Allogeneic transplantation as post-remission therapy for cytogenetically high-risk acute myeloid leukemia: landmark analysis from a single prospective multicenter trial

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ABSTRACT

Background
Allogeneic hematopoietic cell transplantation is considered the preferred post-remission therapy in patients with acute myeloid leukemia cytogenetically defined as being at high risk. To substantiate evidence for allogeneic hematopoietic cell transplantation in first complete remission in these high-risk patients we performed a landmark analysis within a single prospective multicenter treatment trial.

Design and Methods
By the time of analysis, 2,347 patients had been accrued into the AMLCG 99 trial between 1999 – 2007. Out of this population, 243 patients under 60 years old fulfilled the criteria for high-risk cytogenetics. Landmark analyses were performed with a control cohort, who remained in first complete remission at least the median time from complete remission to transplantation in the intervention group.

Results
After standardized induction therapy, 111 patients under 60 years old achieved complete remission. A matched allogeneic donor was identified for 59 patients (30 sibling donors, 29 unrelated donors). Fifty-five patients received an allogeneic hematopoietic cell transplant after a median time of 88 days in first complete remission. Of the remaining 56 patients, 21 relapsed within 90 days after achieving first complete remission and for 7 patients with relevant comorbidities no donors search was initiated, leaving 28 patients given conventional post-remission therapy as the control cohort. The median follow-up of surviving patients was 60.4 months. Patients with an allogeneic donor had substantially better 5-year overall and relapse-free survival rates than the control group (48% versus 18%, P=0.004 and 39% versus 10%, P<0.001, respectively). A survival benefit from transplantation was evident regardless of donor type, age and monosomal karyotype.

Conclusions
Beyond evidence available for subgroups of high-risk patients, the findings of this study establish in a broader manner that allogeneic hematopoietic cell transplantation is a preferable consolidation treatment for patients with acute myeloid leukemia and high-risk cytogenetics.
The study was registered at Clinicaltrials.gov as NCT00266136.

Key words: allogeneic stem cell transplantation, acute myeloid leukemia, high-risk, cytogenetics, first complete remission.

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The online version of this article has a Supplementary Appendix.

Introduction

High-risk acute myeloid leukemia (AML) is characterized mainly by cytogenetic features of the blast population, less often by immunophenotypic abnormalities, more regularly by secondary disease manifestation after myelodysplastic syndrome or cytotoxic treatment of another malignant disease and, finally, by response to induction therapy.[1-5] Molecularly detectable mutations are currently being evaluated for their prognostic role and, consequently, as predictive markers guiding up-front treatment decisions.[6,7] Evidence upon which treatment recommendations can be based must take into consideration this substantial heterogeneity.

Only about 20% of newly diagnosed AML patients are younger than 60 years and hence eligible for conventional allogeneic hematopoietic cell transplantation (HCT). It is obvious that any of the high-risk categories listed above represent rare condition and evidence for defining treatment standards is, therefore, unlikely to derive from single randomized trials. Indeed, most currently available evidence has been derived from cumulative analyses from sequential trials or meta-analyses covering trials conducted over substantial periods of time.[8-11]

From the body of evidence available it has emerged that, in high-risk AML patients, allogeneic HCT should be performed as soon as the patient, disease status and donor availability allow for it.[2,9,10,12-15] Looking for support for this notion, we took the opportunity to analyze patients defined as at high risk according to cytogenetics (complex karyotype, -5/5q-, -7/7q-, abnormal 3q21/3q26, or abnormal 11q23) who underwent allogeneic HCT, comparing their outcomes with those of an appropriate landmark control cohort from one of the largest ongoing AML trials that had enrolled almost 2,400 patients at the time of this analysis.[16,17] This large trial cohort allowed us to focus on patients in first complete remission (CR1) with balanced types of induction therapy, to address questions of donor types and conditioning intensities, to compare patients with different types of cytogenetic high risk including those with monosomal karyotypes (a recently established predictor for very poor prognosis of AML), and to perform multivariate analyses on sufficiently large subgroups. The benefit of allogeneic HCT in CR1 in cytogenetically defined high-risk AML patients has so far not been demonstrated under more stringent comparative conditions in the setting of a single prospective clinical trial.

