

REVIEW

Hematopoietic transplantation from adult unrelated donors as treatment for acute myeloid leukemia

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Transplantation from unrelated donors (URD) is increasingly being used as treatment for hematological malignancies, including acute myeloid leukemia (AML). This increase is the consequence of the availability of more than 11 million URD volunteers and the more efficient donor search process in the recent years. Median time to identify a suitable URD is now 2 months. More than 50% of Caucasian patients have an human leukocyte antigen (HLA)-allele donor match and a one-antigen or allele HLA-mismatched donor may also be acceptable. Complications of URD transplants are particularly frequent and severe, with long-term OS in the registries being 10–20% inferior to HLA-identical sibling transplantation. High resolution DNA techniques for donor and recipient HLA matching have contributed to the survival in experienced centres after unrelated donor SCT approaching that achieved with sibling donors. The introduction of reduced intensity conditioning (RIC) has extended URD transplants to elderly and/or debilitated patients with AML. With this approach, TRM decreases, although graft-versus-host disease-related morbidity and mortality remain a problem. Despite this complication, results after URD transplantation in this age group seem better than those achieved with chemotherapy and/or autologous transplantation. To confirm this possibility, prospective multicenter comparisons of URD transplants after RIC with other treatment options for elderly AML patients have recently been started.

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(AML).¹ This procedure combines the antitumor effect of conditioning regimen with a powerful immune-mediated graft-versus-leukemia (GVL) reaction.² These two components make allogeneic HCT the most effective therapy to prevent leukemia recurrence. Unfortunately, despite the improvements in transplantation technique, this therapy is still associated with substantial treatment-related mortality (TRM) due to toxicity of conditioning regimen, graft-versus-host disease (GVHD) and/or infectious complications.¹

In practice, HCT has a reasonable probability of success only if recipient and donor are closely HLA-matched.³ Only 30% of patients have an HLA-identical sibling, the best scenario, while less than 5% have some other HLA-compatible relative. In the remaining 65–70% who need an allogeneic HCT, the main option is to perform an unrelated donor (URD) search.³ International registries now contain more than 11 million HLA-typed unrelated volunteers, translating into the fact that more than 90% of Caucasian patients have an HLA-A, -B and -DR antigen compatible URD.⁴ Half of these pairs are HLA-allele matched or have a single HLA-A, -B, -C or -DRB1 molecular disparity by high-resolution DNA typing. There is still room for improvement, however, particularly because these proportions in patients from other ethnic origins are lower. The median time to identify a suitable URD has been reduced to approximately 2 months, and two additional months are needed to schedule and perform the stem cell harvest. In view of these limitations, in practice, only 30–40% of donor searches result in URD transplantation. It should also be kept in mind that as leukemia may relapse before this therapy can be carried out, HLA-typing at diagnosis and prompt initiation of URD search in the absence of a family match are mandatory.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a well-established treatment for acute myeloid leukemia

Indications for URD transplants in AML

The European Blood and Marrow Transplant (EBMT) group recently published the current practice of HCT in Europe for a variety of diseases, including URD transplants for AML (Table 1).^{5,6} This practice reflects the general indications for the procedure. The certainty of HCT indication was rated in four categories: standard (S) or generally accepted indication in suitable patients, clinical

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Table 1 Current practice of unrelated donor hematopoietic transplantation for AML in Europe

Disease	Status	Matched URD	Mm URD
AML children	CR1 (low risk)	GNR	GNR
	CR1 (high risk)	CO	GNR
	CR1 (very high risk)	S	CO
	CR2	S	S
	>CR2	D	D
AML adults	CR1 (low risk)	D	GNR
	CR1 (intermediate or high risk)	CO	D
	CR2	CO	D
	CR3, incipient relapse	CO	D
	M3 molecular persistence	CO	GNR
	M3 molecular CR2	CO	GNR
	Relapse or refractory	D	GNR

Abbreviations: CO=clinical option, it can be carried out after careful assessment of risks and benefits; CR1=first complete remission; CR2=second complete remission; CR3=third complete remission; D=developmental, further trials are needed; GNR=generally not recommended; Mm=mismatched; S=standard of care, generally indicated in suitable patients; URD=unrelated donor.

option (CO) when HCT has to be carried out after careful assessment of risk and benefits, developmental (D) if further trials are needed to establish the indication and generally not recommended (GNR) in the remaining cases. It should be emphasized that patients treated for indications included in the CO and D groups, as is the case of all adult AML, should be transplanted in specialist centers with a large experience in the procedure. Only transplants for very high-risk children with AML in first (CR1) or in second complete remission (CR2) are considered S procedures.⁵

The benefit that allogeneic HCT offers to specific groups of AML patients in CR1 is a matter of debate.^{1,7-17} There are no prospective randomized comparisons of URD HCT with other treatment options. In consequence, recommendations for this procedure have to be extrapolated from studies identifying transplantation from an HLA-identical sibling as the best choice, and taking into account the increased mortality using URD. In controlled trials, HLA-identical sibling HCT improved the outcome of patients with high-risk cytogenetics in the EORTC-GIMEMA and US Intergroup studies.^{7,11-13} In the latter experience, HCT also offered better results than intensification chemotherapy (CT) in patients with a favorable karyotype.¹³ In contrast, in the large Medical Research Council series, HLA-identical sibling HCT was the best option for patients with intermediate-risk features.¹⁰ These studies are summarized in a recent meta-analysis showing that allogeneic HCT was of benefit in the high-risk cytogenetics group only.¹⁷

Accordingly, URD HCT is indicated in AML patients in CR1 with adverse cytogenetics at diagnosis. Other adequate situations to perform this procedure are the persistence of initial karyotype abnormalities in morphological remission, and the need for three or more courses to achieve CR. Additional settings where URD HCT may be

a good option are M7 AML, AML with >5% marrow blasts in the marrow on day 15 of induction CT, a low proportion of marrow blasts after treatment but persistent dysplasia, increasing minimal residual disease after CR achievement and the presence of adverse mutations such as internal tandem duplication of the FLT3 gene.^{1,4,18-23} In second CR AML, URD stem cell transplantation (SCT) is a well-established indication, except in the favorable cytogenetics group (t(8;21), inv(16), acute promyelocytic leukemia (APL)). In the latter group, autografting is usually the first option, unless the first remission was of short duration or there is evidence of residual leukemia cells in the graft or in the marrow. Patients who are not in remission are candidates for URD HCT if blast infiltration is less than 30%, and preferably if no leukemia cells are present in the blood.²⁴ In contrast, transplantation in florid relapse should be discouraged outside investigational clinical trials.

