Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase

*Qian Jiang,[1] *Lan-Ping Xu,[1] Dai-Hong Liu,[1] Kai-Yan Liu,[1] Shan-Shan Chen,[1] Bin Jiang,[1] Hao Jiang,[1] Huan Chen,[1] Yu-Hong Chen,[1] Wei Han,[1] Xiao-Hui Zhang,[1] Yu Wang,[1] Ya-Zhen Qin,[1] Yan-Rong Liu,[1] Yue-Yun Lai,[1] and Xiao-Jun Huang[1]

[1]Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China

The relative merits of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and imatinib for chronic myelogenous leukemia in the accelerated phase (AP-CML) have not previously been evaluated. This cohort study was designed to compare the outcomes of imatinib (n = 87) versus allo-HSCT (n = 45) for AP-CML. A multivariate analysis of the total population revealed that a CML duration ≥ 12 months, hemoglobin < 100 g/L, and peripheral blood blasts ≥ 5% were independent adverse prognostic factors for both overall survival (OS) and progression-free survival (PFS). Both treatments resulted in similar survival in low-risk (no factor) patients, with 6-year event-free survival (EFS), OS, and PFS rates of more than 80.0%. Intermediate-risk (any factor) patients showed no difference in EFS and OS, but 6-year PFS rates were 55.7% versus 92.9% (*P* = .047) with imatinib versus allo-HSCT, respectively. Among high-risk (at least 2 factors) patients, imatinib was by far inferior to allo-HSCT, with 5-year EFS, OS, and PFS rates of 9.3% versus 66.7% (*P* = .034), 17.7% versus 100% (*P* = .008), and 18.8% versus 100% (*P* = .006), respectively. We conclude that allo-HSCT confers significant survival advantages for high- and intermediate-risk patients with AP-CML compared with imatinib treatment; however, the outcomes of the 2 therapies are equally good in low-risk patients. All trials were registered with the Chinese Clinical Trial Registry (www.chictr.org) as CHiCTR-TNC-10000955. (*Blood*. 2011;117(11): 3032-3040)

Introduction

Chronic myelogenous 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.[1,2]

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.[3-12] In AP patients, the reported complete hematologic response (CHR) rates for the drug range from 40%-82%. The rates of major cytogenetic response (MCR) and complete cytogenetic response (CCR) range from 24%-49% and 17%-45%, respectively, while major molecular response (MMR) and complete molecular response (CMR) rates range from 11%-50% and 0%-32%, respectively.[7-12] Despite the conferred benefits of imatinib for survival in AP-CML relative to other drug therapies,[9] long-term survival rates remain low. The 7-year follow-up performed by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) CML Working Party reported that event-free survival (EFS), overall survival (OS), and progression-free survival (PFS) rates in AP patients were 15%, 43%, and 37%, respectively.[12]

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only curative treatment for patients in any phase of CML. The literature reports that the 4- or 5-year survival rates for AP-CML treated with allo-HSCT range from 18%-49%.[9,13-16] 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, since the year 2000, allo-HSCT has been reserved for patients with CP-CML who fail to respond optimally to imatinib or other tyrosine kinase inhibitors or those in advanced phases after pretreatment with imatinib or other tyrosine kinase inhibitors.[17-23] Nevertheless, few comparative studies have been performed comparing the outcomes of AP-CML patients treated with imatinib with those treated with allo-HSCT, so the question of whether allo-HSCT is actually superior to imatinib in treating AP-CML remains unanswered.

To clarify the role of allo-HSCT in the treatment of AP-CML in the era of imatinib, we designed a cohort study to compare the outcomes of imatinib- versus allo-HSCT–treated AP-CML patients. We report here our single-center results based on a 9-year follow-up.

Methods

Study protocol

From April 2001 to September 2008, 132 patients treated at Peking University People's Hospital, Peking University Institute of Hematology (Beijing, China), were recruited. Inclusion criteria were: age ≤ 60 years and diagnosis of AP-CML according to the World Health Organization (WHO) classification[24]; adequate performance status (Eastern Cooperative Oncology Group scale 0-2); and lack of any severe pulmonary, cardiac, liver, or renal diseases or any active infection. Subjects could be pretreated with interferon-α or chemotherapy. Patients who had received imatinib or other tyrosine kinase inhibitors or allo-HSCT before the study were excluded. On entering the study, patients were nonrandomly assigned to treatment with imatinib or allo-HSCT based on their own choice. Patients were followed until the end of the study evaluation period in April 2010. Before beginning, the study protocol was approved by the ethics committee

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*Q.J. and L.-P.X. contributed equally to this study.

of Peking University People's Hospital and registered in the Chinese Clinical Trial Registry (registration number ChiCTR-TNC-10000955). Written informed consent was obtained from all patients before their entry into the study in accordance with the Declaration of Helsinki.

According to the WHO 2001 classification criteria, AP-CML was defined by any of the following features: blasts 10%-19% in peripheral blood or bone marrow, basophils $\geq 20\%$, persistent thrombocytopenia ($< 100 \times 10^9$/L) unrelated to therapy or persistent thrombocytosis ($> 1000 \times 10^9$/L) unresponsive to therapy, increasing spleen size, increasing white blood cell count unresponsive to therapy, cytogenetic evidence of clonal evolution (ie, the appearance of additional cytogenetic abnormalities that were not present in the initial specimen at the time of diagnosis of CP-CML), and megakaryocytic proliferation in sizable sheets and clusters associated with marked reticulin or collagen fibrosis and/or severe granulocytic dysplasia.[24]

Therapy

Imatinib. Patients treated with imatinib were enrolled in the Novartis Expanded Access Study (protocol 114) before 2003 and in the Gleevec International Patient Assistance Program (GIPAP) in China after 2003. They were given imatinib at an initial dose of 600 mg (protocol 114) and 400 mg or 600 mg (GIPAP) daily. The dose was then adjusted according to the patient's response and/or toxicity. Patients were evaluated for hematologic, cytogenetic, and molecular responses at frequent intervals. Hematologic response was analyzed weekly for the first 3 months and once a month thereafter. Cytogenetic and molecular responses were analyzed every 3 months for the first 6 months and every 6-12 months thereafter.

