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Long term follow-up of Asian patients with chronic myeloid leukemia (CML) receiving allogeneic hematopoietic stem cell transplantation (HSCT) from HLA-identical sibling—evaluation of risks and benefits

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Abstract Allogeneic hematopoietic stem cell transplantation (HSCT) is the only known curative therapy for patients with chronic myeloid leukemia (CML), but is associated with significant morbidity and mortality. The recent introduction of imatinib mesylate (STI-571) and reduced intensity transplant regimens has made the choice of primary treatment for patients with CML increasingly difficult. We have evaluated the outcome of 53 patients who have received allogeneic HSCT from human leukocyte antigen (HLA)-identical sibling donors between October 1985 and March 2002, determined the variables affecting the outcome, and tried to define indications for this aggressive approach. Successful engraftment occurred in 49 (98%) of evaluable patients. Acute graft-versus-host disease (GVHD) of grade II to IV severity was observed in 63% of the evaluable patients whereas the incidence of chronic GVHD was 57.5%. The Kaplan-Meier estimate of survival at 10 years was 54% [95% confidence interval (CI): 38–70%] and 31% (95% CI: 6–56%) for patients with first chronic phase and more advanced diseases, respectively. Multivariate analysis showed that younger age, absence of grade III-IV GVHD, the use of busulphan and cyclophosphamide (BuCy) as preparative regimen, and transplantation performed after January 1992 were factors associated with improved survival. Patients who were 30 years of age or younger who had transplantation done within 1 year after diagnosis during their first chronic phase of disease had a particularly good prognosis, with a probability of surviving 10 years of 72% (95% CI: 52–92%). We conclude that allogeneic HSCT remains a feasible option for Asian patients with CML. The most favorable outcome is observed in younger patients with early phase of the disease.

Keywords Allogeneic transplant · Chronic myeloid leukemia · Chronic phase · Matched sibling · Graft-versus-host disease · Blast crisis

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Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder that accounts for approximately 20% of all cases of leukemia. The disease is characterized by the presence of Philadelphia (Ph) chromosome, a balanced translocation of the long arm arms of chromosomes 9 and 22 [26]. The median age at presentation is 53 years and the median survival time is 4–5 years. The natural history of CML is progression from a benign chronic phase to a rapidly fatal blast crisis within 3–5 years [33].

In the past 2 decades the therapy of CML has changed with use of hydroxyurea, interferon-alpha (IFN-α), high-dose therapy followed by hematopoietic stem cell transplantation (HSCT), and most recently, imatinib mesylate (formerly STI-571, Glivec, Gleevec). In contrast with other therapies, HSCT is the only curative treatment for CML, which has a 5-year disease-free survival (DFS) approaching 50%, when performed in chronic phase, using stem cells from human leukocyte antigen (HLA)-matched sibling donor [37]. However, the advantage of long-term survival is offset by the risk of early death due to transplant-related complications such as graft-versus-host disease (GVHD) and opportunistic infections, especially in older patients. Although age is clearly an important prognostic variable, the decision for transplantation must be considered individually in the light of other variables that influence outcome such as stage of disease, level of donor and recipient HLA matching, donor-

recipient sex combination, time of diagnosis to transplantation, and viral status of donors and recipients [17, 33].

The recent introduction of the specific BCR-ABL tyrosine kinase antagonist imatinib mesylate [12, 21, 27] and reduced intensity transplant regimens [29] has marked a new era in the treatment of CML. In contrast to the significant mortality and morbidity associated with HSCT using myeloablative preparative regimens [9], these two novel approaches are appealing in view of their great potential in providing safer and well-tolerated therapeutic options. As such, the choice of optimal upfront treatment for patients with newly diagnosed CML has become exceedingly difficult. As most of the reports in the literature focussed predominantly on patients from European and North American centers, there are relatively limited data among the Asian patients with regard to prognostic variables which predict post-transplant outcome. With the objectives of identifying prognostic variables that may give some guidance in the decision-making process for the Asian populations, we analyzed the transplant outcome of the 53 CML patients who have received allogeneic bone marrow or peripheral blood stem cells transplantation from HLA-identical siblings in our institution between 1985 and 2002.

Patients and methods

Patient population

From October 1985 to March 2002, 53 patients with Ph chromosome-positive CML received allogeneic HLA-identical sibling HSCT at our institution. The diagnosis was confirmed by clinical examination and morphologic and cytogenetic analysis of bone marrow immediately before transplantation. All patients provided written informed consent. All evaluations were based on data available on 25 December 2002.

