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Unrelated donor bone marrow transplantation as treatment for chronic myeloid leukemia: the Spanish experience

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ABSTRACT

Background and Objectives. **To analyze the results of unrelated bone marrow transplantation (UDBMT) as treatment for chronic myeloid leukemia (CML) in Spain.**

Designs and Methods. **Eighty-seven consecutive UDBMT performed in 9 centers between October 1989 and February 1998 were evaluated. This represents more than 95% of UDBMT for CML performed in adult transplant centers in Spain during this period. The patients' median age was 31.5 years (range, 12-49). The median interval from CML diagnosis to UDBMT was 30 months (range, 3-160). Seventy-nine percent of transplants were performed during the first chronic phase (1CP).**

Results**. Actuarial probability of survival and disease-free survival at 4 years for the whole series was 24% (95% confidence interval [CI]: 14%-34%) and 20% (CI: 10%-30%), respectively. The cumulative incidence of relapse and transplant-related mortality (TRM) was 7% (CI: 4%-10%) and 71% (CI: 60%-82%), respectively. The main causes of death were graft failure (n=7), infection (n=23), and graft-versus-host disease (GvHD) (n=25). The actuarial probability of acute GvHD grade II-IV and grade III-IV was 56% (CI:46%-66%) and 36% (CI: 26%-36%), respectively. The cumulative incidence of extensive chronic GvHD was 18% (CI: 9%-27%). Univariate analyses showed that the pre-transplant factor with the highest influence on survival was disease status at transplant (30% in 1CP vs. 0% in advanced phases; *p*=0.0001). Other pre-transplant factors influencing survival among patients in 1CP were: patient's age (older than 30 years 11% vs. 48%), interval diagnosis-transplantation (longer than 2 years 17% vs. 55%), donor type (HLA, B, DRB1 identical 32% vs. 25%), CMV serologic status (donor and recipient negative 63% vs. 24%), year of transplantation (before 1995 19% vs. 40%), and conditioning regimen (cyclophosphamide plus total body radiation 40% vs. 16%). The main risk factors had a cumulative effect on survival. Thus, probability of survival ranged from 66% (CI: 39%-93%) in patients in 1CP, under 40 years of age, transplanted from an HLA, A, B, DRB1 identical donor during the first two years after diagnosis, to 0% in those with three or more risk factors.**

Interpretation and Conclusions. **This experience shows that UDBMT used to have a high TRM that has progressively decreased along the years. At the present time, the results are encouraging, particularly when UDBMT is performed under favorable conditions.**

Key words: chronic myeloid leukemia, bone marrow transplantation, unrelated donor BMT

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Hematopoietic cell transplantation (HCT) is the only proven curative therapy for patients with chronic myeloid leukemia (CML). HCT with marrow grafts from HLA-identical siblings have resulted in long-term disease-free survival rates of 40-80% for patients in chronic phase and 10-40% for patients in more advanced phases.[1,2] However, fewer than 30% of otherwise eligible patients have an HLA-identical sibling, and only an additional 5% have a suitable partially HLA-matched related donor.[3] These individuals have a number of therapeutic options such as hydroxyurea, interferon-alpha, or autologous HCT, but there is no evidence that these treatments can cure any patient.[4-6] For this reason, unrelated donor bone marrow transplantation (UDBMT) emerged as a possible therapeutic option, made possible by the large registries of HLA-typed individuals willing to serve as donors.[7,8] Despite its high transplant-related mortality (TRM), after a decade of experience, UDBMT has become a realistic therapeutic option for 25-45% of CML patients who have an adequate unrelated donor.[9-13] This report describes the outcome of the first 87 unselected patients with CML who received an UDBMT in 9 Spanish centers.

Design and Methods

Patient population

We analyzed 87 consecutive patients with CML receiving a bone marrow transplantation from an unrelated donor in 9 Spanish Transplant Centers from October 1989 through to February 1998. Table 1 shows the annual inclusion of patients and the patients' main characteristics. Fifty-two (60%) of these UDBMT were performed during the period 1995-1997. This represents 96% of all UDBMT for CML performed in adult transplant centers in Spain during this period (data provided by the *Organización Nacional de Trasplantes*). Eighty percent of transplants were performed at four institutions (Hospital Clínic [n=38], Hospital La Princesa [n=12], Hospital La Fe [n=11], Hospital Marqués de Valdecilla [n=9]). The median age of the patients was 31.5 years (range, 12 to 49). The median interval from CML diagnosis to UDBMT was 910 days (range, 97 to 4789). Six (7%) BMT were performed during the first year after diagnosis and 22 (25%) during the second year. CML status was as follows: first chronic phase (1CP) in 69 (79%) patients, accelerated phase in 8 (9%), blast crisis in 7 (8%), and second chronic phase in 3 (3%).

