Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study

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Background and Objectives. Numerous studies have reported the feasibility of performing allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning, although results in individual diseases are scarce, with no studies in patients with acute lymphoblastic leukemia (ALL). We sought to analyze the results of reduced intensity conditioning for allografts in adult patients with ALL.

Design and Methods. We report the results of a reduced intensity conditioning regimen followed by allogeneic hematopoietic stem cell transplantation in 27 adult patients with high-risk ALL who were included in four prospective studies.

Results. The median age was 50 years; 23 (85%) patients were beyond first complete remission, 44% were chemorefractory and 41% were Philadelphia chromosome positive. Donors were mismatched related donors or volunteer unrelated donors in 12 cases (44%). The incidence of grades II-IV acute graft-versus-host disease (GVHD) was 48%, and 13 of 18 evaluable patients (72%) developed chronic GVHD. Currently nine patients are alive, with a median follow-up of 809 days (range, 381-1375). The 2-year incidence of transplant-related mortality was 23% (95% CI, 11% to 46%), and the 2-year probability of overall survival was 31% (95% CI, 12 to 48%), while the 2-year incidence of disease progression was 49% (95% CI, 33% to 72%). The 2-year incidence of disease progression in patients with and without GVHD was 35% (95% CI, 19% to 57%) and 70% (95% CI, 47% to 100%), respectively (p=0.05).

Interpretation and Conclusions. This retrospective study suggests that allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning might be a useful therapeutic option for some patients with ALL who are ineligible for standard myeloablative conditioning. However, this treatment modality needs to be evaluated in prospective trials, and should not be employed outside clinical studies.

Key words: reduced-intensity, allogeneic, transplantation, acute lymphoblastic leukemia.

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Allogeneic hematopoietic stem cell transplantation (HSCT) with myeloablative conditioning is a valid treatment option for adults with acute lymphoblastic leukemia (ALL).[1] Several groups of investigators have developed reduced-intensity conditioning regimens for allografting, which may lead to a graft-versus-leukemia (GVL) effect without the toxicities of intense myeloablative conditionings.[2-9] However, experience with reduced intensity conditioning HSCT in ALL is very limited. We herein report results of patients with ALL who were transplanted within four prospective, multicenter studies.

Design and Methods

Patient selection

The study includes 27 consecutive patients with ALL who received an allogeneic HSCT with a reduced intensity conditioning regimen within four multinational prospective studies. Details of each of these protocols have been previously published in detail.[5-9] Up to December 2001, 635 patients had been included in these four groups of prospective studies, and thus only 4.3% of patients suffered from ALL. In all of these studies, patients gave written informed consent for inclusion in the protocols, which were approved by all local ethical committees and local regulatory authorities. All patients were considered unfit for a conventional myeloablative transplant due to age (> 55 years), prior autograft and/or severe comorbidities (pulmonary, cardiac or other dysfunctions that contraindicated standard myeloablative chemoradiotherapy).

The patients' characteristics are shown in Table 1. Their median age was 50 years (range 18-63), and the ECOG performance status was 0-1 in 25 cases (93%). Twenty-four patients (89%) were seropositive for cytomegalovirus (CMV) [n=20] or were seronegative but received stem cells from a CMV-positive donor (n=4). All patients had been treated with one (n=2) or more (n=25) lines of intensive chemotherapy pre-transplant, including a prior autologous transplant in 8 cases. All but two patients had precursor B-lineage ALL. Only 4 patients were in first complete remission (CR) at transplant, while 11 (41%) were in second or third CR and 12 (44%) were chemorefractory (i.e., at the reduced intensity conditioning transplant >30% blasts were found in the bone marrow (BM) in untested relapse or despite recent intensive salvage chemotherapy). The most common cytogenetic abnormality was the Phila-

delphia chromosome (Ph^+), which was found in 11 cases (41%).

The reduced intensity conditioning regimen used in each case is shown in Table 1. In summary, all reduced intensity conditioning protocols included fludarabine (90 to 150 mg /m^2), plus an alkylating agent (melphalan 140 mg/m^2, thiotepa 10 mg/kg) or low-dose (200 cGy) single-fraction total body irradiation (n=1). Three patients from one institution also received cytosine arabinoside (2 g/m^2). All protocols have been previously reported in detail.[5-9] Graft-versus-host disease (GVHD) prophylaxis consisted in cyclosporine A or tacrolimus plus short-course methotrexate (n=24), mycomofetil fenolate (n=1) or CAMPATH-1H (n=2). Infection prophylaxis, grading and treatment of acute and chronic GVHD were done by standard methods.[5-9]

Donors were HLA-identical siblings in 15 cases (56%), volunteer unrelated donors (VUD) in eight (30%) and 1-antigen mismatched related donors in 4 cases (see Table 1 for details). Four of the eight VUD donors had a known alleleic mismatch at the C (n=2) and/or DQB1 loci (n=3). Bone marrow (BM) stem cells were used in 13 cases (48%) and peripheral blood (PB) stem cells in 14 cases (52%).