Patients' characteristics are depicted in Table 1. Forty (75%) patients were in first chronic phase, and 13 (25%) had more advanced disease [five were in accelerated phase, six were in blastic phase, and two were in second chronic phase (after successful treatment of blastic transformation with chemotherapy)].

Table 1 Characteristics of 53 CML patients with allogeneic hematopoietic stem cell transplantation from HLA-matched siblings. *Bu* busulphan, *Cy* cyclophosphamide, *TBI* total body irradiation, *CyA* cyclosporin A, *MTX* methotrexate, *PDS* prednisolone, *ATG* antithymocyte globulin, *IFN* interferon-α, *CMV* cytomegalovirus

	Chronic phase	Advanced disease
Patients (*n*)	40	13
Sex		
Male	21	7
Female	19	6
Age (years)		
Median	27	30
Range	3–40	15–40
Interval from diagnosis to transplantation (months)		
Median	7.1	12.3
Range	1.9–49.4	2.1–49.2
Conditioning regimen		
Bu + Cy	34	8
Cy + TBI	5	5
Bu + Cy + ATG	1	-
Number of marrow cells transplanted ($\times 10^8$/kg recipient's body weight)		
Median	2.7	2.8
Range	1.6–9.0	1.9–3.9
GVHD prophylaxis		
CyA + MTX	39	12
CyA + MTX + PDS	-	1
CyA alone	1	-
Engraftment (days)		
Median	16	18
Range	10–30	12–29
CMV status (donor/recipient)		
–/–	8	0
+/+	15	4
+/–	4	0
–/+	1	0
Unknown	12	7
Donor-recipient gender match (donor→recipient)		
Male→male	12	3
Male→female	7	2
Female→female	14	3
Female→male	7	5
Prior IFN therapy		
Yes	14	1
No	26	12
Year of transplant		
Before 1992	8	4
After January 1992	32	9

Donors

All donors were HLA-identical at the A, B, DRB1 loci with their respective recipients. HLA matching for donors and recipients has been based on conventional serologic typing methods. All patients except one received bone marrow from their HLA-identical siblings. One patient received granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cell (PBSC) from his HLA-identical sibling.

Transplantation procedure and supportive care

Before transplantation, 43 (81%) patients received a BuCy regimen which consisted of oral busulfan (1 mg/kg of body weight every 6 h over 4 days) in combination with intravenous cyclophosphamide (60 mg/kg of body weight per day ×2 days) and 10 (19%) patients received the CyTBI regimen which consisted of intravenous cyclophosphamide (60 mg/kg of body weight per day ×2 days) in combination with fractionated total body irradiation (TBI) 2 Gy twice daily for 3 days. Antithymocyte globulin was added to the BuCy regimen in one (1.9%) of the patients.

GVHD prophylaxis regimen consisted of cyclosporin in combination with methotrexate [34] in 51 patients (96.2%), cyclosporin in combination with tacrolimus (FK506) in 1 patient (1.9%), and cyclosporin in combination with methotrexate and prednisolone in 1 patient (1.9%).

All transplants were performed in reverse isolation rooms. All patients were given gram negative bacterial prophylaxis, which was begun 1 day before conditioning regimen and continued until neutrophil engraftment. Since January 1993, all patients were randomly assigned to either oral fluconazole 200 mg/day, syrup itraconazole 200 mg/day or low-dose intravenous amphotericin B

0.2 mg/kg per day up to a maximum of 10 mg/day, as prophylaxis against fungal infections. Broad-spectrum antibiotics were used to treat initial episodes of fever. High-dose amphotericin B (0.5–1.0 mg/kg per day) was initiated for patients with suspected or proven fungal infections. All patients undergoing HSCT from 1991 onwards were given subcutaneous granulocyte colony-stimulating factor (G-CSF) 5 μg/kg per day until absolute neutrophil count exceeded 500/mm^3. Since 1991, all patients were given cytomegalovirus (CMV) prophylaxis using ganciclovir from day +28 to day +84. CMV reactivation was determined weekly either by pp65 antigen in blood leukocyte (between 1994 and 1998) or by polymerase chain reaction (PCR) assay (from 1998 onwards). All blood products were irradiated (2500 cGy) and filtered before they were infused. Immunoglobulin was administered to all patients in a dose of 500 mg/kg weekly from day −7 to day +54.