Transplantation procedures

Preparative regimens and graft-versus-host disease (GvHD) prophylaxis varied according to the transplant center and time (Table 2). In summary, 70 (80%) patients followed a regimen that included cyclophosphamide (Cy) and total body irradiation (TBI) and 17 (20%) a regimen containing Cy and busulfan. In 24 (28%) and 12 (14%) cases, respectively, ATG and/or thiotepa were added to the preparative regimen. Donor marrow was T-cell depleted in 23 (26%) cases. T-cell depletion was performed by monoclonal antibodies in 11 (13%) and by counterflow elutriation in 12 (14%). All patients received cyclosporine alone (n=1) or associated with methotrexate (n=55; 63%), methylprednisolone (n=15; 17%), or both (n=16; 18%) as GvHD prophylaxis. Table 2 also shows serologic CMV status and sex relation between donor and recipient.

Table 1. Patients' characteristics.

Period analyzed	10/89-02/98
Patients evaluated	87
Annual inclusion of patients	
1989-1990	2
1991	5
1992	8
1993	10
1994	8
1995	15
1996	21
1997	16
1998 (January-February)	2
Disease status	
First chronic phase	69 (79%)
Accelerated phase	8 (9%)
Blast crisis	7 (8%)
Second chronic phase	3 (3%)

	Whole series (n= 87)	1CP (n= 69)
Age		
Median (range) years	31.5 (12-49)	32 (12–49)
Mean (±SD)	31.2 (±9.6)	31.1 (±9.8)
Sex		
Male/Female	52/35	42/27
Interval diagnosis-UDBMT		
Median (range) days	910 (97-4,789)	868 (97–4,789)
Diagnosis to BMT < 1 year	6 (7%)	4 (6%)
Diagnosis to BMT < 2 years	28 (32%)	22 (32%)

SD = standard deviation; 1CP = first chronic phase.

Table 2. Transplantation procedures and donor matching.

	Whole series (n=87)	*1CP (n= 69)*
Cytoreductive therapy		
Cy + TBI	52 (60%)	41 (59%)
Cy + TBI + ATG	6 (7%)	4 (6%)
Cy + TBI + thiotepa + ATG	12 (14%)	12 (17%)
Bu + Cy	10 (11%)	7 (14%)
Bu + Cy + ATG	6 (7%)	5 (7%)
Bu + Cy + etoposide	1 (1%)	--
TBI containing regimen	70 (80%)	57 (8%)
ATG containing regimen	24 (28%)	21 (30%)
GvHD prophylaxis		
CyA alone [+ TCD]	1 (1%)/ [1; 1%]	1 (1%)/ [1; 1%]
CyA + MTX [+ TCD]	55 (63%)/ [8; 8%]	42 (61%)/ [7; 10%]
CyA + methylPDN [+TCD]	15 (17%)/ [12; 14%]	15 (22%)/ [12; 17%]
CyA + MTX + methylPDN [+TCD]	16 (18%)/ [2; 2%]	11 (16%)/ [1; 1%]
BMT with T-cell depletion	23 (26%)	21 (30%)
Donor-recipient histocompatibility*		
Matched by serologic methods	22 (25%)	16 (23%)
Matched by DNA-methods	50 (57%)	41 (59%)
Mismatched	15 (17%)	12 (20%)
Minor mismatched	6 (7%)	6 (9%)
Major mismatched	9 (10%)	6 (9%)
Sex relation		
male to male	32 (37%)	26 (38%)
male to female	22 (25%)	15 (22%)
female to male	20 (23%)	16 (23%)
female to female	13 (15%)	12 (17%)
CMV serologic status		
recipient and donor –	16 (18%)	11 (16%)
recipient – and donor +	14 (16%)	10 (14%)
recipient +	52 (60%)	44 (64%)
unknown	5 (6%)	4 (6%)

*Cy: cyclophosphamide; TBI: total body irradiation; Bu: busulfan; ATG: antithymocyte globulin; PDN: prednisolone; TCD: T-cell depletion; 1CP: first chronic phase. *Class I antigens determined by serologic methods in all cases and class II antigens by DNA methods in 56 cases (45 in 1CP).*

HLA typing and donor matching

In all cases HLA-A and B loci were tested using serologic methods. Seventy-four (85%) pairs matched for these class I loci, four pairs had one minor mismatch (cross-reactive disparity), three one major mismatch and two more than one mismatch. Class II loci were tested by serologic methods (plus mixed-lymphocyte-culture assay in most cases) in 31 pairs (36%) or by DNA-based methods in 56 (64%). All pairs tested by serologic methods matched for DR locus. Fifty pairs (57%) tested by DNA-based methods matched for DRB1 locus; 2 had 1 minor mismatch (match by serologic methods but distinct HLA-D specificity) and 4, 1 major mismatch.

