 21% myeloid blasts. FISH detected the BCR/ABL fusion gene in 78% cells. Chimerism analysis showed that the percentage of donor genes was 19%. The patient progressed to the BC, and was treated with 100 mg/day dasatinib.

Patient 4: A 33-year-old woman diagnosed with CP CML in her 29th week of gestation in May 2011. A complete blood count showed the following: WBC count, 518.4×10^9 /L with 5% blasts; hemoglobin, 6.0 g/dl; and platelets, 383×10^9 /L. Bone marrow aspirate examination revealed 1.5% myeloid blasts. FISH showed the BCR/ABL fusion gene in 88.6% of cells and a possible deletion of the ASS gene. The patient was initially treated with leukapheresis and hydroxyurea. One month later, her peripheral blood WBC count decreased to 1.14×10^9 /L, while her platelet count increased to 619×10^9 /L. At this stage, she opted for an induced abortion. Two months after the initial diagnosis, she underwent

an allo-HSCT; the donor was her HLA-identical sister. the 4.97×10^6 /kg CD34+ cells were obtained and transplanted, and the BuCy conditioning regimen was used when cells were transplanted (BuCy: the dose of busulfan 0.8 mg/kg was administered every 6 h for a total of 12 doses. Cyclophosphamide 60 mg/kg/day were administered intravenously for 2 days following the completion of the busulfan treatment, simustine MeCCNU, 250 mg/m², a single dose oral). One month after the transplantation, CCyR was achieved; the BCR/ABL fusion gene was undetectable on FISH, and chimerism analysis showed complete donor conversion. However, in April 2012, she developed BC, and the bone marrow aspirate showed 30% myeloid blasts. FISH detected the BCR/ABL fusion gene in 80% cells, and chimerism analysis of the bone marrow showed 30% donor genes. In May 2012, she began treatment with nilotinib at a dose of 200 mg twice daily, which was subsequently reduced to 300 mg/day due to intolerance. The characteristics of the patients are listed in Table 1.

Donor hematopoietic stem cell mobilization and isolation

Using G-CSF (10 μ g/kg •d) the mobilization of peripheral blood stem cell donor. Monitoring of blood cell every day, in the fifth days on acquisition. Using COBE Spectra™ blood cell separator machine, Auto-PBSC collection procedures (software version 6.1) were apheresis. Femoral venous access catheter for blood collection, held until the end of the collection. Treatment volume was 2 times the total blood volume, flow rate of 35 ~ 50 ml / min, with ACD-A solution as an anticoagulant, the blood flow velocity and the ratio of (10 to 12): 1. Acquisition time of 200 to 300 minutes, collecting about 200 ml. Surgery for oral or intravenous calcium supplements to prevent hypocalcemia caused by anticoagulants. Flow chamber and sent for collection of blood cell morphology analysis room count, when gathering material mononuclear cells ($5.0 \sim 8.0$) $\times 10^8$ /kg, CD34 + cells ($2.0 \sim 4.0$) $\times 10^6$ /kg the end of with the collection. The peripheral blood stem cells rapidly through the patient's jugular vein catheter quickly infusion to the patient, before reinfusion give 5% sodium bicarbonate 150 ml and dexamethasone 2.5 mg intravenous drip.

Donor hematopoietic stem cell transplantation

Four patients diagnosed CML in blastic crisis were treated with allogeneic peripheral blood stem cell transplantation in this study. The busulfan and cyclophosphamide (BU-CY) conditioning regimen consisted of busulfan (0.8 mg/kg) administered every 6 h for 12 days and cyclophosphamide (CTX) (60 mg/kg) administered once a day for 2 days. Each donor received granulocyte colony stimulating factor (G-CSF) (300 μ g) twice a day for 5 days for mobilization. A median of 12 L (3 times the total blood volume) of donor blood was processed and collected. Each recipient received monocyte count (MNC) $8 \pm 2 \times 10^8$ /kg and/or $5 \pm 1 \times 10^6$ /kg CD34+ cells of body weight. All patients and their donors gave written informed consent, and this study was approved by Institutional Review Board and the Ethics Committee at Southeast University.

GVHD prophylaxis

All patients received immunosuppressive therapy before allo-HSCT.

