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Allogeneic hemopoietic stem cell transplantation for patients with high risk acute lymphoblastic leukemia: favorable impact of chronic graft-versus-host disease on survival and relapse

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Abstract

Background and Objective. **The best post-remission therapy for patients with acute lymphoblastic leukemia (ALL) is controversial, and hemopoietic stem cell transplantation (HSCT) is one therapeutic option. The goal of this study is to describe long term results of HSCT in high risk ALL patients.**

Design and Methods. **Between 1978 and 1996, 170 patient with ALL and a median age of 22 years (1-49), underwent an allogeneic HSCT from HLA-identical siblings (n=149), family mismatched donors (n= 18) or unrelated HLA matched donors (n=3); 92% of patients had at least one adverse prognostic factor for high risk ALL at diagnosis; one third (33%) were in first remission (CR1) and the majority (85%) received an unmanipulated HSCT with cyclosporin-methotrexate prophylaxis of graft-versus-host disease (GvHD).**

Results. **After a median follow-up of over 6 years, 59 patients are alive and 111 patients have died of leukemia (46%) or transplant related complications (54%). The actuarial 10 year survival is 53%, 38% and 20%, for patients in CR1, CR2 or advanced phase, respectively. The actuarial survival of patients with (n=24) or without (n=46) cytogenetic abnormalities, grafted in CR1/CR2 was respectively 45% and 48% (p=0.5). The year of transplant had a significant impact in multivariate analysis on transplant related mortality (TRM) (p=0.0009) but not on relapse (p=0.3). Chronic GvHD was the most important favorable prognostic factor for survival (p=0.0014) and relapse (p=0.0019).**

Interpretation and Conclusions. **This study confirms that long term survival can be achieved with HSCT in ALL patients, even those with cytogenetic abnormalities. Transplant mortality has been significantly reduced in recent years, whereas leukemia rate relapse has remained unchanged: the latter is influenced by the occurrence of chronic GvHD. Immune intervention post-HSCT may be considered to address this problem.**

Key words: acute lymphoblastic leukemia, hemopoietic stem cell transplant, graft-versus-host disease, graft-versus-leukemia

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Acute lymphoblastic leukaemia is the most common type of leukemia in children and represents 20% of cases of leukemia in adults. Most patients with ALL achieve a complete remission with the current induction chemotherapy, but only 10-30% of adult patients become long term survivors.[1,2] There is no definite answer at present as to which is the best post-remission therapy for these patients. Some studies showed that for patients with advanced disease, bone marrow transplantation (BMT) is superior to chemotherapy (CT),[3,4] but for patients in first complete remission this is controversial.[5,6] Some data support the use of more intensive therapy, including BMT, in patients with risk factors predicting treatment failure after chemotherapy, such as high white blood cell counts, age > 30 years, cytogenetic abnormalities, and a long interval to achieve first remission.[7-9] In patients without adverse factors, the probability of continued remission at 5 years ranges between 37% and 72%.[10] The impact of these variables on the outcome of bone marrow transplantation is also controversial.[11,12]

Bone marrow transplantation results in an overall survival of 20-60%[13,14] in different studies, with a transplant related mortality (TRM) of 20-50%, and a significant relapse risk of >30%, especially in patients with advanced disease. A possible graft-versus-leukemia (GvL) effect of allogeneic cells, is supported by a lower but not significant relapse rate after HLA-identical sibling BMT versus identical twin BMT,[15,16] a lower relapse rate in patients with vs without GvHD,[16] and a higher relapse rate after T cell depletion.[17]

We report here our experience with allogeneic BMT in 170 ALL patients. The influence of graft-versus-host disease on the outcome of patients is discussed.

Materials and Methods

Patients' characteristics

Patients underwent HSCT in our unit, between 1978 and 1996, after signing informed consents. Patients' characteristics are shown in Table 1. One hundred and seventy patients (104 males and 66

Table 1. Patients' characteristics at diagnosis.