In summary, 72 pairs matched by serologic methods (n=22, 25%) or DNA-based methods (n=50, 57%), 6 (7%) had one minor mismatch (4 in class I and 2 in class II antigens), and 9 (10%) had a major mismatch (5 in class I and 4 in class II) (Table 2). Loci C, DQ, and DP were evaluated only occasionally and were not taken into account to perform this analysis.

Engraftment, GvHD and relapse

Neutrophil and platelet engraftment were considered to have occurred on the first of 3 consecutive days with an absolute neutrophil count ≥ 500/μL or ≥20,000/μL self-sustained platelets, respectively. The analysis of graft failure was limited to patients who survived at least 28 days and was defined as the absence of an absolute neutrophil count of more than 500/μL for at least 3 consecutive days. A decrease in absolute neutrophil count to below 200/μL for at least 3 consecutive days after initial engraftment was considered as secondary graft failure. Acute GvHD was graded as 0-IV[14] and chronic GvHD was defined as none, limited, and extensive[15] in patients surviving more than 100 days without relapse. Relapse was defined by either morphologic recurrence of leukemia or by sustained evidence of the Philadelphia chromosome.

Statistical analysis

All evaluations were based on data available on July 1, 1998. The data of one patient who received a second BMT were censored at the time of the second transplant. Descriptive statistics were calculated and reported. The estimated probability of neutrophil and platelet engraftment, survival (SRV), and disease free survival (DFS) were evaluated by the Kaplan-Meier method.[16] Estimates of incidence of chronic GvHD, relapse, and TRM were obtained using cumulative incidences[17] in which death or relapse without chronic GvHD, death without relapse, or death due to relapse, respectively, were considered as competing events. The Mantel-Cox test[18] was used to assess the impact of various pre-transplant variables (see Table 4) on neutrophil and platelet recovery, acute GvHD, SRV, and DFS. For the purposes of this analysis the patient's age, the number of cells infused in unmanipulated BMT, the number of BMT per year in the transplant center, the year of BMT, and the interval from diagnosis to transplantation, were treated as categorical variables (see Table 4). Due to the low number of pairs with a minor mismatch, the HLA-matching status was also categorized as being HLA identical or not by either serology (locus A, B and DR) or DNA methods (locus A, B and DRB1). Additionally, patients having an HLA-match by DNA methods were also compared with the remaining patients. A Cox proportional-hazard model[19] was used for quantifying the relation between SRV and the above mentioned pre-transplant variables. The selection of factors with an important effect on the rates of graft failure and relapse was based on a forward stepwise procedure.[20] p values of 0.05 or less were considered to indicate statistical significance. To test whether pre-transplant risk factors were cumulative for individual patients, we used a modified version of a recently published score system.[2] The risk score for an individual patient was the sum of the following five risk factors: status (0 for 1CP, 1 for more advanced phases); age of recipient (0 for < 40 years, 1 for ≥ 40 years); sex combination (0 for all except 1 for male recipient/female donor); time from diagnosis to BMT (0 for < 24 months, 1 for > 24 months); and donor type (0 for HLA, A, B, DRB1 identical, 1 for other donors). All statistical analyses were performed with BMDP statistical software.[20]

Results

Table 3 shows the incidence of the main post-transplantation events among patients at risk. The median (range) number of infused mononucleated cells was 3.2×10^8/kg (0.2-6.3) among patients receiving unmanipulated bone marrow and 0.6×10^8/kg (0.2-0.9) in those receiving a T-cell depleted BMT.

