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Original Article

Prior exposure to imatinib does not impact outcome of allogeneic hematopoietic transplantation for chronic myeloid leukemia patients: a single-center experience in china

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Abstract: Objective: We conducted a retrospective single-center study of 106 patients to investigate the impact of prior exposure to imatinib before allogeneic hematopoietic stem cell transplantation (allo-HSCT) on outcome of HSCT for chronic myeloid leukemia (CML) in china. Methods: Patients were divided into imatinib and non-imatinib group according to whether receiving imatinib therapy before transplantation or not. Hematopoietic engraftment, prognosis, congestive heart failure (CHF), hepatic veno-occlusive disease (HVOD), graft versus host disease (GVHD), hemorrhagic cystitis and infections were compared between the two groups in early stage of transplantation (within 100 days after transplantation). Results: Compared to non-imatinib group, imatinib group neither had a significantly longer engraftment time nor higher incidence of HVOD, GVHD, hemorrhagic cystitis and infections ($P > 0.05$). However, imatinib group tended to have a statistically higher incidence of CHF (29.6% vs 8.6%, $P = 0.037$) and a higher 0.5-year transplant-related mortality (TRM) (27.8% vs 5.9%, $P = 0.001$). The estimated 10-year relapse-free survival (RFS) and 10-year overall survival (OS) were not statistically significant between the two groups (79.6% vs 62.4% $P = 0.432$, 68.9% vs 55.5% $P = 0.086$, respectively). Conclusion: Thus, prior exposure to imatinib before transplantation does not influence the hematopoietic engraftment and incidence of early transplant-related complications. While, imatinib therapy pre-HSCT probably increases the risk of CHF and TRM in early stage of post-HSCT, and this effect can be enhanced in older age patients. However, Imatinib therapy doesn't impact RFS and OS on a long view.

Keywords: Imatinib, chronic myelogenous leukemia, allogeneic hematopoietic stem cell transplantation, early transplant-related complications, congestive heart failure

Introduction

Chronic myelogenous leukemia (CML) is a malignant clone disease which occurs in the hematopoietic stem cells [1]. The treatment goal is to achieve complete cytogenetic response (CCyR) as soon as possible and deeper molecular remission, and improve life quality and gain functional cure [2, 3]. Allo-HSCT is currently the only way to completely cure CML. While, since the tyrosine kinase inhibitors (TKIs) such as imatinib mesylate emerged, the first-line therapy status of allo-HSCT in the treatment of CML is being challenged, and allo-HSCT is downgraded to the second line treatment of CML by the national comprehensive cancer network (NCCN) [4-6]. However, TKIs drugs such as imatinib is extremely expensive, most of the patients in China could not afford for a long time, and during the period of taking imatinib, there are still many patients with CML developing disease progression or resistance. Chinese CML patients are usually younger than westerners, and they are often more eager and promising to cure. In combination with China's special national conditions, allo-HSCT is still the indispensable treatment of CML in china [7, 8].

Imatinib belongs to TKIs drugs, which have various pharmacological effects, and its side effect is diverse [9, 10]. It is of great clinical importance to study whether prior exposure to imatinib influences the outcome of transplantation for chronic myeloid leukemia. It also need to be discussed whether the CML patients with an imatinib therapy history previously have an increased risk when undergoing allo-HSCT. The principal purpose of this study was to clarify the above two questions.

Patients, materials and methods

Patient characteristics

We retrospectively examined a cohort of 106 patients who received a first full allo-HSCT between May 2003 and May 2013 in NanFang Hospital, Southern Medical University. 106 patients were divided into imatinib group and non-imatinib group according to whether had an imatinib therapy history before transplantation. Non-imatinib group did not receive imatinib or any other TKIs before. Imatinib doses ranged from 400 to 800 mg/day, and stopped using at nearly 30 days before the day of cell infusion (day 0). Moreover, this retrospective analysis of patients was approved by our hospital institutional review board.

Definitions

Neutrophil engraftment was defined as having occurred on the first of three consecutive days with counts > 0.5×10^9/L. Platelet engraftment was defined as having occurred on the first of seven consecutive days with platelets > 20×10^9/L and without platelet transfusions. The early transplant-related complications such as CHF, HVOD, GVHD, hemorrhagic cystitis and infections were confined to occur in the first 100 days after transplantation. HVOD, GVHD, hemorrhagic cystitis were defined according to the Seattle criteria [11]. CHF was defined according to ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 [12]. Bacterial infection was defined as having a clear clinical symptoms such as fever or chills, symptoms were relieved obviously after use of antibiotics, and blood, urine or sputum culture was positive. Fungal infection was defined as having a clear lung imaging performance and could be relieved after antifungal treatment, blood and sputum culture or skin biopsy was positive. Viral infection was defined as a routine blood or urine test showed that virus nucleic acid was greater than 1000 Copies/ml.

