RESEARCH ARTICLE

Imatinib Mesylate Versus Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Chronic Myelogenous Leukemia

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Abstract

Purpose: To compare the relative merits of imatinib and allogeneic hematopoietic stem cell transplantation (allo-HSCT) for chronic myelogenous leukemia (CML). Materials and Methods: This cohort study was designed to compare the outcomes of imatinib (n=292) versus allo-HSCT (n=141) for CML, the clinical data of these patients being retrospectively analyzed so as to compare the event free survival (EFS) and overall survival (OS) between these two groups with patients in the chronic phase (CP) and advanced phases, including accelerate (AP) and blast phases (BP). Results: (1) Patients treated with imatinib (278 in the CP) demonstrated superior EFS, OS, 5-year EFS and 5-year OS rates of 88.5% versus 70.0% (P<0.05), 93.2% versus 80.0% (P<0.05), 84% versus 75.0% (P<0.05) and 92% versus 79.0% (P<0.05), respectively, to those treated with allo-HSCT (120 patients in the CP). (2) Both treatments resulted in similar survival, with EFS and OS rates of 42.9% versus 47.6% (P>0.05), 42.9% versus 57.1% (P> 0.05), respectively, for imatinib (14 patients in the AP and BP) and allo-HSCT (21 patients in the AP and BP). Conclusions: Imatinib confers significant survival advantage (EFS and OS) for CML patients with CP compared with allo-HSCT treatment. However, the outcomes are equally good with both treatments in AP and BP patients.

Keywords: Chronic myelogenous leukemia - imatinib - allogeneic stem cell transplantation - survival analysis

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Introduction

Chronicmyelogenous leukemia (CML) typically progresses through 3 phases: the chronic phase (CP), the accelerated phase (AP), and the blast phase (BP). AP-CML is associated with median survival ranging from 6-24 months and generally leads to a rapidly fatal BP (Goldman et al., 2003; O'Brien et al., 2014). Tyrosine kinase inhibitors (TKIs) are an important new class of molecular targeted chemotherapeutic drugs that specifically inhibit oncogenic tyrosine kinases to kill cancer cells by regulating cancer proliferation, invasion, metastasis and angiogenesis. Over the past 10 years, the introduction of imatinib mesylate, a selective BCR-ABL kinase inhibitor, has been considered the first-line therapy for all phases of CML, but allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only curative treatment for patients in any phase of CML, especially for patients in the AP and BP (Ruiz et al., 2016). The allo-HSCT has been reserved for patients with CML who fail to respond optimally to imatinib or other TKIs (e.g drug resistance mutation, can not tolerance) or those in advanced phases after pretreatment with TKIs or those the suitable donor was finded (Hehlmann et al., 2007; Hochhaus et al., 2009; Saussele et al., 2010; Barrett et al., 2015; Moslehi et al., 2015). The prognosis of AP/BP-CML patients is poor, TKIs may be effective, but maintain a very short time. Nevertheless, few comparative studies have been performed comparing the outcomes of CML patients treated with imatinib or other TKIs with those treated with allo-HSCT, so the question of whether allo-HSCT is actually superior to imatinib in treating CML remains unanswered. To clarify the role of allo-HSCT in the treatment of AP-CML in the era of imatinib, we designed a study to compare the outcomes of imatinib (n=292) versus allo-HSCT (n=141) treated CML patients, the clinical data of these patients were retrospectively analyzed.

Materials and Methods

Patient characteristics

From April 2005 to October 2012, 292 patients treated with imatinib and from March 2011 to October 2012, 141 patients treated with allo-HSCT at First Affiliated

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Hospital of Soochow University, Jiangsu Institute of Hematology (Suzhou, China) were included for study. The diagnosis was base on bone marrow aspirate and MICM (Morphology, Immunology, Cytogenetics, Molecular) (Thompson et al., 2015). Imatinib group: 185 male,107 female, the median age was 37 years (range 5~75 years), 278 CP, 5 AP, 9 BP. Allo-HSCT group: 93 male, 48 female, the median age was 34 years (range 7~62 years), 120 CP, 5 AP,16 BP (Table 1).