Engraftment

Seven (8%) patients died without engraftment during the first 28 days after transplantation and 80 were evaluable for engraftment. Primary graft failure occurred in 8 patients (10%). Seven of these patients died from infectious complications on days ranging from 37 to 164 (median, 47 days); while one patient who survived had a recovery of autologous hematopoiesis with recurrent chronic myeloid leukemia on day 29 after BMT. In 4 cases a back-up marrow was administered unsuccessfully to reconstitute hematopoiesis. No variable included in the regression analysis predicted this complication. The median time to neutrophil recovery (500/μL) was 22 days (range, 8 to 39). Nineteen patients with neutrophil engraftment never reached self-sustained platelet counts exceeding 20,000/μL. The median time to platelet recovery for the remaining patients was 25 days (range, 10 to 300). Neutrophil engraftment (mean ±SD) was reached faster in BMT performed since 1995 (500/μL: 25.3±6.3 vs. 20.4±4.4 days, p=0.0003; 1,000/μL: 30.5±7.1 vs. 23.6±6.7 days, p=0.0006). Platelet engraftment was significantly slower among patients receiving T-cell depleted grafts (20,000/μL: 91±100 vs. 28.5±15.1 days, p=0.003). Four (5%) engrafted patients developed secondary graft failure (on days +65, +69, +131, +182); in all of them this complication contributed to death.

Graft-versus-host disease

The actuarial probability of acute GvHD grade II-IV and grade III-IV was 56% (CI: 46%-66%) and 36% (CI: 26%-46%), respectively. The risk of acute GvHD was

Table 3. Post-transplantation events.

	Whole series (n=87)	*1CP (n= 69)*
Primary graft failure (n=80)*	8 (10%)	6 (9%)
Engraftment	(n= 72)*	(n= 59)*
≥500 neutrophils/μL (days)	(n= 72) 22 (8-39)	(n= 52) 22 (8 – 39)
≥20,000 platelets/μL(days)	(n= 42) 25 (10-300)	(n= 25) 25 (10 – 300)
GvHD		
acute grade II-IV	(n= 79)* 35 (44%)	(n= 62)* 32 (52%)
acute grade III-IV	28 (35%) 20 (32%)	
chronic limited GvHD	(n= 40)* 13 (33%)	(n =34)* 11 (32%)
chronic extensive GvHD	14 (35%)	13 (38%)
Relapse	(n= 45)* 6 (13%)	(n= 40)* 4 (10%)
Survival		
Alive	24 (28%)	24 (35%)
Dead	63 (72%)	45 (65%)
Causes of death**		
Primary graft failure	7 (11%)	5 (7%)
Relapse	4 (5%)	2 (3%)
Infection	23 (37%)	19 (28%)
Unclassified	9 (14%)	7 (10%)
Fungal	4 (6%)	4 (6%)
Cytomegalovirus	7 (11%)	5 (7%)
Bacterial	3 (5%)	3 (4%)
Graft-versus-host disease	25 (40%)	17 (25%)
Diffuse alveolar hemorrhage	3 (5%)	1 (1%)
Idiophatic pneumonitis	3 (5%)	3 (4%)
Veno-occlusive disease	3 (5%)	1 (1%)
Secondary graft failure	4 (6%)	3 (4%)
Hemorrhage	4 (6%)	4 (6%)
Sudden death	1 (2%)	1 (1%)
Karnofsky performance score		
100%		17 (71%)
90%		5 (21%)
70%		2 (8%)

**= patients at risk (surviving more than 28 days for engraftment; with engraftment for acute GvHD; surviving more than 100 days for chronic GvHD and relapse); ** in several patients more than one cause of death was considered.).*

not significantly associated with patients' age, sex of patient-donor pairs, disease status, interval diagnosis-BMT, conditioning regimen, number of marrow cells transplanted, degree of compatibility between donor and recipient, or use of ATG in preparative regimen. The only variable associated with a significantly lower risk of acute GvHD was the use of T-cell depletion as GvHD prophylaxis (GvHD grade II-IV 40% vs. 62%, p=0.058; and grade III-IV 10% vs. 45%, p=0.028). The cumulative incidence of chronic GvHD and extensive chronic GvHD was 36% (CI: 25%-47%) and 18% (CI: 9%-27%), respectively, among the 40 patients who survived more than 100 days without relapse. The only variable associated with a significantly higher risk of chronic GvHD was a previous acute GvHD grade II-IV.

Relapse

Six patients relapsed after a median of 89 days (range, 29 to 318); the cumulative incidence of relapse was 7 percent (CI: 1%-13%). In two cases the UDBMT had been performed in blast crisis; in the remaining 4, in first chronic phase. Two of these patients in chronic phase are alive (one after a second UDBMT – not included in the analysis – and the other one is in stable chronic phase, two years after relapse).