Conditioning regimen

Eighty-two patients received BuCy conditioning regimen, busulfan was administered continuously for 4 hours through a central venous catheter at 1.6 mg/kg every 12 hours on days -7 to -4, cyclophosphamide 60 mg/(kg·d) was given daily on days -3 to -2, and cytarabine 4 g/(m^2·d) was given daily on days -9 to -8 (25 of the 82 patients did not use cytarabine). Nine patients received cyclophosphamide and total body irradiation (irradiated dose 4.5 Gy on days -5 and -4, respectively). The remaining 15 patients mostly in accelerated phase or blast crisis phase received other intense conditioning regimens [13, 14]. More specifically, they received TBI + CY + Etoposide/Teniposide (n = 6), Fludarabine + Cytarabine + TBI + CY/Etoposide (n = 4), GIAC (n = 3) and Fludarabine/Idarubicin + Cytarabine + BU + CY (n = 2).

GVHD prophylaxis regimen

Cyclosporine A [CsA, 2.5 mg/(kg·d), with serum valley value maintained at 150-250 ng/ml, given from day -10] plus methotrexate (MTX, 15 mg on day + 1, and 10 mg on day + 3 and + 6) were administered in the patients undergoing HLA matched sibling donor transplantation for GVHD prophylaxis. CsA, MTX and mycophenolate mofetil (MMF, 0.5 g twice a day on days -10 to + 28) were used in the patients undergoing one locus HLA-mismatched sibling donor transplantation. CsA, MTX and human anti-thymocyte globulin [ATG, Genzyme, 1.5-2.5 mg/(kg·d) on days -5 to -2] in the patients undergoing HLA matched unrelated donor, or more than one locus HLA-mismatched sibling donor transplantation. The patients undergoing HLA-mismatched unrelated donor or haplo-identical transplantation received CsA + MTX +ATG +MMF as GVHD prophylaxis [15-17].

Supportive care and prophylaxis

Pre-transplant cardiac function was determined in all patients using both electrocardiogram and echocardiogram, or multiple gated acquisition scan. Before check in sterile laminar flow ward, patients need to perfect the rel-

Table 1. The characteristics of the patients

	IM Group (n = 36)	Non-IM Group (n = 70)	*P* Value
Sex			
Male	22 (61.1%)	40 (57.1%)	0.83*
Female	14 (38.9%)	30 (42.9%)	
Age, years, Median (range)	29.5 (12-51)	32 (13-52)	0.894†
Disease stage, no. (%)			
CML BC	12 (33.3%)	2 (2.9%)	
CML AP/CP2/CP3	5 (13.9%)	4 (5.7%)	0.001‡
CML CP1	19 (52.8%)	64 (91.4%)	
Time interval from diagnosis to transplant, months, no. (%)			
≥ 12	16 (44.4%)	19 (27.1%)	
< 12	20 (55.6%)	51 (72.9%)	0.08*
Donor type, no. (%)			
Unrelated donor, other	19 (52.8%)	31 (44.3%)	0.42*
HLA-identical sibling donor	17 (47.2%)	39 (55.7%)	
Donor recipient sex combination, no. (%)			
Female donor, male recipient	10 (27.8%)	19 (27.1%)	1.00*
All other	26 (72.2%)	51 (72.9%)	
Conditioning regimen, no. (%)			
BU/CY	19 (52.8%)	63 (90.0%)	
TBI/CY	5 (13.9%)	4 (5.7%)	0.000‡
Others♥	12 (33.3%)	3 (4.3%)	
GVHD Prophylaxis with ATG, no. (%)			
Yes	18 (50.0%)	43 (61.4%)	0.30*
No	18 (50.0%)	27 (38.6%)	
MNC of graft (10^8/Kg), Mean ± SD	7.86 ± 1.94	6.73 ± 2.27	0.019†
Transplantation Time, years			
May 2003-Apr 2008	9 (25.0%)	47 (67.1%)	0.00*
May 2008-May 2013	27 (75.0%)	23 (32.9%)	
Stem cell source			
BM	1 (2.8%)	9 (12.9%)	
PB	23 (63.9%)	51 (72.9%)	0.030‡
BM + PB	12 (33.3%)	10 (14.2%)	
IM therapy duration, months, Median (range)	5.5 (0.25-72)	0	
EBMT Score, no. (%)			
Low risk group (score 0-2)	11 (30.6%)	46 (65.7%)	
Intermediate risk group (score 3-4)	20 (55.6%)	20 (28.6%)	0.003‡
High risk group (score 5-7)	5 (13.8%)	4 (5.7%)	