	No.	*(%) or (range)*
All patients	170	
Recipient age (yr), median(range)	22	(1-49)
Patients < 16 years old	44	
median (range)	12	(1-16)
Recipient gender, (male/female)	106/64	
Donor age median, (range)	24	(1-62)
Donor gender, male/female	91/79	
WBCC at diagnosis (x10^9/L), median (range)	14.2	(0.3-300)
Cytogenetics		
normal	65	(38%)
unknown	66	(39%)
abnormal	39	(23%)
Ph+	17	
others	22	
FAB classification		
L1	23	(14%)
L2	83	(49%)
L3	6	(4%)
unknown	58	(34%)
Immunology		
B	101	(59%)
T	20	(12%)
unknown	49	(29%)
Extramedullary disease		
spleen	66	(40%)
CNS	no/yes	160/10
CNS prophylaxis	no/yes	135/35

Abbreviations: WBCC= white blood cell counts; FAB = French- American-British; Ph= Philadelphia; CNS= central nervous system.

Table 2. Transplant characteristics.

	No.	*(%)*
Disease status at HSCT		
1st CR	56	(33%)
2nd CR	64	(38%)
>2nd CR	50	(29%)
Days from diagnosis to HSCT median (range)	342	(101-4413)
WBCC at transplantation (x10^9/L) median (range)	4	(0-180)
Conditioning regimen		
CY+TBI	129	(76%)
CY+BU	12	(7%)
Other	29	(17%)
Donor		
HLA id siblings	149	(88%)
HLA fam mis	18	(10%)
MUD	3	(2%)
GvHD prophylaxis		
MTX	12	(7%)
CS+MTX	136	(80%)
TCD	22	(13%)
Number of infused cells (x10^8/kg BW) median (range)	2.8	(0.031-23.3)
Engraftment (PMN > 500) median days (range)	14	(8-34)
Acute GvHD		
0-I	88	(52%)
II	55	(32%)
III-IV	27	(16%)
Chronic GvHD (118 patients)		
no	39	(33%)
limited	49	(42%)
extensive	30	(25%)
Causes of death		
Leukemia	51	(46%)
Transplant related	60	(54%)
Survival		
N. of pts. alive	59	(34%)
Follow-up (days), median (range)	2660	(22-5631)

Abbreviations: HSCT= hemopoietic stem cell transplants; CR= complete remission CY= cyclophosphamide; TBI= total body irradiation; BU= busulfan; HLA= human leukocyte antigen; PBSC= peripheral blood stem cells; fam mis= family mismatched; MUD= matched unrelated donor; MTX= methotrexate; CS=cyclosporin; TCD= T cell depletion; GvHD= graft-versus-host disease.

females) with a median age of 22 years (24.4 years for male and 21 for female patients) took part in the study. Fifty-six patients were in first complete remission (CR1), 64 patients in second remission (CR2) and 50 patients had more advanced disease (>CR2). Of the patients 16 years old or younger, 7 were in CR1, 26 in CR2 and 11 had more advanced disease. According to the French-American-British (FAB) classification, most patients had L2-ALL (n=83), or L1-ALL (n=23); only 6 patients had L3-ALL. The distribution of cell lineages was B-cell in 101 patients (59%), T-cell in 20 (12%). The cell type was unknown in 48 patients (29%), most of whom were diagnosed and treated before the use of monoclonal antibodies for typing or the use of fluorescence-activated cell sorters (FACS). Thirty-nine patients had an abnormal karyotype at diagnosis, 65 had a normal karyotype and in 66 patients the karyotype was unknown. Seventeen of 39 patients with an abnormal karyotype had Ph-chromosome positive ALL. Sixty-six patients (40%) had a large spleen at diagnosis, whereas CNS involvement was present in only 10 patients (5%). Cranial radiation as prophylaxis was given to 35 patients (21%). One hundred and fifty-seven patients (92%) had at least one high risk factor at diagnosis (age >30 years, white blood cell counts > 25×10^9/L at diagnosis, abnormal karyotype mainly the presence of Philadelphia chromosome and other translocations or multiple abnormalities, interval to achieve remission longer than 4 weeks, extramedullary disease).