Cause of death

Sixty-three (72%) patients died after UDBMT. Their median follow-up after UDBMT was 66 days (range, 12 to 631). Seven patients died from complications of graft failure and 3 due to leukemia relapse. In the remaining 53 patients, the main cause contributing to death was GvHD (25 cases, 40%). Infection was the major cause of death in 23 patients (37%). Diffuse alveolar hemorrhage (n=3), idiopathic pneumonitis (n=3), veno-occlusive disease (n= 3), secondary graft failure (n=4), and hemorrhage (n=4) were causes of death in the remainder. The cumulative incidence of TRM in this series was 71% (CI: 60%-82%). Among patients in first chronic phase, TRM was 77% (CI: 60%-94%) up to 1995 vs. 56% (CI: 40%-72%) after this date (p=0.17).

Survival

The actuarial probabilities of SRV and DFS at 4 years for the entire group were 24% (CI: 14%-34%) and 20% (CI: 10%-30%), respectively. The median follow-up of surviving patients was 1.8 years (range, 0.1 to 7). The Karnofsky performance status scores among patients with more than 1 year of follow-up were: 100% in 10 patients, 90% in 4, and 70% in 2. When survival was analyzed according to the disease

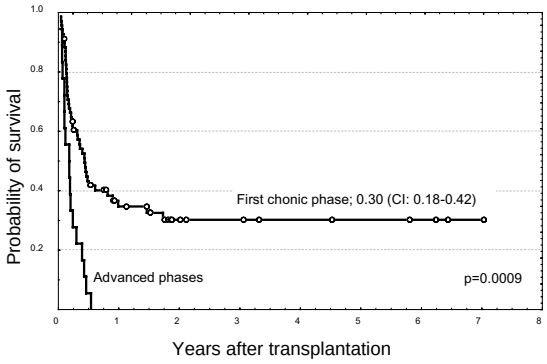

Figure 1. Actuarial probability of survival in patients with chronic myeloid leukemia in first chronic phase or with more advanced disease.

Table 4. Actuarial probability of survival (standard error) in patients receiving an UDBMT in first chronic phase: univariate analysis.

Variable	*n*	*Pts in 1CF (n=69)*	*p value*	*n*	*pts. in 1CF ≥ 1995 (n=43)*	*p value*
BMT year						
< 1995	26	0.19 (0.08)	ns	–	–	–
≥ 1995	43	0.40 (0.08)		–	–	–
BMT center						
≥ 5 UDBMT/year	50	0.31 (0.07)	ns	15	0.42 (0.14)	ns
< 5 UDBMT/year	19	0.29 (0.11)		28	0.40 (0.10)	
Patient age						
< 20 years	12	0.67 (0.16)	.006	7	0.83 (0.15)	.066
20-29 years	21	0.40 (0.11)		17	0.41 (0.13)	
30-39 years	23	0.14 (0.12)		16	0.30 (0.12)	
≥ 40 years	13	0.08 (0.07)		3	0	
< 31 years	33	0.48 (0.09)	.001	24	0.53 (0.17)	.029
≥ 31 years	36	0.11 (0.07)		19	0.15 (0.12)	
Sex match						
female to male	16	0.40 (0.13)	ns	9	0.56 (0.11)	ns
remaining cases	53	0.27 (0.07)		34	0.36 (0.09)	
HLA match						
matched by DNA	41	0.32 (0.09)	ns	34	0.45 (0.09)	ns
remaining patients	28	0.25 (0.10)		9	0.22 (0.14)	
CMV status						
both CMV (–)	11	0.63 (0.15)	.044	7	0.86 (0.13)	.008
remaining patients	53	0.24 (0.07)		32	0.33 (0.19)	
Graft manipulation						
T-cell repleted	48	0.16 (0.09)	ns	35	0.50 (0.18)	ns
T-cell depleted	21	0.35 (0.07)		8	0.38 (0.08)	
Conditioning						
Cy+TBI	41	0.40 (0.08)	.023	30	0.46 (0.10)	ns
other regimes	28	0.16 (0.08)		13	0.25 (0.13)	
Cy+TBI	41	0.40 (0.08)	.082	30	0.46 (0.10)	.009
Bu+Cy	7	0.18 (0.16)		3	0	
ATG containing	21	0.15 (0.09)	ns	10	0.30 (0.15)	ns
non-ATG	48	0.37 (0.07)		33	0.43 (0.10)	
Interval Dx-BMT						
less than 2 years	24	0.55 (0.11)	.004	17	0.62 (0.12)	.023
more than 2 years	45	0.17 (0.06)		26	0.26 (0.09)	

ns = non significant; 1CP = first chronic phase; Dx = diagnosis; Cy = cyclophosphamide; Bu = busulfan; TBI = total body irradiation; ATG = antithymocyte globulin.

status at transplantation we observed that no patients receiving an UDBMT in accelerated, blastic, or second chronic phase survived vs. 30 percent (CI: 18%-42%) of patients receiving the transplant in 1CP (p=0.0001) (Figure 1).

