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Prognostic factors of patients with acute myeloid leukemia (AML) allografted in first complete remission: an analysis of the EORTC-GIMEMA AML 8A trial

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Summary:

The Leukemia Cooperative Groups of the EORTC and the GIMEMA conducted a prospective randomized phase III trial, in order to assess the value of autologous BMT (ABMT) *vs* a second intensive consolidation course (IC2), following a common intensive consolidation course (IC1) for patients with AML. Patients with an HLA-identical sibling donor were not randomized, but were included in an allogeneic BMT (alloBMT) program. This is an analysis of prognostic factors which influence the outcome of treatment after alloBMT in first complete remission (CR). The study included 730 patients <46 years of age in CR, 270 having a histocompatible sibling donor. In 169 of these patients alloBMT was performed in first CR. Early remitters (122 patients achieving CR with one course of treatment) had a DFS at 3 years of 67%, significantly longer than that of 44% for late remitters (47 patients achieving CR after more than one course of treatment) ($P = 0.006$). The relapse risk for early *vs* late remitters was 16 and 40% at 3 years ($P = 0.001$) and the treatment-related mortality (TRM) at 2 years was 21 *vs* 27%. Age appeared to be a prognostic factor for TRM, WBC for DFS, whereas the FAB classification was not of prognostic importance. Patients with poor risk cytogenetic abnormalities showed a trend towards a higher relapse risk. Patients transplanted shortly after achieving CR appeared to have a worse prognosis than those transplanted further into remission. Overall, the number of courses of induction therapy needed to achieve CR was the most important prognostic factor for outcome after allogeneic BMT.

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Intensification of induction chemotherapy regimens[1,2] and improvement of supportive care have significantly increased the rate of complete remission (CR) in acute myeloid leukemia (AML).[1,3–7] Thus, 60 to 80% of adult patients younger than 60 years of age achieve a CR after one to three courses of induction treatment.[3] However, with conventional consolidation and maintenance chemotherapy the duration of CR has remained relatively short, with the median remission duration ranging from 10 to 20 months in most studies and reported 5-year disease-free survival (DFS) rates of less than 25%.[3–6,8] Intensification of post remission therapy has recently resulted in DFS rates of 39%.[9] High doses of chemotherapy followed by autologous bone marrow transplantation or autologous peripheral blood stem cell infusion is gaining support with DFS at 3 years ranging from 31 to 79%.[10,11] However, due to potential reinfusion of leukemic cells and the absence of the graft-versus-leukemia effect, the relapse risk remains a concern, ranging from 29 to 52%.[10] Intensive chemoradiotherapy followed by alloBMT has resulted in long-term DFS in 45 to 60% of cases, if alloBMT is performed in first CR.[12] The reported relapse risk ranges from 12 to 44%.[13] The role of alloBMT is difficult to determine as the treatment results are biased when comparing them with that of other treatment modalities. AlloBMT for AML patients in first remission is generally restricted to patients with an HLA-identical sibling donor. Selection of patients for BMT who are in good condition occurs, excluding patients who have persistent infections or other medical complications. Bias also occurs because of the variation in interval between achieving CR and performing BMT.[4] Therefore patients who relapse rapidly are differentially excluded. The results obtained by alloBMT, when performed during first CR, are mainly due to the activity of combined high-dose cyclopho-

sphamide and supralethal total body irradiation (TBI).[14] AlloBMT may also confer an immunologically mediated graft-versus-leukemia effect.[12,15] The major reasons for failure following alloBMT are toxicities related to the transplant procedure itself,[14] such as graft-versus-host disease, interstitial pneumonia and other infections.[12] Approximately 20% of patients die from transplant-related complications within 6 months. The incidence of transplant-related complications increases with advancing age and most centers do not perform BMTs in patients who are more than 45 years of age.[12]