Transplantation

The transplantation characteristics are shown in Table 2. The conditioning regimen was cyclophosphamide (CY) 60 mg/kg/day for two consecutive

days intravenously, followed by fractionated total body irradiation (TBI) (9.9-12 Gy in 3-6 fractions), or CY 120 mg/kg with busulphan (BU) 4 mg/kg/day *per os* for 4 days or thiotepa (TT) 15 mg/kg in two days. One hundred and forty-nine patients received HLA-identical sibling unmanipulated bone marrow (BM) (n=141) or peripheral blood (PB) (n=8) grafts; 18 patients received family mismatched donor grafts and 3 matched unrelated donor grafts (MUD). The prophylaxis for acute GvHD was mainly cyclosporin A (CSA) with a short course of methotrexate (MTX) (n=136), MTX alone (n=12) and in 22 patients *in vivo* T cell deletion (TCD) using the monoclonal antibody CAMPATH-1. The median number of infused cells was 2.8×10^8 MNC/kg BW (range 0.031-23.3×10^8 cells/kg BW), transfused over 24 hours after the last dose of TBI (signed as day 0).

Graft-versus-host disease (GvHD): definitions and grading

Acute graft-versus-host disease was scored according to standard morphologic, clinical and biochemical criteria based on the involvement of skin (% of skin area involved), liver (serum level of bilirubin) or intestine (volume of diarrhea and/or ileus). Acute GvHD was graded in five degrees: 0 or absent, grade I, II, III, IV according to the participation of each one of this organs.[18] Chronic graft-versus-host disease was also diagnosed according to morphologic criteria and was graded as absent, limited or extensive. Only patients alive on day +100 or beyond were eligible for chronic GvHD evaluation and outcome analysis.[19]

Statistical analysis

Statistical analysis was done using the NCSS statistical software. Chi-square test and Fisher's exact test were used to compare groups; Kaplan Meier curves were used to estimate survival, relapse rate and transplant related mortality.[20] Log rank tests were used to compare survival curves. Univariate and multivariate analysis for prognostic factors on survival and relapse rate were calculated using the Cox model.[21]

Results

Engraftment

Engraftment was defined as occurring on the first of three consecutive days on which there was an absolute number of polymorphonuclear neutrophils (PMN) over 0.5×10^9/L. The median day to achieve PMN > 0.5×10^9/L was 14 days (range 8-34). Median platelet counts ($\times10^9$/L) between days 0-20 were 25 (6-93), between days 21-50 were 80 (9-241), between days 51-100 were 96 (12-226) and beyond day +100 from HSCT were 181 (12-302). Median platelet counts were significantly lower in patients who died of transplant related complications in the interval from day 21 to day 50 (42 vs 101, p=0.0005) and in the interval from day 51 to day 100 (37 vs 113, p<0.00001).

Acute graft-versus-host disease (aGvHD)

The median time for development of aGvHD was 14 days (range 4-60). aGvHD was scored in 88 patients (52%) as grade 0-I, in 55 (32%) as grade II and in 27 patients (16%) as grade III-IV. Patients developing grade 0-I, II and III-IV GvHD had an actuarial transplant mortality (TRM) of 29%, 31% and 73% (p=0.009). Their actuarial relapse was respectively 56%, 44% and 18% (p=0.04) and their probability of survival 28%, 40%, 20% for the 3 groups, with grade II aGvHD having the best one (p=0.6) (Figure 1A).

Chronic graft-versus-host disease (cGvHD)

One hundred and eighteen patients were alive 100 days after transplantation and were evaluable for cGvHD. This was scored as absent in 39 (33%), limited in 49 (42%) and extensive in 30 patients (25%). The occurrence of cGvHD was more frequent in patients who had received BU in addition to CY as conditioning regiment than in those who had received TBI (p=0.02). Patients developing no, limited or extensive chronic GvHD had an actuarial TRM of 10%, 10% and 27%, respectively (p=0.4). The actuarial relapse rate was 72%, 39% and 27% (p<0.0001) and the actuarial survival was 27%, 56% and 46% respectively (p=0.01) for the three groups (Figure 1B).

