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Chronic myeloid leukaemia

Fate of chronic myeloid leukemia patients treated with allogeneic bone marrow transplantation or chemotherapy and/or interferon at a single center: long-term results

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Summary:

From April 1981 to February 2000, 105 patients with chronic myeloid leukemia (CML) underwent BMT from HLA-identical related donors at a single center. Eighty-eight patients were in chronic phase (CP), 11 patients in accelerated phase and six patients in blast crisis. Ten of these patients received a second BMT (BMT2). Comparison of BMT in CP with chemotherapy and/or α-IFN ($n = 70$) was also made. Patients were given cyclophosphamide (CY) and single-dose TBI (CYTBI, $n = 38$) or busulfan (BU) and CY (BUCY, $n = 67$). Overall 54 patients are alive and 52 of them are disease-free with a median follow-up of 11.3 (range 1.1–19.4) years. Ten-year disease-free survival (DFS) in CP patients was better after BUCY, 61% (95% CI, 47–68%) than after CYTBI, 41% (95% CI, 23–61%) ($P = 0.07$). For 88 patients who received a transplant in CP, results were significantly improved when BMT was performed within 1 year after diagnosis ($P = 0.02$) or at an age $\leqslant$25 years old ($P = 0.01$). Ten-year survival in patients who received BMT in CP was better than in patients treated with chemotherapy (56% *vs* 10%; $P = 0.0001$) or α-IFN-based treatment (33%; $P = 0.09$) with survival curves crossing at 4.2 years and at 4 years, respectively. The probability of DFS after BMT2 was 60% (95% CI, 26–87%). CP patients who received BMT after CYTBI had a higher probability of relapse and transplant-related mortality than patients receiving BUCY (53% and 58% *vs* 9% and 34%; $P = 0.002$ and $P = 0.08$, respectively). All but six patients are currently on no medication and have resumed all activities without any limitation. These long-term results confirm that allogeneic BMT is the only curative approach for CML patients and should be offered to all patients with a suitable donor as soon after diagnosis as possible.

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Currently, the approach to patients with chronic myeloid leukemia (CML) has become difficult because of the availability of non-transplant strategies such as interferon (IFN) and more recently STI571 which offer the possibility of long-term disease control for some patients without allogeneic transplantation.[1,2] However, despite improvements in overall survival after IFN-based therapies[3–5] allogeneic BMT remains the only proven curative therapy for CML.[6–9] Improved control of complications such as graft-versus-host disease and infections during the last decade has reduced treatment-related mortality and increased survival rate in CML patients. More than 50% of patients who received a transplant in chronic phase are free of disease more than 10 years after transplantation.[10] Hesitancy by patients or their treating physicians in choosing the optimal time of transplant frequently leads to delay in transplantation which compromises success rates. In fact, results of transplant are inferior in patients receiving BMT in accelerated or second chronic phase (15% to 40%) and in blast crisis (0 to 25%)[6,7,11–14] highlighting the importance of performing the transplant early in the course of the disease. Few studies reported a comparison of allogeneic BMT with chemotherapy alone or IFN-based therapies in CML patients.[15–17] These multi-institutional studies demonstrate the early survival advantage for α-IFN-based treatments due to negligible therapy-related mortality as compared to BMT which is characterized by the early survival disadvantage due to high transplant-related mortality in the short term. The early survival advantage for α-IFN-based treatments is time-limited. In fact, survival curves for BMT show at least half of the patients remain alive disease-free 5 to 10 years after transplant, while similar curves for α-IFN-based treatments show a continuous relapse rate over time, with the curves crossing at about 5 to 6 years showing a long-term survival advantage for BMT.

The median follow-up in most BMT-studies for CML is less than 5 years. The majority of patients relapse within 3 years following BMT. However, occasional patients who had leukemia relapse more than 10 years after transplant have been reported,[18,19] which emphasizes the importance of long-term follow-up for these patients. Also, long-term

follow-up is necessary to evaluate the probability of secondary malignancies and to study the quality of life of BMT survivors. In this study we showed the fate of CML patients treated with BMT or non-BMT approaches at a single center with a longer follow-up.