IM: imatinib mesylate; AP: accelerated phase; BC: blast crisis; CP1: first chronic phase; CP2: second chronic phase; CP3: third chronic phase; BU: busulfan; CY: cyclophosphamide; TBI: total body irradiation; GVHD: graft-versus-host disease; ATG: anti-thymocyte globulin; MNC: mononuclear cell; BM: bone marrow; PB: peripheral blood; EBMT: European Blood and Marrow Transplantation. ♥Other intense conditioning regimens (n = 15): TBI + CY + Etoposide/Teniposide (n = 6); Fludarabine + Cytarabine + TBI + CY/Etoposide (n = 4); GIAC (n = 3); Fludarabine/Idarubicin + Cytarabine + BU + CY (n = 2). *Fisher exact test; †Independent sample t test; ‡Pearson χ^2 test.

evant physical examination, laboratory tests and relevant clinical department consultations, to eliminate transplantation contraindications. Generally, the complete blood counts, electrolyte, liver function, renal function and myocardial enzyme levels as well as other biochemical

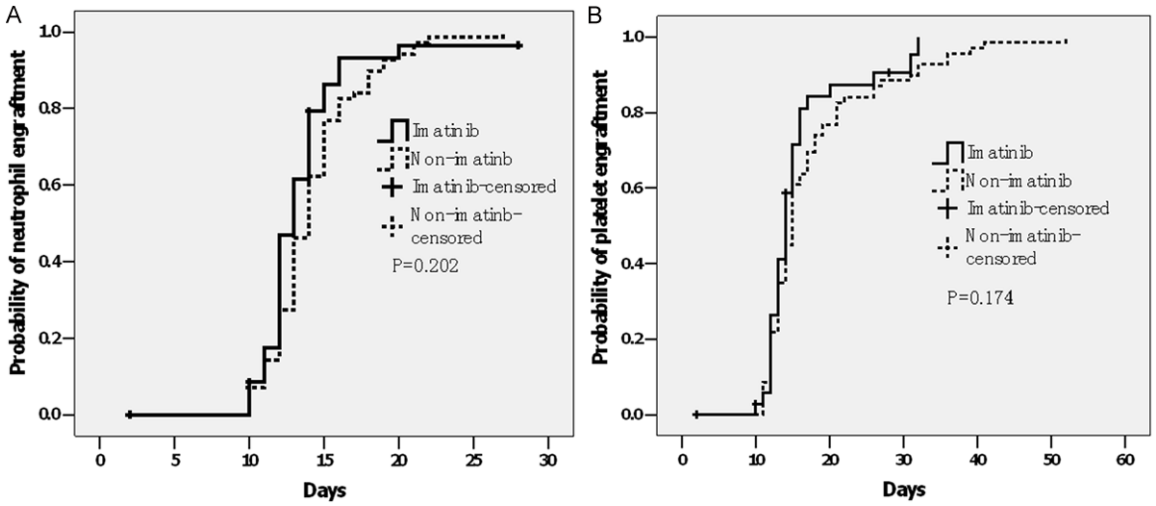

Figure 1. A. The cumulative incidence of neutrophil engraftment at 30-day was 96.6% and 100%, respectively (P = 0.202). B. The cumulative incidence of platelet engraftment at 60-day was 100% and 100%, respectively (P = 0.174).

markers were routinely tested every several days during transplantation. All patients received granulocyte colony-stimulating factor (G-CSF, 300 μg/d) from day +3 post-transplantation until achievement of neutrophil engraftment. Patients were applied for red blood cells or platelet transfusions if hemoglobin levels were ≤ 70 g/L and platelet count ≤ 20.0 × 109/L.

Oral sulfamethoxazole and norfloxacin were administrated from the beginning of preparation therapy to all patients for prophylaxis of bacterial infection. Acyclovir or Ganciclovir was given daily from the beginning of preparation therapy to engraftment for prophylaxis of viral infection. Low molecular weight heparin (Fraxiparine, 0.2 mg, intravenous injection, every 8 hour) and prostaglandin E (Alprostadil, 10 mg, intravenous injection, every 8 hour) were used from the beginning of the conditioning to engraftment for HVOD prophylaxis. Mesna was administrated before and after the intravenous cyclophosphamide therapy for the prophylaxis of hemorrhagic cystitis.