Patients who were discharged after transplantation were enrolled in our long-term follow-up program. Outpatient visits were performed at least monthly during the first 6 months and then at 3-month intervals during the first 2 years after transplantation. After 2 years, the patients were usually seen at 6-monthly to yearly intervals.

Engraftment, GVHD, and relapse

Neutrophil engraftment was considered to have occurred on the first of 3 consecutive days in which the absolute neutrophil count exceeded 500/mm^3. Platelet engraftment was considered to have occurred on the first of 7 consecutive days in which the platelet count exceeded 20,000/mm^3 without platelet transfusions. From 1995 onwards, the presence of donor cells was demonstrated by the detection of informative variable number tandem repeat (VNTR) polymorphism [2]. Graft failure was defined as the failure to achieve absolute neutrophil count of more than 500/mm^3 for at least 3 consecutive days, a decreased absolute neutrophil count to below 200/mm^3 for at least 3 consecutive days after initial engraftment, or documentation of the loss of donor cells by the VNTR studies.

Acute and chronic GVHD were diagnosed and graded according to standard criteria [31, 35, 36]. The probability of chronic GVHD was evaluated in patients who survived for at least 100 days in clinical remission with sustained engraftment. Steroid refractory acute GVHD was defined as grade 2 to 4 GVHD that progressed after 3 days of methylprednisolone at a dose of 2 mg/kg, or grade 2 to 4 GVHD that recurred after tapering the dose of methylprednisolone.

Relapse was defined by either morphologic recurrence of leukemia or the detection of Ph chromosome on at least two occasions. Marrow cytogenetic studies were scheduled on days 28 and 84 and then 6–12 monthly depending on patients' clinical outcome.

Statistical analysis

Results of the study were analyzed as of 25 December 2002. Prognostic factors influencing overall survival (OS), relapse, and development of GVHD were investigated. In evaluation of engraftment, patients who died before day +22 without engraftment were considered not evaluable and censored at time of death. Patients who died after day +22 without engraftment were considered as graft failures and for analysis of engraftment were censored at death or at day +42, whichever came first.

Disease-free survival (DFS) was defined as survival without morphologic evidence of recurrent leukemia or Ph chromosome in either the marrow or blood. The time to event was defined as time from first transplant to time of hematological relapse, death, or last contact in remission. Probabilities of overall survival, DFS, relapse, treatment-related mortality, and acute or chronic GVHD were calculated by the method of Kaplan and Meier [22] and the levels of significance were calculated by the log-rank statistic [25]. Patients who were never free of disease after transplant (n=2) were excluded from analyses of relapse.

For the purpose of analysis, the patients' age and the interval from diagnosis to transplantation were treated as categorical variables. The time to development of GVHD, relapse, or death was also examined by the univariate Kaplan-Meier method and stepwise Cox regression analysis [10]. All variables found to have a p value of less than 0.20 in univariate analyses were considered candidate variables for multivariate analysis.

Pretransplant risk factors scoring system

To test whether pretransplant risk factors were accumulative for individual patients, we used a modified version of a published score system by Gratwohl et al. [17]. The risk score for an individual patient was the sum of the following four risk factors: disease stage (0 for first chronic phase, 1 for accelerated phase, and 2 for blast crisis or higher chronic phase), age of recipients (0 for <20 years, 1 for 20–40 years, and 2 for >40 years), donor-recipient gender match (0 for all, except 1 for male recipient/female donor), and time from diagnosis to transplantation (0 for <12 months, 1 for >12 months). The lowest possible score on this scale is 0, which applies to patients who receive a graft from an HLA-identical sibling donor within 12 months of diagnosis, in first chronic phase, below the age of 20 years, and is not male with a female donor. The highest possible score on this scale is 6, which applies to a male patient, over the age of 40 years, who receives a graft in blast crisis from a female HLA-identical sibling donor, beyond 12 months from diagnosis.

Results

Engraftment

Three patients died before day 22 after transplantation, leaving 50 patients evaluable for engraftment. Primary graft failure occurred in one patient (2%). This patient received a second marrow infusion 28 days after the first marrow infusion. Neutrophil engraftment occurred on the 28th day of the second marrow infusion, but the patient succumbed to interstitial pneumonitis 2 months later.