Patients in first chronic phase. Univariate analysis (Table 4) among these patients showed that factors associated with improved survival were (Figure 2): patient's age (p=0.001), negative CMV serologic status in donor and patient (p=0.044), conditioning regimen with Cy and TBI (when compared with the remaining regimens [p= 0.023] or with busulfan and Cy [p=0.08]), and interval from diagnosis to BMT less than two years (p=0.004). In multivariate analyses the variables associated with a better survival were patient's age, conditioning with Cy and TBI, interval of less than two years from diagnosis to transplant, and UDBMT performed after 1995 (Table 5).

Patients in 1CP receiving an UDBMT after 1995: the probability of survival was 19% (CI: 3%-35%) before 1995 vs. 40% (CI: 24%-56%) after 1995. Among this subgroup of patients, univariate analysis showed that factors associated with better survival were (Table 4): patient's age (p=0.029), donor and patient with negative CMV serologic status (p=0.008), and interval from diagnosis to BMT less than two years (p=0.023). In multivariate analysis the variables that best correlated with survival were patient's age, interval less than two years after diagnosis, and patient and donor matched by DNA methods.

Risk assessment. Figure 3 shows the cumulative effect on survival of the five main pre-transplant risk factors. The probability of survival ranged from 66% (CI: 39%-93%) in cases with no risk factors, which applies to a patient in 1CP below age of 40 years, who receives a graft from an HLA, A, B, DRB1 identical donor, within 2 years of diagnosis) to 0% in those with three or more risk factors.

Discussion

This report analyzes the results of UDBMT performed in nine Spanish centers between 1989 and 1998. The series includes more than 95% of UDBMT performed for CML in Spain during this period, and is representative of this type of transplantation activity. In our experience, as in others,[2,7-11] TRM of this procedure was very high. The cumulative incidence of TRM has decreased notably over the years (77% vs. 56% before and after 1995, respectively) and with an adequate candidate selection (26% in patients with favorable risk factors). Nevertheless, TRM was clearly higher than that observed after BMT from HLA-identical siblings, which contrasts with recent reports from single institutions.[12] As in previous studies,[7-13,21,22] the main causes of TRM were graft rejection, infections, and GvHD.

The incidence of graft failure in our series was somewhat higher than that observed by some authors after unmanipulated UDBMT[10] but similar to that reported by others,[8,9,13] although we were unable to identify factors predicting graft failure. In this series the infusion of a *back-up* autologous bone marrow was unsuccessful for recovering hematopoiesis in all cases in which this measure was used, a fact that was also