Cytogenetics

Karyotypic analysis was available for 104 patients. Seventeen had Ph-chromosome positive ALL, 22 had other abnormalities [t(4;11)(n=3); t(1;19)(n=2); multiple abnormalities (n=6); trisomy 8 (n=2); aneuploidy (n=1); polyploidy (n=3), other (n=5) [t(11;13), -21, -17del17q; -8; hyperdiploidy)], and 65 had a normal karyotype (Table 1). Fourteen of 39 patients, with an abnormal karyotype, are alive (34.5%) at a median interval of 1948 days (range 84-3674). Among patients with Ph^+-ALL, 5/17 are alive (30%) at a median interval of 2295 days (range 179-3661). The actuarial survival of patients grafted in CR1/CR2 with (n=24) or without (n=46) cytogenetic abnormalities was respectively 45% and 48% (p=0.5) (Figure 2).

Transplant related mortality (TRM)

The overall actuarial transplant mortality at 10 years was 38%. There has been a reduction of TRM with time, especially in the last years: 35% before 1992 vs 10% in 1992-97 (p=0.01)(Figure 3). In multivariate analysis the year of transplant (p=0.004), female recipients (p=0.004), aGvHD (p=0.01), T cell depletion (p=0.03) and the use of donors other than HLA-identical siblings (p=0.03) were significant predictors of TRM (Table 3A). These factors remained predictive also after step down analysis. White blood cell counts at transplantation, number of infused cells, donor gender, donor age, WBC at diagnosis and disease status had no significant impact on TRM.

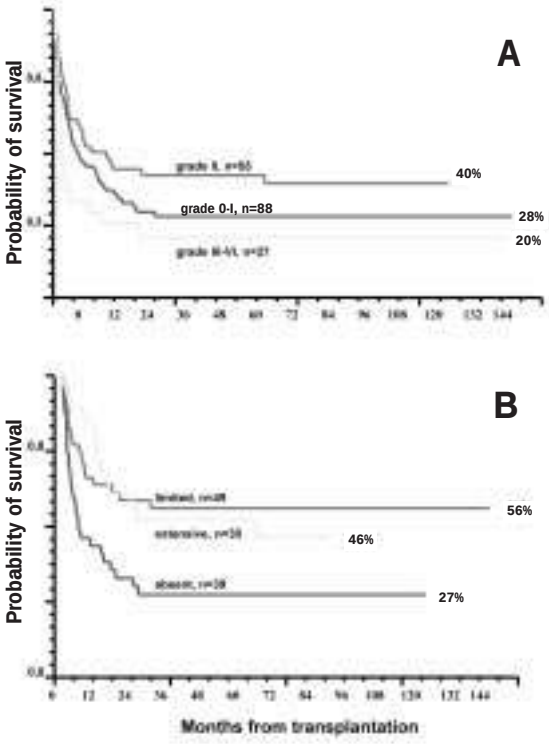

Figure 1. The effect of acute GvHD (Panel A) and chronic GvHD (Panel B) on survival: patients with grade O-I aGvHD have lower mortality, but higher relapse, such that survival is comparable with patients with aGvHD grade III-IV.
Panel B shows the effect of chronic GvHD on survival in patients alive on day 100 (n=118): there is a significant survival advantage for patients with limited or extensive cGvHD over patients without cGvHD.

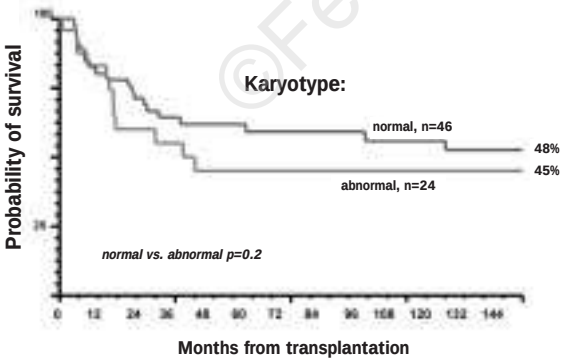

Figure 2. Actuarial survival for patients in CR1 and CR2 according to the karyotype at diagnosis: survival is 48% for patients with normal karyotype and 45% for patients with abnormal karyotype (p=0.5).

