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Original article ■

Early Hematopoietic Cell Transplantation Results in Higher Overall Survival and Leukemia Free Survival Compared to Conventional Chemotherapy in High Risk Acute Myeloid Leukaemia (AML) Patients

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SUMMARY

Between 1996 and 2004, a total of 708 patients were enrolled in the AML ´96 and 2002 studies of the East German Study Group. Of those, 138 patients (19.5%) had unfavourable cytogenetics defined as complex karyotype, del (5q)/-5, del (7q)/-7, abn (3q26) and abn (11q23). Seventy-seven (56%) patients achieved CR1 after induction chemotherapy and were eligible for HCT.

HCT was performed after a median of two cycles of consolidation chemotherapies in the AML ´96 and one cycle in the AML 2002 (p=0.03). After a median follow-up of 21 months, OS amounted 73±14%, 50±14% and 14±8% at 3 years for patients after related HCT, unrelated HCT and chemotherapy, respectively (p=.008). Differences in outcomes were mainly due to a lower relapse incidence (26±13% for related and 48±15% for unrelated HCT) in patients after HCT compared to a higher relapse incidence in patients undergoing consolidation chemotherapy (89±8%; p=.003). Treatment-related mortality was low and not statistically significantly different between the three treatment groups (10±9%, 14±10% and 6± 6% for related, unrelated and chemotherapy; p=0.98).

We conclude that early HCT from related or unrelated donors led to significantly better OS and LFS compared to chemotherapy in patients with unfavourable karyotype.

Key words: **AML, hematopoietic stem cell transplantation, transplant-related mortality, overall survival**

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) following myeloablative conditioning has been established as an important treatment strategy to reduce relapse risk of patients with AML (1). However, it is also known that allogeneic HCT is associated with an increase in treatment-related mortality (TRM), which adversely affects outcome (2). Cytogenetic analysis has enabled to unravel in part the heterogeneity of AML, such that three cytogenetic prognostic profiles (favourable, intermediate and unfavourable) are currently in common use (3). Although randomised controlled trials are the gold standard for the evaluation of treatment efficacy, they have not proven feasible in the assessment of the role of SCT in haematological malignancy. Genetic randomisation offers an alternative strategy that has been adopted in a number of recent studies (4-10). Three such donor versus no-donor studies have recently suggested that HCT results in superior leukemia free survival (LFS) in patients with AML in CR1 (4-6). While a MRC study showed improved survival in patients with an intermediate risk AML (5), an EORTC/GIMEMA study showed for the first time that patients with AML in CR1 aged younger than 46 years with bed risk cytogenetics assigned to allo-HCT from related donors has a significantly better outcome than for those who were planned to undergo an auto - HCT (6). In a more recent study, the HOVON-SAKK group evaluated their results together with those of the previous MRC, BGMT and EORTC studies in a metaanalysis. Results revealed a significant benefit of 12% in overall survival (OS) by donor availability for all patients with AML in CR1, who did not have a favourable cytogenetic profile (10).

Here we address the question of whether the use of early HCT in patients with poor risk AML favourably impacts DFS and OS. The outcome of patients with poor risk AML in CR1 with a matched related or unrelated donor HCT has been compared with the outcome of patients without a donor receiving chemotherapy.

METHODS

Patient Characteristics

Between July 1997 and August 2006, 708 patients below the age of 60 years with newly diagnosed, de novo and secondary AML were enrolled in the prospectively randomized controlled AML´96 and AML 2002 studies (Table 1).

Only patients with FAB M3 or APL were excluded. Seventy six patients (20%) in the OSHO AML '96 and 62 (18%) in the OSHO AML 2002 trial had unfavourable karyotype, with 38 (50%) and 39 (63%) of them achieving CR1, respectively. Continuous CR1 before HCT or consolidation chemotherapy (CT) was observed in 22 and 37 patients respectively. The median time from last chemotherapy to HCT/CT was 76 (range, 15-150) days, 70 (range, 10-292) days and 67 (range, 33-106) days in the related, unrelated and CT groups respectively ($p=0.40$). According to the aim of the AML 2002 study, HCT was performed earlier than in the AML '96 study after reaching CR.