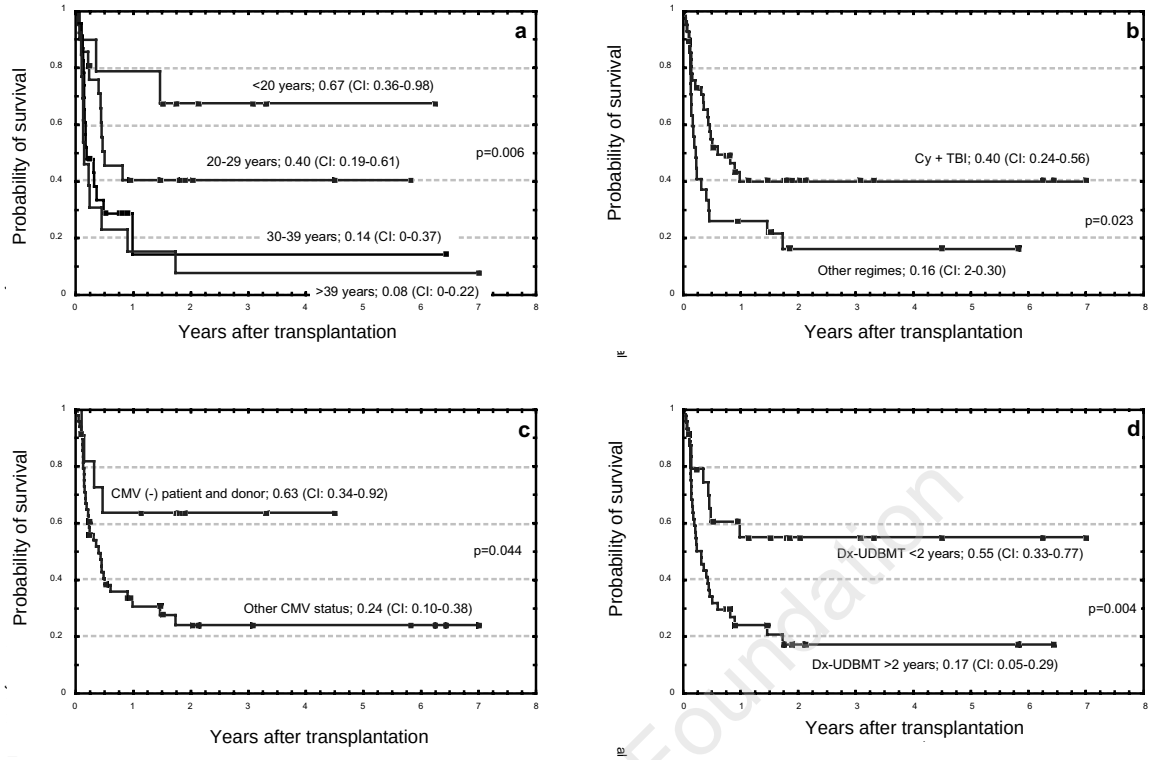

Figure 2. Actuarial probability of survival in patients with chronic myeloid leukemia in first chronic phase depending on several pre-transplant variables; a) patient's age; b) conditioning regimen; c) CMV serologic status; and d) interval diagnosis-UDBMT.

observed by other authors.[11] Unfortunately, we had insufficient information on disparity of class I HLA alleles to analyze the possible correlation of this with graft failure as other authors have recently done.[23]

The actuarial probability of acute GvHD was also similar to that reported in other series.[10,11,13] This complication contributed to death in 40% of cases. The only factor associated with a low incidence of GvHD was the use of T-cell depletion as GvHD prophylaxis.[8,13,24] Unfortunately, this incidence did not result in improved survival, probably due to the high incidence of delayed engraftment, secondary graft failure, and infections among T-cell depleted transplant recipients. We did not observe the previously reported effects of factors such as patient's age,[8,10] donor's sex,[10,13] or donor/recipient matching[23,25] on GvHD incidence. This could be explained, in part, by the low number of patients included in our series and the fact that T-cell depletion was mostly applied to patients at high risk of GvHD (old patients, mismatched donors, female donors with previous pregnancies, etc.). Some groups involved in this study have recently adopted the *early* cyclosporine prophylaxis described by the Genoa group[12] but the experi-

Table 5. Probability of survival. Multivariate analysis.

Pre-transplant variable	*Better prognosis*	*Hazard ratio (95% CI); p value*			
		1CP		*1CP ≥1995*	
Patient's age	< 31 years	4.6 (2.0-10.6)	.001	5.6 (1.8-17.0)	.007
Interval Dx-UDBMT	< 2 years	3.0 (1.2-7.3)	.006	4.1 (1.3-13.0)	.007
Cytoreductive regimen	Cy + TBI	2.6 (1.3-5.4)	.036	–	–
UDBMT year	≥1995	2.2 (1.0-4.9)	.051	–	–
Matching	Matched by DNA	–	–	6.0 (1.9-19.3)	.010

1CP = first chronic phase; Dx= diagnosis.

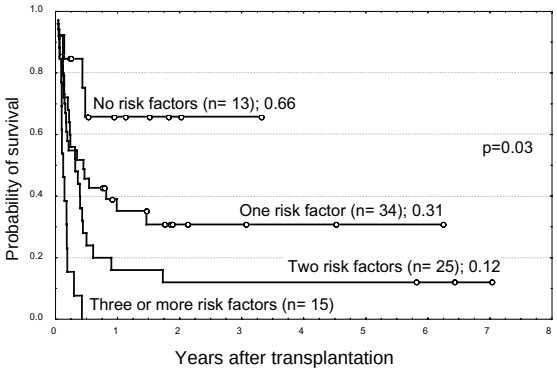

Figure 3. Actuarial probability of survival according to main pre-transplant risk factors.

ence is too brief to draw any conclusions about its usefulness.

Infection was the primary cause of death in 37 percent of the patients, CMV being the proved or suspected agent in most cases. Of note, among UDBMT performed after 1995, we observed excellent results in patient/donor pairs with a negative CMV serologic status (probability of survival 86% vs. 33%; p=0.008). The impact of prophylactic (or pre-emptive) ganciclovir or foscarnet and fluconazole to prevent CMV and fungal infections has recently been emphasized but could not be analyzed in this series.[10,12]

The cumulative incidence of relapse in this report was lower than that described by other authors.[9,10] This may be a consequence of the high TRM and short follow-up (median 1.8 years) of this series. Relapses were mainly observed among patients with advanced disease. All patients but one who relapsed died shortly after; thus there was no opportunity to administer donor lymphocytes.