Statistics

The statistical analyses were performed using SPSS version 13.0 software package. All statistical tests were two-sided, and P value less than 0.05 was used to indicate statistical significance. Differences between groups were evaluated by the Pearson χ^2 test and Fisher exact test on the appropriate cross-tabulations for the discrete variables, and by independent sample t test for the continuous variables. The Log-Rank test was used for comparing the survival curves. Kaplan-Meier method was used to estimate cumulative incidence of engraftment and chronic GVHD (cGVHD), 0.5-year TRM, OS and RFS. Multivariate logistic analysis was conducted to analyze risk factors for CHF, and the Cox regression model was used for analyzing prognostic factors for 0.5-year TRM, OS and RFS. Multivariate analysis considered the following factors: sex, age, disease stage, time interval from diagnosis to transplant, donor type, donor recipient sex combination, conditioning regimen, GVHD prophylaxis with ATG, mononuclear cell (MNC) number of graft, transplantation time, stem cell source and imatinib therapy.

Results

Patient demographics and pre-transplant characteristics

Table 1 shows the median time of imatinib therapy duration was 5.5 (rang; 0.25-72) months for imatinib group. There were no statistically significant difference in sex, age, time interval from diagnosis to transplant, donor type, donor recipient sex combination, GVHD Prophylaxis with ATG between the two groups (P > 0.05). However, the difference in disease stage, conditioning regimen, MNC of graft, transplanta-

Table 2. The comparison of engraftment and early transplant related complications between two groups

	IM Group (n = 36)	Non-IM Group (n = 70)	*P* Value
Engraftment time, days, mean (95% *CI*)			
ANC	13.55 (12.37-14.73)	14.32 (13.58-15.07)	0.202*
PLT	15.89 (13.86-17.91)	17.83 (15.73-18.76)	0.174*
GVHD grade, no. (%)			
No	13 (36.1%)	36 (51.4%)	
1-2	17 (47.2%)	30 (42.9%)	0.115†
3-4	6 (16.7%)	4 (5.7%)	
CHF, no. (%)	9 (29.6%)	6 (8.6%)	0.037‡
Hepatic veno-occlusion disease, no. (%)	2 (5.6%)	3 (4.3%)	1.000‡
Hemorrhagic cystitis, no. (%)	9 (29.6%)	19 (27.1%)	1.000‡
Bacterial infection, no. (%)	8 (22.2%)	7 (10.0%)	0.139‡
Fungal infection, no. (%)	3 (8.3%)	4 (5.7%)	0.687‡
Viral infection, no. (%)	5 (13.9%)	14 (20.0%)	0.595‡

IM: imatinib mesylate; ANC: absolute neutrophil count; GVHD: graft-versus-host disease; CHF: congestive heart failure; CI: confidence interval. *Log-Rank test; †Pearson χ^2 test; ‡Fisher exact test.

tion time and stem cell source were statistically significant ($P < 0.05$). Imatinib group subjects tended to have a higher proportions with accelerated phase or blast crisis, as well as a longer time interval from diagnosis to transplant, etc. All these factors contributed to the statistically higher EBMT Score [18] of imatinib group. Consequently, imatinib group patients were more probably to receive intense conditioning regimens and inclined to be transplanted higher MNC of graft.

Engraftment

Since imatinib therapy is associated with adverse hematological toxicity [19], we looked specifically at the impact of imatinib on engraftment. Neutrophil and platelet engraftment time are shown in **Figure 1** and **Table 2**. The imatinib patients took, on average, 0.77 fewer days to reach ANC (absolute neutrophil count) > 0.5 × 10^9/L compared to the non-imatinib individuals, and the difference was not statistically significant ($P = 0.202$). The imatinib patients did, on average, 1.94 days faster to reach PLT > 20 × 10^9/L than the non-imatinib individuals, and the difference was not statistically significant either ($P = 0.174$).

Early transplant-related complications

The cumulative incidence of acute GVHD (aGVHD) at day 100 was higher in the imatinib group (63.9%) compared with the non-imatinib group (48.6%), but the difference was not statistically significant ($P = 0.154$). The composition of different grades of aGVHD was either not statistically different ($P = 0.115$). There was also no significant difference between the imatinib and non-imatinib groups with regard to the cumulative incidence of HVOD (5.6% vs 4.3%, $P = 1.000$) and hemorrhagic cystitis (29.6% vs 27.1%, $P = 1.000$). However, the cumulative incidence of CHF at day 100 in imatinib group was obviously higher than non-imatinib group (29.6% vs 8.6%, $P = 0.037$).

The cumulative incidence of bacterial, fungal and viral infection at day 100 were not statistically different between the two groups ($P < 0.05$). In imatinib group, eight patients developed bacterial infections, 6 cases blood culture positive, 2 cases urine culture positive. In non-imatinib group, seven patients developed bacterial infections, 4 cases blood culture positive, 3 cases sputum culture positive. There were 3 cases of pulmonary fungal infections in imatinib group. Correspondingly, four cases of fungal infections in non-imatinib group, 2 were pulmonary, 2 were buccal, respectively. Five patients in imatinib group developed blood CMV virus infections. While, fifteen patients in non-imatinib group developed viral infections, 13 blood CMV virus positive, and 1 urine BK virus positive.