Design and Methods

Study Population

Between May 1999 and May 2007 2,347 patients 16 years old or more (with no upper age limit) who had a previously untreated AML, except for acute promyelocytic leukemia, or suffered from high-risk myelodysplastic syndrome (refractory anemia with excess blasts in transformation) were included in the AMLCG 99 trial.[16,17] At diagnosis, samples of bone marrow aspirates were examined for chromosomal abnormalities using standard banding techniques and classified according to the International System for Human Cytogenetic Nomenclature.[2] A monosomal karyotype was defined as two or more monosomies, or a single monosomy in the presence of structural abnormalities.[18,19] Two hundred and forty-three patients 21-59 years of age with a known unfavorable karyotype with or without monosomal karyotype, as detailed above, were considered in the present analysis (*Online Supplementary Figure S1*). According to the study protocol of the AMLCG99 trial, an unfavorable karyotype was defined as a complex karyotype, -5/5q-, -7/7q-, abnormal 3q21/3q26, or abnormal 11q23 throughout the whole study period. The trial was approved by the ethics committees of the participating centers and was conducted in accordance with the Declaration of Helsinki. Written informed consent was provided by all participants. The study was registered at Clinicaltrials.gov as NCT00266136.

Study design and treatment

Before treatment started, all patients were randomly assigned upfront to one of the two induction therapies: thioguanine, cytarabine, and daunorubicin (TAD) – high-dose cytarabine and mitoxanthrone (HAM) or HAM-HAM. In the same step patients were randomly assigned to post-remission therapy with either prolonged maintenance or autologous HCT. After achieving complete remission, patients received consolidation with one course identical to the TAD induction regimen. For maintenance treatment, patients were given monthly courses of cytarabine, and as a second agent from course to course, daunorubicin, thioguanine or cyclophosphamide, with the second agent changing in a rotating sequence. Maintenance was continued for 3 years. After recovery from TAD consolidation, patients younger than 60 years who were randomly assigned to autologous HCT received busulfan/cyclophosphamide conditioning before reinfusion of autologous stem cells. Independently of the random assignment it was recommended per protocol that younger patients with histocompatible family donors should proceed to allogeneic HCT in CR1. In January 2002, the protocol was amended by recommending allogeneic HCT also from matched unrelated donors for patients under 60 years old with an unfavorable karyotype as consolidation therapy in CR1. The search for a related or unrelated stem cell donor was initiated immediately after the diagnosis of high-risk AML had been made. Until transplantation patients received conventional consolidation and maintenance treatment according to the protocol. Patients with a suitable donor and no contraindications (defined by the treating physicians) underwent allogeneic HCT according to the policies of the transplant center.

Post-induction/pretransplantation characteristics

Complete remission (CR) was defined according to standard morphological criteria; morphological CR with incomplete blood count recovery (CRi; absolute neutrophil count < $1x10^9$/L and/or platelet count < $100x10^9$/L) was included for this transplant analysis. Pre-transplantation comorbidities were assessed using the HCT comorbidity index (HCT-CI).[20]

HLA typing and matching

Patents and donors were typed at least for HLA-A, -B and –DRB1. After July 2001 all patients and donors were tested at least for HLA-A, and -B by at least intermediate-resolution DNA typing and HLA-DRB1 and DQB1 by high-resolution techniques. High-resolution typing of patients and donors for HLA-A, -B, -C, -DRB1 and -DQB1 was performed after April 2005.[21]

Statistical analyses

Data were analyzed as of April 1, 2010. The primary objective of this analysis was to compare allogeneic HCT and conventional chemotherapy as consolidation therapy in AML patients with an unfavorable karyotype in CR1. Overall survival was measured from the start of treatment until death. Relapse-free survival was counted from the achievement of CR1 until relapse or death in CR. Outcome comparisons were performed by landmark analy-

ses, i.e. only patients with CR1 lasting 90 days or more were included in the control cohort in order to account for the median time from CR1 to transplantation (88 days) in the HCT comparison groups. Significances were calculated for overall survival and relapse-free survival by the log-rank test, and for multivariate analyses by logistic and Cox regression. Outcome measures were evaluated according to treatment received (*as treated*: allogeneic HCT in CR1 *versus* conventional treatment) and according to intended treatment (*intention to treat*: recommended allogeneic HCT, initiation of donor search and identification of a suitable allogeneic donor as defined per protocol *versus* recommended allogeneic HCT, initiation of donor search but without identification of a suitable donor as defined per protocol in patients who were otherwise eligible for an allogeneic transplant). The probabilities of relapse and non-relapse-related mortality were calculated using cumulative incidence estimates to accommodate competing risks (*mortality* in this analysis refers to number of deaths per number of patients involved in the evaluation). For analysis of non-relapse mortality, failure was defined as death during a continuous complete remission. For analysis of relapse, failure was defined as clinical or hematologic recurrence of AML at any site.