Allo-HSCT. Before allo-HSCT, it was recommended that patients receive short-term imatinib therapy at a dose of 400 mg daily for < 3 months. For those patients who could not afford imatinib, an increasing dose of hydroxyurea $\pm$ interferon-α or combination chemotherapy was recommended. The transplantation protocol was similar to those described previously.[25-30]

Conditioning was performed as follows. In human leukocyte antigen (HLA)–-matched sibling transplants, patients received a regimen consisting of 80 mg/kg hydroxyurea orally on day -10, 2 g/m^2/d cytarabine intravenously on day -9, 4 mg/kg/d busulfan orally before 2008 and 3.2 mg/kg/d busulfan intravenously after 2008 on days -8 to -6, 1.8 g/m^2/d cyclophosphamide intravenously on days -5 to -4, and 250 mg/m^2 of methyl-N-(2-chloroethyl)-N′-cyclohexyl-N-nitrosourea orally on day -3. In cases of HLA-mismatched/haploidentical sibling or unrelated donor transplants, patients received a regimen similar to that for HLA-matched patients, except for the addition of 4 g/m^2/d cytarabine on days -10 to -9 and 2.5 mg/kg/d antithymocyte globulin (SangStat) intravenously on days -5 to -2.

Donor stem cells from bone marrow or peripheral blood stem cells (PBSCs) were mobilized with recombinant human G-CSF (rhG-CSF). In HLA-matched or -mismatched sibling/haploidentical transplants, neither bone marrow nor PBSCs were manipulated and were infused fresh. In unrelated donor transplants, either bone marrow or PBSCs were infused.

A combination of cyclosporine, mycophenolate mofetil, and short-term methotrexate (MTX) was given for acute graft-versus-host disease prophylaxis. Methotrexate was administered intravenously at 15 mg/m^2 on day $+1$ and then at 10 mg/m^2 on days $+3$ and $+6$ in HLA-matched sibling transplants. An additional 10 mg/m^2 was administered on day $+11$ in HLA-mismatched/haploidentical sibling or unrelated donor transplants. Cyclosporine (1.25 mg/kg twice a day) intravenously was started on day -9 and was continued until patients could tolerate oral medication. Thereafter, cyclosporine (3.25 mg/kg twice a day) was given orally with trough levels targeted to 150-250 ng/mL, then tapered based on the presence or absence of severe graft-versus-host disease. It was standard practice to taper cyclosporine gradually beginning at 3 months, completing withdrawal by 6 months after HLA-matched sibling or unrelated donor transplants and by 9 months after HLA-mismatched/haploidentical sibling transplants. Mycophenolate mofetil (1 g daily) orally was begun on day -9 and was discontinued after engraftment in HLA-matched sibling transplants. In unrelated donor transplants, mycophenolate mofetil was tapered from 1 g to 0.5 g daily after engraftment and was discontinued on day $+30$. In HLA-mismatched/haploidentical sibling donor transplants, mycophenolate mofetil was tapered from day $+30$ and was discontinued until day $+60$. Steroids and/or second-line immunosuppressants were used for graft-versus-host disease management. Prophylactic drugs were administered to prevent infection by bacteria, fungi, and viruses.

Serial measurements of BCR-ABL transcript levels in bone marrow after HSCT were performed at 1, 2, 3, 6, 9, 12, 18, and 24 months after transplantation, as well as once a year thereafter. Immunosuppressant withdrawal and either imatinib therapy or modified donor lymphocyte infusion were the interventions used to deal with disease relapse, as has been described elsewhere.[30,31]

Response criteria. The hematologic response criteria were defined as follows.[1] CHR was defined as myeloblast count $\leq 5\%$ in bone marrow, no myeloblasts in peripheral blood, neutrophil and platelet counts of at least 1.5×10^9/L and 100×10^9/L, respectively, and no evidence of extramedullary involvement.[2] The criteria for marrow response were similar to those for CHR, but with neutrophil and platelet counts of at least 1.0×10^9/L and 20×10^9/L, respectively.[3] Return to CP was defined as $< 10\%$ myeloblasts in peripheral blood and bone marrow, $< 20\%$ peripheral basophils, and no extramedullary involvement other than in liver or spleen. Sustained responses were required to last at least 4 weeks. The cytogenetic response was defined as complete (0% Philadelphia chromosome–positive [Ph$^+$] cells), partial (1%-35% Ph$^+$ cells), minor (36%-65% Ph$^+$ cells), minimal (66%-95% Ph$^+$ cells), or none ($> 95\%$ Ph$^+$ cells). MCR was defined as either a complete or partial response. MMR was defined as a 3-log reduction in BCR-ABL transcript levels compared with the standard baseline levels of BCR-ABL transcript, which was 31% (range 10%-87%), the median level of bone marrow samples calculated from 42 newly diagnosed CP-CML patients at our hospital before imatinib therapy. CMR was defined as an undetectable BCR-ABL transcript level.