The median times to neutrophil recovery and platelet recovery for all evaluable patients were 17 days (range: 10–30 days) and 24 days (range: 16–97 days), respectively. The disease status at transplantation, prior interferon therapy, number of marrow cells infused, and time from diagnosis to transplantation were not found to significantly influence the median time to engraftment.

Graft-versus-host disease

The incidence of various stages of acute and chronic GVHD is presented in Table 2. Of 50 evaluable patients, 31 (62%) developed grade 2–4 acute GVHD (aGVHD) and 18 of them (36%) had grade 3–4 acute GVHD. The estimated probability of developing grade 2–4 acute GVHD was 62% at 100 days. The risk of acute GVHD was not significantly associated with patients' age, sex of patient-donor pairs, disease status, conditioning regimen, and the time from diagnosis to transplantation.

Chronic GVHD was seen in 23 (56%) of 41 patients who survived without relapse for at least 100 days. Chronic extensive GVHD was seen in nine (21.9%) of

Table 2 Incidence of GVHD

	Chronic phase (n=40) n (%)	Advanced phase (n=13) n (%)	Total (n=53)
Acute GVHD			
Early death[a]	1 (25%)	2 (15.4%)	3
None	8 (20%)	3 (23.1%)	11
I	7 (17.5%)	1 (7.7%)	8
II	9 (22.5%)	4 (30.8%)	13
III	13 (32.5%)	2 (15.4%)	15
IV	2 (5%)	1 (7.7%)	3
Chronic GVHD			
Early death[b]	6 (20.6)	6 (46.1)	12
None	16 (34.4)	2 (15.4)	17
Limited	12 (30)	2 (15.4)	14
Extensive	6 (15)	3 (23.1)	9

[a] Three patients died at <day +28 without acute GVHD
[b] Twelve patients died at <day +100

these patients. The estimated probability of developing chronic GVHD was 62% at 30 months. There was no impact of patients' age, sex of patient-donor pairs, disease status, conditioning regimen, and the time from diagnosis to transplantation on the risk of chronic GVHD.

Relapse

Relapse occurred in 12 of 30 chronic phase patients (40%) and 3 of 11 advanced phase (27%) patients. For patients with disease in chronic phase, the median time to relapse was 13.8 months (range: 1.9–37.4 months) and the median time from diagnosis to transplantation was 8.6 months (range: 2–25 months). Whereas for patients with advanced diseases, the median time to relapse was 38.6 months (range: 9.6–85.5 months) and the median time from diagnosis to transplantation was 12.3 months (range: 6.1–32.9 months). Multivariate Cox regression analysis did not reveal any predictive factors that are associated with increased risk of relapse.

Cytogenetic relapse was the most common type of relapse and this was observed in 11 patients (73%). Three patients (20%) presented with hematological evidence of relapse and one patient (7%) presented with molecular relapse before evidence of cytogenetic relapse was demonstrated. At the most recent follow-up, 11 of the 15 patients (73%) were alive 286–3996 days after transplantation, and 9 were in complete remission (5 molecular remission, 4 complete cytogenetic remission) after discontinuing immunosuppressive therapy (1 patient), receiving treatment with IFN-α (2 patients), receiving donor lymphocyte infusion (4 patients), or receiving therapy with imatinib (2 patient). Four died eventually because of uncontrolled leukemia or complications of therapy. With a median follow-up of 33 months (range: 2–67 months) from the time of relapse, the probability of survival for 5 years after relapse was 71% (95% CI: 47–95%).

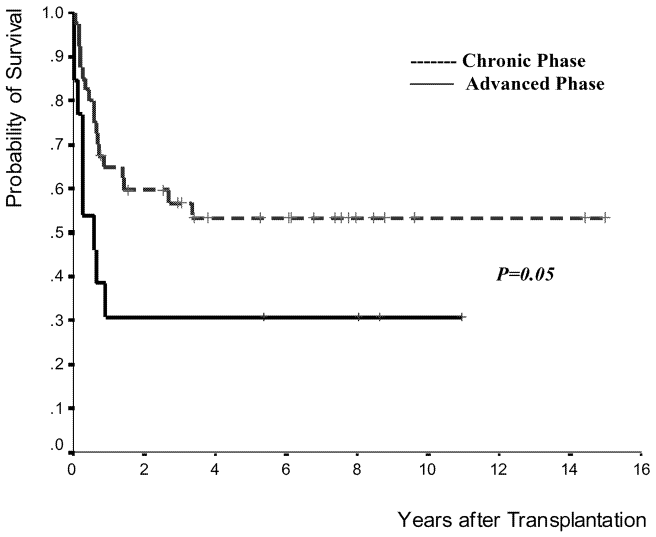

Fig. 1 Overall survival in 40 chronic phase and 13 advanced phase patients receiving allogeneic haematopoietic stem cell transplantation for CML