Results

Patients' characteristics

The start of induction therapy of all prospectively enrolled 243 AML patients less than 60 years old with an unfavorable karyotype was between August 1999 and May 2007. After induction therapy with either TAD-HAM (123 patients) or HAM-HAM (120 patients), 111 patients achieved a CR1 (CR/CRi) within a median of 58 days (range, 12-113 days). As previously described, both induction therapies resulted in comparable outcomes.[16,17] For landmark analyses, a minimum of 90 days of CR was required after achieving CR1, leaving a study cohort of 90 patients (21 patients relapsed within 90 days after achieving CR1 and were excluded from further analyses). A suitable allogeneic donor could be identified for 59 patients (a sibling donor for 30 and an unrelated donor for 29). Fifty-five patients underwent allogeneic HCT after a median of 88 days in documented CR1 (Table 1). The control cohort for landmark analyses of survival data consisted of 35 patients treated with conventional post-remission therapy (including autologous HCT in six cases). The median follow-up of all surviving patients was 60.4 months (range, 11-105 months), that for patients undergoing allogeneic HCT was 60.4 months, while that for patients receiving conventional consolidation therapy was 58.2 months.

Post-remission treatment

TAD consolidation therapy was given to 61/90 patients (30/55 patients undergoing allogeneic HCT and 31/35 patients receiving conventional treatment) and at least one cycle of maintenance therapy was administered to 19/90 patients (5/55 patients and 14/35 patients, respectively). Six out of 31 patients without a donor underwent autologous HCT according to the protocol.

Due to comorbidities/infections, four patients with an allogeneic donor did not proceed to transplantation in CR1 and were, therefore, included in the *as treated* control cohort. No suitable donor could by identified for 24 patients while in continued CR1 (control cohort for *intent to treat* analyses). For seven additional patients, only considered in the *as treated* analyses, no donor search was initiated because of comorbidities and/or severe infection associated with induction therapy.

Among the subjects undergoing allogeneic HCT, 38 patients (69%) received standard intensity conditioning and 17 (31%) received reduced intensity conditioning, as previously defined.[22] Total body irradiation (8-12Gy)-based standard intensity conditioning was used in 29 patients. Conditioning regimens and prophylaxis against graft-*versus*-host disease were chosen according to the

Table 1. Characteristics of the patients, diseases and donors.

Characteristics	allogeneic HCT (n=55)	control (n=35)
Median age, years (range)	45 (21-59)	49 (23-59)
age 18–30 years, n. (%)	10 (18)	4 (11)
age 31–40 years, n. (%)	11 (20)	6 (17)
age 41–50 years, n. (%)	19 (35)	8 (23)
age 51–59 years, n. (%)	15 (27)	17 (49)
Sex, n. (%)		
male	26 (47)	18 (54)
female	29 (53)	17 (46)
Disease diagnosis, n. (%)		
AML FAB M0	7 (13)	1 (3)
AML FAB M1	10 (18)	6 (17)
AML FAB M2	21 (38)	6 (17)
AML FAB M4	4 (7)	5 (14)
AML FAB M5	9 (16)	11 (31)
AML FAB M6	1 (2)	3 (9)
AML FAB M7	2 (4)	1 (3)
AML unclassified	1 (2)	2 (6)
Karyotype, n. (%)		
complex	33 (60)	24 (69)
non-complex	22 (40)	11(31)
monosomal karyotype	18 (33)	9 (26)
non-monosomal karyotype	36 (66)	26 (74)
Median time from start of induction therapy to documented CR/CRi, days (range)	54 (12-100)	57 (17-113)
Median time from documented CR1 to HSCT, days (range)	88 (8-199)	-
Median time CR1 to relapse, days (range)	545 (189-1645)	229 (105-1081)
relapse between 90–120 days after CR1, n.	0	2
relapse between 121–180 days after CR1, n.	1	8
relapse >180 days after CR1, n.	16	19
Comorbidity status at CR1, n. (%)		
HCT-CI 1-2	30 (58)	21 (60)
HCT-CI 3-4	16 (27)	11 (31)
HCT-CI >4	9 (16)	3 (9)
Donor characteristics, n.		
HLA-identical sibling	27	3
matched unrelated (6/6 HLA match)	1	-
matched unrelated (8/8 HLA match)	16	1
matched unrelated (10/10 HLA match)	4	-
mismatched unrelated (≤7/8 HLA match)#	1	-
mismatched unrelated (≤9/10 HLA match)#	6	-
Reasons why HCT was not performed, n. (%)		
co-morbidities and / or severe infections	-	11
no sibling / no matched donor	-	24

HCT: hematopoietic cell transplantation; AML: acute myeloid leukemia; CR1: first complete remission; CRi, incomplete remission (bone marrow blasts <5%, no extramedullary AML manifestation, incomplete recovery of platelet and/or neutrophil cell counts), HCT-CI: hematopoietic cell transplantation comorbidity index; HLA: human leukocyte antigen. #Allele and/or antigen mismatch.

policies of the individual centers. Six patients received an allogeneic bone marrow graft (11%) and 49 an allogeneic peripheral blood stem cell graft (89%), all without *in vitro* T-cell depletion. No graft failure was reported within the study population. The cumulative incidence of acute graft-*versus*-host disease grade II – IV was 33% and that of chronic graft-*versus*-host disease was 44% (limited disease in 11 patients and extensive disease in 13 patients).