Donor selection

Ideally, URD donor and recipient should be closely, genetically HLA-matched. Recent data support that it is important not only to share the same HLA-alleles, but also that they belong to the same HLA haplotypes so as to minimize non-detectable disparities.^{20,25} Several studies have analyzed whether there is a different impact of disparities at HLA class I vs II antigens and alleles on transplantation outcome and results are controversial.²⁶⁻³³

A study from Seattle revealed that differences in one or more class I antigens or two or more alleles were associated with an increased risk of graft failure; in contrast, a single HLA-class I allele difference did not favor this complication. A National Marrow Donor Program (NMDP) report³¹ with 1874 URD transplants and a Japanese study³² on 1298 donor-patient pairs revealed that differences at HLA-A, -B, -C or -DRB1 independently increased the risk of acute GVHD.

The effect of disparity on survival was investigated in the mentioned NMDP study,³¹ Mismatches for HLA-A, -B, -C and -DRB1 loci were associated with decreased survival as compared to full match, whereas mismatch for DQB1, DQA, DPB1 and DPA had no significant impact. Additionally, a recent study showed a similar outcome when antigen mismatch occurred within or outside cross-reactive groups.³⁴

In 2007, the NMDP has published a study clarifying previous controversial findings. This NMDP report includes 3857 URD transplants performed between 1988 and 2003.³⁵ Donor-recipient pairs were typed for HLA-A, -B, -C, -DRB1, -DQB1, -DQA1, -DPB1 and -DPA1 by high-resolution typing methods. As in the previous NMDP study, the authors demonstrated that full matching for HLA-A, -B, -C and -DRB1 (total eight) was associated with the best survival. A single mismatch at A, B, C or DRB1 increased the relative risk (RR) of death (RR = 1.23, 95% CI: 1.11-1.36, $P=0.0001$) and decreased 9% of the 1-year survival, from 52% for fully matched pairs to 43% in the presence of one mismatch. HLA mismatches by low- or high-DNA resolution testing (antigen or allele

mismatch) were associated with a similar deleterious effect. In contrast to a previous report showing that a single HLA mismatch had an adverse impact only in patients transplanted for early disease,³³ in this study the differences were apparent in all disease risk categories. The impact of individual HLA-loci mismatch was also studied. A single HLA-A mismatch was associated with increased mortality (RR = 1.36, 95% CI: 1.17–1.58, $P < 0.0001$), with a similar adverse trend being observed in the case of DRB1 mismatch (RR = 1.48, 95% CI: 1.05–1.85, $P = 0.0005$). Of note, mismatches at two HLA loci increased mortality risk as compared to single mismatches, with an additional 10% decrease in survival at 1 year (43 vs 33%).

In summary, high-resolution DNA typing of HLA-A, -B, -C and -DRB1 alleles is necessary for optimal URD donor selection. The best survival is associated with full eight HLA matching. A single antigen or allele HLA mismatch is acceptable, particularly, in urgent transplants. Single HLA-B or -C mismatches are better tolerated than HLA-A or -DRB1 mismatches, whereas HLA-DQ or -DP disparities seem not to have effect on survival. Disparities for two loci, detected by either high- or low-resolution testing, further increase mortality and consequently these transplants are not recommended if other treatment options are possible.

Results

Results of URD transplants for AML have been communicated and/or published by the two largest registries, the EBMT group and the Center for International Blood and Marrow Transplant Research (CIBMTR). It has to be emphasized that these results are somewhat outdated since the main published series include patients transplanted more than 5 years ago. The 5-year survival of 606 adults receiving myeloablative conditioning and URD transplantation and included in the EBMT database was 44% (V Rocha, personal communication). Leukemia-free survival (LFS) at 2 years in an earlier report from the same group was 40% for AML patients transplanted in CR1 and 36% for those in CR2.³⁶ In a CIBMTR study including 476 recipients of URD HCT for AML, adjusted overall and LFS at 3 years were 44 and 43%, respectively, in CR1 whereas in CR2 of AML, the corresponding values were both 33% at 3 years.³⁷ Cumulative incidences of relapse at 5 years were 13% in CR1 patients and 15% after CR2 transplants. This low incidences of relapse may indicate a strong GVL effect which unfortunately was counterbalanced by a high transplant-related mortality, 51% at 5 years in CR1 patients and 53% after URD HCT transplants for AML in CR2. Again, this study may not reflect the current results of both URD and autologous transplantation since patients were treated before 1997. The improvement in the results of URD SCT observed in recent years is reflected in Figure 1 showing the experience from our own group.