Cause of death

Twenty-seven (51.9%) patients died after transplantation. Their median follow-up after transplantation was 166 days (range: 6–1219 days). The cause of death included graft failure in 1, relapse in 4, infection in 14, GVHD in 5, veno-occlusive disease in 1, and hemorrhage in 1.

Survival

The probabilities of OS and DFS at 10 years were 48% (95% CI: 34–62%) and 43% (95% CI: 29–57%), respectively. The median follow-up of surviving patients was 6.8 years (range: 0.8–15 years). Patients in first chronic phase had an overall survival superior to those in more advanced phase [54% (95% CI: 44–64%) vs 31% (95% CI: 6–56%), p=0.05] (Fig. 1). Disease-free survival was more favorable for patients with first chronic phase as compared with those with advanced disease although the difference was not statistically significant [47% (95% CI: 31–63%) vs 31% (95% CI: 6–56%), p=0.17].

A multivariable analysis identified age, grade 3–4 acute GVHD, the use of cyclophosphamide, and TBI as preparative regimen and transplant performed before 1992 as the four factors which are associated with increased risk of death (Table 3). Patients who were over 30 years of age had a significantly higher risk of death than patients who were less than 30 years of age (relative risk: 4.59, 95% CI: 1.67–12.63%). Their 8-year OS was only 16% (95% CI: 7–25%), and this was significantly inferior to the 63% (95% CI: 55–71%) seen among patients who were younger than 30 years of age. Multivariate Cox regression analysis also identified the age of more than 30 years (p=0.02), the use of cyclophosphamide and TBI preparative regimen

Table 3 Univariate and multivariate analysis of mortality of 53 patients with CML receiving allogeneic HSCT from HLA-identical siblings. *IFN* interferon-α, *TBI* total body irradiation, *GVHD* graft-versus-host disease

Variable	*n* (%)	*p* value		Relative risk (95% confidence interval)
		Univariate analysis	Multivariate analysis	
Patient's age		0.001	0.006	
≤30 years	36 (68)			1.0
>30 years	17 (32)			4.59 (1.37–6.80)
Status at transplant		0.06		
First chronic phase	40 (76)			
Advanced disease	13 (24)			
Prior IFN therapy		0.22		
Yes	15 (28)			
No	38 (72)			
Interval from diagnosis to transplant		0.098		
>1 year	18 (34)			
≤1 year	35 (66)			
TBI-based conditioning regimen		0.005	<0.001	
Yes	10 (81)			5.71 (2.34–13.89)
No	43 (19)			1.0
Donor-recipient gender match		0.592		
Female→male	12 (23)			
Others	41 (77)			
Acute GVHD grade 2–4		0.388		
Yes	30 (57)			
No	23 (43)			
Acute GVHD grade 3–4		0.048	0.008	
Yes	18 (34)			4.47 (1.48–13.52)
No	35 (66)			1.0
Chronic GVHD		0.392		
Yes	23 (43)			
No	30 (57)			
Steroid-resistant GVHD		0.064		
Yes	10 (19)			
No	43 (81)			
Year of transplant		0.002	<0.001	
≥1992	41 (77)			1.0
<1992	12 (23)			6.79 (2.55–18.08)

(p=0.006), development of grade 3–4 acute GVHD, and transplant performed before the year of 1992 (p=0.004) as adverse prognostic variables for DFS.

Patients who were 30 years of age or younger who had transplantation done within 1 year after diagnosis during their first chronic phase of disease had a particularly good prognosis. In this subgroup of 18 patients who were considered to be at "good risk," the probability of surviving 10 years was 72% (95% CI: 52–92%) (Fig. 2). This is significantly superior to the 10-year OS of 37% (95% CI: 21–53%) seen among the poorer risk group patients (i.e., age>30 years, had transplantation done more than 1 year from initial diagnosis, or in advanced phase of disease during transplantation) (p=0.02). These 18 good-risk patients also had a trend towards better DFS at 10 years as compared to the poorer risk group patients, although the difference is not statistically significant [61% (95% CI: 37–85%) vs 33% (95% CI: 17–49%), p=0.07].