Survival according to treatment received

At the time of last follow-up, 33 of 90 patients were alive (27/55 patients after allogeneic HCT in CR1 and 6/35 control patients). Patients who underwent allogeneic HCT in CR1 had substantially better 5-year overall survival and relapse-free survival rates than comparable patients given conventional post-remission therapy (48% *versus* 16%, P=0.001 and 40% *versus* 13%, P<0.001, respectively) (Figure 1). Both for the entire group and those patients transplanted, only age (≤40 years *versus* >40 years) had a significant impact on overall survival (54% *versus* 28%, P=0.001 and 69% *versus* 37%, P=0.011, respectively) (Table 2). Comparing allogeneic HCT in CR1 with conventional treatment in the subgroups of patients 40 years and less or over 40 years of age showed that the survival benefit of allogeneic HCT was independent of age (overall survival 69% *versus* 25%, P=0.026 and 37% *versus* 15%, P=0.032, respectively). Patients transplanted from a matched related or a matched unrelated donor had similar survival rates (hazard ratio for overall survival 0.77, 95% confidence interval 0.35–1.68, P=0.51) (Table 3).

Survival according to intended treatment

To eliminate factors such as pre-existing comorbidities, which might worsen the outcome of the control group, we performed an *intent to treat* analysis on the basis of donor availability. In consequence, four of the 35 patients receiving conventional therapy who had a matched related (n=3) or unrelated donor (n=1) were added to the transplant group (*Online Supplementary Figure S1*). In the remaining 31 patients, allogeneic HCT in CR1 was not intended because of a protocol recommendation/no suitable donor (24 patients) or pre-existing comorbidities (7 patients, all excluded from the *intent to treat* analysis). Comparing all 59 patients with identified allogeneic donors with the remaining 24 landmark control patients confirmed the benefit of allogeneic HCT with regard to overall survival (48% *versus* 18% P=0.004) and relapse-free survival (39% *versus* 10% P=0.001) also on the basis of intended treatment (Figure 2).

Relapse and non-relapse mortality

Of the 90 patients analyzed in this study, 47 had a relapse; 18/55 patients relapsed after allogeneic HCT and 29/35 patients after conventional post-remission therapy (Figure 3). Relapse was fatal in 41 patients (13/55 and 28/35 patients, respectively). The median time from CR1

Table 2. Comparison of outcome in different subgroups of patients.

	Allogeneic HCT (as treated)			Conventional consolidation therapy			All patients		
	n	5-year OS	*P* value	n	5-year OS	*P* value	n	5-year OS	*P* value
Age									
≤40 years	22	69% (48-90)	0.011	10	25% (0-55)	0.155	32	54% (34-74)	0.001
>40 years	33	37% (20-55)		25	15% (0-31)		58	28% (16-40)	
Karyotype									
complex aberrations	33	57% (39-76)	0.084	24	10% (0-24)	0.029	57	37% (24-51)	0.971
other#	22	37% (18-59)		11	34% (4-64)		33	36% (19-54)	
monosomy	18	57% (23-75)	0.343	9	-	0.005	27	38% (18-58)	0.858
no monosomy	37	44% (27-62)		26	23% (5-42)		63	37% (24-50)	
Comorbidities									
HCT-CI 0-2	30	58% (40-77)	0.258	21	17% (0-34)	0.220	51	41% (27-55)	0.339
HCT-CI 3-4	16	37% (10-63)		11	27% (0-54)		27	32% (12-51)	
HCT-CI >4	9	37% (0-74)		3	-		12	28% (0-57)	
Status prior to HCT									
hematologic remission	17	50% (25-76)	0.801						
incomplete remission*	35	54% (36-72)							
Donor									
related	27	43% (22-64)	0.723						
unrelated	28	55% (36-75)							
Conditioning									
standard Intensity	38	47% (30-64)	0.855						
reduced Intensity	17	54% (38-80)							
Therapy (as treated)									
HCT	55	49% (35-64)	0.001						
no HCT	35	17% (4-31)							
Therapy (intent to treat)									
donor				4	25% (0-69)	0.866	59	48% (34-62)	0.004
no donor				24	10% (0-24)		24	18% (1-35)	