Single institutions have published different approaches with the aim to decrease mortality and improve survival after URD SCT. The Seattle team tried to optimize the donor–recipient pair selection process by incorporating molecular HLA-typing more than 10 years ago.¹⁹ They

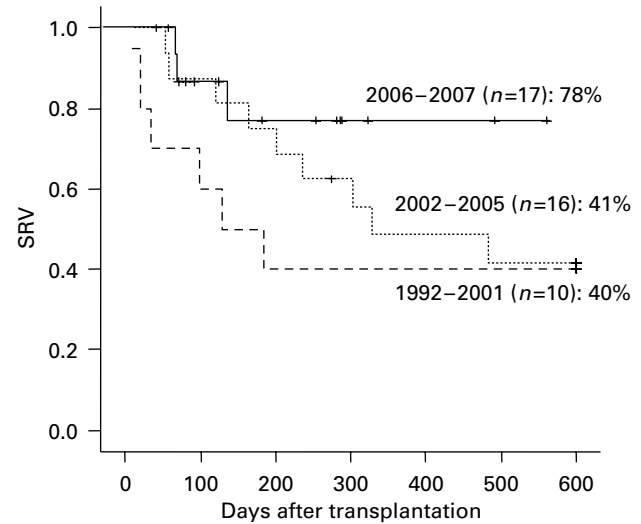


Figure 1 Probability of survival (SRV) after unrelated donor hematopoietic transplantation at the Hospital de la Santa Creu i Sant Pau of Barcelona, in patients with non-advanced disease (first or second remission of malignancies, chronic myelogenous leukemia in any chronic phase, myelodysplastic syndrome with low proportion of blasts, aplastic anemia, thalassemia). Impact of year of transplantation.

used a standard conditioning regimen, infused T-cell-replete marrow and administered fluconazol prophylaxis and preemptive ganciclovir. This group reported their updated experience in 161 patients treated with URD BMT for primary AML. Median age of the series was 30 years.¹⁹ Twenty-six patients (16%) were younger than 18 years of age and 135 (82%) were adults. Donors and patients were HLA-matched in 103 (64%) cases whereas one-antigen mismatch was present in 58 (32%) pairs. Ninety-six percent of patients received conditioning for BMT with cyclophosphamide and TBI. GVHD prophylaxis consisted of cyclosporine and MTX in 83% of transplants. After a median follow-up of 3 years, 5-year LFS was CR1 ($n = 16$) 50%, CR2 ($n = 40$) 28%, other CR ($n = 8$) 27, relapse ($n = 81$) 7% and primary induction failure ($n = 16$) 19% (Figure 2a). Cumulative incidences of relapse were 21, 20, 44 and 63%, respectively (Figure 2b). An important observation from the study, consistent with a previous finding from the same group,²⁴ was that a marrow cell dose above the median value of $3.5 \times 10^8/\text{kg}$ had a significantly favorable prognostic impact, by decreasing TRM and improving LFS in patients transplanted in remission (Figures 3a and b). Remarkably, adults in CR2 who received a high marrow cell dose had a 5-year LFS of 47% (Figure 3c).

Other groups have investigated modifications of the myeloablative conditioning, infused partially T-cell-depleted grafts and/or modified the GVHD prophylaxis. The St Louis group administered a single dose of 550 Gy TBI plus cyclophosphamide (CY) as preparative treatment and triple GVHD prophylaxis with CYA, MTX and corticosteroids;³⁸ LFS at 3 years was 57% in AML patients in CR1 and 41% in those in subsequent CR. Of note, regimen-related mortality was only 3%. The MD Anderson transplant team used a myeloablative regimen that included fludarabine plus high-dose intravenous busulfan and they

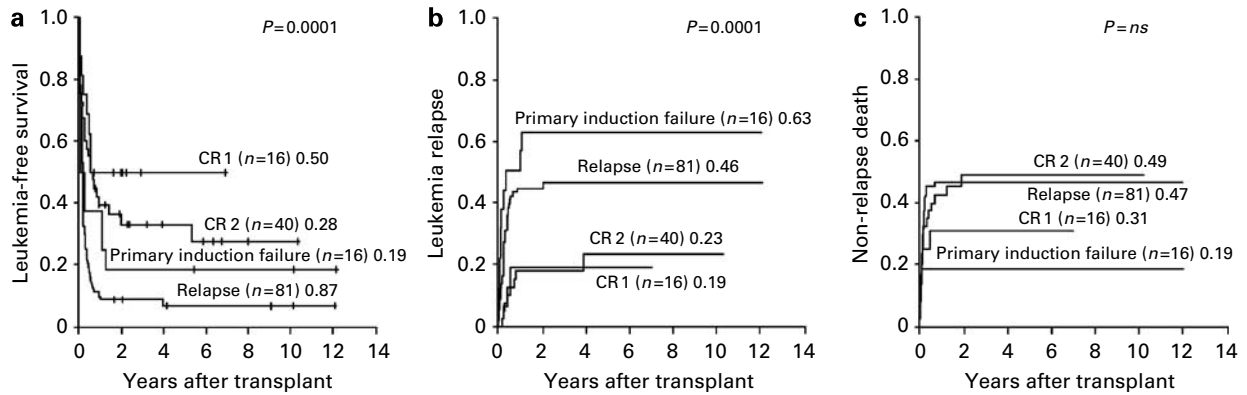


Figure 2 Outcome of marrow transplantation from unrelated donors as treatment for acute myeloid leukemia. The Seattle experience in 161 patients (Sierra *et al.*¹⁹); (a) leukemia-free survival, (b) cumulative incidence of relapse; (c) cumulative incidence of non-relapse death.