Outcome definitions. EFS was defined as the time elapsed between the commencement of treatment (with either imatinib or allo-HSCT) and the appearance of 1 of the following events: the absence of hematologic response at 3 months; the loss of previously obtained CHR, MCR or CCR; posttransplantation molecular relapse; relapse in AP or BP; or death from any cause. Posttransplantation molecular relapse was defined as positive BCR-ABL transcripts confirmed in 2 consecutive assays after previously achieving a CMR, or a persistent BCR-ABL transcript increase of more than 1-log. OS was defined as the time from the beginning of treatment to death from any cause. PFS (for responsive patients in the imatinib group and engrafted patients in the allo-HSCT group) was defined as the time elapsed from the beginning of treatment to a relapse in AP or BP. In the allo-HSCT group, relapse was defined to include hematologic, cytogenetic, and molecular relapse.

Cytogenetic and molecular analysis. Cytogenetic analysis was performed by the G-banding technique. Bone marrow specimens were examined on direct short-term (24-hour) cultures, and at least 20 metaphases were analyzed. BCR-ABL transcripts were detected by analyzing bone marrow with nested reverse transcriptase polymerase chain reaction (PCR) before 2004 and with quantitative real-time PCR after 2004. The normalization ratios of BCR-ABL transcript levels in the quantitative PCR analysis were obtained through comparison with the levels of ABL transcript, as reported previously.[32]

Statistical analysis. The Mann-Whitney U, χ^2 (for continuous variables), and Fisher exact (for categorical variables) tests were used to compare differences between the groups. The Kaplan-Meier method was used to assess statistical significance 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, and PFS. The log-rank test was used to identify such prognostic factors. Factors at a level of $P < .2$ were included as variables in the Cox regression model. Factors with an effect significant at the $P \leq .05$ level were interpreted as being independently predictive of the outcomes. All statistical analyses were performed with SPSS Version 13.0 software.

Results

A total of 132 patients with AP-CML were enrolled in the study, 87 in the imatinib group and 45 in the allo-HSCT group. Selected characteristics of the patients before treatment are

Table 1. Patient characteristics

Variable	Imatinib	Allo-HSCT	*P*
No. of patients	87	45	
Age, y			.000
Median (range)	44 (22-60)	34 (10-59)	
Sex, no. (%)			.368
Male	51 (58.6)	30 (66.7)	
Female	36 (41.4)	15 (33.3)	
CML duration, mo			.006
Median (range)	26 (.5-192)	5 (2-80)	
Interval from CML diagnosis to AP, mo			.001
Median (range)	17 (0-191)	2 (0-75)	
Interval from onset AP to treatment, mo			.063
Median (range)	1 (0-66)	3 (1-11)	
Disease status at diagnosis of CML, no. (%)			.535
AP	19 (21.8%)	12 (26.7%)	
CP	68 (78.2%)	33 (73.3%)	
Previous combined chemotherapy for AP, no. (%)			.000
No	53 (60.9)	41 (91.1)	
Yes	34 (39.1)	4 (8.9)	
Splenomegaly, no. (%)			.314
No	58 (66.7)	26 (57.8)	
Yes	29 (33.3)	19 (42.2)	
WBC count, × 10^9/L			.000
Median (range)	9 (1.2-238)	30 (2-280)	
Hemoglobin, g/L			.764
Median (range)	112 (45-162)	106.5 (53-152)	
Platelet count, × 10^9/L			.002
Median (range)	340 (13-2415)	819 (18.5-2338)	
PB blasts, %			.285
Median (range)	0 (0-19)	0 (0-13)	
PB basophils, %			.712
Median (range)	8 (0-56)	10 (0-34)	
BM blasts, %			.103
Median (range)	3 (0-19)	5.3 (0-18.5)	
AP features, no. (%)			
Blasts ≥ 10%	16 (18.4)	12 (26.7)	.270
Basophils ≥ 20%	23 (26.4)	7 (15.6)	.157
Persistent thrombocytopenia	13 (14.9)	4 (8.9)	.325
Persistent thrombocytosis	12 (13.8)	16 (35.6)	.004
Increasing spleen size	29 (33.3)	19 (42.2)	.314
Clonal evolution only	10 (11.5)	3 (6.7)	.541
Hematologic features only	49 (56.3)	38 (84.4)	.001
Both of the clonal evolution and hematologic features	28 (32.2)	4 (8.9)	.003

WBC indicates white blood cell; PB, peripheral blood; and BM, bone marrow

listed in Table 1. Several distinct differences between the 2 groups were evident. Patients in the imatinib group were significantly older and had a significantly longer CML duration and interval from CML diagnosis to AP, higher rates of prior combined chemotherapy and hematologic AP features with clonal evolution, lower rates of hematologic AP features only, and lower white blood cell and platelet counts compared with those in the allo-HSCT group.

Identification of prognostic factors

Because of some significant differences between the 2 groups in terms of their pretreatment characteristics, we analyzed the association of those characteristics with survival. Factors associated with adverse EFS and PFS included CML duration ≥ 12 months, being in CP at the time CML was diagnosed, hemoglobin < 100 g/L, platelet count < 100 × 10^9/L, and peripheral blood blasts ≥ 5%. Factors predictive of adverse OS included the above-mentioned factors as well as bone marrow blasts ≥ 10%, as shown in Table 2.

A multivariate analysis of the total study population, which included variables for the pretreatment characteristics and the patient's therapy of choice (imatinib or allo-HSCT), revealed that CML duration ≥ 12 months and hemoglobin < 100 g/L were independent adverse predictors of EFS, OS, and PFS. In addition, peripheral blood blasts ≥ 5% was an independent adverse factor affecting OS and PFS, and bone marrow blasts ≥ 5% was associated with shorter EFS. Only imatinib therapy was associated with shorter PFS, as shown in Table 3.