Treatment protocols

The AML 96 study addressed the question of the optimal cytosine arabinoside infusion rate for induction chemotherapy and the use of related or unrelated HCT in high risk patients after two consolidation therapies. Treatment in the AML 96 study involved one cycle of induction chemotherapy with an anthracycline in combination with two different applications of intermediated dose of cytarabine. This cycle was repeated once if no CR was achieved. In the event of CR, patients received two consolidation cycles and were assigned either to a third consolidation chemotherapy, if no related or unrelated donor was available, or to HCT from related or unrelated donor.

The AML 2002 study aimed at improving CR rate by testing two different chemotherapy regimens in patients not achieving CR after one induction cycle, at decreasing toxicities using one in comparison to two consolidation therapies in patients with favourable and intermediate risk karyotype and at improving survival in patients with unfavourable cytogenetics performing early HCT in CR1. One of the induction arms of the AML´96 study was used in the AML 2002. Patients in CR with intermediate and favourable cytogenetics were randomly assigned to treatment with one or two cycles of chemotherapy followed by autologous or allogeneic HCT. In contrast, patients with unfavourable cytogenetics were allocated to allogeneic HCT as soon as possible if a related or unrelated donor was available. Complex abnormalities (i.e.,defined as at least three unrelated cytogenetic clones),-5q, -7q, abn (3q26) and abn(11q23) were considered unfavourable cytogenetics.

Approval for both studies was obtained from the University of Leipzig Medical Ethical Committee and a written consent was obtained from all participating patients.

Table 1. *Overview of patient flow in the AML ´96 and AML 2002 studies*

Trial	n	Unfavourable Karyotype n	CR n	CR1 before HCT or CT n (%)	Therapy			
					HCT			CT
					Autologous	Related	Unrelated	
AML ´96 1997-2002	371	76 (20%)	38 (50%)	22 (29%)	1 (4%)	5 (23%)	4 (18%)	12 (55%)
AML 2002 2002-8/2006	337	62 (18%)	39 (63%)	37 (60%)	4 (11%)	7 (19%)	17 (46%)	9 (24%)
Total	708	138 (19,5%)	77 (56%)	59 (43%)	5 (8%)	12 (20%)	21 (36%)	21 (36%)

CR-complete remission; HCT-hematopoietic cell transplantation; CT-chemotherapy

HLA Typing and Matching

All related and unrelated donor-recipient pairs were selected on the basis of serologic matching for human leukocyte antigen (HLA) class I and molecular matching for HLA-DRB1. Three unrelated pairs had one HLA-A or HLA-B antigen mismatches. In addition, retrospective allele level typing was performed in the majority of donor-recipient pairs for HLA A, -B, -C, -DQB1, and -DPB1 alleles using direct automated fluorescent methods, as described (11).

Transplant Procedure

All patients were conditioned with conventional preparative regimen consisting of 12 Gy total body irradiation delivered at 0.07 to 0.20 Gy/min from day -6 to -4 using linear accelerators followed by cyclophosphamide 60mg/kg/body weight on days -3 and -2. Granulocyte colony-stimulating factor mobilization and harvest of peripheral blood mononuclear cells (G-PBMC), infusion of donor hematopoietic cells and antimicrobial prophylaxis were performed as previously reported (12).

All patients received cyclosporine A (CsA) from day -1 and long-course methotrexate (MTX) for GvHD prophylaxis. CsA was applied at a dose of 5mg/kg divided in two doses over 4 hours and according to daily determined plasma level (200ng/ml). MTX was given intravenously at a dose of 15mg i.v. on days +1, +3, +6 and +11. All patients received leukovorin 15 mg i.v. on day +4, +7 and +12 24 hours after MTX. In unrelated transplants ATG, (ATG-S, Fresenius, Bad Homburg, Germany) was given over 6 hours from day -5 to day -3 with premedication (250 mg prednisone i.v.). Toxicities were determined using the National Cancer Institute Common Toxicity Criteria, Version 2.0. The local investigators performed GvHD grading using standard criteria (12, 13). Engraftment was defined as the first of three consecutive days when the patient's neutrophil counts exceeded 0.5 x 10^9/l.