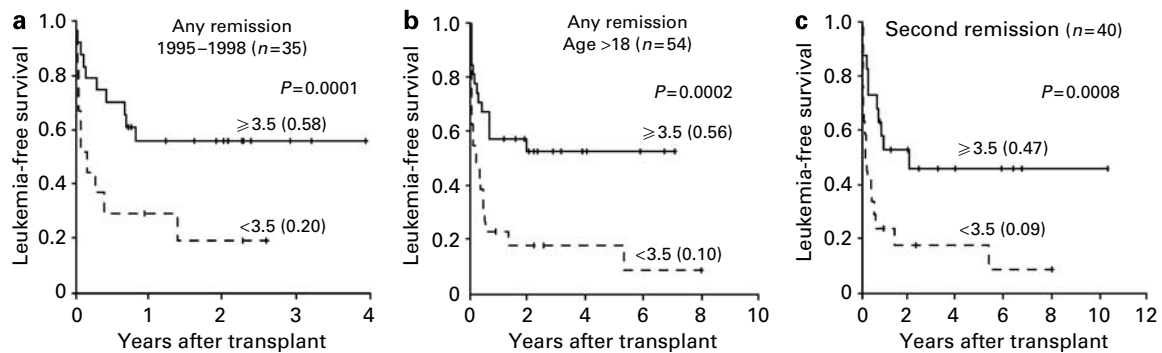


Figure 3 A high marrow cell dose improves leukemia-free survival after unrelated donor marrow transplantation as treatment for acute myeloid leukemia in remission; (a) patients in remission transplanted between 1995 and 1998; (b) adults in any remission, (c) patients in second remission. From Sierra *et al.*¹⁹

administered GVHD prophylaxis with tacrolimus and MTX.³⁹ Donors were HLA-compatible related ($n=60$) or unrelated ($n=36$). Actuarial 1-year overall survival (OS) and event-free survival (EFS) were 81 and 75%, respectively, for patients transplanted in CR without impact of donor type on these results. The Calgary group used a similar conditioning with fludarabine and IV busulfan (BU) with the addition of antithymocyte globulin (ATG), CYA and a short course of MTX.⁴⁰ In transplants from alternate donors, 100 days and 2-year TRMs were only 8 and 19%, respectively.

Until these encouraging results from single centers are confirmed, outside specific clinical trials the conventional CY-TBI and BU-CY regimens are the standard for conditioning URD SCT for AML. It should be noted that in case of administering BU, particularly when oral route is used, dose adjustment according to the blood levels seems to improve the outcome.⁴¹

Factors influencing outcome

As in other HCT settings, disease stage has a strong impact on outcome, confirmed in the recent NMDP analysis.³⁵ Patients transplanted in CR have better results than those with active disease (primary refractory or in relapse)

(Figures 2a-c).¹⁹ Patients in relapse with a low leukemia burden have a better outcome than those with overt disease. In the Seattle experience, patients with $<30\%$ blasts in the marrow and without blasts in the blood had a 5-year LFS of 30% (Figure 4), results were similar to those achieved in CR2 patients.²⁴ In contrast, patients with blasts in the blood had a dismal outcome at 2 years. In the Ohio University series of patients with AML in relapse, those with $<20\%$ blasts in the marrow at transplant had a 2-year survival of 33% as compared with 5% in the group with $\geq 20\%$ ($P=0.04$);⁴² regarding circulating blasts, only patients with $<5000/\mu\text{l}$ at transplantation survived 2 years (18 vs 0%, $P=0.003$).⁴²

Treatment-related mortality in children who receive an URD SCT for AML is usually lower than that in adults. The Italian Group of SCT (Gruppo Italiano per il Trapianto Midollo Osseo) analyzed the results of URD SCT in 423 patients below 19 years of age treated at 31 centers between September 1989 and December 2000. TRM at 100 days was 32% before 1998 and 21% thereafter ($P=0.003$).⁴³ However, due to the high-risk features of the disease, LFS for patients with AML or MDS was only 38% at 3 years. The Seattle team reported a 47% LFS at 3 years in children with acute leukemia (AL) in CR1 or CR2 and poorer results in CR3 or relapse, 10% at 3 years.⁴⁴ The St Jude group reported a particularly good outcome in a series

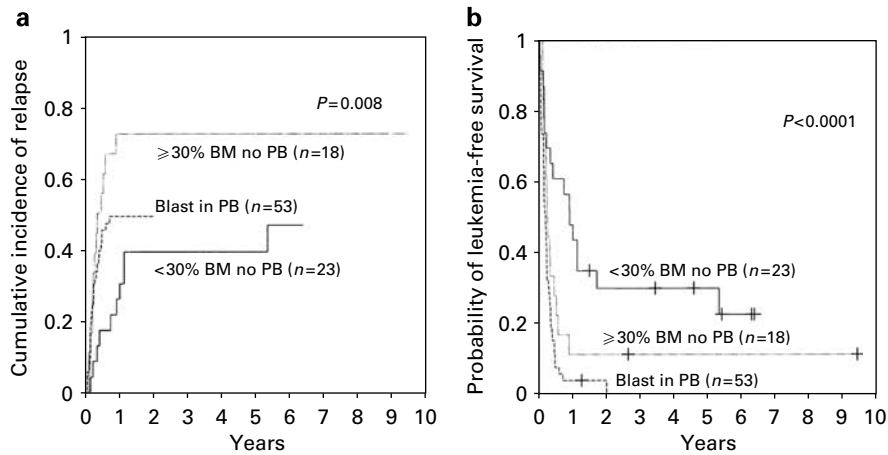


Figure 4 Cumulative incidence of relapse (a) and leukemia-free survival (b) after marrow transplantation from unrelated donors as treatment for acute leukemia: impact of bone marrow (BM) and peripheral blood (PB) blasts on outcome. From Sierra *et al*.²⁴

of 22 children with AL in CR1 or CML in chronic or accelerated phase, LFS was 73% at 2 years.⁴⁵ The CIBMTR reported a 54% LFS at 3 years in patients younger than 18 months with AL in CR1 and 30% for those with more advanced disease.⁴⁶ The EBMT group reported the results of URD SCT in children.⁴⁷ Patients transplanted with T-cell-depleted BM had OS and EFS at 2 years of 41 and 37%, respectively, whereas the corresponding values in recipients of unmanipulated BM were 49 and 43%. In the recent NMDP study, patients up to 30 years of age had improved survival as compared to those of 31- to 45-year-olds (RR of death 1.51, 95% CI: 1.36–1.67, $P < 0.0001$), and to those of recipients with an age above 45 (RR = 1.79, 95% CI: 1.59–2.02, $P < 0.0001$).³⁵

Together with age, cytogenetics at diagnosis is considered a strong prognostic indicator in AML. However, information available on the predictive value of this parameter in URD SCT recipients is limited. Recently, Tallman *et al*.²¹ analyzed 261 patients with AML in CR1 and 299 patients in CR2 who received a matched URD. LFS at 5 years was similar for patients in the favorable (29%), intermediate (30%) and unfavorable (29%) cytogenetics risk groups. Surprisingly, the results achieved in CR2 were similar or even better than those in CR1, with 5-year LFS in the three categories of 42, 35 and 45%, respectively. From these findings, the authors concluded that cytogenetics seems to have little influence on the results of URD SCT for AML; consequently, patients in the poor risk category are candidates for this procedure.