Chimerism analysis

After transplant, serial samples of PB and BM cells were analyzed for degrees of donor-recipient chimerism using a polymerase chain reaction (PCR) technique in all evaluable cases. In eight cases both granulocyte and T-cell chimerisms were studied, while in 13 cases unfractionated nucleated cells were analyzed.

Minimal residual disease (MRD)

A method of monitoring MRD post-transplant was used in 15 cases (56%). In 9/11 patients with Ph+ ALL BM samples were studied by a reverse transcriptase qualitative PCR for the bcr/abl transcript. In 10 patients immunophenotypic detection of blasts by flow cytometry was the method for monitoring MRD.[10,11] Both methods were simultaneously used in 5 cases with Ph^+ ALL. In one patient a PCR for the rearranged immunoglobulin heavy chain gene was used.[9]

MRD was defined to be present when there were > 0.1% aberrant lymphoblasts by immunophentoyping in morphologically and cytogenetically normal BM and/or when there were PCRs positive for the specific marker detected pretransplant.

Statistical analysis

The probability of overall survival was estimated from the time of transplantation using Kaplan-Meier product-limit estimates, while the probabilities of transplant-related mortality (TRM), disease progression and acute and chronic GVHD were calculated using cumulative incidence estimates. Univariate Cox regression was used to analyze the association of various variables with disease progression, with GVHD included as a time-dependent covariate. A multivariate Cox regression analysis was not done because of the small number of patients.

Results

Patients received a median of 4.7×10^6/kg $CD34^+$ cells (range 2.1 to 9). Early procedure-related toxicities were mild in most cases, although there was one early death from multiorgan failure (patient UK1). Thus, only 26 patients were truly evaluable for engraftment and GVHD.

Hematologic recovery and infections

Donor-derived hematologic recovery occurred in all 26 evaluable cases. Neutrophils decreased to < 0.5×10^9/L in all cases and recovered at a median of 13 (range 10 to 30) and 16 (13 to 21) days after transplant in recipients of BM and PB, respectively; however, 9/13 recipients of BM received granulocyte colony-stimulating factor post-transplant, as opposed to 2/14 recipients of PB (p=0.004). The median times to reach a stable platelet count >20×10^9/L were 17 (12-32) and 13 (10-21) days, respectively. Nineteen patients (70%) developed febrile neutropenia, with three cases of bacteremia and one candidemia. CMV was reactivated in only four patients, which represents a 180-day probability of developing CMV infection of 18%. Two patients died from an infectious complication; UK1 died on day +18 from multiorgan failure after *Candida krusei* fungemia, and MDA8 died on day +90 with pulmonary and cerebral aspergillosis after grade II acute GVHD.

Acute and chronic GVHD

Acute GVHD occurred in 17 patients (63%); the reaction reached grade I in four cases, grade II in six, grade III in four and grade IV in three cases. The 100-day incidence of grade II-IV acute GVHD was 48%. Thirteen of 18 evaluable patients (72%) developed chronic GVHD, which was extensive in seven cases (39%).

Chimerism

Around day +30, 17 of 21 (81%) patients studied had complete donor chimerism (CDC) in PB and/or BM, and on days +90 to +100 the rate of CDC in BM or PB was 17/18 (94%). There were no primary or secondary graft failures. CDC was confirmed in fractionated PB T cells and granulocytes in eight cases, while in the other 13 patients only unfractionated nucleated cells were tested.

Table 1. Patients' characteristics and outcome.