*Univariate analyses of risk factors in transplanted or control groups (percentages, 95% confidence intervals). Median follow-up of surviving patients after transplantation in CR1: 60.4 months; median follow-up of surviving patients receiving conventional consolidation therapy: 58.2 months. Abbreviations: OS, overall survival; HCT, hematopoietic cell transplantation; HCTCI, hematopoietic cell transplantation comorbidity index. #, -5/5q-, -7/7q-, abnormal 3q21/3q26, or abnormal 11q23. *bone marrow blasts <5%, no extramedullary AML manifestation, incomplete recovery of platelet and/or neutrophil cell counts.*

to relapse after allogeneic HCT was 545 days (range, 177-1645 days) while that for patients receiving conventional therapy was 229 days (range, 105-1081 days). Interestingly, only 4/21 patients (19%) transplanted from matched unrelated donors relapsed in contrast to 13/27 patients (48%) transplanted from matched related donors (P=0.022). In contrast, transplantation from matched related donors resulted in three non-relapse-related deaths (11%) as compared to ten deaths (36%) in patients transplanted from matched unrelated donors (P=0.123). Of the 35 control patients, two died in CR (1 after an allogeneic HCT in second CR and 1 due to an infection).

Subset analyses

A monosomal karyotype was found in 27 of the 90 patients with high-risk cytogenetics at diagnosis of AML (33% of patients undergoing allogeneic HCT in CR1 and 26% of patients receiving conventional post-remission therapy). As shown by univariate and multivariate analyses, monosomal karyotype was an adverse prognostic factor in patients not transplanted from an allogeneic donor in CR1, but not in patients undergoing allogeneic HCT (Tables 2 and 3).

A small subset of ten patients with documented CR/CRi (median age 45 years, 5 transplanted from matched related donors and 5 from matched unrelated donors) received sequential reduced intensity conditioning therapy.[23] These patients showed a tendency to a higher overall survival rate after 5 years (75%) compared to patients receiving other conditioning regimens (43%; P=0.068).

Discussion

AML with poor-risk cytogenetics in patients less than 60

Table 3. Multivariate analyses of outcome.

Variable	n	Hazard ratio	95% CI	Overall P
Overall survival for all patients				
Patients' age				
≤40 years		32	1.00	0.011
>40 years	58	2.2	1.21-4.14	
Therapy				
HCT	55	1.00		0.003
no HCT	35	2.35	1.35-4.10	
Karyotype				
no monosomy	27	1.00		0.260
monosomy	63	1.40	0.78-2.50	
Overall survival of transplanted patients				
Patients' age				
≤40 years	22	1.00		0.032
>40 years	33	2.63	1.09-6.36	
Comorbidities				
HCT-CI ≤2	30	1.00		0.237
HCT-CI ≥3	25	1.59	0.74-3.43	
Karyotype				
no monosomy	18	1.00		0.849
monosomy	37	0.93	0.42-2.06	
Donor				
matched related	27	1.00		0.509
unrelated	28	0.77	0.35-1.68	
Overall survival of non-transplanted patients				
Patients' age				
≤40 years	10	1.00		0.461
>40 years	25	1.42	0.56-3.58	
Karyotype				
no monosomy	9	1.00		0.024
monosomy	26	2.90	1.15-7.27	

HCT: hematopoietic cell transplantation; HCT-CI: hematopoietic cell transplantation comorbidity index; CI: confidence interval.