Several factors such as age, peripheral WBC, French–American–British (FAB) classification and cytogenetic abnormalities have been described as prognostic factors in AML.[13,16–19] However, these factors are often not independent, but interrelated and reproducibility between studies has been low due to heterogeneity of the studies. The importance of these factors is therefore unclear. The objective of this analysis was to identify factors present at diagnosis which are of prognostic importance for the relapse risk, treatment-related mortality (TRM) and disease-free survival (DFS) after allogeneic bone marrow transplantation in first complete remission. The aim was to evaluate whether known prognostic factors for achieving CR (WBC, FAB, age, cytogenetics) are still of prognostic value after alloBMT. In other words, the aim was to analyze whether bone marrow transplantation has any influence on factors which were initially of prognostic importance. The second aim was to investigate those factors related to the responsiveness of patients to chemotherapy, for instance, the time between diagnosis and the assessment of CR or the number of courses to reach CR, and also the interval between CR and alloBMT. What was the outcome of those patients transplanted rapidly after achieving CR, without full hematological and clinical recovery? The third objective was to explore the influence of treatment-related factors such as conditioning regimen and prevention of graft-versus-host disease (GVHD).

The AML 8A protocol of the EORTC Leukemia Cooperative Group in collaboration with GIMEMA was the first prospective study comparing alloBMT with ABMT and intensive consolidation chemotherapy. More than 1000 patients have been prospectively registered in this study. A comparison of the three treatment options has recently been published.[20]

Patients and methods

Study design

The AML 8A was a prospective trial conducted between November 1986 and April 1993 by the EORTC LCG and GIMEMA, involving 60 European centers.

Entry criteria

Patients with untreated newly diagnosed AML, with ⩾30% blast cells in bone marrow smears, aged between 10 and 45 years old were included in the study. Blast crises of chronic myeloid leukemia and leukemias arising after other myeloproliferative diseases or myelodysplastic disorders of more than 6 months duration were ineligible. Patients with severe heart, renal, hepatic or neurological concomitant disease were excluded. All patients were informed of the treatment and the involved risks, and gave their formal consent.

Methods

Patients were registered at diagnosis and induction treatment was subsequently given. The induction regimen consisted of daunorubicin (DNR): 45 mg/m^2 on days 1, 2 and 3, i.v. push injection; Ara-C: 200 mg/m^2 continuous i.v. infusion each day from days 1 to 7.

Evaluation of response was done at 4 weeks. In cases of partial remission a second induction cycle was administered whereas resistant cases received salvage therapy which was given outside the protocol and consisted mainly of high-dose Ara-C and m-AMSA or the MEC regimen (mitoxantrone, etoposide and Ara-C).

Patients entering CR after one or two courses of induction therapy received a first intensive consolidation course, 4 weeks after the beginning of the (last) induction course. Intensive consolidation consisted of: Ara-C 500 mg/m^2 by a 2-h i.v. infusion, every 12 h for 6 days and of amsacrine (AMSA) 120 mg/m^2 intravenously, on days 5, 6 and 7.

CR was confirmed by blood and BM examination 3 weeks after the end of this consolidation course. At that time, where there was an HLA-A and B identical sibling the MLC was performed, followed eventually by an alloBMT. This can be considered as a randomization by genetic chance. Patients not elected for alloBMT, with confirmed CR were randomized for either a second intensive consolidation or for autologous BMT.

The conditioning regimen for alloBMT was left to the discretion of the clinician and consisted of cyclophosphamide 60 mg/kg/day on 2 consecutive days and total body irradiation, either 9–10 Gy in a single fraction or 12 Gy in four to six fractions over 2 or 3 days, with lung blocks after 6, 8 or 10 Gy, respectively. Alternately, in 31% of alloBMT patients the conditioning regimen consisted of a combination of busulfan 4 mg/kg/day on days −6 to −3 and cyclophosphamide 60 mg/kg/day on days −2 and −1. Prophylaxis for GVHD following alloBMT consisted of cyclosporin A alone (37%), cyclosporin A and methotrexate (50%) and other (2%). Eleven percent of the patients received no treatment for the prevention of GVHD. T cell depletion of the transplant before reinfusion was performed in 24 patients (17%), mainly by counterflow elutriation or with Campath-1-G.

Some centers from the GIMEMA group excluded their promyelocytic (M3) acute leukemia patients, and gave treatment with protocols specific for this subtype of AML.