Therapy

Imatinib group: The CP-CML patients and AP/BP-CML patients were treated with imatinib at an initial dose of 400 mg daily and 600~800mg daily respectively. The dose was then adjusted according to the patient's response and/or toxicity. Patients can adhere to medication during the period of treatment until drug resistance. Patients not tolerating side effects of imatinib were excluded.

allo-HSCT group

Source of stem cells: 30 peripheral blood stem cells (PBSCs) transplantation, 111 bone marrow transplantation. Donor type: 96 sibling HSCT, 29 human leukocyte antigen (HLA)-matched unrelated donor HSCT, 15 haploid-HSCT, 1 identical twins HSCT. Patients received conditioning regimen: 4 total body irradiation plus cyclophosphamide (TBI+Cy), 126 Busulfan plus cyclophosphamide (Bu+Cy), 11 nonmyeloablative HSCT (Table 2).

Follow up

433 patients were followed up according to telephone, mail, hospital registration system and so on. Follow up destination: to follow-up or death. The median follow up time of imatinib group was 40 months (range 2~93 months) ; the median follow up time of allo-HSCT groups was 49 months (range 1~127 months).

Statistical analysis

Considering the number of AP-CML and BP-CML patients are less, We combine AP-CML and BP-CML patients together each group for analysis. All statistical analyses were performed with SPSS Version 20.0 software. The Kaplan-Meier method was used to assess statistical signficance in the time-to-event analyses. We performed univariate and multivariate analyses to determine whether any of the selected factors were predictive of EFS, OS. The log-rank test was used to identify such prognostic factors. Factors with an effect signficant at the P<0.05 level were interpreted as being independently predictive of the outcomes.

Results

Comparison between the imatinib and allo-HSCT groups

1. The overall treatment effect: Imatinib group: 252 event free survival (EFS) patients (CP, n=246; AP/BP, n=6), At the last follow-up, 265 patients were alive (CP, n=259; AP/BP, n=6), twenty-seven patients died (CP, n=19; AP/BP, n=8), whom were died of advanced disease or imatinib-resistance caused by BCR-ABL kinase domain mutations and so on.

Allo-HSCT group: 94 EFS patients (CP, n=84; AP/BP, n=10), At the last follow-up, 108 patients were alive (CP, n=96; AP/BP, n=12), 33 patients died (CP, n=24; AP/BP, n=9), whom were died of graft-versus-host disease (GVHD) (n=23), Lung infection (n=9, one of whom underwent secondary poor graft function), relapse of primary disease (n=1). Treatment-related mortality was 22.7% (32/141, the relapse of primary disease was excluded).

2. CP-CML: In CP-CML patients, patients treated with imatinib was significantly superior, with EFS, 5-year EFS, OS and 5-year OS rates for imatinib (n=278) and allo-HSCT (n=120) of 88.5% versus 70.0% (P=0.001) (Figure 1), 84.0% versus 75.0% (P<0.001) (Figure 2), 93.2.5% versus 80.0% (P=0.001), and 92.0% versus

Table 1. Patient Characteristics

Variable	Imatinib	Allo-HSCT	P
No. of patients	292	141	
Age, y			
Median (range)	37 (5~75)	34 (7~62)	
Sex, no.(%)			
Male	185 (63.4)	93 (66.0)	
Female	107 (3.66)	48 (34.0)	
Disease status at diagnosis of CML, no. (%)			
CP	278	120	
AP	5	5	
BP	9	16	
Follow-up time, m			
Median (range)	40 (2~93)	49 (1~127)	
CP			
No. of Patients	278	120	
EFS rate (%)	88.5	70	0.001
5-year EFS rate (%)	84	75	0.001
OS rate (%)	93.2	80	<0.001
5-year OS rate (%)	92	79	<0.001
AP and BP			
No. of Patients	14	21	
EFS rate (%)	42.9	47.6	0.688
OS rate (%)	42.9	57.1	0.437
No. of EFS	252	94	
CP	246	84	
AP and BP	6	10	
No. of survivals	265	108	
CP	259	96	
AP and BP	6	12	
No. of deaths	27	33	
CP	19	24	
AP and BP	8	9	

Table 2. Patient Characteristics of allo-HSCT Group

Variable	allo-HSCT
Source of stem cells, no.(%)	
PBSCs	30 (21.2)
BM	111 (78.7)
Donor, no.(%)	
Sibling	96 (68.0)
Unrelated	29 (20.5)
HLA-haploidentical	15 (10.6)
Identical twins	1 (0.7)
Pretreatment method, no.(%)	
TBI/Cy	4 (2.8)
Improved BU/Cy	126 (89.3)
NST	11 (7.80)