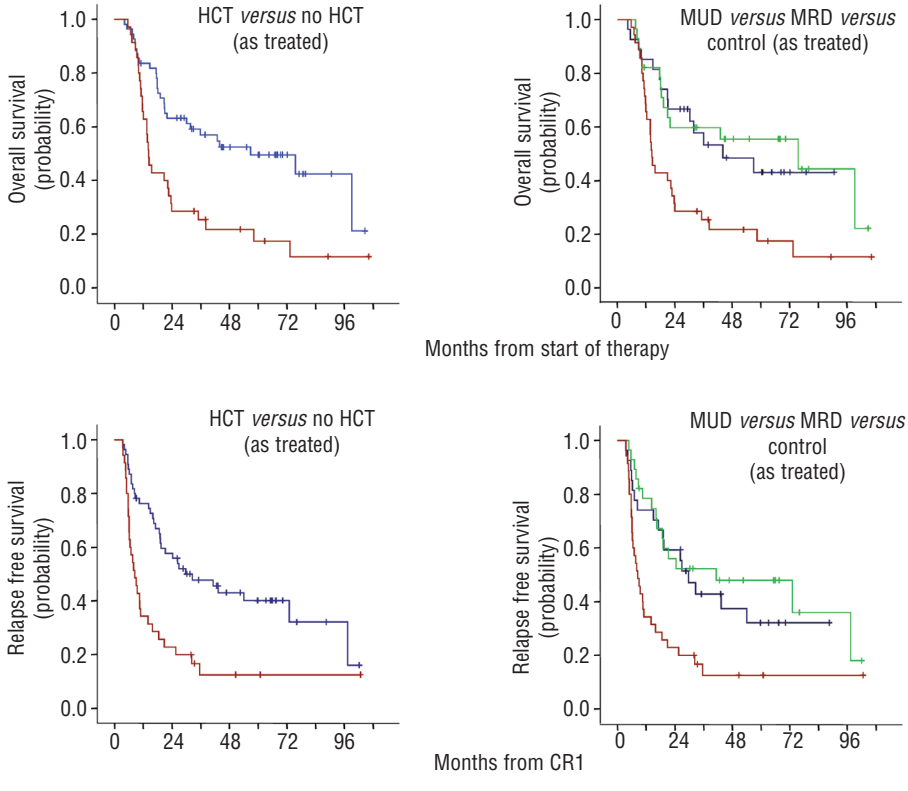

Figure 1. Survival plots for comparison groups. HCT, hematopoietic stem cell transplantation; CR1, first complete remission. Patients transplanted in CR1 (—), landmark control group (—). MUD, matched unrelated donor (—); MRD, matched related donor (—).

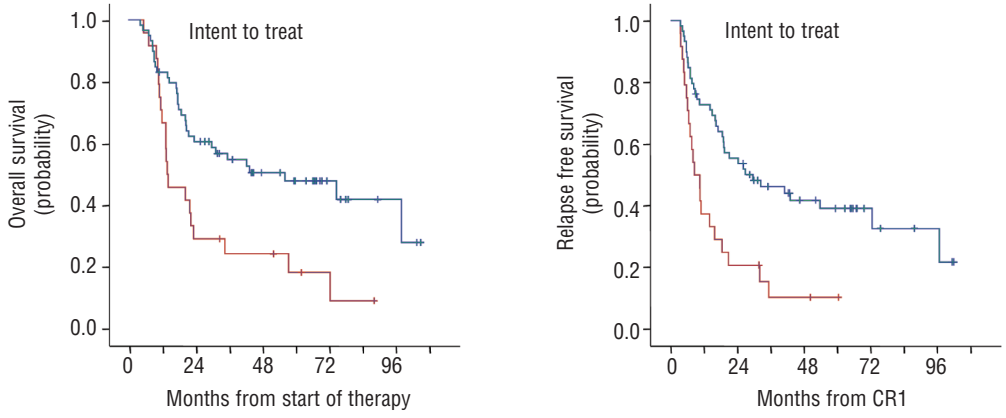

Figure 2. Survival plots for corresponding intent to treat analyses (recommended allogeneic HCT, initiation of donor search and identification of a suitable allogeneic donor as defined per protocol (—); *versus* patients with recommended allogeneic HCT, initiation of donor search but without identification of a suitable donor as defined per protocol for patients who otherwise were eligible for an allogeneic transplant(—).

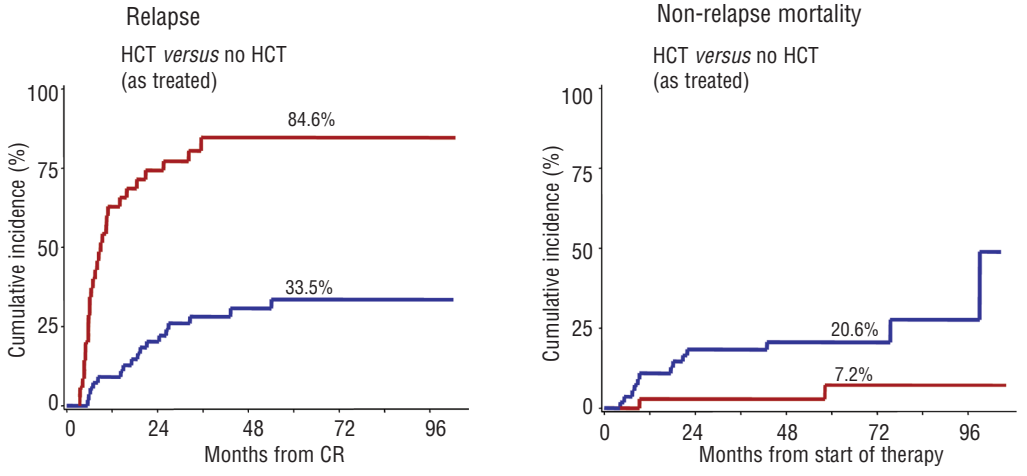

Figure 3. Cumulative incidences of relapse and non-relapse mortality. Transplanted patients are represented by blue and landmark controls by red.

years of age is a rare disease and has a dismal prognosis. Accordingly, most evidence for treatment recommendations stems from meta-analyses or alternative cumulative evaluations of different, at best sequential, clinical trials.[2,8-14] These limitations hold true specifically for the role of allogeneic HCT in front-line treatment. Only recently, data from two prospective analyses were reported which strongly favor allogeneic HCT from matched related or unrelated donors in the first-line treatment of high-risk AML patients defined by either cytogenetics and/or failure of induction treatment.[11,15]