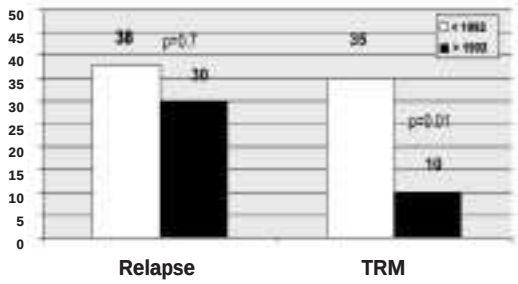

Figure 3. Risk of transplant mortality (TRM) and relapse in patients grafted < 1992 (white bars) or ≥ 1993 (black bars). Reduced transplant mortality (TRM) (p=0.01) in patients with ALL in first or second complete remission (CR1+CR2) (right part of the graph) compared with no significant reduction in the risk of relapse (p=0.7) (left part of the graph).

Leukemia relapse

The overall actuarial relapse rate was 48%. The probability of relapse was greater for patients with advanced disease (24% in CR1 vs 54% in CR2 (p=0.004) vs 72% in >CR2 (p=0.0003)(Figure 4). In multivariate analysis significant predictors were disease status at transplantation, (p=0.0001) and cGvHD (p=0.001) (Table 3B). After step down analysis, factors remaining significant were cGvHD (p=0.0002), phase of the disease (p=0.0004) and recipient age (p=0.01) with older patients having a higher risk of relapse. Other variables were not significant: in particular the year of transplant had no effect (p=0.3) on relapse: this is outlined in Figure 3, showing the risk of relapse for patients in CR1/CR2 grafted ≤ 1992 or ≥1993.

Survival

Fifty-nine patients (35%) are alive with a median follow-up of 2660 (range 71-5631) days. The overall probability of survival at 10 years is 31%. There is an effect of disease status on survival as expected: 53%, 38%, and 20% 10-year actuarial survival, for patients in CR1, CR2 and more advance disease respectively. In multivariate analysis on all patients, excluding chronic GvHD, the year of HSCT had the most significantly impact (Table 3B); recipient age and donor compatibility were also important (Table 3B). When patients surviving after day +100 and *eligible* for cGvHD were analyzed, then cGvHD itself (p=0.0017) and disease status (CR1 vs >CR1 p=0.002) were highly predictive (Table 3D). Data at diagnosis (white blood cells, cytogenetic abnormalities, age, extramedullary disease) did not appear to influence survival significantly. After step down analysis factors remaining significant were: cGvHD (p=0.0002) and disease status (p=0.0004).

Table 3. Multivariate Cox analysis.

	Baseline value	*Compared value*	*RR*	*95% CI*	*p*
A. Transplant mortality (170 patients: not including cGvHD)					
Year of HSCT	continuous		0.90	(0.84-0.97)	0.004
Recipient gender	male	female	2.27	(1.29-4.00)	0.004
Acute GvHD	O-I	II	0.98	(0.50-1.91)	
	II	III-IV	2.55	(1.26-5.18)	0.018
GvHD prophylaxis	unmanip	TCD	2.25	(1.05-4.79)	0.036
HLA compatibility	HLA ident	mismatched	2.64	(1.05-6.66)	0.039
Recipient age	continuous		1.03	(1.00-1.06)	0.053
B. Survival (170 patients; not including cGvHD)					
Year of HSCT	continuous		0.91	(0.86-0.96)	0.001
Disease status	continuous		1.50	(1.14-1.96)	0.003
Recipient age	continuous		1.03	(1.01-1.05)	0.016
HLA comp	HLA ident	mismatched	2.41	(1.17-4.97)	0.017
C. Relapse (118 patients alive on day ≥ 100; including cGvHD)					
Disease status	CR1	>CR1	4.56	(1.93-10.82)	0.0006
Chronic GvHD	absent	limited	0.43	(0.21-0.88)	
		extensive	0.23	(0.08-0.61)	0.006
D. Survival (118 patients alive on day ≥ 100; including cGvHD)					
Chronic GvHD	absent	limited	0.35	(0.18-0.70)	
	limited	extensive	0.21	(0.08-0.54)	0.0017
Disease status	CR1	>CR1	3.02	(1.49-6.13)	0.0022