Patients and methods

Patient population

One hundred and five consecutive patients with CML and a median age of 31 years (range 10–53) who received BMT from HLA-identical sibling donors ($n = 102$), identical twin ($n = 2$) or HLA phenotypically identical relative donor ($n = 1$) between April 1981 and February 2000 at Pesaro BMT Center were evaluated. Marrow metaphases from all patients examined prior to transplant contained the Ph chromosome and/or molecular rearrangements (BCR-ABL) considered characteristic of CML. Ten patients who relapsed following the first BMT received a second transplant and one of them received a third transplant. Informed consent was obtained from each patient or their guardians. The patient demographic data are shown in Table 1. Characteristics of 88 chronic phase patients who underwent BMT (BMT patients) and 70 patients who received chemotherapy or α-IFN-based treatment (non-BMT patients) are shown in Table 2. HLA typing for HLA-A, B, DR and DQ alleles was performed by standard microcytotoxicity assays on all patients with CML under 55 years old. BMT was offered to patients who had an HLA-identical donor, while patients lacking such a donor continued or started chemotherapy alone or in combination with α-IFN. In the non-BMT cohort 53 patients (76%) were HLA typed, 10 patients (14%) did not have siblings and seven patients (10%) were not typed. Three of these patients had an HLA-identical sibling donor but refused transplant. Comparisons were made between chronic phase patients who received transplant with those given non-transplant treatments. Because most patients were assigned to receive non-transplant treatments due to the lack of matched donor this process in part can be considered as 'genetic randomization' with an intention-to-treat analysis.[20] BMT and non-BMT patients were matched for any clinical and hematologic features, including the Sokal score[21] other than for age and sex. It should be emphasized that non-BMT patients received different doses of IFN and five of them started IFN many years after therapy with busulfan and/or hydroxyurea.

Transplant procedure

Thirty-eight patients received cyclophosphamide (CY, 60 mg/kg/day for 2 days) followed by single-dose total body irradiation at 10 Gy (CYTBI) with lung shielding as the conditioning regimen (Table 1). When an interim analysis showed an increased mortality and relapse rate, conditioning with CYTBI was discontinued and the preparative regimen was modified to include busulfan (BU) and CY (BUCY) in June 1986. Initially patients <35 years old were given BU 4 mg/kg/day × 4 days and CY 50 mg/kg/day × 4 days while patients ⩾35 years old received the same dose of BU but a reduced dose of CY (60 mg/kg/day × 2 days). From 1997 all patients received the last regimen regardless of age. Three patients with poor pre-transplant performance scores were given reduced doses of BU and CY. The assessment and grading of acute and chronic GVHD were made according to accepted criteria.[22,23] Patients received unmanipulated marrow infusion the next day after TBI or 36 h after the last dose of CY. The median marrow cell dose infused was 2.4×10^8/kg (range $1.0–4.6 \times 10^8$/kg). All patients were maintained in strict isolation in single rooms with positive pressure HEPA-filtered air and were given prophylactic broad-spectrum antibiotics, acyclovir, amphotericin B (from September 1986) and trimethoprim/sulfamethoxazole for prophylaxis of *Pneumocystis carinii*. All blood products administered were irradiated to 30 Gy.

Table 1 Patients, disease and transplant characteristics

	No.	*Values*
Median age, y (range)	105	31 (10–53)
⩽25		25
25–35		47
35–45		24
>45		9
Sex: Female/Male	105	58/47
Median WBC at Dx, x10^9/l (range)	100[a]	150 (26–795)
Median platelets at Dx, x10^9/l (range)	100[a]	545 (100–1760)
Median spleen size at Dx, cm (range)	99[a]	5 (0–16)
Myelofibrosis pre BMT, No. (%)	101[a]	54 (53)
Disease phase, No. (%)	105	
Chronic		88 (84)
Accelerated		11 (10)
Blast crisis		6 (6)
Prior therapy, No. (%)	105	
Busulfan		16 (15)
Hydroxyurea		34 (32)
Busulfan + hydroxyurea		29 (28)
Interferon or hydroxyurea + interferon		26 (25)
Interval from Dx to transplant, No. (%)	105	
<12 months		51 (49)
12–36 months		37 (35)
<36 months		17 (16)
Median donor age, y (range)	105	31 (4–56)
Patient/donor pair sex mismatched, No. (%)	105	53 (51)
Year of BMT, No. (%)	105	
1981–1985		23 (22)
1985–1990		36 (34)
>1990		46 (44)
Conditioning regimen, No. (%)	105	
CY120TBI 10		38 (36)
BU16 CY200		41 (39)
BU16 CY120		23 (22)
BU14 CY90–120		3 (3)
GVHD prophylaxis, No. (%)	103[b]	
MTX		18 (17)
CsA		11 (11)
CsA + short MTX ± methylprednisolone		74 (72)

[a]Not available for all patients.
[b]Two patients who received syngeneic BMT were not given GVHD prophylaxis.