The relevance of HLA compatibility on TRM and survival has already been discussed. The best scenario is HLA matching between donor and recipient in 8 or 10 alleles, whereas each HLA disparity increases cumulative mortality in approximately 10%.³⁵

A marrow cell dose above the median of 3.5×10^8 nucleated cells per kilogram decreased TRM and improved LFS in patients with AML transplanted in remission (Figures 3a–c).¹⁹ Patients receiving a high marrow cell dose had higher median neutrophil counts and fewer episodes of neutropenia below $0.5 \times 10^9/l$ during the initial 15 weeks after BMT and faster recovery of self-sustained platelet

counts. Patients who received a marrow cell dose below the median were more likely to die due to bacterial infections and pneumonia. For unclear reasons, in the same report, a CMV seronegative status in donor and recipient was associated with fewer relapses and more prolonged leukemia-free interval than positivity in either the patient or the donor.¹⁹ More frequent is the finding of the NMDP report, where CMV seropositive patients had an increased risk of death, regardless of the CMV serostatus of the donor.³⁵

The beneficial impact of a high marrow cell dose on the outcome of URD HCT for AML provided the background to investigate transplantation of peripheral blood (PB) progenitor cells in this setting. It is remarkable that survival beyond 1 year was 67% in the preliminary experience in 27 AML patients in CR1 who received a PB URD HCT in Seattle.²⁰ Long-term results are unknown, however, and late morbidity and mortality are possible, since extensive chronic GVHD seems particularly frequent if URD and PB stem cells are used. It will be of major interest to know the results of the ongoing Blood and Marrow Transplant Clinical Trials Network (CTN) protocol, which prospectively compares BM vs PB as hematopoietic source for URD transplantation. <https://web.emmes.com/study/bmt/index.html>

An important study from Seattle has recently identified the comorbidities with significant impact on TRM after transplantation.⁴⁸ The analysis of 1055 patients who received related (58%) or unrelated (42%) grafts allowed design of an HCT comorbidity index (HCT-CI) with more discriminant power than the previously reported Charlson's comorbidity score.⁴⁹ They used a training group of patients to develop the HCT-CI and demonstrated its value in a validation set. In the latter, TRM at 2 years was 14% in score 0 group, 21% in score 1 or 2 patients and 41% in those with a score of 3 or more, with the respective 2-year survivals being 71, 60 and 34%. Recently, the same group has shown that the combination of HSC-CI and disease stage is useful to predict the outcome after transplantation using either high-dose or reduced intensity conditioning (RIC).⁵⁰ It is therefore crucial to know the

HCT-CI to compare the results of future published experiences. This statement has been recently demonstrated in a comparison of transplants for AML in CR1 performed at the Fred Hutchinson Cancer Research Center and those treated at the MD Anderson Cancer Center in Houston. Without considering the HCT-CI the results seemed superior in Seattle, whereas survival was the same at the two institutions after adjusting for comorbidities.⁵¹

Interestingly, modern studies of polymorphisms in molecular genotype of URD-recipient pairs seem to provide useful prognostic information. In a series of 196 URD transplants for AL, investigators from the Anthony Nolan Research Institute have found that single nucleotide polymorphisms (SNPs) in the NOD2/CARD15 gene of donor and/or recipient associate with increased risk of relapse and death.⁵² The authors hypothesize that this finding may be attributed to a decreased GVL effect, in the presence of SNPs, as compared to donors and recipients with the wild-type gene.

In addition to patient and disease features, procedure characteristics have been investigated as potential factors influencing the outcome. Since GVHD is the main cause of nonleukemic death, the impact of *in vivo* and *in vitro* T-cell-depletion has been analyzed. T-cell-replete transplantation associates with increased frequency and severity of GVHD whereas T-cell depletion leads to more infections, post-transplant lymphoproliferative disorders and disease recurrences. Despite the latter, some teams have obtained encouraging results with *in vivo* T-cell depletion using ATG or alemtuzumab (Campath 1H). Among others, Marks *et al.*⁵³ in a series of 39 AML patients, who received Campath 1m T-cell-depleted URD marrow and a median age 10 years, reported a 61% survival at 44 months.

To conclude about the role of T-cell depletion, it is necessary to wait for the results from randomized trials in the setting of URD SCT for AML and other indications. A prospective comparison testing the value of *in vivo* T-cell depletion with ATG as part of conditioning regimen has just finished recruitment, but the results are not available yet. Trials to test the value of alemtuzumab in allogeneic HCT are ongoing. Before the data from these studies are known, the decision to perform a T-cell-replete or -depleted (usually *in vivo*) procedure is a transplant center choice, mainly based on its experience and the presence of HLA mismatching between donor and recipient.

URD HCT vs other transplant options

URD vs autologous transplants

Retrospective analyses from the EBMT and the CIBMTR compared the results of autologous and unrelated transplants (Table 2).^{36,37} These studies have the limitation of including patients transplanted more than a decade ago, before 1997. For this reason, their conclusions may not be fully valid today, since significant improvements in HLA matching and supportive measures have occurred, increasing the survival of URD transplant recipients in recent years. The results of these comparative studies are summarized on continuation.