Causes of failure

One hundred and eleven patients died at a median follow-up interval of 88 months (range 1-187) from transplant. The main cause of death was leukemia (n=51) followed by aGvHD (n=17) (n=10), interstitial pneumonia (IP)(n=6), rejection (n=5), ARDS (n=5), heart failure (n=4), multiorgan failure (n=4), chronic GvHD (n=3), hemorrhage (n=3), hepatitis (n=2), second tumor (n=1).

Discussion

We have confirmed in this study that long term survival can be achieved with allogeneic hemopoietic stem cell transplants in ALL patients if performed in the early phase of the disease, even in the presence of cytogenetic abnormalities. Over the past 10 years there has been a significant reduction of transplant mortality but not of leukemia relapse.

Phase of disease and patients' age have been known for a long time to predict the outcome of allogeneic BMT;[5,12,22] the median age in this series was 22 years, indicating that half of the patients were adults, up to the age of 49. The combined effect of phase and patient age should be considered carefully when an adult with ALL in first remission is referred for transplantation: delaying the graft until first relapse may have a different effect in children or adults: in this series the survival of patients less than 20 years old with disease beyond CR1 was 61% as compared to only 43% for adults in the same phase (data not shown). In other words waiting may significantly reduce the chance of long term survival in adults with ALL, especially because in this study we have confirmed a very pronounced effect of age on survival and on relapse. In addition comparative studies of BMT versus CT have never shown that BMT patients have a disadvantage.[5]

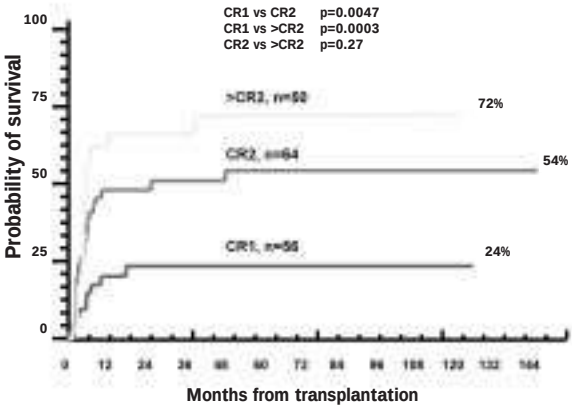

Figure 4. The effect of disease status on actuarial relapse rate in 170 patients with ALL. The difference between patients in first remission (CR1) and second remission (CR2) is significant (p=0.0047) whereas between CR2 and patients with more advanced disease it is not (p=0.27).

Cytogenetic abnormalities (especially Ph-chromosome positive, translocations t(4;11), t(1;19), multiple chromosomal abnormalities) have been associated with a bad prognosis with current conventional CT.[2] In this series the presence of cytogenetic abnormalities at diagnosis did not significantly influence the overall survival or the relapse rate in patients in CR1/CR2: over 35% of these patients are surviving in the long term (median 64 months). These results are in agreement with other reports,[23-25] showing encouraging results produced by bone marrow transplantation in Ph-chromosome positive ALL, and suggesting that patients with abnormal karyotypes and a suitable donor should be transplanted as early as possible after the achievement of complete remission.

Transplant mortality is a very important issue when advising a patient as to whether he or she should undergo a transplant: major problems are acute GvHD and infections. Improved treatment of infections, especially CMV with pre-emptive or prophylactic use of gancyclovir, and other measures, such as increased number of infused marrow cells, have resulted in an overall reduction of TRM over the years: 35% before 1992 and 10% currently; these results are in agreement with other reports.[14,26] This is an important message for patients considering HSCT in the early phase of disease, although late effects such as sterility and second tumors should also be taken in to account. In our series only one patient has died of a second tumor.