Definitions of disease stage and relapse

CML phases were defined according to published criteria.[24] Relapse was defined as the detection of Philadelphia (Ph)-positive metaphases on two or more separate occasions

Table 2 Comparison of BMT and non-BMT chronic phase patients

	BMT patients		*Non-BMT patients*		*P*
	No.		*No.*		
Median age, y (range)	88	31 (10–53)	70	43 (14–55)	0.001
⩽25		19		10	
25–35		40		13	
35–45		21		20	
>45		8		27	
Sex: Female/Male, No.	88	50/38	70	25/45	0.006
Median WBC at Dx, x10^9/l (range)	88	150 (30–540)	68[a]	140 (30–650)	0.14
Median platelets at Dx, ×10^9/l (range)	88	570 (100–1760)	67[a]	480 (120–950)	0.25
Median spleen size at Dx, cm (range)	88	5 (0–16)	66[a]	5 (0–18)	0.09
Myelofibrosis pre BMT, No. (%)	88	39 (44)			
Sokal score at Dx, No. (%)	80*		67[a]		0.12
Low risk		47 (59)		50 (68)	
Intermediate risk		26 (32)		15 (29)	
High risk		7 (9)		2 (3)	
Therapy, No. (%)	88		70		
Busulfan		14 (16)		16 (23)	
Hydroxyurea		32 (36)		20 (29)	
Busulfan + hydroxyurea		21 (24)		10 (14)	
Interferon or hydroxyurea + interferon		21 (24)		24 (34)	
Interval from Dx to transplant, No. (%)	88				
<12 months		46 (52)			
12–36 months		30 (34)			
>36 months		12 (14)			
Year of diagnosis <1990, No. (%)	88	55 (63)	70	47 (67)	0.10

[a]Not available for all patients.

after day 60 or hematological evidence of recurrent CML. In this report, persistence or recurrence of BCR-ABL rearrangement in either marrow or blood not followed by a reappearance of Ph chromosome was not considered relapse. Transient cytogenetic relapse was defined if there was recurrence of Ph-positive metaphases, which resolved spontaneously without therapeutic intervention. Transplant-related mortality was defined as death due to causes other than disease recurrence. Patients were censored at the time of relapse or at last follow-up.

Detection of minimal residual disease

Marrow and peripheral blood standard cytogenetic studies, Southern blot hybridization for BCR and, from 1992, non-quantitative RT-PCR for BCR-ABL transcripts were routinely performed at 30 days, 60 days, 6 months and 1 year after transplantation and annually thereafter as previously described.[9] FISH on interphase nuclei to detect BCR-ABL-positive cells (IP-FISH; Vysis, Stuttgart, Germany) after transplant was also used. Chimerism assessment was performed by FISH in sex-mismatched and by VNTR-PCR in sex-matched donor–recipient pairs.

Statistical analysis

Characteristics of the transplant and non-transplant groups were compared using the χ^2 test for categorical variables and the Wilcoxon two-sample test for continuous variables. Primary outcome variables were survival, disease-free survival (DFS), transplant-related mortality and relapse and were calculated by the method of Kaplan and Meier[25] and the log-rank test was used to assess differences between groups. DFS was defined as survival without cytogenetic and/or morphologic evidence of recurrent leukemia in either the marrow or peripheral blood. In the BMT cohort, survival was calculated from the date of transplant and in the non-BMT cohort from diagnosis to death or to last follow-up. For analysis of relapse, surviving patients were censored at the time of second transplant. Association between DFS and potential prognostic variables listed in Table 1 was tested in univariate analyses using log-rank statistics. Variables significant at the $P < 0.1$ level were assessed in multiple logistic regression analysis using the GB-STAT statistical package.[26] The results were analyzed as of 31 March 2001.