In patients with AML in the EBMT analysis, relapse was lower and TRM was higher in patients receiving URD as compared to autologous transplants, which led to similar LFS in the two groups.³⁶ The same impact of URD transplantation on relapse and mortality was also observed in the CIBMTR report, although in contrast to the EBMT analysis, a LFS advantage for autologous transplantation was demonstrated in CR1 patients.³⁷

Preliminary results of the only prospective comparison were recently communicated.^{20,54} In the German AML 01/99 study high-risk AML patients (adverse cytogenetics and/or >5% blasts on day 15 of treatment) were treated after CR1 consolidation with autologous or URD transplantation. URD transplants were performed in the more recent period of the trial in patients with an HLA-matched volunteer. In contrast with the results of retrospective studies, survival at 4 years was better (56%) after URD than after autologous transplantation (23%, $P=0.01$). These findings support the usual approach of starting an URD search in patients with high-risk AML without a family HLA match.

URD vs umbilical cord blood transplants

Three studies have compared the outcome of unrelated umbilical cord blood (UCB) and URD BMT in adults.⁵⁵⁻⁵⁷ Interestingly, the EBMT/Eurocord report gave specific information to evaluate the results obtained in AL patients in first and second remission (Table 3).⁵⁶ Neutrophil engraftment was delayed in the UCB group in all three studies. Acute GVHD was less frequent or less severe in two of these reports.^{57,58} Chronic GVHD incidence was higher after UCB transplantation in the International Bone

Table 2 Results of unrelated donor compared to autologous transplantation for AML

Diagnosis (registry)	Stage	Unrelated		Autologous		Time (years)	P-value
		N	LFS (%)	N	LFS (%)		
AML (EBMT)	CR1	25	40	50	48	2	0.17
	CR2	46	36	92	43	2	0.67
AML (CIBMTR)	CR1	193	43	482	53	3	0.02
	CR2	263	33	177	39	3	0.17

Abbreviations: AML = acute myeloid leukaemia; CIBMTR = the Center for International Blood and Marrow Transplant Research; CR1 = first complete remission; CR2 = second complete remission; EBMT = the European Blood and Marrow Transplant group; LFS = leukemia-free survival; N = number of patients.

Results of the EBMT and CIBMTR retrospective analyses.

Table 3 Leukemia-free survival after unrelated cord blood or matched unrelated donor hematopoietic transplantation as treatment for acute leukemia

	<i>UCB transplant</i> 2 years LFS (95% CI)	<i>Matched URD</i> 2 years LFS (95% CI)	P-value
<i>Type of leukemia</i>			
Acute myeloid leukemia	32 (25–39)	42 (39–45)	0.18
Acute lymphoid leukemia	34 (27–41)	33 (30–36)	0.21
<i>Status of the disease</i>			
First complete remission	43 (33–53)	49 (45–53)	0.31
Second complete remission	44 (32–56)	47 (43–50)	0.64
Advanced	23 (17–29)	19 (16–22)	0.92

Abbreviations: CI = confidence interval; LFS = leukemia-free survival; UCB = umbilical cord blood; URD = unrelated donor transplantation. EBMT-Eurocord experience.

Marrow Transplant Registry (IBMTR) experience,⁵⁵ but there was less extensive disease than after URD BMT. The relapse rate was similar after UCB transplantation and URD BMT. Transplant-related mortality was increased after UCB transplantation in the IBMTR series and decreased in the single center Takahashi experience,^{55,57} whereas it was equivalent after UCB and URD BMT in the EMBT/Eurocord study.⁵⁶ The main conclusions of these reports were as follows: (a) Laughlin *et al.* from the IBMTR concluded that following UCB, transplantation survival was comparable to that of one-antigen mismatch URD BMT and inferior to fully matched URD BMT; (b) Rocha *et al.* from the EBMT found that matched URD and UCB transplantation had an identical outcome; (c) Takahashi *et al.* obtained clearly superior results after UCB than those after URD transplants.

The mentioned studies provide a strong background to consider UCB as a valid hematopoietic stem cell source for transplantation in adults.⁵⁸ In practice, most teams favor this type of transplant when it is unlikely to obtain cells from an HLA-matched URD on a short-term basis. In a minority of well-experienced teams, UCB transplantation is preferred to matched URD.

URD vs haploidentical transplants

Haploidentical-related transplants have classically been associated with unacceptably high TRM due to conditioning regimen toxicity and opportunistic infections. The relapse rate was also high since the GVL effect was abrogated as a consequence of intense ‘*ex vivo*’ T-cell depletion of the graft. In recent years, the haploidentical transplantation technique has been refined with encouraging results. The Perugia group reported a remarkable 48% EFS at 2 years in 42 AML patients transplanted in remission.⁵⁹ The investigators at St Raffaele Hospital of Milano have also achieved encouraging results with the post-transplant infusion of T-cells transfected with the thymidine kinase suicide gene, which allows an early and effective immune restoration.⁶⁰ These experiences support the investigation of this transplantation modality in patients who lack an HLA-compatible family donor and need an allogeneic procedure on a short-term basis. There are no studies comparing URD SCT and haploidentical transplantation in patients with AML. On the other hand, a

retrospective comparison of UCB and haploidentical transplants has recently been communicated. Of note, no significant differences in LFS were observed between the two transplant modalities in patients with AML.⁶¹

URD transplantation after reduced intensity conditioning

RIC regimens for allogeneic transplantation are increasingly being used to extend this procedure to elderly and debilitated patients. In Europe, more than 40% of allogeneic transplants are currently performed after RIC.⁶² AML is a frequent indication for this strategy, since median age of these patients is above 60 years and they have a very poor outcome with other treatment alternatives.⁶³ In the absence of an HLA-identical sibling, URD transplantation after RIC is currently an option.^{64–92}