The risk of relapse has not significantly changed with time[14] and remains a major problem in ALL possibly due to selection of patients with high-risk leukemia. In this series the vast majority (92%) had at least one risk factor at diagnosis of their disease, such as cytogenetic abnormalities, high white blood cell count, extramedullary disease and age > 30 years.[2] In the present series there is a trend for a lower risk of relapse with time in patients grafted in CR1-CR2, but not so in patients with advanced disease: the overall risk in the latter is 72% at 8 years which poses two questions: is it reasonable to transplant a patient knowing that the relapse risk is over 70% and the overall survival not more than 20%? And of course the second question is: can we do something about it? A recent report suggests that intensification of the conditioning regimen is associated with an unacceptable toxicity even in patients in first complete remission.[27] Alternatively other manipulations, such as pre-conditioning treatment, could address this problem.[28]

Chronic GvHD has been reported to have a positive influence on leukemia relapse.[22] We confirm a favorable impact of cGvHD on relapse but, differently from others, also on survival: patients with no cGvHD had a 27% probability of surviving 10 years, compared to 56% and 46% for patients with limited and extensive cGvHD respectively. In other words if an ALL patient survives 100 days after transplant, and is thus *eligible* for developing cGvHD, it is much better to have some degree of cGvHD, because this will be highly protective against leukemia relapse and will translate into a survival advantage. We have also shown a favorable effect of acute GvHD on relapse, as already described,[22] which overcomes the negative effect on transplant mortality: in fact patients with grade III-IV aGvHD had comparable survival to patients with grade 0-I aGvHD. Best results were seen in patients with aGvHD grade II.[29,30]

One option would, therefore, be to modulate GvHD, but past attempts have not always been successful. No prophylaxis for acute GvHD is a deleterious strategy which results in severe and hyperacute GvHD, with concomitant infectious complications and poor graft function.[31,32] On the other hand we have shown that low dose cyclosporin has a significant impact on leukemia relapse,[33] suggesting that modulation of *in vivo* immunosuppression is possible in the setting of a mild conditioning regimen.

Donor lymphocyte infusions (DLI) can exert significant antileukemic effect in patients relapsing after allogeneic bone marrow transplantation: over 80% of patients with CML, approximately 30% of patients with AML, whereas only occasional patients with ALL will respond to DLI.[34] The reasons for these differences are unknown: higher number of clonogenic cells and greater resistance to an immune effect, have been taken into consideration.[35]

It is interesting that, in spite of these negative results of DLI in ALL, we and others have shown a pronounced effect of acute and chronic GvHD on leukemia relapse in ALL patients after allogeneic hemopoietic stem cell transplants. The effect is so relevant that it translates into a survival advantage. One hypothesis for the effect of acute and chronic GvHD and for the lack of effect of DLI in acute lymphoblastic leukemia, may be that the former prevent leukemia relapse, possibly when the tumor burden is low, whereas DLI is supposed to treat leukemia relapse when the tumor burden is high.

We believe that these data suggest that improvement of the outcome in ALL will come at present only if we can address the issue of leukemia relapse: prophylactic donor lymphocyte infusions may be considered early after BMT, possibly given in escalating doses.[36] The use of leukemic specific T clones or of biologic modifiers, capable of modulating antigen expression on target cells (IFNs) or on antigen presenting cells (GM-CSF),[37,38] may be alternative approaches.

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PZ is a recipient of an educational grant from the Blood Bank Center, "St. Andrews" General Hospital of Patras, Greece, and is supported by the National Health System of Greece. PZ was responsible for data analysis and writing the manuscript. MTvL, TL, FG, DO, SB, NM, GB, MI, GF were responsible for the patients' care. MS performed the cytogenetic examinations. AB was responsible for the conception of the study, its interpretation and writing of the paper.

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Disclosures

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