Patients	Patient 1	Patient 2	Patient 3	Patient 4
age	28	52	36	33
BCR/ABL (Fish) before treatment	55%	45.6%	78%	80%
BCR/ABL (Fish) after treatment	1.3%	5.3%	0	0
BCR/ABL (PCR) before treatment	42%	32%	35%	47%
BCR/ABL (PCR) after treatment	0.53%	1.2%	0.01%	0.01%

Table 1: Characteristics of patients, TKIs-II combined with allo-HSCT.

Cyclosporin A (CsA) and methotrexate (MTX) were administered as a GVHD prophylaxis treatment. The regimen consisted of 3 mg/kg of intravenous CsA with a target blood level of 200-400 ng/L and a short course treatment of MTX (15 mg on day 1 and 10 mg on days 3, 6, and 11, respectively). If GVHD was successfully treated at that point, the dose was gradually reduced, and ended on the sixth month.

Engraftment and chimerism analysis

The neutrophil engraftment start point was defined as the first day of 3 consecutive days when the absolute neutrophil count (ANC) exceeded $0.5 \times 10^9/L$. The platelet engraftment start point was defined as the first day of 3 consecutive days when the platelet count exceeded $20 \times 10^9/L$ independently without a platelet transfusion. Donor cell engraftment was assessed in Peripheral Blood (PB) nucleated cells by quantitative Polymerase Chain Reaction (PCR) of variable numbers of tandem repeats, blood cell counts, Bone Marrow (BM) examination, cytogenetic and molecular analysis.

Result

One month after the transplantation, the patient 1 showed a Complete Molecular Response (CMR) and has remained stable for 22 months without dasatinib, BCR/ABL fusion gene detected in 0/500 cells on FISH, RT-PCR was 0%. Two months after this, the patient 2 achieved a CCyR, and the BCR/ABL fusion gene was undetectable on FISH after transplantation two months. Three months after the transplantation, he achieved a CMR and has remained progression free and BCR/ABL fusion gene negative for 23 months. The patient 3 was treated with dasatinib. After 1 month of treatment, his complete blood count returned to normal. After 2 months, he achieved an MCyR, and the BCR/ABL fusion gene was detected in only 4.0% of cells on FISH. After 3 months, he achieved a CCyR, and the BCR/ABL fusion gene was detectable 0/500 on FISH, RT-PCR was 0.01%. At this stage, chromosome analysis of the bone marrow showed complete donor conversion. The patient has been in a stable condition for 21 months, and the BCR/ABL fusion gene has remained undetectable on FISH. In May 2012, the patient 4 began treatment after 2 weeks, her peripheral blood cell counts had returned to normal. One month later, she achieved a CCyR, with 0% myeloid blasts in the bone marrow. The BCR/ABL fusion gene was detectable 0/500 on FISH, RT-PCR was undetectable and chimerism analysis showed complete donor conversion. She has been stable and progression free achieved a durable 25 month follow-up.

Discussion

Presentation in BC is uncommon but carries a poor prognosis. BC is less responsive to conventional chemotherapy, and the post-HSCT survival rate among patients with BC is low due to high relapse rates and treatment-related mortality. Data on transplantation during BC are discouraging. The European Group for Blood and Marrow Transplantation (EBMT) [7] analyzed 167 CML-BC patients who had undergone allo-HSCT between 1980 and 1990. They found that the 2-, 5-, 10- and 15-year Overall Survival (OS) rates were 21%, 18%, 16% and 14%, respectively [7].

Some studies have suggested that imatinib has no deleterious or beneficial effect on transplant outcomes [8]. Lee et al. analyzed 216 IM⁺ and 216 IM⁻ allograft recipients with advanced-phase CML suggested that the use of imatinib before HSCT was not associated with treatment-related mortality, relapse, leukemia-free survival or overall survival [9].

Dasatinib is a multitargeted tyrosine kinase inhibitor of BCR-ABL and SRC Family Kinases (SFKs). It effectively inhibits the active