The outcome of patients transplanted during blast crisis was extremely poor; no patient has survived more than 1 year after transplant. The median survival was 70 days (range: 6–328 days). All these patients died as a consequence of transplant-related complications or relapse.

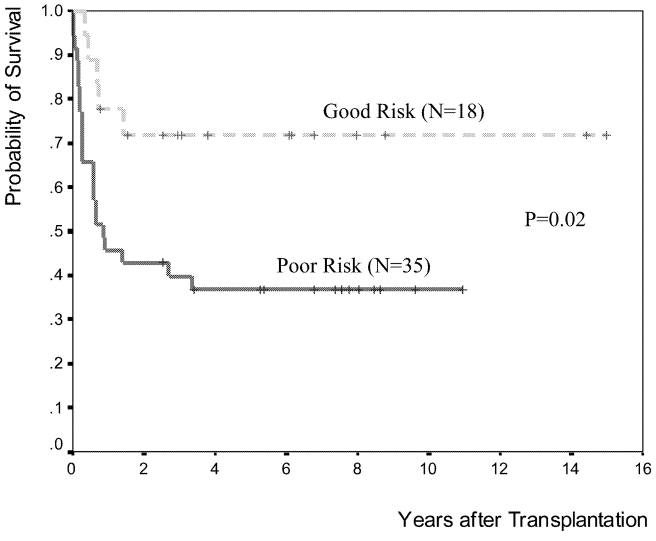

Fig. 2 Overall survival according to the risk group. The good-risk patients consisted of 18 patients who were ≤30 years of age, in first chronic phase, and had HSCT done within 1 year from initial diagnosis had a 10-year OS of 72% compared with the inferior 10-year OS of 37% for the remaining poorer-risk patients (p=0.02)

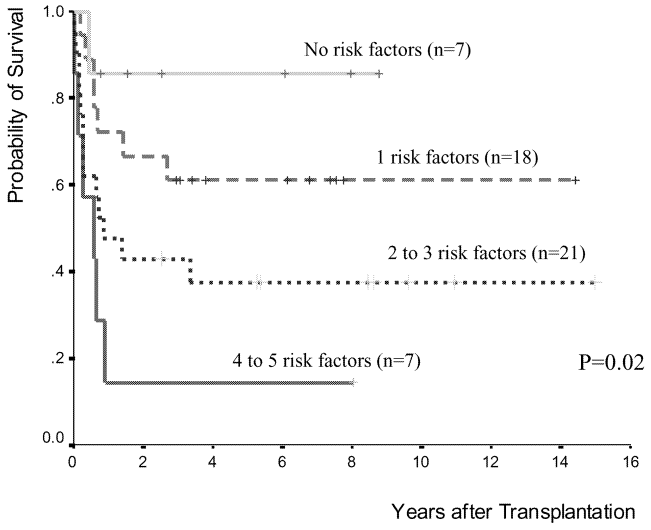

Fig. 3 Probability of overall survival of 53 patients receiving HSCT from HLA-identical siblings according to the main pre-transplant risk factors

Risk-score analysis

Figure 3 shows the accumulative effect on survival of the four main pretransplant risk factors. The probability of survival ranged from 86% (95% CI: 73–99%) in patients with no risk factors to 14% (95% CI: 1–27%) in those with four or more risk factors (p=0.02).

Comparison of transplantation outcome before and after 1992

We also compared the outcome of patients who received HSCT before and after January 1992. There were no significant differences among the two groups of patients for any of the clinical features with regard to age, gender, interval between diagnosis to transplant, conditioning regimen, stage of disease, risk factor score, prior IFN-α therapy, and donor-recipient gender combination. The OS and DFS were significantly superior among the patients who received transplantation after January 1992. The transplant-related mortality was significantly lower among patients transplanted after January 1992 (41% vs 76%, p=0.03). The superiority in the OS is similarly demonstrated among patients receiving transplantation after January 1992 when the comparison was done according to the risk scores. In patients with risk score of 0 or 1, the 8-year OS was 75% (95% CI: 65–75%) for patients transplanted after January 1992 vs 25% (95% CI: 3–47%) for those transplanted before January 1992 (p=0.03). In patients with risk score of 2 or more, the 10-year OS was 39% (95% CI: 28–50%) for patients transplanted after January 1992 vs 13% (95% CI: 1–25%) for patients transplanted before January 1992 (p=0.08).