Survival

The median time to follow-up for the imatinib and non-imatinib groups was 1.38 (range,

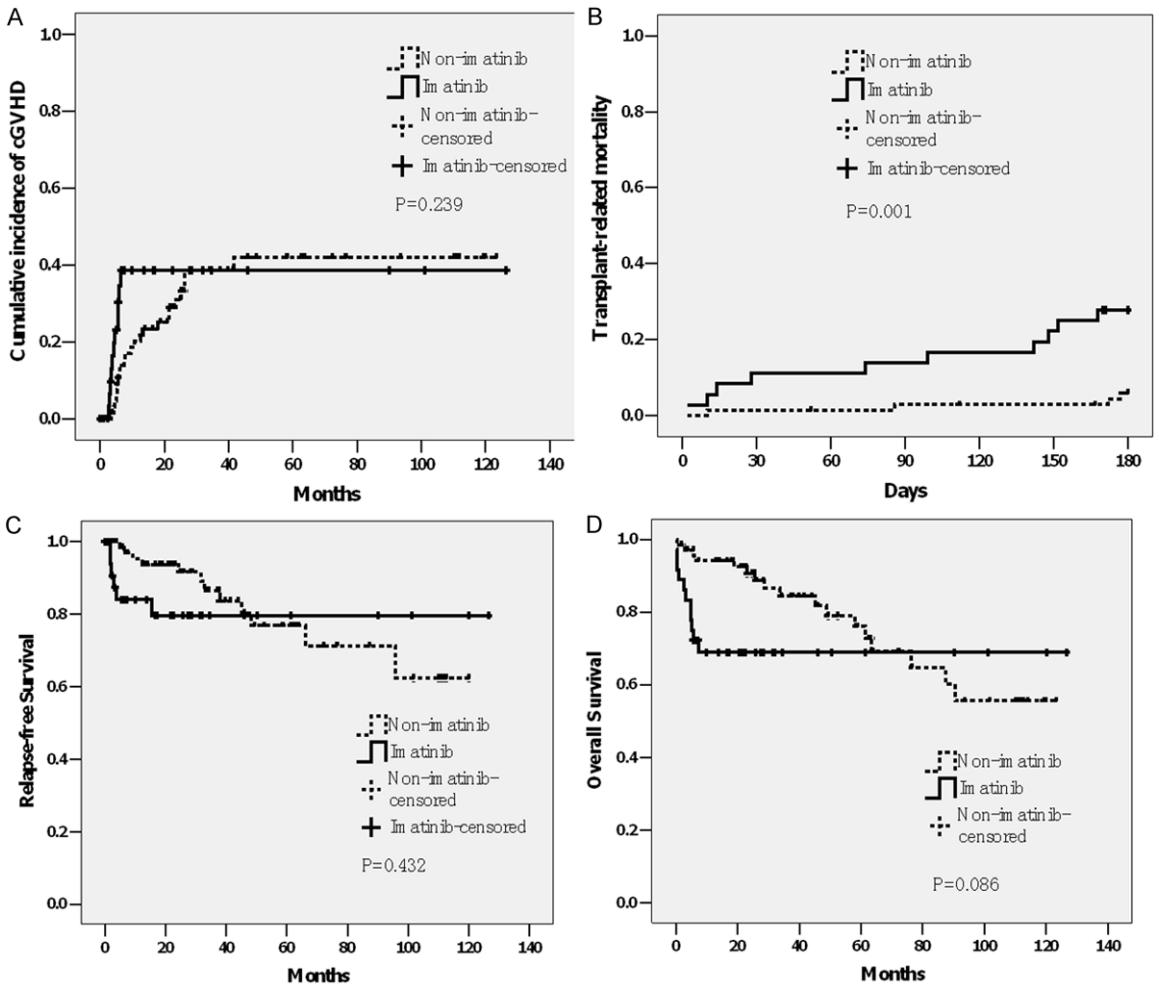

Figure 2. Cumulative incidence of cGVHD, transplant-related mortality (TRM), relapse-free survival (RFS) and Overall survival (OS). A. The estimated cumulative incidence of cGVHD at 10-year was 38.6% and 42.0%, respectively (*P* = 0.239). B. The 0.5-year TRM was 27.8% and 5.9%, respectively (*P* = 0.001). C. The estimated 10-year RFS was 79.6% and 62.4%, respectively (*P* = 0.432). D. The estimated 10-year OS was 68.9% and 55.5%, respectively (*P* = 0.086).