Imatinib therapy

Eighty-seven patients were treated with imatinib, 49 (56.3%) of whom received a daily dose of 600 mg and 38 (43.7%) of whom received 400 mg daily. Seventy-four patients (85.1%) achieved a CHR, 5 (5.7%) achieved a bone marrow response, 4 (4.6%) returned to CP, and 4 (4.6%) showed no hematologic response. The median follow-up was 32 months (range, 1-108 months) for all 87 patients and 45 months (range, 7-108 months) for the 53 living patients. Forty-three (49.4%)

Table 2. Factors associated with EFS, OS, and PFS

		EFS			OS			PFS			
Variable	No. of patients	No. of events	6-year EFS rate (%)	*P*	No. of deaths	6-year OS rate (%)	*P*	No. of patients	No. of progression	6-year PFS rate (%)	*P*
Total	132	57	60.6		41	63.0		127	39	63.2	
Age, y				.954			.390				.395
< 40	61	25	53.5		19	62.9		59	19	60.9	
≥ 40	71	32	47.3		22	59.8		68	20	64.9	
Sex				.059			.148				.253
Male	81	40	45.3		28	57.8		77	25	64.4	
Female	51	17	55.8		13	69.8		50	14	60.9	
CML duration, mo				.000			.001				.000
< 12	61	11	80.0		7	86.9		59	4	92.0	
12-36	26	17	32.0		12	49.7		25	12	51.2	
> 36	45	29	32.2		22	48.4		43	23	42.5	
Disease status at diagnosis of CML				.008			.036				.009
AP	31	6	76.3		4	83.7		47	3	88.4	
CP	101	51	44.2		37	58.3		80	36	56.8	
Splenomegaly				.658			.610				.284
Yes	48	21	48.9		15	63.1		46	16	61.8	
No	84	36	52.9		26	63.3		81	23	64.3	
WBC count, × 10^9/L				.301			.341				.297
< 30	92	42	49.3		31	61.4		88	30	60.4	
≥ 30	40	15	51.1		10	63.4		39	9	69.0	
Hemoglobin, g/L				.005			.002				.025
< 100	46	25	39.6		20	47.4		42	17	53.8	
≥ 100	86	32	56.6		21	70.9		85	22	68.1	
Platelet count, × 10^9/L				.000			.000				.000
< 100	17	12	29.4		10	38.2		14	8	42.9	
100-450	51	23	52.0		19	56.1		50	20	55.5	
> 450	64	22	53.8		12	72.9		63	11	74.5	
PB blasts, %				.002			.004				.004
< 5	118	48	52.4		34	68.7		114	32	65.6	
≥ 5	14	9	35.7		7	45.1		13	7	46.2	
PB basophils, %				.447			.045				.681
< 5	54	23	56.0		20	60.7		52	15	68.1	
≥ 5	78	34	43.3		21	63.4		75	24	58.7	
BM blasts, %				.073			.059				.107
< 10	107	43	51.2		31	63.8		105	31	62.0	
≥ 10	25	14	42.4		10	55.7		22	8	63.6	
AP features				.051			.337				.028
Clonal evolution only	13	3	76.9		3	72.5		12	1	90.0	
Hematologic features only	87	37	49.6		27	61.9		85	26	63.3	
Both of the above	32	17	36.2		11	40.6		30	12	49.6	
Therapy				.008			.023				.000
Imatinib	87	45	39.2		34	51.4		83	37	48.3	
Allo-HSCT	45	12	71.8		7	83.3		44	2	95.2	

PB indicates peripheral blood; and BM, bone marrow

patients achieved an MCR, 41 (47.1%) achieved a CCR, 30 (34.5%) achieved an MMR, and 16 (18.4%) achieved a CMR.

Forty-five patients (51.7%) developed events (median, 9 months; range, 1-70 months), including an absence of hematologic response by 3 months (n = 4), loss of CHR (n = 16), and relapse to AP (n = 25). The 6-year EFS rate was 39.2% (95% CI, 32.7%-45.7%), and median EFS was 49 months. Thirty-four patients (39.1%) died (median, 13.5 months; range, 1-86 months) because of an absence

Table 3. Multivariate analysis of adverse prognostic factors associated with EFS, OS, and PFS

	EFS			OS			PFS		
Variable	Estimated HR	95%CI	*P*	Estimated HR	95%CI	*P*	Estimated HR	95%CI	*P*
CML duration ≥ 12 mo	4.5	2.3-8.7	.000	3.4	1.4-7.9	.005	5.5	1.9-15.8	.002
Hemoglobin < 100 g/L	2.0	1.2-3.5	.009	2.3	1.2-4.4	.009	2.0	1.0-3.8	.036
PB blasts ≥ 5%				2.5	1.0-6.0	.041	3.5	1.5-8.3	.005
BM blasts ≥ 10%	2.0	1.1-3.7	.029						
Imatinib therapy							8.6	2.0-37.0	.004

HR indicates hematological response; PB, peripheral blood; and BM, bone marrow

of hematologic response (n = 2) or disease progression (n = 32). The 6-year OS rate was 51.4% (95% CI, 44.3%-58.5%), and median OS was 80 months. Among the 83 responding patients, a total of 37 patients (44.6%) progressed to AP (n = 26) or BP (n = 11; median, 10 months; range 2.5-68 months). The 6-year PFS rate was 48.3% (95% CI, 41.8%-54.8%), and median PFS was 70 months.