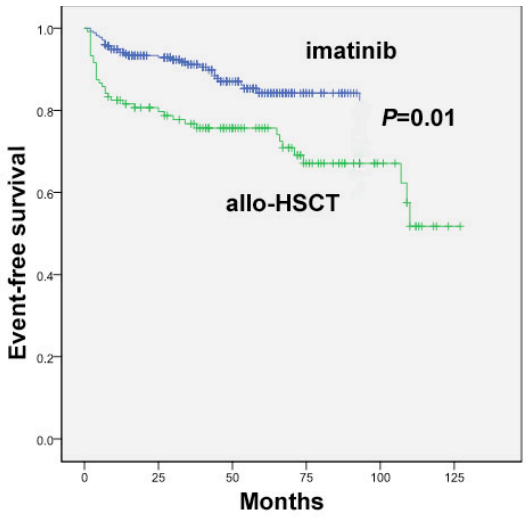

Figure 1. Event-Free Survival of CP-CML Patients

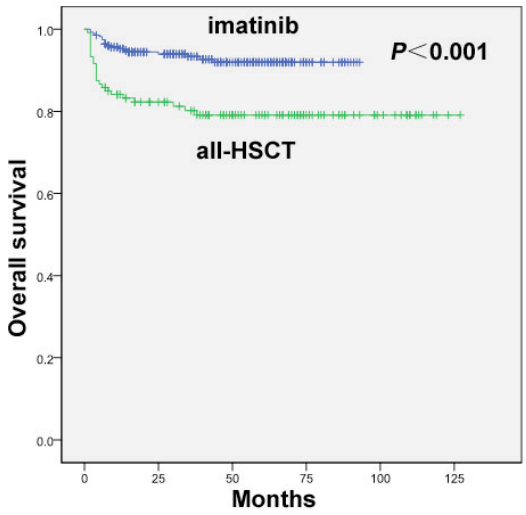

Figure 2. Overall Survival of CP-CML Patients

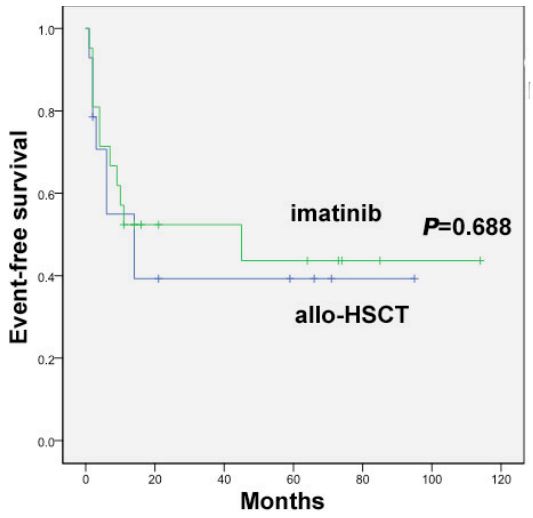

Figure 3. Event-Free Survival of AP/BP-CML Patients

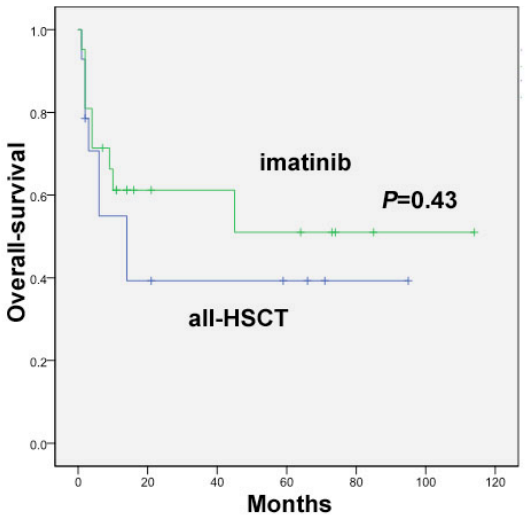

Figure 4. Overall Survival of AP/BP-CML Patients

79.0% (P=0.001), respectively.

3. AP/BP-CML: Among AP/BP-CML patients, imatinib (n=14) was no significant difference from allo-HSCT (n=21), with EFS and OS rates of 42.9% versus 47.6% (P=0.688) (Figure 3)and 42.9% versus 57.1% (P=0.437) (Figure 4), respectively.