Results

Engraftment

Four patients who died before 21 days were not evaluable for engraftment. None of the evaluable patients had rejection or graft failure. The median times to a granulocyte count of $>0.5 \times 10^9$/l and a platelet count of $>20 \times 10^9$/l were 25 days (range 13–43) and 22 days (range 12–42), respectively.

Graft-versus-host disease (GVHD)

Thirty-eight (38%) out of 100 evaluable patients developed grade II–IV acute GVHD (aGVHD) and 23 of them (23%) had grade III–IV aGVHD. There was no difference in the

incidence of grade II–IV aGVHD in patients who received CYTBI or BUCY as conditioning (data not shown). Patients who received CsA+sMTX had a lower incidence of aGVHD than patients given MTX or CsA (30% *vs* 55%, respectively; $P = 0.01$). Thirty-eight of 75 evaluable patients developed chronic GVHD (cGVHD): 12 patients (16%) had limited and 26 patients (34%) extensive cGVHD.

Toxicity

Transplant-related toxicity (TRT) was graded according to published criteria[27] and is shown in Table 3. Toxicity evaluated in various organ systems was not statistically significant in patients who received CYTBI or BUCY regimen. No patient developed either clinical or autopsy-proven liver VOD.

Infections

Seventy patients developed one or more episodes of Gram(−) and/or Gram(+) infections. The incidence of fungal infections (Candida species or Aspergillosis) was 33% with prevalence of Candida species (24%). Most episodes of fungal infections (21%) were observed before 1987 when prophylaxis with amphotericin B had not been introduced in our patients. Thirteen percent of patients developed cytomegalovirus infection. Patients who received CYTBI or BUCY had similar incidences of infectious complications (data not shown). There was no significant difference in the incidence of interstitial pneumonia in patients given CYTBI or BUCY (16% *vs* 12%, respectively).

Mortality

Overall, 51 (48.5%) patients died, 26 of them (51%) within 100 days after transplant. Forty-seven patients (44.7%) died from transplant-related causes and four patients (3.8%) from their original disease. Causes of death are shown in Table 4. The main cause of death was pneumonia (57%). Acute and/or chronic GVHD or liver failure were major contributing causes of death in 47% and 23% of patients, respectively. Mortality was higher in patients who received BMT in accelerated phase or blast crisis (82% and 83%, respectively). In CP patients the probability of mortality was higher after CYTBI at 58% (95% CI, 38% to 76%) than after BUCY at 34% (95% CI, 22% to 47%) ($P = 0.08$).

Table 3 Transplant-related toxicity

	CYTBI		*BUCY*	
	Grades 2–3	*Grade 4*	*Grades 2–3*	*Grade 4*
Oral mucosa	19 (50)	3 (7.8)	42 (62.8)	2 (2.9)
Kidney	1 (2.6)	—	4 (5.9)	—
Heart	—	—	1 (1.4)	—
Gut	7 (18)	1 (2.6)	18 (26.8)	2 (2.9)
Liver	3 (7.8)	3 (7.8)	9 (13.4)	5 (7.4)
Bladder	7 (18)	1 (2.6)	8 (11.9)	5 (7.4)
CNS	1 (2.6)	—	2 (2.9)	1 (1.4)

Values in parenthesis are percentages.

Table 4 Causes of early and late death in patients after BMT

	Patients, n = 51
Interstitial pneumonia:	14
Fungal	2
Pneumocystis carinii	3
Cytomegalovirus	3
Idiopathic	6
No interstitial pneumonia	15
Liver failure	12
Original disease	4
Acute GVHD	2
Chronic GVHD	2
Hemorrhagic cystitis associated with disseminated Herpes zoster	1
Sepsis	1

Relapse

Relapse occurred in 12 out of 88 chronic phase (14%) and four out of 17 advanced phase (24%) patients ($P = 0.3$). The median time to relapse for CP patients was 52 (range 16–80) months. Nine out of 29 patients who received CYTBI and three out of 59 patients receiving BUCY in CP relapsed. The probability of relapse in patients who received transplant while in CP was significantly lower after conditioning with BUCY at 9% (95% CI, 2% to 18%) than after CYTBI at 53% (95% CI, 26% to 73%) (Figure 1). The latest relapse occurred at 6.5 years after transplant in a patient who received CYTBI. In all but one patient cytogenetic relapse preceded hematologic relapse. Multiple regression analysis revealed that only conditioning with CYTBI predicted high relapse rate (odds ratio (OR) 3.45 (95% CI, 1.12 to 10.65; $P = 0.004$) in CP patients.