At the last follow-up, 7 patients had been enrolled in the clinical trials on the second-generation tyrosine kinase inhibitors sponsored by Novartis Pharmaceuticals or Bristol-Myers Squibb in China. These patients were switched to nilotinib or dasatinib because of a lack of cytogenetic response on imatinib therapy (n = 6) or to relapse (n = 1). Another 7 patients had volunteered to undergo allo-HSCT, including 3 with no hematologic response and 1 that developed relapse, 2 in CHR, and 1 in MMR. Thirty-nine patients remained on imatinib therapy, including 1 (2.6%) in AP, 2 (5.1%) in CP but with a loss of CHR, 36 (92.3%) in CHR, 33 (84.6%) in CCR, 29 (74.4%) in MMR, and 16 (41.0%) in CMR.

Allo-HSCT

Forty-five patients were treated with allo-HSCT. Thirty-two (71.1%) of the patients were treated with short-term imatinib and all achieved a CHR before transplant. Thirteen patients (28.9%) received other therapy before transplant: 2 were treated with combined chemotherapy and 11 were treated with hydroxyurea ± interferon-α; none of them returned to a second CP.

Nineteen patients (42.2%) underwent allo-HSCT from an HLA-matched sibling donor; 23 (51.1%) were from HLA-mismatched/haploidentical siblings or donors, including donors with 1 HLA antigen mismatch (n = 4) and 2 to 3 HLA antigen mismatches (n = 19). Three patients (6.7%) underwent transplants from unrelated donors with 1 HLA antigen mismatch.

All but 1 patient (97.8%) engrafted successfully. Twenty-one (47.7%) of the 44 engrafted patients developed acute graft-versus-host disease (17 with grades I or II and 4 with grades III or IV), and 6 (14.0%) of the 43 patients surviving at least 3 months developed chronic graft-versus-host disease (3 had limited cases; 3 had extensive cases). Forty-three of the patients surviving more than 3 months were analyzed for cytogenetic and molecular responses, and 41 (95.3%) had achieved a CMR at 3-6 months; 2 (4.7%) of these patients were without CMR at 6 months and achieved a CMR after receiving donor lymphocyte infusion. Among the 44 engrafted patients, 5 (11.4%) presented a molecular relapse at a median of 13 months (range, 12-24 months) after transplantation. After receiving imatinib, 4 patients achieved a sustained CMR lasting 36 months (range, 20-69 months); 1 patient progressed to a hematologic relapse in CP after 24 months on imatinib therapy, then was changed to nilotinib and achieved an MMR after 6 months. Two patients (4.5%) developed a hematologic relapse, 1 in AP at 12 months and the other in BP at 13 months. These patients did not respond to imatinib, donor lymphocyte infusion, or chemotherapy, and died 6 months and 3 months later, respectively. Among all 45 patients, 12 (26.7%) developed events (median, 12.5 months after transplant; range, 1.7-41 months), including transplantation-related mortality (graft failure, n = 1; severe infection, n = 2; or graft-versus-host disease, n = 2), molecular relapse (n = 5), and relapse in AP or BP (n = 2). Among the 7 patients who developed a molecular or hematologic relapse, 2 had undergone HLA-matched sibling transplants and 5 had received HLA-mismatched/haploidentical sibling transplants. Seven patients (15.6%) died (median, 16 months after transplant; range, 1.7-41 months) because of transplantation-related mortality (n = 5) and relapse in the advanced phase (n = 2). The median follow-up was 51 months (range, 1.7-108 months) for all 45 patients and 65 months (range, 19-108 months) for the 38 living patients. The 6-year EFS, OS, and PFS rates were 71.8%, 83.3%, and 95.2%, respectively (with 95% CI of 64.8%-78.8%, 77.4%-89.2%, and 91.9%-98.5%, respectively), and median EFS, OS, and PFS had not yet been reached. The 6-year probability of relapse was 17.1% (95% CI, 11.2%-23.0%).

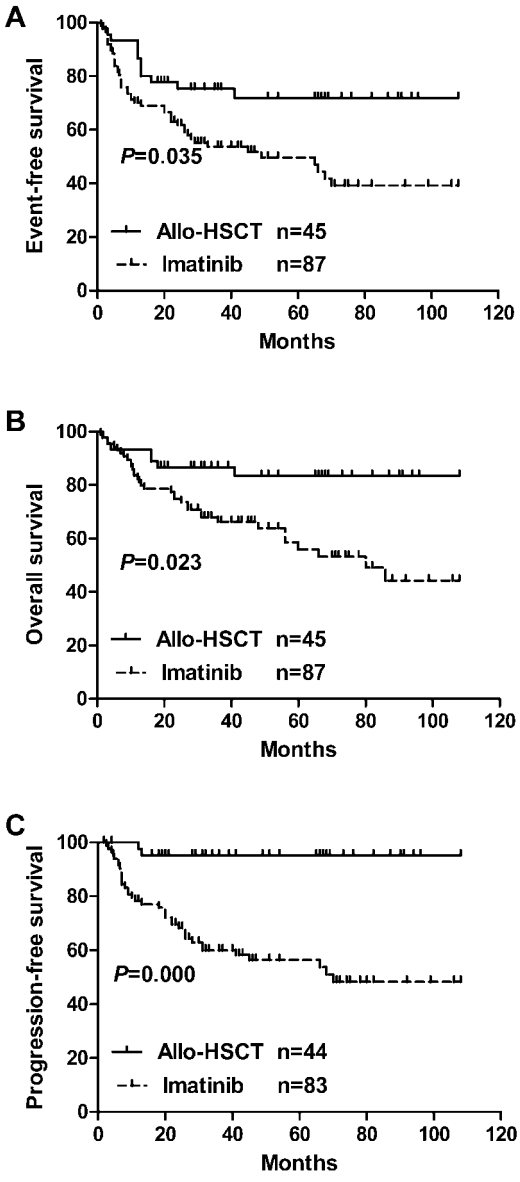

Figure 1. Survival of the entire cohort by therapy. (A) Event-free survival. (B) Overall survival. (C) Progression-free survival.