0.005-10.39) and 3.19 (range, 0.027-10.13) years, respectively. The estimated cumulative incidence of cGVHD at 10-year post-HSCT was lower but not significant between the imatinib group (38.6%) and non-imatinib group (42.0%) (*P* = 0.239) (**Figure 2A**). Eleven patients in the imatinib group died of transplant related causes compared with 4 in the non-imatinib group, providing statistically significant TRM at 0.5-year post-HSCT in the imatinib group compared with the non-imatinib group (27.8% vs 5.9%, *P* = 0.001) (**Figure 2B**).

In a longer follow-up, eleven patients from the imatinib group and 17 from the non-imatinib group died of relapse or all kinds of complications (30.5% vs 24.3%). Six patients from the imatinib group and 12 from the non-imatinib group have relapsed after HSCT (16.7% vs 17.1%). Estimated RFS and OS at 10-year was 79.6% and 68.9% for the imatinib group compared with 62.4% and 55.5% for the non-imatinib group (*P* = 0.432 and 0.086, respectively) (**Figure 2C**, **2D**).

In the multivariate logistic regression analysis, age (*OR* = 1.24, 95% *CI* 1.07-1.44, *P* = 0.006), transplantation time (May 2003-Apr 2008) (*OR* = 47.55, 95% *CI* 2.29-988.92, *P* = 0.013) and imatinib therapy (*P* = 0.033) were the independent risk factor for CHF. In Cox regression analysis, age (*HR* = 1.10, 95% *CI* 1.01-1.19, *P* = 0.038) and imatinib therapy (0-12 vs 0 months) (*HR* = 6.47, 95% *CI* 1.36-30.85, *P* = 0.019)

Table 3. Multivariate analyses of risk factors for CHF, 0.5-year TRM, RFS and OS

Risk factor	CHF†		0.5-Year TRM‡		RFS‡		OS‡	
	OR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	P
Sex								
Male	1.00		1.00		1.00		1.00	
Female	0.25 (0.03, 1.92)	0.181	1.11 (0.24, 5.07)	0.896	3.03 (0.75, 12.15)	0.119	2.63 (0.93, 7.42)	0.069
Age	1.24 (1.07, 1.44)	0.006	1.10 (1.01, 1.19)	0.038	1.01 (0.94, 1.09)	0.755	1.02 (0.97, 1.08)	0.503
Disease stage	0.133		0.916		0.068		0.332	
CML CP1	1.00		1.00		1.00		1.00	
CML AP/CP2/CP3	5.26 (0.28, 98.01)	0.266	1.56 (0.19, 12.69)	0.680	3.80 (0.74, 19.55)	0.110	2.89 (0.58, 14.38)	0.195
CML BC	0.22 (0.01, 3.62)	0.287	1.32 (0.18, 9.53)	0.786	8.38 (1.20, 58.61)	0.032	2.46 (0.57, 10.60)	0.227
Time interval from diagnosis to transplant	0.98 (0.94, 1.01)	0.200	1.00 (0.97, 1.02)	0.769	1.01 (0.99, 1.04)	0.376	1.00 (0.98, 1.02)	0.914
Donor type								
Unrelated donor, other	1.00		1.00		1.00		1.00	
HLA-identical sibling donor	25.14 (0.51, 1248.64)	0.106	0.89 (0.04, 20.71)	0.943	2.75 (0.51, 14.92)	0.241	2.88 (0.69, 12.06)	0.147
Donor recipient sex combination	1.00		1.00		1.00		1.00	
Female donor, male recipient	0.72 (0.05, 11.19)	0.814	0.80 (0.14, 4.40)	0.795	0.47 (0.11, 2.08)	0.322	0.56 (0.19, 1.61)	0.278
All other								
Conditioning regimen	0.203		0.325		0.466		0.418	
BU/CY	1.00		1.00		1.00		1.00	
TBI/CY	0.00 (0.00)	0.998	0.14 (0.01, 2.08)	0.152	3.41 (0.47, 24.60)	0.224	0.52 (0.09, 2.87)	0.453
Others	0.06 (0.00, 1.31)	0.074	0.37 (0.05, 2.96)	0.348	1.78 (0.16, 19.44)	0.637	0.34 (0.07, 1.72)	0.191
GVHD Prophylaxis with ATG								
Yes	1.00		1.00		1.00		1.00	
No	7.49 (0.36, 157.20)	0.195	3.51 (0.18, 68.43)	0.408	0.30 (0.05, 1.83)	0.191	0.70 (0.19, 2.58)	0.592
MNC of graft (10^^{8}/Kg)	1.08 (0.71, 1.63)	0.716	0.89 (0.65, 1.23)	0.483	1.00 (0.74, 1.33)	0.963	0.85 (0.69, 1.04)	0.107
Transplantation Time								
May 2008-May 2013	1.00		1.00		1.00		1.00	
May 2003-Apr 2008	47.55 (2.29, 988.92)	0.013	1.68 (0.31, 9.08)	0.545	0.77 (0.14, 4.33)	0.767	1.64 (0.53, 5.05)	0.388
Stem cell source	1.00		1.00		1.00		1.00	
PB		0.430		0.957		0.978		0.288
BM	6.90 (0.28, 168.70)	0.236	1.12 (0.07, 17.07)	0.933	0.77 (0.05, 11.08)	0.846	0.22 (0.02, 2.11)	0.187
BM + PB	0.70 (0.10, 4.65)	0.708	1.26 (0.27, 5.87)	0.767	0.89 (0.18, 4.51)	0.892	1.38 (0.47, 4.12)	0.560
IM therapy, months		0.033		0.055		0.546		0.650
0	1.00		1.00		1.00		1.00	
0-12	35.00 (2.28, 536.48)	0.011	6.47 (1.36, 30.85)	0.019	0.84 (0.20, 3.50)	0.841	1.28 (0.45, 3.65)	0.644
≥ 12	89.69 (1.09, 7357.86)	0.046	13.42 (0.57, 317.59)	0.108	0.17 (0.01, 4.01)	0.271	2.80 (0.30, 26.20)	0.368