Endpoints and statistical methods

Data were analyzed as of August 2006. Patients who died without evidence of relapse and progression were considered to have died of non-relapse causes. OS and DFS were estimated by the Kaplan-Meier method from the date of achieving CR1. The event for OS was death due to whatever the cause and patients were censored at the date of last contact if alive.

RESULTS

Donor availability and consolidation treatment applied

Between October 1st 1997 and August 1st 2006, 708 patients were included in two consecutive AML'96 and AML 2002 studies. One hundred and thirty eight patients were found to have an unfavourable karyotype and were identified as poor risk AML. Of these, 77 patients (56%) went into CR and donor search was initiated. Of the patients receiving further consolidation therapy, 18 died from relapse of the disease or from toxicity. Finally, 59 patients were in CR1 before CT or HCT. An HLA-identical sibling donor was available in 12 of the 59 patients (20%), 5 patients underwent autologous HCT (which are not included in this analysis) and the remaining 42 (72%) underwent unrelated donor search. Twenty one patients (36%) had a HLA-matched unrelated donor and received an unrelated HCT, while the remaining 21 patients without a donor were treated with consolidation chemotherapy. At the time of analysis, the median follow-up of patients following diagnosis was 21 (range 4 to 96) months calculated from first diagnosis. Patient characteristics of the donor and no-donor groups are presented in Table 2.

Table 2. *Characteristics of the high risk AML patients treated by HCT and chemotherapy (CT)*

	HCT		CT	p-value HCT vs. CT
	Related	**Unrelated**		
N	12	21	21	
Age; median (range) years	36 (17-51)	46 (23-59)	49 (16-60)	n.s.
de novo / secondary AML	12 / -	17 / 4	15 / 6	0.12
CR after 1st course	5	17	17	0.20
CR after 2nd course	7	4	4	
no. of consolidations; median (range)	1* (1 - 2)	2* (0 - 3)		
AML 96	0** (0 - 1)	1** (0 - 3)	2	p = 0.03
AML 2002			2	(96 vs. 2002)
	p = .03	p = .20		
CR -> HCT / CT; Median (range) days	76 (15-150)	70 (10-292)	67 (33-106)	0.4

CR-complete remission; HCT-hematopoietic cell transplantation; CT-consolidation chemotherapy

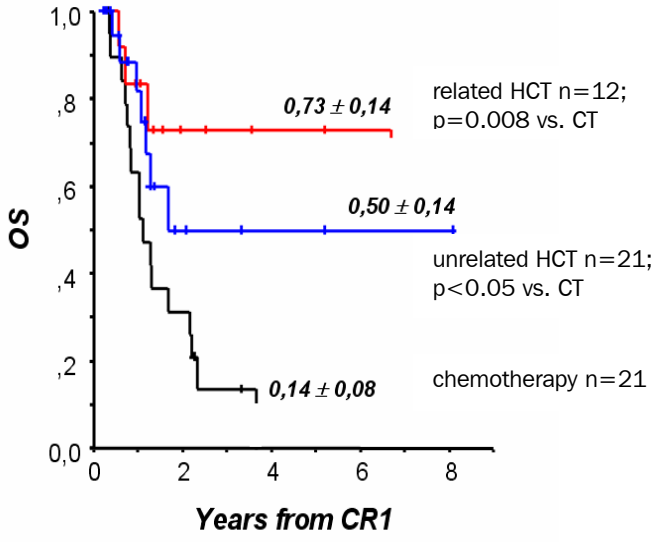
The two groups are comparable with respect to age, type of AML (de novo or secondary), and time interval from CR to HCT or CT. As expected, the numbers of consolidation courses before HCT were higher in patients treated in the AML ´96 study amounting to median 1 (range 1-2) for patients with related HCT and median 2 (range 0-3) for unrelated HCT. In the AML 2002, HCT were performed after median 0 (0-1) consolidation therapies for related HCT and after median 1 (0-3) consolidation courses for unrelated HCT (number of consolidation AML ´96 vs. 2002 p=0.03, Table 2).