Statistical analysis

The DFS was calculated from the date of alloBMT until the date of first relapse or date of death in first CR. For the calculation of the cumulative risk of relapse over time, the same type of analysis as for DFS was made, except for patients who died in first CR, who were censored at time of death. Treatment-related mortality (TRM) was calculated

from the date of alloBMT until the date of death in first CR (date of relapse = censored observation). The duration of survival corresponds to the time from alloBMT to the date of death.

Actuarial curves were calculated according to the Kaplan–Meier technique.[21] The standard error (s.e.) was calculated according to the Greenwood formula.[22] The Kaplan–Meier estimate at 3 years ± 1.96 s.e. generally represents the 95% confidence interval. The differences between curves were tested for statistical significance using the two-tailed logrank test.[23] In cases of ordered variables, the logrank test for linear trend was used. The stratified logrank test has been used to test for relative prognostic importance of one variable regarding another one (eg white blood cell count according to the number of courses of induction therapy to achieve a complete remission). The relative risk (RR) of having an event per time unit in one category of patients *vs* another one ('baseline' category) was estimated using the O/E ratio technique;[24] the 95% confidence interval of the RR was computed for two categorical variables using the odds-ratio technique.[24]

Results

Patient characteristics

Nine hundred and fifty-two newly diagnosed, untreated patients, less than 46 years of age, were registered in the study. The median age was 32 years (range: 11 to 45), 51% of the patients were male, 49% female. The distribution of FAB types was as follows: M1, 16%; M2, 33%; M3, 6%; M4, 20%; M5, 19%; M6, 4%; M7, 1%; unknown, 1%. The median white blood cell count was 16.6×10^9/l (range: 0.20 to 376.0×10^9/l). Out of 952 patients registered 31 patients were either ineligible or inevaluable, because of inadequate diagnosis or missing data.

Remission-induction therapy

All 921 eligible and evaluable patients, less than 46 years old, were treated according to the protocol with remission-induction therapy. Five hundred and two patients achieved complete remission (CR) after one course (55%). In addition, 110 patients achieved CR after a second course of remission-induction therapy (12%) and 118 after one or two courses of salvage therapy. Altogether, 730 out of 921 patients achieved complete remission (79%).

Ninety-three percent of patients achieving CR after one or two induction courses received a first intensive consolidation course. This information is not available for the patients who were given salvage therapy. The overall DFS at 3 years for the 730 patients achieving CR was 37% (s.e. = 1.9%).

Donor availability and allogeneic bone marrow transplantation

Family HLA-typing was reported in 650 patients (89%) of the 730 patients included in the analysis. Two hundred and seventy patients had an HLA-identical sibling donor and 380 did not. One hundred and ninety-nine patients with a histocompatible sibling eventually underwent transplantation. Reasons for not performing alloBMT were: refusal by patient or donor, patient lost to follow-up, toxic or early death, relapse before alloBMT, medical decisions and toxicity of treatment (Table 1).

One hundred and seventy patients were transplanted in first complete remission and 29 at another stage of the disease.

Description of patients allografted in first CR

The median age of patients allografted in first complete remission was 32 years (range: 13–45, mean 31.25), 54% were male and 46% female. The distribution of FAB types was: M1, 14%; M2, 42%; M3, 5%; M4, 20%; M5, 15%; M6, 2%; unknown, 2%. The median white blood cell count at diagnosis was 13.7 x 10^9/l (range: 0.40 to 360.0×10^9/l). The mean time from diagnosis to complete remission was 42 days (range: 20 to 137 days; median: 32 days) and the mean time from CR to allogeneic bone marrow transplantation was 116 days (range, 4 to 338 days; median, 106 days).

Overall results

The date of alloBMT was missing for one patient, so this patient was excluded from the analysis. Median follow-up from alloBMT for the 169 patients transplanted in first CR was 3 years and 5 months (range, 3–89 months). The disease-free survival at 3 years for these patients was 60% (s.e. = 3.9%) and the relapse risk 23% (s.e. = 3.7%). The treatment-related mortality at 2 years was 22% (s.e.= 3.4%) (Figure 1). In fact 35 patients have died in first CR, all but five within 6 months of transplantation. The cause of death for these patients is: interstitial pneumonitis (seven patients), other infections (nine patients), hemorrhage (three patients), GVHD (nine patients), liver veno-occlusive disease (one patient), cardiovascular disease (one patient), other toxicities (three patients) and other causes (two patients).