At the last follow-up, 38 patients were alive, 4 of whom were on imatinib (n = 3) or nilotinib (n = 1) therapy. All 38 (100%) patients were in CCR, 37 (97.4%) were in CMR, and 1 (2.6%) was on nilotinib therapy in MMR.

Comparison survivals between the imatinib group and the allo-HSCT group

Comparing the 2 cohorts, patients treated with allo-HSCT had significantly longer EFS ($P = .008$), OS ($P = .023$), and PFS ($P = .000$) than those treated with imatinib. The Kaplan-Meier survival curves are shown in Figure 1.

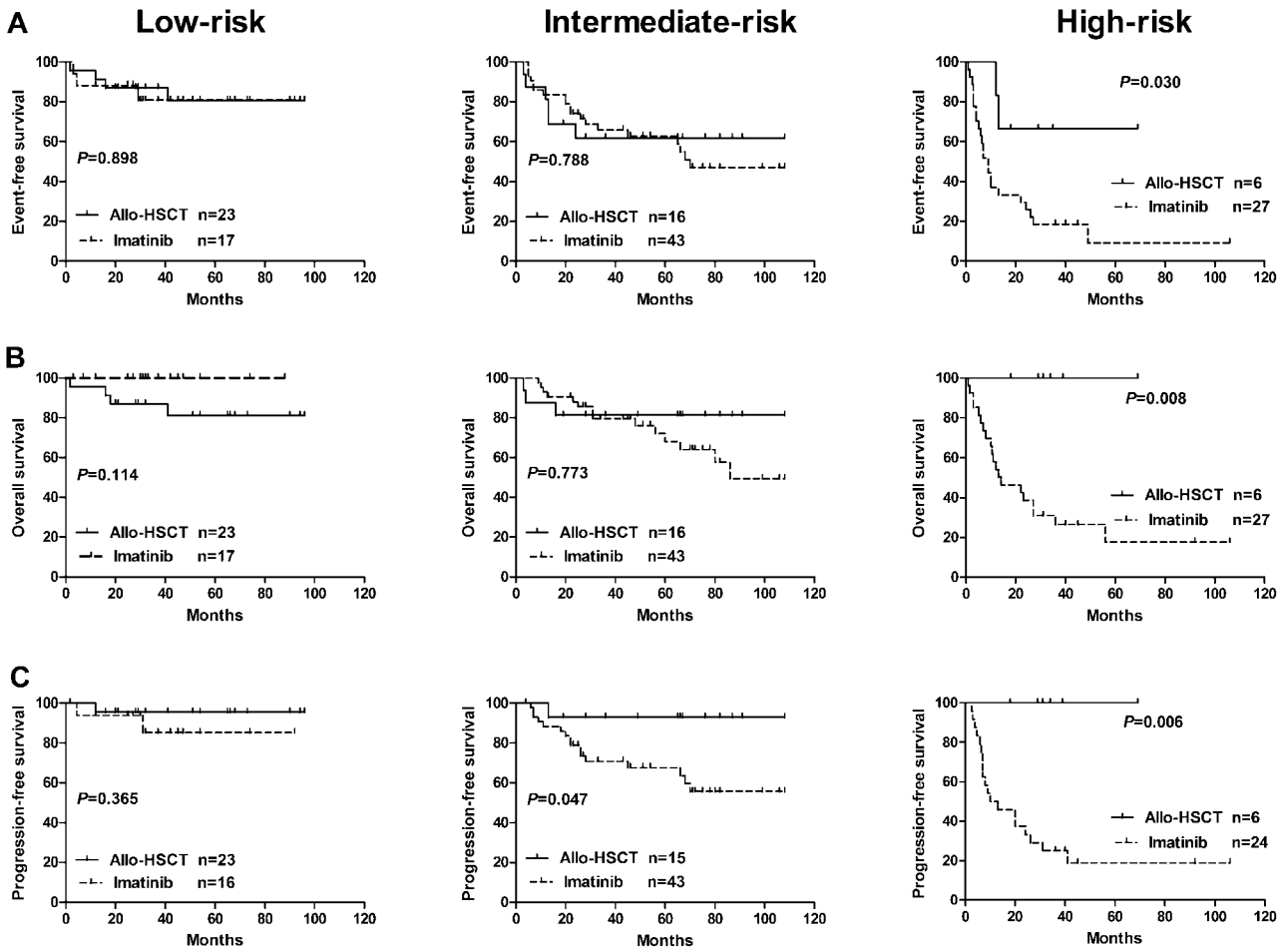

Figure 2. Survival in low-, intermediate-, and high-risk patients by therapy. (A) Event-free survival. (B) Overall survival. (C) Progression-free survival. In low-risk patients, 6-year EFS, OS, and PFS rates were 80.9% vs 80.7% ($P = .898$), 100% vs 81.2% ($P = .114$), and 85.2% vs 95.2% ($P = .365$) in the imatinib group vs the allo-HSCT group, respectively. In intermediate-risk patients, 6-year EFS, OS, and PFS rates were 47.1% vs 61.9% ($P = .788$), 61.3% vs 81.3% ($P = .773$), and 55.7% vs 92.9% ($P = .047$) in the imatinib group vs the allo-HSCT group, respectively. In high-risk patients, 5-year EFS, OS, and PFS rates were 9.3% vs 66.7% ($P = .030$), 17.7% vs 100% ($P = .008$), and 18.8% vs 100% ($P = .006$) in the imatinib group vs the allo-HSCT group, respectively.