Survival, relapse incidence, non-relapse mortality, engraftment and graft failure

All patients engrafted at a median of 16 (range 10-26) days after HCT. With a median follow-up of 21 (range 11-62) months, 14 (range 3-96) months and 15 (range 3-19) months, 8 of the 12 patients after matched related HCT, 14 of the 21 patients after unrelated HCT and 4 of the 21 patients after CT were alive. Of these, 7, 13 and 4 patients respectively were in continuous CR1. OS was best for related HCT 73±14%, followed by unrelated HCT 50±14% and consolidation chemotherapy 14±8% (p<0.05; Figure 1a).

Factors associated with better OS and lower risk of relapse were younger age (p=0.008) and HCT (p=0.001). Similarly LFS was significantly better after sibling HCT (67±14%) and unrelated HCT (44±14%) compared to the chemotherapy group (11±7%; p=0.002; Figure 1b).

The main reasons for these differences were due to decreased relapse incidence after HCT (26±13% in related and 48±15% in unrelated HCT) compared to the chemotherapy group (89±8%; p<0.003; Figure 2) without increase in non-relapse mortality between the three treatment groups (10±9%, 14±10% and 6±6% for related, unrelated and CT, respectively; p=n.s.; Figure 3).



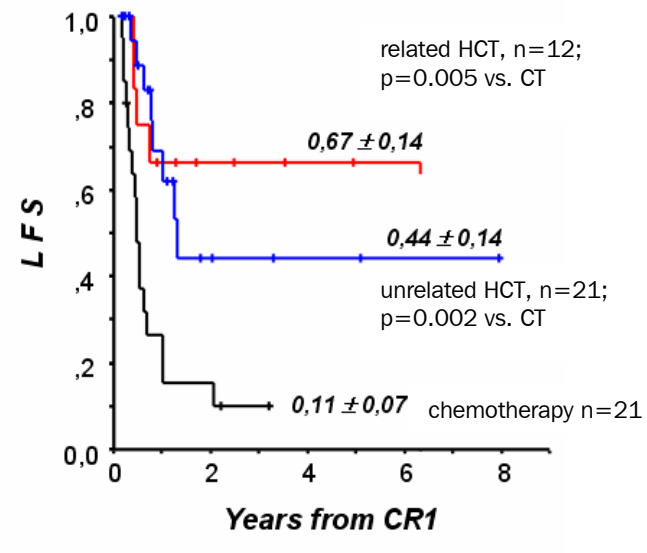


Figure 1. *Overall survival (a) and leukaemia free survival; (b) of patients with AML in CR1 according to treatment*