Discussion

Allogeneic HSCT is probably the only treatment that can cure patients with CML. The disease-free survival at 5 years may reach 70% in allografted patients [6, 18]. Cure is probably mediated by the combined effects of the high-dose chemotherapy and immune-mediated graft-versus-leukemia (GVL) effect. In no other disease is there such clear evidence that the GVL effect plays a crucial role in eradicating leukemia after allografting. For now, it is generally accepted that allogeneic transplant soon after diagnosis should continue to be offered as an option for selected patients [15].

Most of the published data has focussed predominantly on patients from North America and European centers. Data pertaining to Asian populations remain sparse [24, 28]. The result of the present study provides further evidence that allogeneic transplantation from matched sibling donors is a feasible procedure able to cure a significant proportion of patients with CML. In the context of our patients, the best result is achieved if the transplant is carried out in patients who are 30 years of age or younger, with transplantation done within 1 year after diagnosis during their first chronic phase of disease.

Our results concur with previous studies that patients with blast crisis have extremely poor outcome despite transplantation [3, 4, 37, 38]. Alternative treatment options by including imatinib [13, 20, 23, 32] or accrual into the research protocol should therefore be considered in this group of patients.

Previous studies [8, 14, 16, 18, 19] have found a significant relation between the duration of disease before transplantation and the probability of survival: the probability of survival was higher among those transplanted within 1 year of diagnosis compared to those who were transplanted after 1 year of diagnosis. The same trend relating shorter duration of disease (less than 1 year) before transplantation to a higher probability of survival was observed in this series (10-year overall survival of 56% vs 33%, data not shown), but it lacked statistical significance (p=0.09). However, given the favorable outcome among young patients who had transplantation done within 1 year during the chronic phase of disease, allogeneic transplantation should remain a serious option until it becomes clear that other treatment options (such as imatinib) can achieve similar or better results.

Gratwohl et al. [17] have demonstrated that the main pretransplant risk factors are cumulative for individual patients with CML having allogeneic transplantation. The reliability of this scoring system in estimating survival was recently confirmed by the International Bone Marrow Transplant (IBMT) Registry [30]. We evaluated this finding in our series using the same variables but modifying the scores slightly. In contrast to their series which includes both related and unrelated donors, our series only included patients with matched sibling transplant. Hence, the variable for donor type was not included for summation of the risk factors. The cumulative impact of risk factors on outcome is shown in Fig. 3. The survival

among the different risk groups was found to be statistically different, and is in agreement with the published results. The curves in both the original and the current study emphasized the strong prognostic value of the risk score. The dismal outcome seen among the high-risk patients emphasizes the urgent need to explore the alternative therapeutic approach.

GVHD remains a major cause of mortality and morbidity in patients receiving allotransplantation. In the present study, the incidence of grade 2–4 acute GVHD and chronic GVHD was found to be 63% and 57%, respectively. It is the direct cause of death in about 20% of the patients. The development of grade 3–4 acute GVHD was found to be a negative factor for survival. In contrast to other published studies, we did not find any impact of patients' age, donor-recipient gender match, disease status, conditioning regimen, GVHD prophylaxis regimen, and the time from diagnosis to transplantation on the risk of acute and chronic GVHD. Nevertheless, optimizing the control and treatment of GVHD is of critical importance, not only to improve the outcome of transplantation but also to improve the quality of life for patients.

HLA typing of class I and II antigens has been defined by serological methods among the patients and recipients in the current series. This may have partially contributed to the high incidence of acute and chronic GVHD. In an effort to improve the accuracy of HLA typing, we have recently employed PCR-based typing techniques to identify the compatibility between donor and recipient at HLA DR beta-1 alleles. It remains to be seen whether the use of molecular techniques has any impact on the incidence of GVHD and the outcome of patients.