and inactive conformations of BCR-ABL and also inhibits the SFKs implicated in imatinib resistance. In vitro studies have shown that dasatinib has 325-fold greater potency than imatinib in cells transduced with unmutated BCR-ABL and is active against all tested BCR-ABL mutations, except one (T315I), that confer imatinib resistance [10]. In a phase II clinical trial [3], dasatinib was administered to patients with imatinib-resistant and imatinib-intolerant CML-BC. The results of an 8-month follow-up showed that dasatinib induced major hematologic responses in 34% Myeloid BP (MBP)-CML and 31% lymphoid BP (LBP)-CML patients, MCyR in 31% MBP-CML and 50% LBP-CML patients and CCyR in 26% MBP-CML and 43% LBP-CML patients. The myeloid BC (MBC)-CML and Lymphoid BC (LBC)-CML patients who achieved major hematologic responses had not experienced disease progression at the 8-month follow-up [3]. These outcomes were similar to those of another international, phase II clinical trial [11], in which dasatinib was administered orally (70 mg twice daily) to 10⁵ MBP-CML and 48 LBP-CML patients. After a minimum follow-up of 12 months, major hematologic responses were induced in 34% MBP-CML and 35% LBP-CML patients. MCyR was attained in 33% MBP-CML and 52% LBP-CML patients, while CCyR was attained in 26% MBP-CML and 46% LBP-CML patients. The median progression-free survival was 6.7 months in MBP-CML patients and 3.0 months in LBP-CML patients. The median OS was 11.8 months in MBP-CML patients and 5.3 months in LBP-CML patients [11].

TKIs-II can produce a rapid and significant effect in CML BC. CML patients undergoing allo-HSCT may receive a TKI-II (dasatinib or nilotinib) after failure of imatinib treatment. Jabbour E analyzed the outcomes of 12 patients, most of whom had advanced CML (AP, 6; BP, 5) and who had received dasatinib (n=2), nilotinib (n=7) or both (n=3) before undergoing HSCT. Of the 12 patients, nine achieved a molecular response, including four complete and five major responses. After a median follow-up of 10 months, seven patients were alive and showed a molecular response, while five patients had died, including four who died of disease progression [5]. The authors concluded that previous treatment with a TKI-II did not increase transplant-related toxicity. A high rate of molecular responses was achieved after HSCT, despite the fact that all patients underwent transplantation while they were in an imatinib-refractory, advanced disease stage [5]. TKIs-II have the potential advantage of rescuing patients after failure of imatinib therapy, and allowing these patients to undergo transplantation with a smaller disease bulk, which should improve disease control after HSCT [5]. Breccia et al. administered pre-SCT dasatinib treatment to two CML-BC patients (treatment duration, 8 and 6 months), who achieved a CCyR and a CHR [12]. Similarly, Gotoh et al. [13]. reported the case of a patient with imatinib- and nilotinib-resistant, Ph-positive CML-BC. Before dasatinib therapy, this patient was found to have a F359V BCR-ABL mutation. He was treated with dasatinib before allo-HSCT, and eventually achieved molecular remission [13].

The GVL effect is believed to destroy leukemia cells through an antitumor T-cell and natural killer (NK)-cell immune response. A mechanism has been proposed to account for antitumor T-cell and NK-cell dysfunction: secretion of suppressive factors such as transforming growth factor β 1 [14,15] and interleukin 10 [16], in the leukemia microenvironment. Thus, for a lower leukemia burden, the GVL effect will be greater due to the less stringent downregulation of the antitumor T-cell immune response mediated by the decreased secretion of suppressive factors. Some reports have suggested that high-dose chemotherapy induced severe cytoreduction, allowing the development of a more potent GVL effect [17,18]. A recent study has indicated that the achievement of a MCyR before allo-HSCT may improve the

prognosis of CML-BC patients [19]. Another report has indicated that dasatinib might enhance the GVL effect [20].