In an attempt to determine whether choice of therapy contributed to the survival differences among patients with or without common poor prognostic factors (CML duration ≥ 12 months, hemoglobin < 100 g/L, and peripheral blood blasts $\geq 5\%$) for OS and PFS before treatment based on the multivariate analyses of the total population, we categorized the entire cohort into low risk (possessing none of the factors, n = 40), intermediate risk (possessing any one of the factors, n = 59), or high risk (possessing at least 2 factors, n = 33).

In low-risk patients, data collected at a median follow-up of 47 months (range, 7-96 months) from the 35 living patients suggested that choice of therapy did not influence outcome. This conclusion was confirmed by at the absence of significant differences in EFS, OS, and PFS between the imatinib (n = 17) and allo-HSCT (n = 23) groups, with 6-year EFS, OS, and PFS rates of more than 80.0%. In intermediate-risk patients, after a median follow-up time of 66.5 months (range, 11-108 months) for the 42 surviving patients, EFS and OS did not differ in terms of therapy, with 6-year EFS and OS rates for imatinib (n = 43) and allo-HSCT (n = 16) of 47.1% versus 61.9% ($P = .788$) and 61.3% versus 81.3% ($P = .773$), respectively. Although more AP patients in the imatinib group developed relapses compared with those in the allo-HSCT group, 6-year PFS rates were 55.7% versus 92.9% ($P = .047$), respectively. In high-risk patients, the median follow-up was 37.5 months (range, 18-106 months) for the 12 living patients, and treatment with allo-HSCT was significantly superior, with 5-year EFS, OS, and PFS rates for imatinib (n = 27) and allo-HSCT (n = 6) of 9.3% versus 66.7% ($P = .030$), 17.7% versus 100% ($P = .008$), and 18.8% versus 100% ($P = .006$), respectively. These findings are shown in Figure 2.

Current responses of surviving patients in the imatinib group versus the allo-HSCT group

Differences between the surviving patients in each group, based on an evaluation of data collected at their last follow-ups, are shown in Table 4. Significantly higher proportions of MCR, CCR, MMR, and CMR were found in the allo-HSCT group compared with the imatinib group.

Discussion

Today, imatinib allows doctors to rescue patients with AP-CML, but almost half of these patients relapse within 4-5 years.[5-12] Although allo-HSCT represents the only potential cure for CML in all phases, imatinib's effectiveness for many patients has made treatment decisions more complex. As a consequence, the number

Table 4. Current hematological, cytogenetic, and molecular responses of surviving patients by therapy

	Imatinib	Allo-HSCT	*P*
No. of surviving patients	39	38	
Median follow-up (range), mo	47 (25-108)	65 (18-108)	.658
CHR, no. (%)	36 (92.3)	38 (100)	.240
MCR, no. (%)	33 (84.6)	38 (100)	.025
CCR, no. (%)	33 (84.6)	38 (100)	.025
MMR, no. (%)	29 (74.4)	38 (100)	.001
CMR, no. (%)	16 (41.0)	37 (97.4)	.000

of patients receiving allo-HSCT for CML has decreased substantially, particularly CP patients.[13] However, it is widely accepted that allo-HSCT can play an important role in the treatment of CML in the advanced phase.[20-23] To our knowledge, this is the first report based on a cohort, comparative study that has been designed to evaluate the value of allo-HSCT for AP-CML compared with imatinib in the era of tyrosine kinase inhibitors. Because it was impossible to design a randomized study to compare the 2 treatment approaches in patients with AP-CML in China for both ethical and practical reasons, we compared the outcomes of the 2 therapies among patients who had freely chosen one or the other treatment.

Based on a 9-year follow-up, our data for the imatinib group showed 6-year EFS, OS, and PFS rates (39.2%, 51.4%, and 48.3%, respectively) that were similar to those reported elsewhere in the literature.[7-12] Our experience had shown that survival rates (6-year EFS, OS, and PFS rates of 71.8%, 83.3%, and 95.2%, respectively) for patients treated with allo-HSCT were superior to those reported in other studies. According to a study by the European Group for Blood and Marrow Transplantation (EBMT), the probability of survival at 5 years after treatment was 29% among 444 patients with AP-CML undergoing allo-HSCT between 1980 and 1990.[13] The most recent International Bone Marrow Transplant Registry (IBMTR) update analyzed CML patients undergoing marrow (n = 273) and PBSC (n = 117) myeloablative transplantations in second CP/AP between 1998 and 2006. The estimated 5-year survival rates in that study were 32% ± 6% and 36% ± 10%, respectively.[16] Several factors might have contributed to our superior transplantation outcomes. First, the initial reduction of the leukemia load via short-term treatment with imatinib as a bridging therapy seemed to result in lower transplantation-related mortality and better chances of long-term survival, both of which have been shown to largely depend on disease status at the time of transplantation. In our study, 32 (71.1%) patients achieved a second CP with short-term imatinib therapy before transplantation. In support of this interpretation is the significantly higher probability of survival after allo-HSCT treatment for first CP-CML patients with a reduced disease burden because of treatment with imatinib, as reported by Lee et al.[33] Second, posttransplantation monitoring of BCR-ABL transcripts by quantitative PCR and tyrosine kinase inhibitors or modified donor lymphocyte infusion intervention guided by minimal residual disease levels might have contributed to these improved outcomes. Several trials have demonstrated that the quantification of BCR-ABL transcripts after allo-HSCT was predictive of relapse,[34,35] and that individualized intervention (tyrosine kinase inhibitors and donor lymphocyte infusion) based on the minimal residual disease level can decrease relapse and improve survival.[30] Data from our institute showed that of 28 patients with CML with high BCR-ABL transcript levels after transplantation who received imatinib and/or modified donor lymphocyte infusion, 25 achieved a durable CMR.[30] Third, most patients with a shorter interval between the initial diagnosis of CML and transplantation (the median CML duration in the current study was 5 months) were more likely to have better outcomes according to the EBMT risk scale.[21]