The large data pool of the prospective AMLCG 99 trial, comprising almost 2400 patients enrolled at the time of this examination, enabled us to perform an analysis focusing on patients with high-risk cytogenetics aged less than 60 years, who achieved a CR1 after balanced induction treatment.[17]

The control cohort in our landmark comparisons certainly represents a positive selection as a minimal duration of CR1 was required in order to compensate for time from CR1 to transplantation in the intervention group. Landmark analysis was also used in a recent report by Schlenk *et al.* on the role of HCT in first-line treatment of high-risk AML. More than 80% of AML patients in this prospective cohort comparison were defined as being at high risk due to failure of induction treatment.[15] This study also described a significant benefit of transplantation on the overall survival of patients with poor-risk cytogenetics (also including abn(12p), abn(17p) as high-risk cytogenetic abnormalities, in contrast to our study) in their multivariable regression model. The authors also ascertained an overall survival benefit for transplant recipients irrespective of whether the graft was from a matched related or unrelated donor. Their conclusions are, therefore, largely in line with the findings of the present study, although they refer to a mixed population of high-risk patients with either induction failure or poor cytogenetics.

In contrast, our prospective cohort comparisons are restricted to genetically high-risk patients in CR1 after balanced induction treatment, allowing us to compare outcomes of this specific high-risk population with an accordingly defined control group. The data clearly underscore that survival outcome after transplantation of a graft from a matched unrelated donor is certainly not worse than that after a related donor transplant. Since higher ranking evidence from randomized controlled trials will not be easily obtained in this rare disease entity, and with existing evidence some such trials may not even be ethically justifiable, there is little chance that data will appear that would question rather than corroborate our main finding. Consequently, together with existing data, we present here firm evidence that despite substantial non-relapse fatality rates of up to 20% with the transplants regimens used in this study, the benefit on survival end-points demonstrates that allogeneic HCT from matched related

or unrelated donors in CR1 should be considered the standard of care for AML patients with high-risk cytogenetics.[24] This conclusion also applies generally to patients aged less than 60 years, irrespectively of whether they belong to the age category less than or 40 years old, which benefits most, or to the category over 40 years old, which also shows a significant survival benefit. However, eligibility and donor matching criteria, transplant regimens and the extension of transplants to elderly patients require refinement in future studies and bear the potential for improving transplant outcome in this AML population.[20,21,23,25-27]

It might be asked whether allogeneic HCT in this setting can be postponed to first relapse. Although this question appears to be very reasonable for AML patients with intermediate cytogenetic risk, current consensus and the few data available suggest that an allogeneic HCT in CR1 should not be delayed in this population. Reports indicating a successful outcome after relapse with a curative potential of approximately 30% are highly selective and relate only to patients who have survived their relapse and remain fit enough to receive a transplant.[28,29] The predicted overall survival of relapsed AML patients in this setting is exceedingly poor, being no more than about 10%.[18,30]

Finally, the comparatively large numbers of patients cytogenetically defined as high-risk accrued in this study also enabled us to address the role of rare subgroups such as patients with monosomal karyotype within the whole cohort of cytogenetically high-risk patients. In both univariable and multivariable analyses, monosomal karyotype was confirmed as a factor conferring the worst outcome in the control group.[18,19] Surprisingly, monosomal karyotype was overcome as a prognostic factor in patients undergoing allogeneic HCT in CR1.

The main weaknesses of our conclusions depend on the fact that they were not derived from a randomized controlled trial specifically designed to address our key question. In consequence, imbalances of, for example, age groups or AML phenotypes and a remaining uncertainty of potential donor availability in the control group (the main limitation of all donor *versus* no donor comparisons) are also potential limitations of our study. On the other hand, randomized trials are unlikely to be feasible because of the rareness of the subentity under investigation and may even be of ethical concern. With these considerations in mind, it appears appropriate to conclude that allogeneic HCT in cytogenetically defined high-risk patients, with or without a monosomal karyotype, in CR1 who are eligible for a transplant and have a suitable donor is the current standard of care in first-line post-remission treatment. Our analyses further highlight the need to agree on standards on how to develop high-level evidence treatment guidelines for rare subentities.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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References