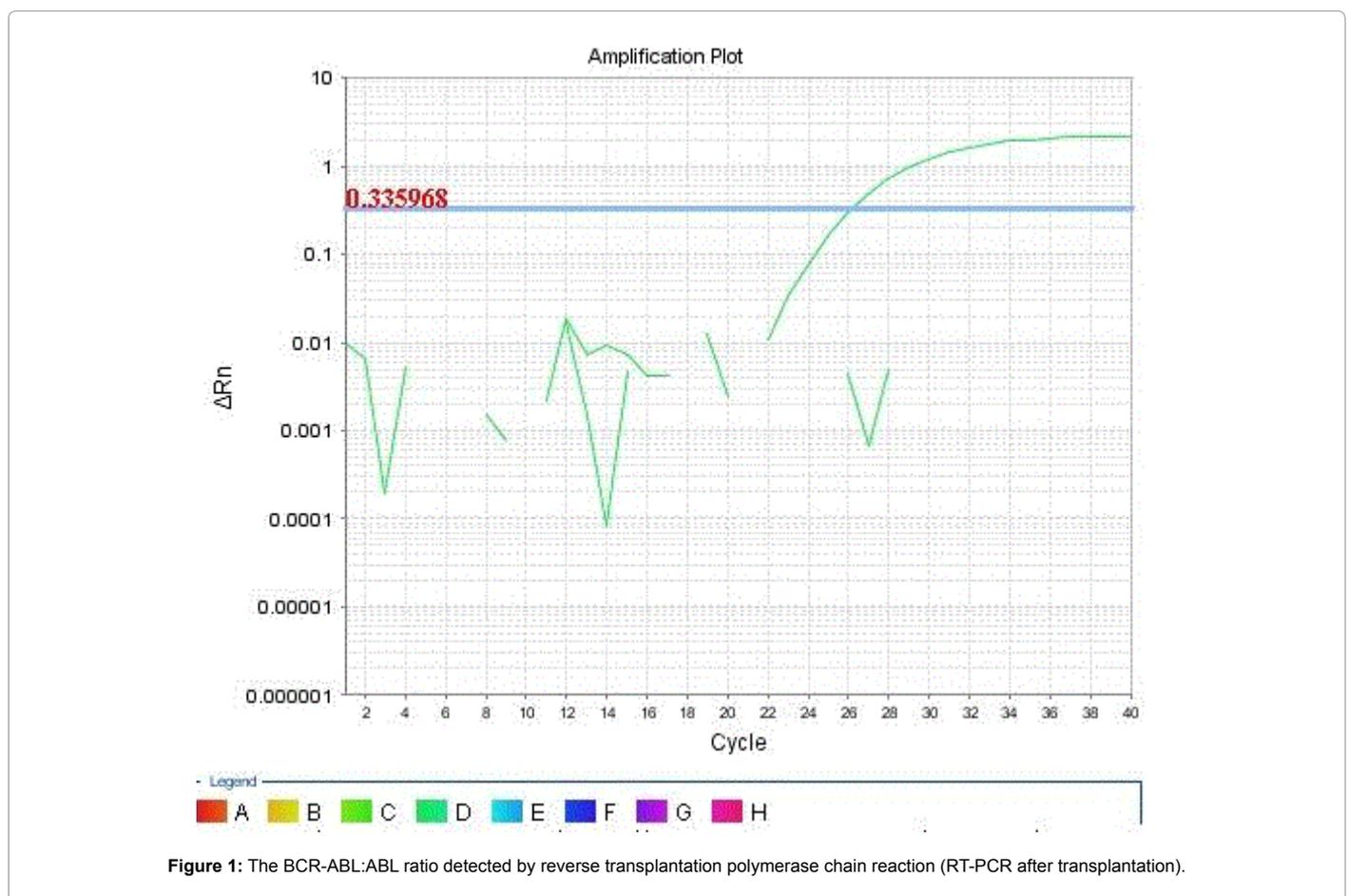
In our study, patients 1 and 2 received imatinib during BC or AP, but did not achieve remission or became worse. However, both patients achieved MCyR soon after their treatment regimen was changed to TKIs-II. With a smaller disease bulk, the subsequent allo-HSCT induced CMR in both patients (after 1 and 3 months). Both patients are alive and disease free survival at 22 and 23 months after allo-HSCT. It has become clear that high-dose chemotherapy does not eradicate malignancy in many CML patients and that the therapeutic benefit of allo-HSCT is largely related to an associated immune-mediated, Graft-Versus-Leukemia (GVL) effect. Compared with imatinib, TKIs-II may induce cytogenetic or molecular responses more quickly and more effectively in CML patients [21,22], reducing the pretransplant tumor burden to a greater degree [23]. Therefore, we speculate that TKIs-II can reduce the pretrans-plant tumor burden to a greater degree and enhance the effect of GVL (Figure 1), GVL and tumor burden are negatively correlated. Consequently, the success rate of allo-HSCT may be increased, and the relapse rate may be reduced.

The prognosis of patients who relapse into BC after allo-HSCT is very poor. Donor lymphocyte infusion (DLI) is considered the standard management for CML relapse after HSCT, but this treatment has very limited success when administered to CML patients who relapse with BC [24,25]. Imatinib is now an alternative to DLI in the management of patients relapsing after transplantation, but this treatment also has a poor outcome in patients who relapse with BC. Recently, the Chronic

Leukemia Working Party of the EBMT reported a retrospective analysis of 128 patients treated with imatinib for relapse after allogeneic transplantation. The CCyR was 22% for the patients in BC, at a median follow-up of 9 months; the estimated 2-year survival for BC patients was only 12% [26]. DeAngelo et al. administered imatinib to 15 CML patients who relapsed after transplantation, including four patients in the AP and one in the BP. Only one of these patients achieved CMR (Figure 2) [27].