BCR-ABL monitoring

Forty-five patients did not have PCR results. A total of 423 RT-PCR studies in 60 patients were performed on marrow and/or blood. Eight patients had transient PCR positivity: seven patients within 60 days and one patient at 6–9 months after BMT. Only three of 45 evaluable patients (6.6%) had

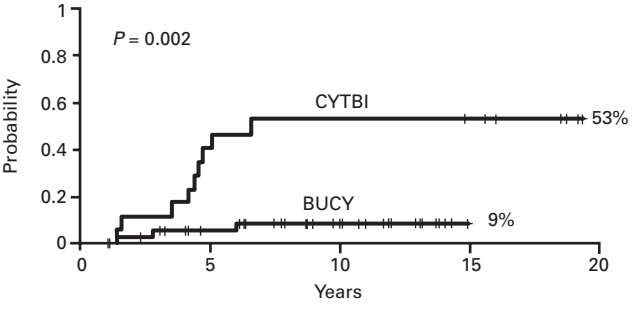

Figure 1 The probability of cytogenetic and/or hematologic relapse in chronic phase CML patients after conditioning with CYTBI or BUCY.

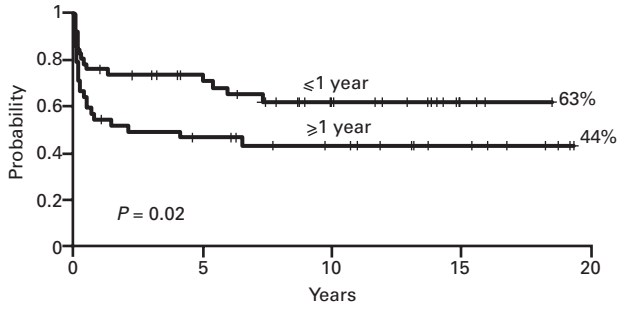

Figure 2 The probability of disease-free survival for patients with chronic phase CML undergoing allogeneic transplant less than 1 year or more than 1 year.

positive PCR beyond 1 year: at 30 months, at 48 months and at 108 months. The first two patients also had cytogenetic relapse while the last patient is in complete cytogenetic and hematological remission after more than 5 years despite persistent PCR positivity. One patient who had intermittent positive PCR results (at 6 months and at 3 years) is in molecular remission after more than 3 years. In 11 out of 16 patients who had a relapse it occurred before the PCR test had been introduced into our center. In all five remaining patients PCR positivity preceeded relapse.

Survival and disease-free survival

Transplant patients: Overall 54 patients (51.4%) are alive. Fifty-two patients are disease-free survivors with a median of 11.3 years (range 1.1–19.4 years) from transplantation. Two patients who had a cytogenetic relapse only (one of them after syngeneic BMT2) are on interferon treatment at more than 3 and 4 years, respectively. The 10-year probability of DFS (95% confidence intervals) for the entire group of patients was 49% (39% to 59%), while it was 55% (47% to 68%), 18% (2% to 51%) and 17% (0 to 41%) in chronic phase, accelerated phase, and blast crisis, respectively. Patients who underwent transplantation while in CP had better DFS after conditioning with BUCY (61% (52% to 77%)) than CYTBI (41% (23% to 61%)) ($P = 0.07$). DFS was significantly higher in CP patients who received transplant within 1 year of diagnosis (63% (54% to 82%)) or at the age ⩽25 years old (73% (49% to 91%)) than in patients receiving transplant beyond 1 year of diagnosis (44% (30% to 61%)) or at age >25 years old (49% (38% to 63%)) (Figures 2 and 3). Multiple logistic regression analyses showed that CP (OR 0.75 (95% CI, 0.68 to 0.85) $P = 0.001$), transplant within 1 year from diagnosis (OR 2.22 (1.13 to 4.4) $P = 0.019$), patient age ⩽25 years (OR 0.46 (0.23 to 0.91) $P = 0.023$), and the absence of grade II-IV aGVHD (OR 0.97 (0.95 to 1.08) $P = 0.012$) were associated with better DFS.