Pat.	Age (yr)/ Sex	PS (ECOG)	Risk features at RIC allograft Cytogen.	Status	Failed prior autograft	Stem cell source	Donor type /HLA mismatch	Conditioning (reference)	GVHD prophylaxis	Acute GVHD, grade	Chronic GVHD	Outcome
SP4	59 / M	0	Ph+	CR1	No	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	III	NE	Died, pneumonia day +46
MDA6	51 / M	1	Ph+, -7	CR1	No	BM	1 Ag MM child	Flu-Mel[5]	Tacrolimus-MTX	No	No	Relapse day +182, died +214
MDA8	57 / F	1	Ph+	CR1	No	PB	HLA-id sib.	Flu-Mel[5]	Tacrolimus-MTX	II	NE	Died,infection on day +90
SP1	62 / M	0	Ph+	CR2	No	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	I	No	Relapse day +154, died +235
SP5	60 / M	1	Ph+	CR2	No	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	II	No	Relapse day +266, died +303
SP11	62 / M	1	Ph+	CR2	No	PB	HLA-id sib.	Flu-TBI[3]	CsA-MMF	I	Ext.	Relapse day +321, alive +497
SP10	34 / M	0	Ph+	CR3	Yes	BM	VUD / C mismatch	Flu-Mel [8]	CsA-MTX	I	Ext.	AWD day + 546
MDA2	46 / F	2	Ph+	CR3	No	BM	1 Ag MM sib.	Flu-Mel-Ara-C[5]	Tacrolimus-MTX	IV	Ext.	Died, cGVHD day +474
SP2	63 / F	1	Ph+	1ry. Refr.	No	PB	HLA-id sib.	Flu-Mel [8]	CsA-MTX	No	Ext.	AWD day + 1233
SP3	42 / M	1	Ph+	Refr. Rel.	Yes	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	No	NE	Relapse day +56, died +236
MDA4	25 / F	1	Ph+	Rel.	No	BM	1 Ag MM sib.	Flu-Mel-Ara-C[5]	Tacrolimus -MTX	Limited III		Relapse day +197, died +229
IT1	50 / M	0	Normal	CR1	No	BM	HLA-id sib.	Flu-Cy-TT[9]	CsA-MTX	II	No	AWD day + 1243
UK2*	18 / M	0	–	CR2	Yes	BM	VUD	Flu-Mel-CAMPATH[6,7]	CsA-CAMPATH	No	No	AWD day + 1375
MDA7	54 / M	1	Hyperdip.	CR2	No	BM	1 Ag MM child	Flu-Mel[5]	Tacrolimus-MTX	II	Limited	AWD day + 812
SP6	60 / M	1	t(1;19)	CR2	No	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	No	Ext.	AWD day + 816
UK1	27 / F	1	Complex	CR2	Yes	BM	VUB / DQB1 mismatch	Flu-Mel-CAMPATH[6,7]	CsA-CAMPATH	NE	NE	Died from MOF on day +18
SP12	62 / M	0	Hyperdip.	PR2	Yes	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	III	Ext.	AWD day + 381
MDA9	29 / M	1	Complex	CR3	No	BM	VUD	Flu-Mel[5]	Tacrolimus-MTX	IV	NE	Relapse day +67, died +95
SP8	37 / M	0	+3,+18, 5p-	Rel.	Yes	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	II	Ext.	AWD day + 690
IT2	49 / M	1	Normal	Rel.	No	PB	HLA-id sib.	Flu-Cy-TT[9]	CsA-MTX	III	Limited	Relapse day +253, died +305
MDA5	28 / M	0	Hyperdip.	Rel.	Yes	BM	VUD / C and DQB1 mismatch	Flu-Mel[5]	Tacrolimus-MTX	IV	NE	Died, aGVHD day +83
A11	50 / F	1	–	Rel.	No	BM	VUD	Flu-Mel-Ara-C[5]	Tacrolimus -MTX	No	Limited	Relapse day +343, died +632
SP7	54 / F	1	Normal	Refr. Rel.	No	PB	HLA-id sib.	Flu-Mel[8]	CsA-MTX	No	Limited	Relapse day +267, died +399

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SP9*	23 / M	1	Normal	Refr. Rel.	Yes	PB	HLA-id sib.	Flu-Mel [8]	CsA-MTX	I	Limited	Relapse day +165 died +255
MDA1	41 / F	1	Normal	Refr. Rel.	No	PB	HLA-id sib.	Flu-Mel[5]	Tacrolimus-MTX	II	NE	Relapse day +67, died +285
MDA3	30 / M	1	Normal	Refr. Rel.	No	BM	VUD / DQB1 mismatch	Flu-Mel [5]	Tacrolimus-MTX	No	NE	Relapse day +99, died +319
MDA10	55 / M	1	Normal	Refr. Rel.	No	BM	VUD	Flu-Mel [5]	Tacrolimus-MTX	No	NE	Died, infection on day +49

**T-lineage acute lymphoblastic leukemia. M: male; F: female; PS: performance status; Ph+: Philadelphia-chromosome positive; 1ry Refr.: primary refractory; Refr. Rel.: refractory relapse; CR1, CR2, CR3: first, second and third complete remission, respectively; HLA-id sib.: HLA-identical sibling; VUD: volunteer unrelated donor; 1 Ag MM: one antigen mismatched; Flu: fludarabine; Mel: melphalan; Ara-C: cytosine arabinoside; Cy: cyclophosphamide; TT: thiotepa; TBI: total body irradiation; CsA: cyclosporine A; MTX: short-course methotrexate; MMF: mycomofetil fenolate; GVHD: graft-versus-host disease; AWD: alive without disease; NE: not evaluable.*

Responses and outcome

All 26 evaluable patients achieved a morphologic CR in BM early post-transplant, although four cases showed rapid leukemia progression within 100 days post-transplant.