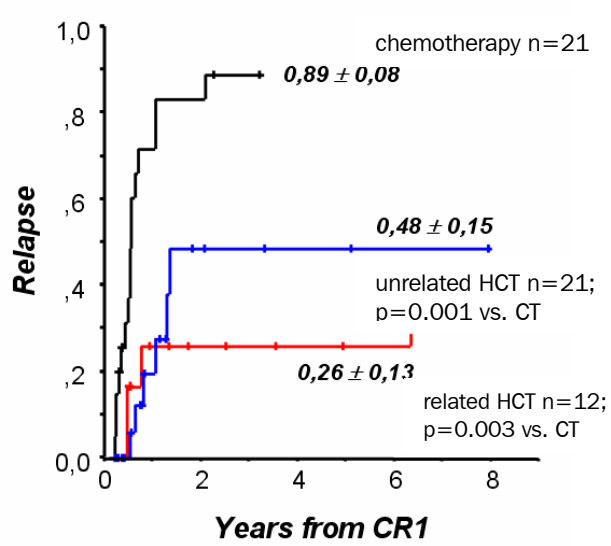


Figure 2. *Relapse incidence of patients with AML in CR1 according to treatment*

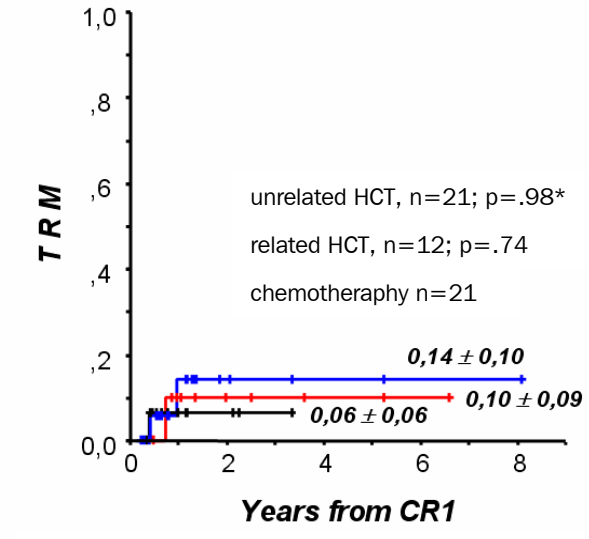


Figure 3. *Non-relapse mortality of patients with AML in CR1 according to the treatment*

DISCUSSION

The role of HCT for AML in CR1 has progressed from early reports on syngenic marrow transplantation to the extensive data now available (4-6, 10, 11) providing evidence for a superior LFS in the group assigned to HCT. However, none of the studies to date has been able to show a benefit in OS in adult AML undergoing HCT, an issue of extensive debate in the hematology community in recent years (8, 14). A possible explanation for the lack of a significant difference in OS of patients with AML treated with chemotherapy, autologous SCT or allo-SCT could be the relatively small number of AML cases coupled to the pathobiological heterogeneity of the disease. Subgrouping of AML according to risk categories leads to smaller groups and reduces the power of the statistical analysis (7, 9). The cooperative group has run two successive trials in adult AML <60 years, in which HCT has been standard treatment for all patients achieving CR and having HLA-identical related donor and in all high risk AML patients who have an HLA-identical related or unrelated donor. The aim of the study was to perform an allogeneic HCT in high risk AML-patients as soon as possible after achieving CR1. The present study shows that 95% of high risk AML patients achieving CR1 were indeed evaluated for transplant and 72% of patients have undergone allogeneic HCT in AML 2002. This number of performed HCT is far higher than in the AML 96 study (41%). The main reason is a lower relapse rate and mortality following consolidation therapy even before HCT or CT. In fact, while 16 patients in CR either relapsed or died of toxicity of consolidation therapy prior to transplant, only 2 patients relapsed before HCT or CT in the AML 2002 study. Although the data is based on a small cohort of patients drawn from two different study cohorts with a short median follow-up time, limiting the interpretation of the multivariate analysis, this is the first study showing that not only LFS but also OS was significantly better in allogeneic HCT compared to a CT group of patients with unfavourable cytogenetics (Figure 2). The significant difference in 3-year LFS and OS was due to the lower relapse incidence. Indeed, a strong reduction of relapse was observed in the HCT compared to the CT patients (Figure 3). This is consistent with other studies (4-6) showing a significant increase in LFS and lower relapse incidence in the donor group, coupled to a higher TRM which adversely affects OS in the donor group.

A very important result of our study was the fact that the TRM of 10% and 14% in HCT (related and unrelated HCT, respectively) was not significantly different to that of the CT group (6%, p=.98 and p=.74, respectively). The TRM in our study is also low compared to previously published data reporting TRM in matched related HCT of 23% (4), of 17% (6) and 25% (10), all of which were statistically different to the CT group. Similarly, among patients with AML in CR1 (median age 34

years) undergoing non-T-cell depleted, matched sibling SCT following standard Cy/TBI or Bu/Cy conditioning, TRM was 23% to 25% at 1-year (15). The TRM observed in our study in matched and partially matched unrelated HCT (14%) is also much lower than recently reported on 236 consecutive prospectively analysed patients (16). This may contribute to the difference in OS among our group of patients compared to those previously published (4-6). It may also be relevant that the analysis in our study concentrates on a high risk group of patients with unfavourable karyotype rather than on all AML patients.