In the subset of patients with two favorable factors (age ⩽25 years and transplant within 1 year from diagnosis; $n = 12$) DFS at 10 years was 83% (52% to 98%); patients with age >25 years and transplant beyond 1 year from diagnosis ($n = 33$) had a DFS of only 36% (19 to 55%) ($P = 0.005$). In the cohort of CP patients given BUCY, only transplant within 1 year from diagnosis was associated with significantly better DFS (67% *vs* 50%, $P = 0.049$).

BMT compared with non-transplant treatments: The estimated 10-year overall survival in patients who received BMT in CP was higher at 56% (47% to 68%) than in patients treated with chemotherapy at 10% (7% to 24%) ($P = 0.0001$) or α-IFN-based treatment at 33% (16% to 54%) ($P = 0.09$) with survival curves crossing at 4.2 years and at 4 years, respectively (Figure 4). The 10-year probability of survival in BMT patients with a low Sokal score was 65% (46% to 81%), while it was 38% (20% to 66%) ($P = 0.2$) for patients who received α-IFN-based treatment with curves crossing at 4.3 years. The median follow-up in patients treated with interferon was lower (3.9 years; range 1–12) than in BMT patients. The median survival time had not been reached in BMT patients while it was 7 years and 5 years after α-IFN-based treatment or chemotherapy respectively.

Second transplant

Ten patients who relapsed following the first transplant (BMT1) received a second BMT (BMT2) and one of them a third BMT. Seven of these 10 patients have been reported previously.[28] Eight patients received CYTBI and two patients BUCY as conditioning for BMT1. Relapse occurred in chronic phase ($n = 4$), accelerated phase ($n = 3$) or in blast crisis ($n = 3$). The median age at the time of BMT2 was 30 years (range 15–42 years). There were seven females and three males. The median duration from BMT1 to relapse and to the second BMT was 38.5 (range 3.1–61.5) months and 41 (range 4–83) months, respectively. The median time from relapse to BMT2 was 6.5 months

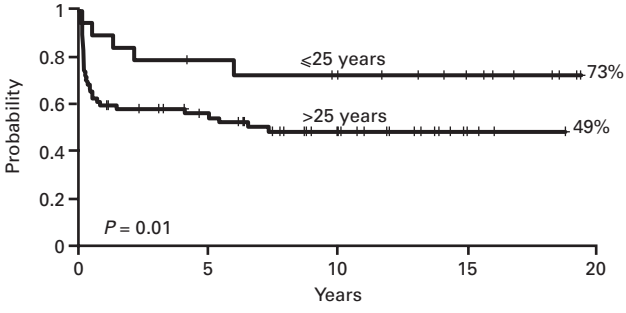

Figure 3 The probability of disease-free survival for chronic phase CML patients undergoing allogeneic BMT according to age at the time of transplant.

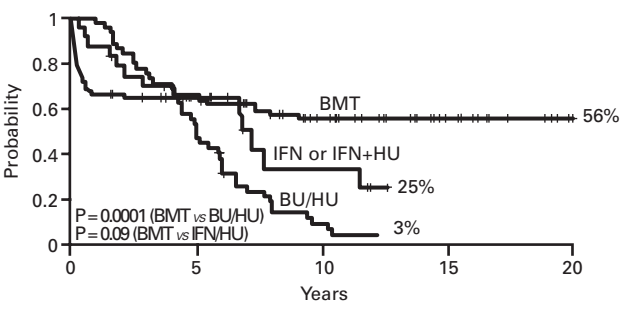

Figure 4 The probability of survival in chronic phase CML patients following allogeneic BMT or chemotherapy (busulfan and/or hydroxyurea) or IFN-based treatment (IFN or hydroxyurea + IFN).