The use of cyclophosphamide and TBI (CyTBI) as preparative regimen, as opposed to busulphan and cyclophosphamide (BuCy), was identified as a risk factor for poorer overall survival in the present series. This may relate to the higher incidence of treatment-related mortality (TRM) in patients given the CyTBI regimen as compared with the BuCy regimen (estimated incidence of TRM at 5 years: CyTBI 90% vs BuCy 37%, data not shown), although the difference may be partially attributed to the significantly higher proportion of patients with advanced disease that were given CyTBI as preparative regimen. Our results differ from previous randomized studies which failed to demonstrate a significant difference in disease-free survival or overall survival between the two regimens [7, 11]. However, BuCy is preferred over CyTBI as it is associated with less acute toxicity, including a shorter period of neutropenia [7] and also increased effectiveness [11]. Its use is further favored by its greater ease of administration, lesser expense, and its association with fewer and less severe delayed effects, including second malignancies, hypothyroidism, and sterility [8].

In the present study, we found that the outcome in term of overall survival, disease-free survival, and treatment-related mortality were more favorable among patients who received HSCT from January 1992 onwards as compared with those performed before 1992. As noted above, comparison of the two groups of patients reveals similar pretransplant characteristics. This improved outcome is likely related to a number of factors, including (1) improvement in the skill of the transplant team, (2) improvement in the ability to control complications such as GVHD, (3) improvement in the supportive care including the use of GCSF that resulted in a shorter period of neutropenia (median days to ANC >500/μl: 19 days vs 15.5 days, p=0.002), (4) the use of antifungal prophylaxis (such as fluconazole and low-dose amphotericin B), (5) better prophylaxis and treatment of CMV infections, including the use of ganciclovir and intravenous immunoglobulin, and (6) an increase in the accuracy of HLA serotyping.

Recently, decisions regarding the appropriate upfront treatment of newly diagnosed patients have become increasingly difficult due to the development of newer treatment modalities such as imatinib and the reduced intensity approach. Imatinib monotherapy has been shown in both phase II and III studies to result in favorable outcome in patients with newly diagnosed or refractory CML [21, 27]. The impressive efficacy of imatinib in inducing cytogenetic response and its acceptable toxicity profile make it a tempting first-line approach. However, there are still a number of unresolved issues pertaining to the use of imatinib as initial therapy for CML. First, it will take several years to establish whether imatinib is curative. Second, it is not known if imatinib treatment failure will return the patient to a chronic phase or if more aggressive disease will evolve that is difficult to treat with transplantation. It is important to note that success in transplantation has also improved over the past few years. Until mature data are available on imatinib, it is still believed that good-risk CML patients should seriously consider HLA-matched sibling HSCT as upfront therapy.

The recognition that eradication of leukemia after allogeneic HSCT depends to a large degree on a lymphocyte-mediated graft-versus-leukemia effect has led in recent years to the concept of using low-dose conditioning regimens designed predominantly to tolerize the patient to lymphoid tissues of the donor. This nonmyeloablative conditioning regimen appears to be an attractive approach in that it is associated with a marked reduction in mortality and morbidity during the peritransplantation period [1, 5]. Data from different centers using a variety of nonmyeloablative conditioning regimens show that some patients have achieved Philadelphia chromosome negativity. However, the rate of molecular negativity and durability of these remissions must be determined from ongoing clinical trials before one can recommend that NMSCT should replace conventional allografting procedures for patients deemed eligible for transplantation. Furthermore, our enthusiasm with this novel and promising approach must be tempered with the realization that the standard concerns of GVHD and infections remain limiting for many patients.

Given the increasing complexity in the choice of primary treatment for patients with CML, it is imperative

for clinicians to weigh the balance between the risks and benefits of each treatment option. We believe that our study will contribute to the decision-making process for allogeneic HSCT for Asian patients with CML.

In summary, the present study showed that patients younger than 30 years of age with newly diagnosed CML in chronic phase fare extremely well with allogeneic HSCT from an HLA-identical sibling. The result provides further compelling argument for offering allogeneic HSCT as upfront therapy to relatively young patients with good risk, for whom a cure is the chief objective. At the present moment, there is no evidence that newer treatment modalities such as imatinib can prolong life more than allogeneic transplantation for the "good-risk" patients. Furthermore, similar to IFN-α, initial treatment with imatinib will significantly delay the interval from diagnosis to transplantation, subjecting those who undergo transplantation to a higher risk of early mortality. The present data do not justify this delay among the good-risk patients who may potentially benefit from early transplantation. Regimen-related mortality and severe acute GVHD remain the major concerns for offering allogeneic transplantation. Future investigations will need to focus on strategies to reduce nonrelapse mortality, in particular, the prevention of GVHD while preserving GVL.

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