It has been generally accepted that cytogenetic analysis performed at diagnosis is the single most valuable prognostic factor for the response to induction therapy in AML (3). In addition, it has been shown that cytogenetic characteristics at diagnosis are also associated with the outcome of postremission treatment (17). However, discrepant results have been obtained regarding relapse risk in cytogenetic defined subgroups of AML (5, 6). The incidence of AML patients with unfavourable karyotype was 20% and 18% in the AML 96 and 2002 studies respectively, which is similar to other reports (30% Slovak et al (18, 19); 21% Burnett et al (5); 21% Suciu et al (6). The estimated 4-year LFS rate in a subgroup of unfavourable cytogenetic AML patients was significantly better in the donor than in the no-donor group (43,4% vs 18.4% with relapse rates of 38.2% vs 75,9% and TRM of 18.4% vs 5.7%) (6). In contrast, LFS, OS and relapse rate at 7-years in another study showed no significant difference in donor versus no donor AML patients with unfavourable cytogenetics (5).

In conclusion, our policy of performing allo-SCT from related or unrelated donor in adult patients with AML early after achieving CR has been effective in patients with unfavourable cytogenetics. Further post transplant strategies might improve the current results especially on the relapse incidence and should be prospectively studied.

* already published in Leukemia (Reference 19)

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REZULTATI RANE TRANSPLANTACIJE HEMATOPOETSKIH ĆELIJA KOD VEĆE STOPE UKUPNOG PREŽIVLJAVANJA I PREŽIVLJAVANJA BEZ PRISUSTVA LEUKEMIJE U POREĐENJU SA KONVENCIJALNOM HEMOTERAPIJOM KOD VISOKO RIZIČNIH BOLESNIKA SA AKUTNOM MIELOIDNOM LEUKEMIJOM

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Sažetak

U periodu od 1996. do 2004. u AML96 i 2002 studiju uključeno je 708 bolesnika. Od toga je kod 138 bolesnika (19,5%) pokazana nepovoljna citogenetika, definisana kao kompleksan kariotip, del (5q)/-5, del (7q)/-7, abn (3q26) i abn (11q23). Sedamdeset i sedam (56%) bolesnika je postiglo CR1 posle indukcije I i moglo da primi alogenu transplantaciju od nesrodnog ili srodnog davaoca.

Transplantacija matičnih ćelija hematopoeze (HCT) je urađena posle 2 ciklusa (medijana) konsolidacione terapije u AML96 i posle samo jednog ciklusa u AML 2002 (p=0.03). Posle praćenja (medijana) od 21. meseca, OS posle 3 godine je iznosio 73±14%, 50±14% i 14±8% za bolesnike posle alogene transplantacije sa srodnim davaocem, sa nesrodnim davaocem i koji su primili citostatsku terapiju (p=0.008). Razlike u preživljavanju su pre svega nastale zbog niske incidence recidiva (26±13% kod srodnih davaoca i 48±15% kod nesrodnih davaoca) u poređenju sa značajno višom incidencom recidiva kod bolesnika lečenih citostatskom konsolidacionom terapijom (89±8%; p<0.003). Smrtnost izazvana lečenjem (TRM) je bila niska i nije se razlikovala u tri ispitivane grupe (10±9%, 14±10% i 6±6% kod HCT od srodnog, HCT od nesrodnog davaoca i citostatske terapije; p=0.98).

Na osnovu gore navedenih rezultata se može zaključiti da je najbolje preživljavanje bolesnika sa visokorizičnom AML (OS i LFS) pokazano u grupi bolesnika koji su odmah posle postizanja CR1 transplantirani od srodnog ili nesrodnog davaoca.

Ključne reči: **AML, transplantacija matičnih ćelija hematopoeze, preživljavanje**