(range 1–57.5). Patients received chemotherapy and/or interferon, to attempt to achieve a remission or a return to chronic phase. Three patients received BMT2 in chronic phase, four patients in accelerated phase and three patients in blast crisis. All patients were given BUCY as conditioning for BMT2. The same donor was used in eight patients and another HLA-identical sibling donor was used in two patients. Seven patients are alive and six of them disease-free with a median of 8.6 years (range 2.4–15). The 10-year probability of DFS was 60% (95% CI, 26%–87%) (Figure 5). Three patients had a relapse at 6 months, 1 and 1.1 year following BMT2, respectively. One of these patients received syngeneic BMT2, and the other two patients received BMT2 in blast crisis and chronic phase, respectively. The last patient who had a second relapse in accelerated phase was given a third BMT after conditioning with CY + fractionated TBI. He was given donor lymphocyte infusion (DLI) for a positive PCR which reappeared at 6 months after transplant and is in complete remission more than 2 years following DLI. Only one patient developed grade II aGVHD and two patients had moderate or severe cGVHD. Three patients died of leukemia, interstitial pneumonia in association with liver failure or severe chronic GVHD, respectively.

Long-term survivors

Median Karnofsky score (KS) of surviving patients is 100% (range 70–100%). Two patients have KS of 80% associated with IFN therapy of relapse, one has KS of 70% associated with cGVHD (off therapy) and six patients who are on treatment for cGVHD have KS of 80–90%. Thirty out of 54 patients (55.5%) are alive and disease-free more than 10 years after transplant. All but six patients are currently on no medication and have resumed all activities without any limitation. One patient developed Hodgkin's lymphoma at 6 years after transplant and had a complete remission following chemotherapy. No other patients developed second malignancies. One woman became pregnant 2.5 years after the first transplant (conditioning with CYTBI) and gave birth to a healthy child; she is disease-free following BMT2. Another woman who received BUCY had a successful pregnancy and delivered healthy twins (7 years after BMT) developed from cryopreserved embryos. Partners of two patients who received CYTBI or BUCY, respectively, had pregnancies 4 years after transplant which resulted in live births.

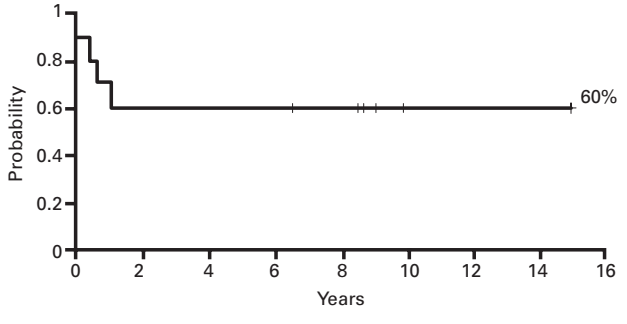

Figure 5 The probability of disease-free survival in CML patients following second allogeneic transplant.

Discussion

The present study indicates that allogeneic BMT in chronic phase CML results in long-term disease-free survival in more than 55% of patients with a median follow-up of 11.3 years. The focus of this report is allogeneic BMT, although comparison of BMT and non-BMT was also made to show what happened to a cohort of patients who were treated at a single center with different treatment modalities. The 10-year survival rate in our BMT patients was higher than in patients treated with non-transplant approaches. Furthermore, the median survival in this study had not yet been attained at 15 years in BMT patients, while in patients treated with conventional chemotherapy or interferon-based treatment it was 5 and 7 years, respectively. However, it should be taken into consideration that the median age of non-BMT patients was significantly higher than in BMT patients, which might have had some negative influence on survival of patients treated with non-transplant approaches. The present study can be considered in part as 'genetically randomized' because the majority of patients treated with non-transplant approaches were HLA typed and lacked an identical sibling donor. Therefore they were given non-transplant therapies. The only randomized ('genetic randomization') comparison of BMT and IFN-based treatment comes from the German CML Study.[17] In this multicenter study patients were allocated according to eligibility for transplant: patients who had a related donor received early BMT while patients lacking such a donor were treated with IFN. During the first 4 years of observation survival was better with IFN and the survival curves were expected to cross at 5 years. Whereas the evidence of this randomization favors early BMT in intermediate and high risk patients, an advantage of BMT in low risk patients can only be expected much later because of short follow-up. There are another two large multicenter trials comparing results of BMT and non-transplant treatments. Gale *et al*[15] compared the survival of 548 patients from the International Bone Marrow Transplant Registry with 196 patients who received rIFN-α or hydroxyurea (HU) in the German CML Study Group. There was a significant survival advantage for HU or IFN in the first 4 years after diagnosis and for transplants starting 5.5 years after diagnosis. In a recent study from the Italian Cooperative Study Group on CML and Italian Group for Bone Marrow Transplantation 10-year survival rates were 55%, 32% and 18% for BMT patients, patients who received α-IFN or chemotherapy, respectively, with the only significant difference being in the chemotherapy group. The median survival time had not yet been reached in the BMT cohort, whereas it was 72 months and 54 months in the α-IFN therapy and chemotherapy cohorts respectively.[16] Although the present study was not a prospective comparison of BMT and non-BMT approaches and the number of IFN-treated patients was small, the data of this report are similar to those reported in the literature.