The median overall follow-up is 304 days (range, 18-1375). Currently nine patients are alive, with a median follow-up of 809 days (range, 381-1375). Eighteen patients died, 12 from ALL and six from transplant-related mortality (TRM). The causes of TRM were attributed to acute GVHD (n=2) and chronic GVHD, aspergillosis, respiratory synctial virus pneumonia and disseminated *Candida krusei* infection (n=1 each). The 2-year incidence of TRM is 23% (95% CI, 11% to 46%), and the 2-year probability of overall survival is 31% (95% CI, 12 to 48%). The 2-year incidence of disease progression is 49% (95% CI, 33% to 72%). In univariate analysis the development of GVHD (defined as acute GVHD grade II-IV and/or chronic GVHD) appeared to confer protection against disease progression. Thus, the 2-year cumulative incidences of disease progression in patients with (n=17) and without (n=10) GVHD were 35% (95% CI, 19% to 57%) and 70% (95% CI, 47% to 100%), respectively (Hazard ratio (HR) for progression 3.3 (95% CI 1.1-9.9), p=0.05) [Figure 1].

Five of the 15 patients (33%) in CR at transplant showed leukemia relapse, whereas 8/12 (60%) of those not in CR at transplant did so, but this variable was not significant in univariate Cox regression analysis (p=0.1); 6/15 and 2/12 patients, respectively, are alive without leukemia. Six out of 11 (54%) patients with Ph+ ALL relapsed, while two are long-term leukemia-free survivors; one of these disease-free survivors was in third CR at transplant while the other was primary chemorefractory. One patient who relapsed (SP11) is alive in cytologic and cytogenetic remission following therapy with imatinib. No other Ph+ patient received this drug either before or after transplantation. Three patients who relapsed received donor lymphocyte infusions, but neither GVHD nor disease responses were observed in any.

Minimal residual disease (MRD)

Fifteen patients had two or more evaluable BM studies for monitoring MRD post-transplant. All seven patients with persistently MRD showed progression of the ALL, while 7/8 patients with at least two consecutive negative MRD studies within the first six months post-transplant have not developed leukemia relapse (p=0.001). Due to the small sample size (with appropriate MRD follow-up), the association between acute and/or chronic GVHD and MRD could not be assessed.

Discussion

Our results confirm that reduced intensity conditioning regimens are well tolerated and highly immunosuppressive in patients with ALL, with no graft failures. However, all reduced intensity conditioning regimens could have a deleterious impact on leukemia-free survival when compared with traditional myeloablative conditioning regimens, and this probably explains why so few patients with ALL have been included in reduced intensity conditioning prospective trials. Recently, a retrospective multicenter study from Germany described 22 reduced intensity transplants.[12] In that study several patients received the transplant as a second allogeneic transplant, a situation that may be best referred to as chemotherapy followed by donor

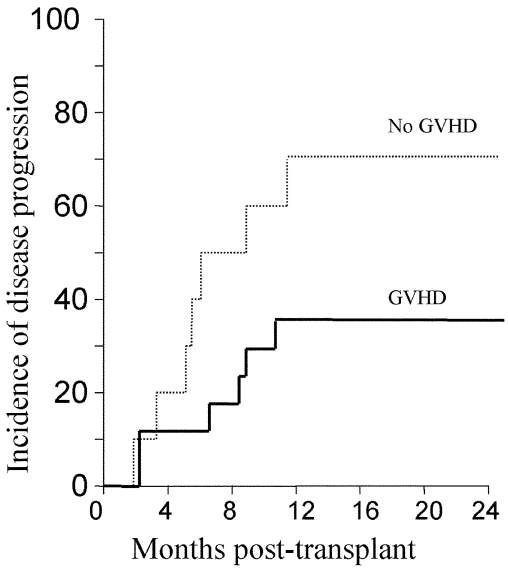

Figure 1. Cumulative incidence of disease progression after allogeneic PBSCT with reduced-intensity conditioning in patients with (n=17) and without (n=10) GVHD (acute grade II-IV or chronic GVHD). The one-year incidence of disease progression in patients with and without GVHD were 35% (95% CI, 19% to 57%) and 70% (95% CI, 47% to 100%), respectively (p=0.05).