CHF: congestive heart failure; TRM: transplant-related mortality; RFS: relapse-free survival; OS: Overall survival; OR: odds ratio; HR: hazard ratio; CI: confidence interval; AP: accelerated phase; BC: blast crisis; CP1: first chronic phase; CP2: second chronic phase; CP3: third chronic phase; BU: busulfan; CY: cyclophosphamide; TBI: total body irradiation; MNC: mononuclear cell; BM: bone marrow; PB: peripheral blood; IM: imatinib mesylate. †Multivariate logistic regression analysis; ‡Cox regression analysis.

were significantly associated with a higher 0.5-year TRM, and disease stage (CML BC vs CP1) was significantly associated with a lower RFS (*HR* = 8.38, 95% *CI* 1.20-58.61, *P* = 0.032). While, all factors studied were not significantly associated with OS in the multivariate analysis (**Table 3**).

Discussion

Imatinib, although generally very well tolerated, has some side effects that may raise concerns regarding the safety of a subsequent allo-HSCT. Its side effects can be divided into the short-term and long-term side effects [9, 10, 20]. Common short-term side effects are gastrointestinal reaction, water-sodium retention, bone marrow suppression, etc. Most short-term side effects appear in the first two years after the treatment, which are mild and can be recovered by decreasing dosage or withdrawal. In recent years, some of the long-term side effects of imatinib are also gradually been recognized, such as cardiac toxicity, bone metabolic abnormalities, liver and lung toxicity, secondary second tumor, etc. These long-term side effects generally take place slowly, develop gradually and imperceptibly, also progress irreversibly. And they have a profound effect on the long-term life quality of the patients. Allo-HSCT usually uses large doses of chemotherapy or radiotherapy as conditioning regimens, and long-term use of immunosuppressive agents is essential after transplantation, etc [21, 22]. Under the intense stress situation, even the imatinib therapy time is short, the early and long-term side effects can appear ahead of time. The impact on clinical outcomes of imatinib therapy prior to preceding allo-HSCT is necessary to be well-known.

Interestingly, though imatinib has a potent bone marrow suppression, we observed that imatinib-treated patients took, on average, even 0.77 fewer days to reach ANC > 0.5 × 10^9/L compared to the non-imatinib individuals, but the difference was not statistically significant (*P* = 0.202). And the imatinib patients did, on average, 1.94 days faster to reach PLT > 20 × 10^9/L than the non-imatinib individuals, the difference was not statistically significant either (*P* = 0.174). Our results are in agreement with a previous report indicating that use of imatinib does not impair donor engraftment. In the study of JM Zaucha, et al [23], it retrospectively analyzed engraftment in 30 patients with BCR/ABL-positive leukemias who received imatinib before HSCT and compared results of 48 age-matched controls who did not receive preceding imatinib, and finally found that both neutrophil and platelet engraftment occurred more rapidly (3.84 fewer days and 6.90 days faster, *P* = 0.18 and 0.22, respectively). This result may indicate that imatinib does not severely affect normal hematopoiesis. Several preliminary studies [24, 25] confirmed that imatinib selectively inhibited in vitro growth of BCR-ABL-positive cells and did not affect BCR-ABL-negative cell lines. What is more, Prejzner W, et al [26] conducted an in vitro experiment showing that therapeutic doses of imatinib inhibited normal progenitor colony formation by only 10-20%.