Recently published reviews have covered RIC transplantation for AML, including the results achieved using related and URD donors (Table 4).^{62,82–84} The conditioning regimen usually included fludarabine and BU, CY or low-dose TBI. Often, ATG or alemtuzumab was added to these drugs to favor engraftment and decrease GVHD.^{65,84–86} Post-transplant GVHD prophylaxis consisted of CYA or tacrolimus and MTX or MMF in most instances. TRM at 1 year was in the order of 25%, a value significantly lower than that observed after conventional transplantation in the same age group.^{89–91} GVHD, particularly chronic GVHD, remains a problem again in this setting, although the development of this complication is crucial to avoid leukemia recurrence.⁹² Disease stage had a significant impact on transplantation results, with best outcome in patients in CR1.⁶² Of note, in the Seattle consortium experience, OS and TRM 2 years after RIC URD transplantation for AML in CR1 were 63 and 27%, respectively (Figure 5b).⁷⁴ The results achieved using related donors were OS 44% and TRM 10% (Figure 5a). The difference observed in OS was due to the decreased incidence of relapse with URD grafts, reflecting a strong GVL effect, particularly relevant after RIC transplantation.

The same authors reported the results of RIC transplants for AML in the group of patients older than 60 years in CR1 or CR2; OS at 2 years was 45% after related transplantation and 55% after URD transplantation.^{62,74} These results are better than the 10–15% achieved with CT (Figure 6), providing background to prospectively compare

Table 4 Hematopoietic transplantation from unrelated donors using reduced intensity conditioning in patients with acute myeloid leukemia

References	Patients N (URD)	RIC	Median age (range) in years	% TRM (time)	Survival (%)
Bornhäuser <i>et al.</i> ⁶⁴	16 (16)	Flu-BU-ATG	47 (16–65)	12	31
Sayer <i>et al.</i> ⁶⁶	113 (62)	Flu-CY-BU or TBI 8 Gy	51 (16–67)	53 (2 years)	32
Bertz <i>et al.</i> ⁶⁷	15 (12)	Flu-BCNU-Mel	64 (60–70)	22 (1 year)	68
Claxton <i>et al.</i> ⁶⁹	17 (11)	Flu-CY ± ATG	59 (28–72)	8	50
Niederwieser <i>et al.</i> ⁶⁸	10 (10)	Flu-TBI 2 Gy	57 (40–61)	30	50
Wong <i>et al.</i> ⁶⁵	13 (13)	Flu-BU or Flu-Mel	61 (55–69)	38	31
Ho <i>et al.</i> ⁸⁵	23 (16)	Flu-BU-Campath	53 (22–70)	15 (1 year)	74
Van Besien <i>et al.</i> ⁸⁶	41 (25)	Flu-Mel-Campath	52 (17–71)	33 (2 years)	39
Ringhoffer <i>et al.</i> ⁸⁷	16 (9)	188 Re or 90Yt antiCD66-Flu ± Mel	63 (56–67)	25 (2 years)	17
Tauro <i>et al.</i> ⁷¹	56 (41)	Flu-Mel-Campath	52 (18–71)	19 (1 year)	41
Schmid <i>et al.</i> ⁷²	75 (44)	Flu-AraC-Amsa-TBI 4cGy-CY-ATG	52 (19–66)	33 (1 year)	42
Hegenbart <i>et al.</i> ⁷⁴	122 (64)	Flu-TBI 2 Gy or TBI 2 Gy alone	57 (17–74)	19 (2 years)	40

Abbreviations: ATG = antithymocyte globulin; Flu = fludarabine; Gy = grays; Mel = melphalan; N = number of patients; RIC = reduced intensity conditioning; TRM = transplant-related mortality.

Modified from Niederwieser *et al.*⁶²

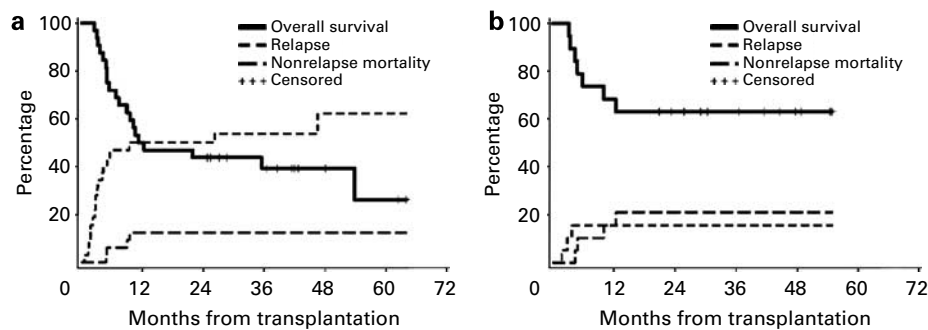


Figure 5 Survival, relapse and non-relapse mortality after allogeneic stem cell transplantation after nonmyeloablative conditioning (fludarabine and 200 cGy) as treatment for acute myeloid leukemia in first complete remission (CR1): the Seattle consortium experience; (a) transplants from related donors ($n = 32$), (b) transplants from unrelated donors ($n = 19$). From Hegenbart *et al.*⁷⁴

the two treatment options. Such a study has started under the auspices of EBMT and several cooperative groups in Europe (D Niederwieser, personal communication, Figure 7).

The results in patients with more advanced AML, refractory or in relapse after treatment, with the combination of CT and RIC (sequential therapy) are also encouraging, leading to sustained LFS at 4 years in 30% of otherwise incurable patients.^{72,78}

In summary, URD HCT is a valid and increasingly used treatment for high-risk AML. The results of this procedure, if performed in well-experienced centers, approach now to the outcome of transplantation from HLA-identical siblings. This fact is mostly the consequence of improved methods for donor and recipient HLA matching at the gene level. Acute and chronic GVHD still are particularly frequent in this setting and cause significant short- and long-term morbidity and mortality. Ongoing prospective studies are analyzing the possible role of *in vivo* T-cell depletion to decrease this complication, and to improve survival and quality of life.