Table 2. Characteristics of patients with and without GVHD, defined as acute grade II-IV or chronic GVHD (% in parentheses).

	Developed GVHD	*Did not develop GVHD*
N. of patients	17	10
Median age (range)	50 (25-63)	46 (18-62)
Male sex	12 (71)	7(70)
HLA-identical sibling donor	11 (65)	4 (40)
GVHD prophylaxis with CsA/FK506+MTX	16 (94%)	8 (80)
Failed prior autograft	4 (24)	4 (40)
In CR at transplant	11 (65)	4 (40)
Ph+ ALL	8 (47)	3 (30)
PB as stem cell source	10 (59)	4 (40)
Disease progression*	6 (35)	7 (70)
Transplant-related mortality	4 (24)	2 (20)
Follow-up, in days	381 (46-1236)	246 (18-1375)

*CR: complete remission; GVHD: graft-versus-host disease; CsA/FK506+MTX: prophylaxis with cyclosporine or tacrolimus plus short-course methotrexate; PB: peripheral blood as stem cell source. *All p values are > 0.1 except for disease progression (see text).*

leukocyte infusions rather than a primary allograft. Four of the 22 patients were alive and disease-free from 5 to 30 months post-transplant, while 7 died from complications. Thus, the 27 patients described herein represent by far the largest series so far reported of patients with ALL who have received a reduced intensity conditioning allograft. On the other hand, several studies have shown that a graft-versus-leukemia effect associated with acute and chronic GVHD leads to a reduction of relapse in ALL after conventional myeloablative allografts.[13-17] Thus, it seemed reasonable to test reduced intensity conditioning allografts in patients who are considered poor candidates for a conventional myeloablative transplant because of a high risk of TRM.

Of note, besides being considered unfit for a conventional myeloablative transplant, patients in this study mostly had very poor prognosis ALL; only four patients were in first CR (two after second-line or salvage chemotherapy), most had poor-risk cytogenetics and 12 were chemorefractory or in overt relapse at transplant. Additionally, 12 donors were either volunteer unrelated donors or mismatched family donors.

With these considerations in mind, a TRM of 23% and a 30% 2-year overall survival with a median follow-up of 756 days appears promising. In a small series of patients it is difficult to detect any possible graft-versus-leukemia effect that may have contributed to these prolonged remissions. However, the 12 patients who had overt ALL at transplant survived leukemia-free for a median of 201 days post-transplant, and two are still alive without disease more than two and three years after the procedure (Table 1). Additionally, of the 11 patients with Ph+ ALL, two are long-term leukemia-free survivors with no detectable MRD. Additionally, the most important observation in our study is that the risk of disease progression post-transplant was lower in patients who developed acute or chronic GVHD than in those who did not. As shown in Table 2, these differences cannot be easily explained by differences in other relevant prognostic factors between the groups. In univariate analysis, the only variable that decreased the HR of progression was GVHD. This observation suggests that a graft-versus-leukemia effect does exist in ALL after a reduced intensity conditioning allograft. These results, however, should be interpreted with caution due to the small sample size, the relatively short follow-up, the few relapses observed and the potential existence of undetected confounding factors.

This retrospective study suggests that allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning might be a useful therapeutic option for some patients with ALL who are ineligible for standard myeloablative conditioning. However, this treatment modality needs to

be evaluated in prospective trials, and should not be employed outside clinical studies.

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Pre-publication Report & Outcomes of Peer Review

Contributions

RM designed the study, acted as data manager and wrote the various versions of the manuscript. SG, JLG and RC acted as data managers from one institution and participated in writing the manuscript. MDC, FFA, JSM and JS were responsible for the patients included in the Spanish protocol and participated in writing the manuscript. SM was responsible for the UK protocol patients, and PC for the Italian patients, and both also participated in writing the manuscript. All Tables and Figures were created by RM.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received December 2, 2002; accepted March 24, 2003.

In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

What is already known on this topic

Little information is available on the use of allogeneic stem cell transplantation with reduced-intensity conditioning regimen in acute lymphoblastic leukemia.

What this study adds

This study shows that allogeneic stem cell transplantation with reduced-intensity conditioning regimen is feasible in selected patients with acute lymphoblastic leukemia.

Caveats

There is no evidence so far that patients with acute lymphoblastic leukemia may benefit from this treatment modality, which should be employed exclusively within prospective clinical trials.