In our study, we found that allo-HSCT conferred survival advantages in terms of EFS, OS, and PFS compared with those treated with imatinib. In addition, allo-HSCT also delivered a higher quality of molecular response than did imatinib (CMR rates of 97.4% vs 41.0%). The better outcome of allo-HSCT compared with imatinib may have contributed to several significant differences between the 2 groups in terms of patients' pretreatment characteristics. Although a multivariate analysis of the total study population, including variables for the pretreatment characteristics and the patient's therapy, found that imatinib therapy did not negatively affect EFS and OS, its only significant relationship was to PFS. After accounting for factors known to adversely affect OS and PFS, we found that the superiority of allo-HSCT (relative to imatinib) in terms of EFS, OS, and PFS was particularly significant among high-risk patients, with 5-year EFS, OS, and PFS rates of 66.7% versus 9.3%, 100% versus 17.7%, and 100% versus 18.8%, respectively. Allo-HSCT was also associated with a lower probability of relapse to the advanced phase among intermediate-risk patients, with 6-year PFS rates of 92.9% versus 55.7% (for imatinib). Long-term observation of high- and intermediate-risk patients treated with imatinib demonstrated that their survival curves continued to decline because of events or disease progression. Based on the good results collected, we recommend early transplantation for previously imatinib-untreated AP-CML patients after achieving a second CP with imatinib. This course of treatment should be weighed against the risk of transplantation-related mortality and the subsequent relapse with imatinib therapy because of advanced disease. In the imatinib group, 11 patients had either switched to the second-generation tyrosine kinase inhibitors or undergone allo-HSCT because of imatinib resistance. Although the second-generation tyrosine kinase inhibitors have been introduced as therapeutic alternatives to allo-HSCT, responsiveness to these drugs might not last long for a substantial proportion of patients with AP-CML.[36,37] Therefore, our findings confirm that allo-HSCT continues to be a viable treatment option for all eligible patients with AP-CML, particularly for high- and intermediate-risk patients.

Kantarjian et al have identified pretreatment anemia and a lack of cytogenetic response after 3 months on imatinib therapy as negative predictors of survival in AP-CML. In that study, the estimated 4-year survival rates were 88% for low-risk patients (ie, those with no negative factors present) and 60% for other patients.[9] The GIMEMA CML Working Party found that the achievement of a CHR or CCR by imatinib was predictive of a better outcome in AP-CML. After a 7-year follow-up, the median survival time had not been reached.[12] These data suggest that a specific cohort with AP-CML had a longer-than-expected rate of survival on imatinib therapy. Our study also identified independent prognostic factors for survival, and showed that low-risk patients treated with imatinib had a similarly good prognosis compared with the findings that have been reported in the above-mentioned literature. Moreover, those undergoing allo-HSCT in the same period had similar outcomes, with 6-year EFS, OS, and PFS rates above 80%. Therefore, we suggest that although AP-CML patients can generally benefit from allo-HSCT, transplantation for those classified as low-risk AP may be delayed. Such patients' responsiveness to imatinib treatment should be carefully monitored; allo-HSCT may be a salvage option for low-risk patients with AP-CML at the time of relapse.

Today, second-generation tyrosine kinase inhibitors are not only used for salvage of imatinib failure, but have also been shown in

randomized prospective trials to be superior for first-presentation CP-CML.[38,39] Whether allo-HSCT was superior to the second-generation tyrosine kinase inhibitors for the previously imatinib-untreated AP-CML patients remains to be determined in another prospective study.

As a limitation to our current study, it has to be stated that the patients were not randomized to receive imatinib or allo-HSCT. In addition, there were significant differences in the demographic characteristics between the 2 groups: the transplantation cohort was younger and the interval from CML diagnosis to AP was shorter than in the imatinib cohort. In addition, the choice of therapy was determined by the patients themselves. Although additional socio-economic factors, which probably influenced the outcomes, cannot be eliminated completely, we do not think that these played an important role.

In summary, our data suggest that allo-HSCT is a viable option for all patients with AP-CML. It is superior to imatinib, conferring significant survival advantages to high- and intermediate-risk patients. In such cases, we recommend that patients receive an early transplantation after achieving a second CP with imatinib. However, the outcomes of imatinib and allo-HSCT are equally good in low-risk patients with AP-CML. For such patients, imatinib may remain the primary option so long as the minimal residual disease is carefully monitored, and allo-HSCT should be considered if there is evidence of imatinib resistance.

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Authorship

Contribution: Q.J. and L.-P.X. designed the research, interpreted the data, and wrote the manuscript; D.-H.L., K.-Y.L., S.-S.C., B.J., H.J., H.C., Y.-H.C., W.H., X.-H.Z., and Y.W. performed the study and contributed to writing the manuscript; Y.-Z.Q. Y.-R.L., and Y.-Y.L. performed research and conducted the molecular and cytogenetic analyses; and X.-J.H. was the principal investigator, designed the research, interpreted the data, and wrote the manuscript.

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Correspondence: Xiao-Jun Huang, Peking University People's Hospital, Peking University Institute of Hematology, No 11 Xizhimen South St, Beijing, 100044, China; e-mail: xjhrm@medmail.com.cn.

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