Several pre-transplant factors had a clear influence on survival; these were disease status at transplant, patient's age, conditioning with cyclophosphamide and total body irradiation, interval between diagnosis and transplantation, CMV serologic status, and DNA-based matching. As other authors have shown,[2,8,9] disease status at BMT emerged as the most important risk factor. In our series, since no patients with advanced disease survived after the procedure, most risk-factor analyses were performed in the subgroup of patients in chronic phase. Additionally, as most UDBMT were performed from 1995 onwards, and the results in this period were clearly better than those observed in the previous years, we also analyzed this subgroup of patients to provide more updated information.

The age of the recipient appeared to be a significant variable in our series as well as in others.[2,8,10,13] TRM increased progressively with age and survival of patients over 40 was rare. Although some centers have reported good results in patients over this age,[10,26] based on our experience, we like the EBMT,[27] do not advise offering UDBMT to patients above 40-45 years. In our series conditioning with Cy and TBI was associated with improved survival. Although the low number of transplants conditioned with Bu and Cy precluded the possibility of drawing definitive conclusions, patients receiving this conditioning had a poorer outcome than those receiving Cy and TBI. This observation needs to be confirmed in a larger series of patients given that several authors have obtained excellent results in UDBMT with Bu-Cy conditioning.[28-30]

Several authors have demonstrated that the duration of the disease before transplant has a major impact on survival.[2,10,11,13] We could not analyze this effect in our series because of the low number of patients receiving an UDBMT during the first year after diagnosis. However, when analyzing the patients receiving their transplant during the first two years, we clearly observed the impact of this factor. This supports the approach of activating an international search donor in CML patients as soon as the lack of a family match is known. Nowadays, the median time it takes to find a matched unrelated donor is around 90 days in Spain (REDMO data, 1998), which makes early UDBMT feasible.

The fact that, in most cases, only the DRB1 locus was evaluated by DNA methods may justify the apparently low influence of mismatching on GvHD and survival in our series.[23,31-33] Similarly, we did not confirm the influence of marrow cell dose on the outcomes observed in studies with a higher number of evaluable patients.[11,34] On the other hand, we did not have enough information to analyze in detail the influence of previous treatment for CML on the results of transplantation.[35-38]

Gratwohl *et al.*[2] have demonstrated that main pre-transplant risk factors are cumulative for individual patients with CML having a BMT. We evaluated this fact in our series using the same variables but modifying their score slightly. Thus, as our analysis included a limited number of patients, all them receiving an UDBMT, risk factors were classified as 0/1; the variable donor type (related/unrelated) was substituted by (HLA, A, B, DRB1 identical/others), disease stage (0/1/2) by (1CP/advanced disease), and patient's age (0/1/2) by (<40/≥40 years). As Figure 3 shows, this risk assessment method was also highly predictive when applied to patients receiving an UDBMT.

In conclusion, this experience demonstrates that UDBMT used to have a high TRM that has progressively decreased over the last years. This improvement is probably a result of more accurate donor/recipient matching, better GvHD and infection prophylaxis, and timing of transplant. At present, the results are especially encouraging when UDBMT is performed in good risk patients. Thus, in our series, patients under 40 years of age with CML in first chronic phase lasting less than two years, and receiving a BMT from an HLA-A, B, and DRB1 matched donor, had an actuarial probability of survival as high as 66%. These results compare with those observed in other multicenter analyses.[2,8,9,11,13] In the near future quicker and better donor selection (typing of HLA-A, B, C, DR and DQ by DNA-methods) and the use of more effective prophylactic measures of GvHD, fungal and viral infections will improve these results.

Contributions and Acknowledgments

EC, JFT and AT conceived and designed the study JFT prepared the questionnaires and collected the data. EC processed and analyzed the data and wrote the paper, which was critically reviewed by JFT, GS, RC and JS. EC, VG, GS, AI, CB, JL, RC and AS collected the data in their respective centers. The order of authorship reflects the contribution of each center to the study.

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Disclosures

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Potential implications for clinical practice

- Despite its high transplant-related mortality, UDBMT is currently a realistic therapeutic option for CML patients who have an adequate unrelated donor.
- Several pre-transplant factors, such as disease status at transplant, patient's age, interval diagnosis-transplantation, degree of HLA compatibility, CMV serologic status and conditioning regimen, have a major impact on survival.

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