1. Schoch C, Kern W, Schnittger S, Buchner T, Hiddemann W, Haferlach T. The influence of age on prognosis of de novo acute myeloid leukemia differs according to cytogenetic subgroups. Haematologica. 2004; 89(9):1082-90.
2. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-74.
3. Byrd JC, Mrozek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002;100(13):4325-36.
4. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. 1998;92(7):2322-33.
5. Mrozek K, Heerema NA, Bloomfield CD. Cytogenetics in acute leukemia. Blood Rev. 2004;18(2):115-36.
6. Thiede C, Steudel C, Mohr B, Schaich M, Schakel U, Platzbecker U, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood. 2002;99(12):4326-35.
7. Schlenk RF, Dohner K, Krauter J, Frohling S, Corbacioglu A, Bullinger L, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008;358(18):1909-18.
8. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. 2000;96 (13):4075-83.
9. Cornelissen JJ, van Putten WL, Verdonck LF, Theobald M, Jacky E, Daenen SM, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood. 2007;109(9):3658-66.
10. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009;301 (22):2349-61.
11. Basara N, Schulze A, Wedding U, Mohren M, Gerhardt A, Junghanss C, et al. Early related or unrelated haematopoietic cell transplantation results in higher overall survival and leukaemia-free survival compared with conventional chemotherapy in high-risk acute myeloid leukaemia patients in first complete remission. Leukemia. 2009; 23(4):635-40.
12. Krauter J, Wagner K, Schafer I, Marschalek R, Meyer C, Heil G, et al. Prognostic factors in adult patients up to 60 years old with acute myeloid leukemia and translocations of chromosome band 11q23: individual patient data-based meta-analysis of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol. 2009;27(18):3000-6.
13. Lodewyck T, Cornelissen JJ. Allogeneic stem cell transplantation in acute myeloid leukemia: a risk-adapted approach. Blood Rev. 2008;22(6):293-302.
14. Messner HA. How good is allogeneic transplantation for high-risk patients with AML? Best Pract Res Clin Haematol. 2006;19(2):329-32.
15. Schlenk RF, Dohner K, Mack S, Stoppel M, Kiraly F, Gotze K, et al. Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian Trial AMLHD98A. J Clin Oncol. 2010;28(30): 4642-8.
16. Buchner T, Berdel WE, Haferlach C, Haferlach T, Schnittger S, Muller-Tidow C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative

Group. J Clin Oncol. 2009;27(1):61-9.
17. Buchner T, Berdel WE, Schoch C, Haferlach T, Serve HL, Kienast J, et al. Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia. J Clin Oncol. 2006;24 (16):2480-9.
18. Breems DA, Van Putten WL, Huijgens PC, Ossenkoppele GJ, Verhoef GE, Verdonck LF, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol. 2005;23(9):1969-78.
19. Medeiros BC, Othus M, Fang M, Roulston D, Appelbaum FR. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the Southwest Oncology Group experience. Blood. 2010;116(13):2224-28.
20. Sorror ML, Storer B, Storb RF. Validation of the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) in single and multiple institutions: limitations and inferences. Biol Blood Marrow Transplant. 2009;15(6):757-8.
21. Lee SJ, Klein J, Haagenson M, Baxter-Lowe LA, Confer DL, Eapen M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007;110 (13):4576-83.
22. Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006;108(3):836-46.
23. Schmid C, Schleuning M, Ledderose G, Tischer J, Kolb HJ. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. J Clin Oncol. 2005;23(24):5675-87.
24. Appelbaum FR. Hematopoietic cell transplantation from unrelated donors for treatment of patients with acute myeloid leukemia in first complete remission. Best Pract Res Clin Haematol. 2007;20(1):67-75.
25. Stelljes M, Bornhauser M, Kroger M, Beyer J, Sauerland MC, Heinecke A, et al. Conditioning with 8-Gy total body irradiation and fludarabine for allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia. Blood. 2005;106 (9):3314-21.
26. Platzbecker U, Thiede C, Fussel M, Geissler G, Illmer T, Mohr B, et al. Reduced intensity conditioning allows for up-front allogeneic hematopoietic stem cell transplantation after cytoreductive induction therapy in newly-diagnosed high-risk acute myeloid leukemia. Leukemia. 2006;20(4): 707-14.
27. Schetelig J, Bornhauser M, Schmid C, Hertenstein B, Schwerdtfeger R, Martin H, et al. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: a report from the cooperative German Transplant Study Group. J Clin Oncol. 2008;26(32):5183-91.
28. Appelbaum FR, Clift RA, Buckner CD, Stewart P, Storb R, Sullivan KM, et al. Allogeneic marrow transplantation for acute nonlymphoblastic leukemia after first relapse. Blood. 1983;61(5):949-53.
29. Blume KG, Beutler E, Bross KJ, Chillar RK, Ellington OB, Fahey JL, et al. Bone-marrow ablation and allogeneic marrow transplantation in acute leukemia. N Engl J Med. 1980;302(19):1041-6.
30. Rowe JM, Tallman MS. How I treat acute myeloid leukemia. Blood. 2010;116(17): 3147-56.