Discussion

Imatinib, the first-generation TKIs, which was the first synthetic targeted anti-tumor drugs and widely used in clinic, but not radically cure CML. allo-HSCT is currently the only curative treatment for patients in any phase of CML. Some patients with suitable donor choose allo-HSCT in order to radical cure. Because recent developments in drug therapy and concerns about transplantation-related mortality have challenged the concept of transplantation as a first-line treatment for CP-CML (Gratwohl et al., 2006). Our data for the CP-CML treated with imatinib group and AP/BP group showed EFS, OS rates (88.5%, 93.2% and 42.9 %, respectively) that were similar to those reported elsewhere in the domestic literature (Castagnetti et al., 2015; Jiang et al., 2015; Sasaki et al., 2016).

Our data suggest that imatinib confers significant survival advantages for patients with AP-CML compared with allo-HSCT treatment. Imatinib as a selective BCR-ABL TKIs has replaced allo-HSCTs as first-line therapy for patients with CP-CML (Schiffer 2007; Firwana et al., 2016; Jabbour,2016; Kujak, et al., 2016). Imatinib was convenient and safe, imatinib can continue to take if therapy effective and no drug resistance, unless there is serious adverse drug reactions and must be stopped. Allo-HSCT must choose a suitable donor firstly, the risk of allo-HSCT was obviously higher than that of imatinib. Possible complications of allo-HSCT include graft-versus-host disease (GVHD), severe infection, hepatic vein occlusion disease (VOD). In our study, transplantation-related mortality of allo-HSCT group (n=120) was 20%. To the end of follow-up, imatinib group (CP-CML) showed EFS, OS rates (88.5%, 93.2%, respectively) that were survival advantages compared with those treated with allo-HSCT. Therefore, we believe that CP-CML patients choose imatinib therapy was more safe and effective.

Our data for both treatments resulted in similar survival in AP/BP-CML patients, with EFS and OS rates, but the size of sample is too small to sure the relationship between them, we need increase the number of cases to conformed the explanation. AP/BP-CML patients have a poor outcome, how to choose the treatment, drug treatment

or allo-HSCT, there is no generally accepted view, such as the first-generation TKIs (imatinib), the second-generation TKIs (nilotinib, dasatinib) or allo-HSCT. But allo-HSCT was particularly important to AP/BP-CML patients, which is the only way to cure CML (Baccarani et al., 2006; Gratwohl et al., 2009; Kujak et al., 2016). Jiang et al conclude allo-HSCT confers significant survival advantages for high and intermediate risk patients with AP-CML compared with imatinib treatment, however, the outcomes of the two therapies are equally good in low-risk patients (Jiang et al., 2011; Xu et al., 2015).

Drug intolerance, primary drug resistance, disease advance or BCR-ABL kinase domain mutations in some patients and so on lead to imatinib failure and need to choose other therapeutic method, such as second-generation TKIs, allo-HSCT. Gene mutation detection should be implemented if the condition allows. Because of mutations and adverse drug reactions (Moslehi et al., 2015), second-generation TKIs were selected (Cortes et al., 2007; Nair et al., 2015). Overcome imatinib resistance, more potent TKIs such as nilotinib, dasatinib, and bosutinib have been developed with demonstrable activity against most of the BCR-ABL kinase domain mutations seen in patients treated with imatinib, with the notable exception of the T315I mutation. Cross resistance can occur between second-generation TKIs and imatinib (Jabbour et al., 2008; Pagnano et al., 2015). Data on allo-HSCT or received a second-generation TKIs as second-line therapy after imatinib failure (e.g. imatinib-resistant CML) are scarce. Allo-HSCT could become the preferred second-line option after imatinib failure for suitable patients with a donor (Saussele et al., 2010).

In conclusion, our data suggest that imatinib conferred survival advantages in terms of EFS and OS compared with those treated with allo-HSCT. AP/BP-CML patients showed no difference in EFS and OS, but the size of sample is too small to sure the relationship between them, we need increase the number of cases to conformed the explanation. Imatinib may remain the primary option for patients with CP-CML, and more safe and effective than allo-HSCT. allo-HSCT or second-generation TKIs should be considered if there is evidence of imatinib resistance or intolerance, some patients achieved response, increasing EFS and OS. patients with AP/BC-CML can be treated with allo-HSCT if the situation permitted, other treatments included the first or second generation TKIs and so on.

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