The cumulative incidence of aGVHD at day 100 and cGVHD in a long time follow-up were not statistically different between patients who did and did not receive imatinib pre-transplant (63.9% vs 48.6% *P* = 0.154, 38.6% vs 42.0% *P* = 0.239, respectively). Nor did the composition of different grades of aGVHD (*P* = 0.115). There was also no significant difference between the imatinib and non-imatinib groups with regard to the cumulative incidence of HVOD (5.6% vs 4.3%, *P* = 1.000) and hemorrhagic cystitis (29.6 vs 27.1%, *P* = 1.000). Previous data about patients undergoing allo-HSCT and receiving imatinib therapy pre-transplant suggested similar conclusions. Stephanie J. Lee, et al [27] retrospectively analyzed 409 CML patients treated with imatinib prior to SCT and 900 CML patients who did not receive imatinib prior to SCT, and concluding that there was no evidence for imatinib affecting the incidence of GVHD (43% vs 42%, *P* = 0.94). Liver toxicity is a potentially fatal complication during hematopoietic stem cell transplantation therapy [28]. There is no doubt that imatinib can induce liver toxicity resulting in a mild increase in transaminases and occasionally increases in bilirubin [20]. However, in our study we did not observe statistically higher incidence of HVOD in patients treated with imatinib prior to HSCT. The possible reason is that liver impairment can be soon relieved with drug withdrawal and dosage reduction. In our study, imatinib was stopped using at nearly 30 days before the day of cell infusion. The fact that small number of our study and most of our patients received imatinib for less than a year also limited our analysis.

There are few data currently available with regard to the cumulative incidence of infections at the first 100 days in patients who received imatinib prior to all-HSCT or not. According to our data, we found no statistically significant difference in bacterial infection, fungal infection and viral infection between the imatinib group and the non-imatinib group (22.2% vs 10.0%, 8.3% vs 5.7%, 13.9% vs 20.0%; P = 0.139, 0.687, 0.595; respectively).

However, the cumulative incidence of CHF at day 100 in imatinib group was obviously higher than non-imatinib group (29.6% vs 8.6%, P = 0.037). The concern that imatinib may lead to cardiac-related toxicities, notably CHF, had been previously described by several investigators [29-32]. But soon after, Atallah E, et al [33] retrospectively analyzed over 1200 leukemia patients receiving imatinib therapy, finding CHF was present in 22 of 1276 (1.7%) patients, and concluding that CHF was a rare event in patients receiving imatinib therapy. The incidence of CHF of our study was far higher than Atallah E, et al reported (14.2 vs 1.7%). This discrepancy was probably attributed to the fact that patients of our study were all in an intense stress situation, undergoing transplantation with large doses of chemotherapy or radiotherapy as conditioning regimens, and long-term use of immunosuppressive agents. Multivariate logistic regression analysis showed that age (*OR* = 1.24, 95% CI 1.07-1.44, P = 0.006), transplantation time (May 2003-Apr 2008) (*OR* = 47.55, 95% *CI* 2.29-988.92, P = 0.013) and imatinib therapy (P = 0.033) were the independent risk factor for CHF.

We observed that imatinib group of our study tended to have poorer prognosis than non-imatinib group in early stage of post-HSCT, imatinib group had a higher 0.5-year TRM (27.8% vs 5.9%, P = 0.001). Cox regression analysis showed that age (*HR* =1.10, 95% CI 1.01-1.19, P = 0.038) and imatinib therapy (0-12 vs 0 months) (*HR* = 6.47, 95% CI 1.36-30.85, P = 0.019) were significantly associated with a higher 0.5-year TRM. However, imatinib therapy did not induce a worse prognosis on a long view. The estimated 10-year relapse-free survival (RFS) and 10-year overall survival (OS) were not statistically significant between the two groups (79.6% vs 62.4% P = 0.432, 68.9% vs 55.5% P = 0.086, respectively). This discrepancy was probably attributed to the fact that imatinib therapy reduced the relapse post-HSCT and had a longer RFS.

In conclusion, on the basis of this retrospective analysis of a cohort of 106 CML patients receiving allo-HSCT, prior exposure to imatinib had no impact on either engraftment or early transplant-related complications such as HVOD, GVHD, hemorrhagic cystitis and infections for CML. Occasionally, we found that imatinib therapy pre-HSCT probably increases the risk of CHF and TRM in early stage of post-HSCT, and this effect can be enhanced in older age patients. Imatinib therapy doesn't impact RFS and OS post-HSCT on a long view.

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Disclosure of conflict of interest

None.

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