In the current study, both patients 3 and 4 underwent allo-HSCT and received TKIs-II after they relapsed with BC. CHR was achieved in several weeks, and CCyR was achieved after 3 months and 1 month in patients 3 and 4, respectively. In both patients, chromosome analysis of the bone marrow showed complete donor conversion. In patient 3, we observed that the chronic GVHD was alleviated during the recurrence of CML. As the CML was treated, the cGVHD re-appeared. Both patients are alive and remain progression free after 21 and 22 months of follow-up.

Several factors might have contributed to our superior TKIs-II combined with transplantation outcomes. First, the initial reduction of the leukemia load via short-term treatment with TKIs-II as a bridging therapy seemed to result in lower transplantation-related mortality and better chances of long-term survival. Secondly, BC patients achieved a second CP with short-term TKIs-II therapy before transplantation with a speed reduced disease burden. Thirdly, TKIs-II combined with HSCT by minimal residual disease levels might have contributed to decrease relapse and improve survival. In addition, TKIs-II combined with allo-



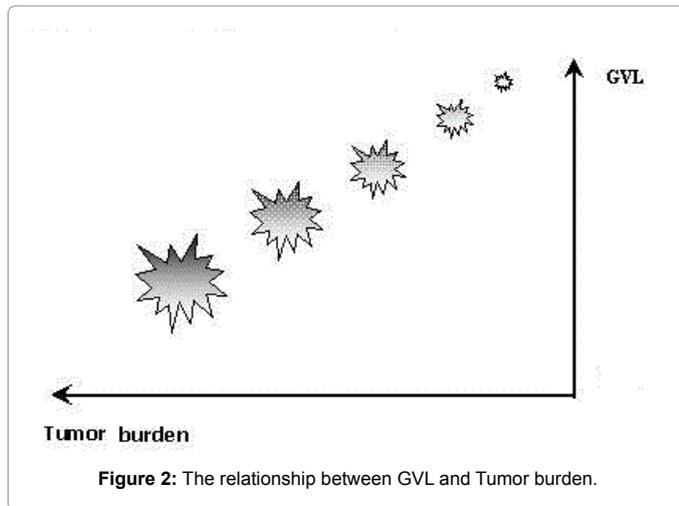


Figure 2: The relationship between GVL and Tumor burden.

HSCT also delivered a higher quality of molecular response than TKIs-II alone.

It has been suggested that the GVL effect is more likely to occur after the achievement of complete donor chimerism [28]. Compared with imatinib, TKIs-II can eliminate leukemic clones resistant to the GVL effect in a shorter time, reducing disease burden to levels below cytogenetic or molecular detection more quickly. The GVL effect mediated by antitumor T-cell and NK-cell immune responses may be re-induced because of the decreased secretion of suppressive factors. An efficient GVL effect may durably suppress residual CML progenitors and reduce recurrence rates. Thus, we suggest that compared with imatinib therapy, early use of TKIs-II may quickly and effectively induce a more long-lasting remission in patients who have relapsed with BC after HSCT. We speculate that the GVL effect may be re-induced because of the decreased disease bulk.

Conclusion

Compared with imatinib, TKIs-II may reduce tumor burden more quickly and to a greater extent (a cytogenetic or molecular remission) and enhance the GVL effect. This enhanced effect may in turn increase the success rate of allo-HSCT and reduce recurrence. DLI has a very limited success in the treatment of CML patients who relapse with BC after allo-HSCT. In such patients, the early use of TKIs-II can eliminate the residual leukemic clones, and reduce the disease burden to levels below cytogenetic or molecular detection. The GVL effect mediated by antitumor T-cell and NK-cell immune responses may be re-induced. This enhanced GVL effect may durably suppress residual CML progenitors after HSCT and reduce recurrence rates. Therefore, we suggest that the reduction of tumor burden using second-generation tyrosine kinase inhibitors, in combination with stem cell transplantation, favorably alters the prognosis of CML in BC. Further well-designed, randomized studies involving a large number of patients are required to evaluate this strategy.

Author Contribution

Jiahua Ding designed and performed the research. Analyzed the data and wrote the paper with Zhengping Yu.

Conflict of Interest

The authors declare no competing financial interests.

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