Previous studies have shown that transplantation within

1 year of diagnosis and younger age have been associated with a significantly better outcome after BMT.[29–31] Our data match with these findings, highlighting that the delay in transplantation can significantly compromise the successful outcome of BMT. Furthermore, we confirm that BMT in an advanced phase of disease is associated with a lower survival rate as has been shown by others.[12–14]

We have found that patients who received conditioning with CYTBI had a lower survival rate than patients receiving the BUCY regimen due to high mortality. It should be emphasized that all patients who received the CYTBI regiment underwent transplant before 1986 and were given a single-agent prophylaxis (MTX or CsA) for GVHD. It is well known that the results of BMT have improved in the last decade due to more effective GVHD prophylaxis and antiviral or antifungal therapies. Therefore, a high mortality rate observed in our patients after CYTBI was probably not only related to conditioning regimen. Furthermore, we observed that chronic phase patients who received CYTBI had an unexpected higher relapse rate than patients receiving BUCY. The results of two randomized studies comparing CYTBI and BUCY are controversial: the Seattle group did not find a significant difference between relapse rates after CYTBI or BUCY,[8,32] while in the French study patients who received TBI-containing regimens had a higher risk of relapse than patients receiving the BUCY regimen.[33] In contrast to our data, the French study showed that the incidence of relapse was significantly lower after single-dose TBI (SDTBI) than fractionated TBI (FTBI). There are discordant results regarding the impact of FTBI or SDTBI on relapse rates. Cosset *et al*[34] reviewed the literature concerning TBI-containing regimens and found the same relapse rate after SDTBI and FTBI in patients who received a transplant for acute and chronic leukemias. No significant association between FTBI and relapse was found in the International Bone Marrow Transplant Registry study.[35] The low incidence of BCR-ABL positivity, cytogenetic and/or hematologic relapse after the BUCY in our patients confirm the results of previous studies which showed that the BUCY regimen may be more effective than CYTBI in eradicating chronic phase CML.[13,32,33,36]

The incidence of transplant-related toxicity was similar in patients who received CYTBI or BUCY. Pneumonia was the main cause of death in our patients. Although there were some data indicating an early toxicity with liver VOD and hemorrhagic cystitis after conditioning with busulfan, the two randomized studies comparing TBICY and BUCY did not confirm such a correlation.[8,33]

The best therapeutic strategy for patients who relapsed after BMT for CML remains to be determined. Several therapeutic options such as donor lymphocyte infusion (DLI),[37] interferon-α[38] or second marrow transplantation[39,40] have been used with various degrees of success. Although second allogeneic hemopoietic stem cell transplant offers a chance of cure, this approach is associated with high treatment-related morbidity and mortality.[37–41] The vast majority of our patients who received the second transplant relapsed after CYTBI and were given BUCY as the conditioning regimen. The BUCY regimen was better tolerated with low incidence of regimen-related toxicity. Despite the fact that most of these patients were in an advanced phase of disease at the time of second transplant, the probability of DFS was higher (60%), highlighting the antileukemic efficacy of the BUCY regimen for second transplant. In the present study, all but one patient who received the second transplant had a relapse beyond 1 year after the first BMT that was strongly associated with better outcome in multivariate analysis in patients receiving a second transplant for leukemia relapse.[42] Only one patient who received CYTBI developed Hodgkin's lymphoma after BMT. No other cases of secondary malignancies have been observed in our patients.

The present long-term single-center study analysis allows for some conclusions. Currently, allogeneic BMT is the only therapy that can cure CML. This study shows that there is a tradeoff between the risk of early transplant-related mortality and the chance of cure by allogeneic BMT. Our data confirm that the BUCY regimen is effective in eradicating the CML clone in the majority of patients and BMT should be carried out as soon after diagnosis as possible if an HLA-identical family donor is available.

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