When compared to autologous transplantation for very high-risk AML in CR1, the results of URD HCT in the recent years may be superior, although updated comparisons of the two procedures are lacking. URD HCT instead of autografting in CR2 of AML is a common practice, excluded the group of patients with favorable

cytogenetics at diagnosis who may benefit the most from autologous transplantation. If the probability of identifying an HLA-matched donor in a short-term basis is low, a single HLA mismatch may be acceptable. Another option in this circumstance is to use UCB progenitors as stem cell source, provided that an adequate dose is available. This transplantation modality is being performed with increasing frequency, being now preferred to HLA-mismatched or even to HLA-matched adult URD HCT at some experienced institutions. Another possibility if the previous options are not possible is to perform a haploidentical transplantation. This is a complex procedure due to the severely impaired immune reconstitution, secondary to the intense T-cell depletion of the graft necessary to avoid lethal GVHD. Refinements of this transplantation technique to improve its safety are currently being investigated.

One of the most important advances in the transplantation field during the recent years has been the introduction of RIC for allotransplants. This has extended the possibility to perform this procedure to patients up to 70 years of age or more. In URD HCT the GVL effect is particularly strong and the results of transplants after RIC in patients with AML could be even better than those achieved after transplantation from HLA-identical siblings. This is the case in preliminary experiences recently published.

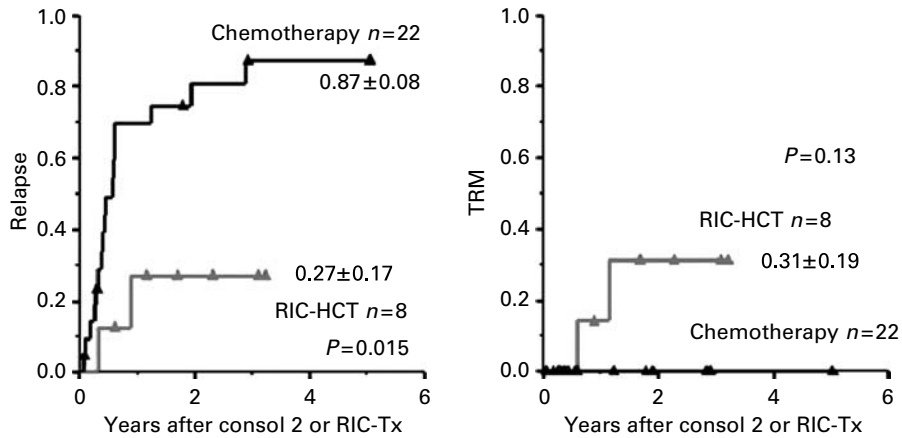


Figure 6 Relapse incidence and transplant-related mortality in patients with high-risk cytogenetic acute myeloid leukaemia reaching CR1 and treated with either chemotherapy or reduced intensity conditioning/hematopoietic cell transplantation (RIC-HCT). From Niederwieser *et al.*⁶²

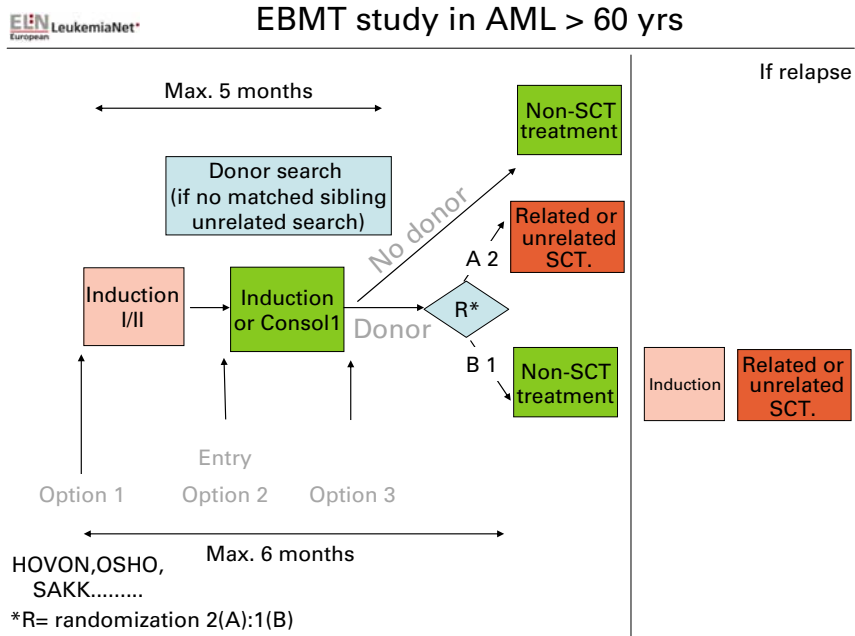


Figure 7 Design of the prospective EBMT-ELN-Intergroup study on the value of hematopoietic transplantation (SCT) after nonmyeloablative conditioning for elderly acute myeloid leukemia (AML) in first complete remission (CR1). Patients with a related or unrelated donor will be randomized between allogeneic transplantation or non-allograft therapy (D Niederwieser, personal communication with permission). SCT, stem cell transplantation.

Further improvements are necessary in the setting of URD HCT. Strategies for donor selection have to be optimized. In this sense, certain HLA mismatches less permissive than others have recently been identified.⁹³ More clear algorithms including the different transplant options for patients without a family match have to be developed. A better control of GVHD and infections is mandatory. The discovery of new approaches to improve efficacy and safety of transplantation is necessary. With this purpose, the combination of RIC with antigen or molecularly targeted antineoplastic therapy, before and after transplant, is now being investigated in clinical trials.

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