Number of courses and time to achieve first complete remission

Patients were divided into early and late remitters. Early remitters were the 122 patients who achieved CR after one

Table 1 Reasons for not performing alloBMT in patients with a histocompatible sibling donor

Reason	*No.*
Refusal	19
Lost to follow-up	2
Toxic/early death	7
Early relapse	15
Medical decision	6
Toxicity	17
Unknown	5
Total	71

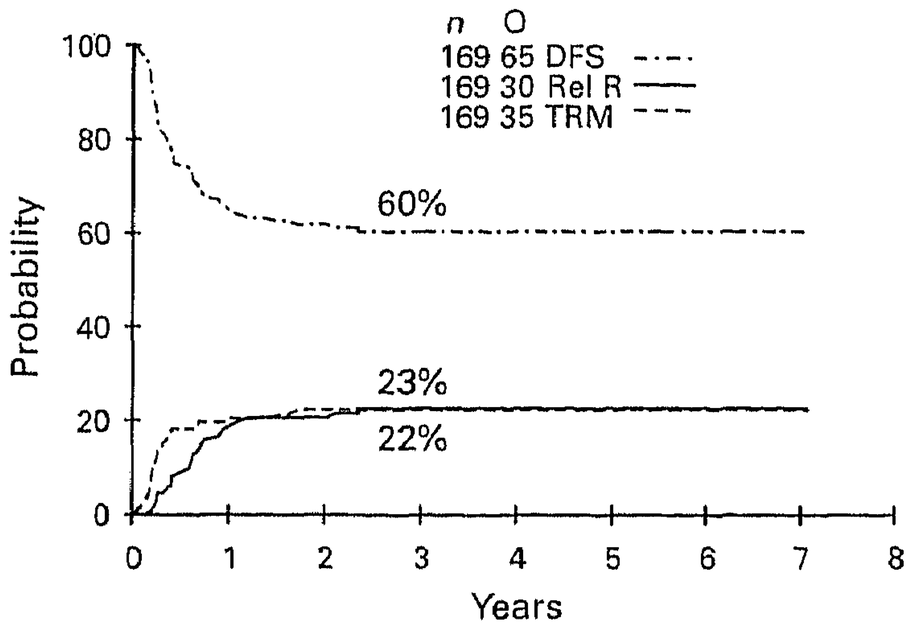

Figure 1 Overall results from BMT. *n* = number of patients; O = observed number of 'events'; Rel R = cumulative relapse risk; TRM = treatment-related mortality (cumulative probability of dying in first CR); disease-free survival = probability of remaining alive in first CR.

course of remission-induction treatment. Late remitters were the remaining 47 patients who needed more courses of remission-induction or salvage treatment to achieve CR. At 3 years there were still 49 early remitters and 10 late remitters at risk. Table 2 shows the results for patients, according to the number of courses to achieve CR (early and late remitters), as well as according to the time taken to achieve CR (<5 weeks, 5–9 weeks, ⩾10 weeks). Early remitters had a significantly longer DFS (Figure 2) (RR, 2.2; 95% confidence interval 1.26–3.87) and a significantly lower relapse risk (Figure 3) compared to late remitters. In fact, the relative risk for the relapse risk for late remitters is 3.97, which means that the chance of them having a relapse per time-unit is 3.97 times higher than that of early remitters (95% confidence interval 1.73–9.13). However, the TRM at 2 years was essentially the same for both groups of patients (RR, 1.35; 95% confidence interval 0.63–2.89). Similarly, patients who achieved complete remission within 5 weeks had a significantly longer DFS and significantly lower relapse risk than patients who needed more than 5 and more than 10 weeks (DFS at 3 years: 66, 57 and 39% respectively, $P = 0.02$ for linear trend; relapse risk at 3 years: 83, 74 and 59 respectively, $P = 0.01$ for linear trend).

Interval between CR and alloBMT

Patients allografted quickly (within 8 weeks) after achieving CR had a shorter DFS at 3 years post-transplant, compared to patients allografted after 8, 16 and 24 weeks of complete remission, but this difference was not significant (Table 2). The relapse risk observed at 3 years and TRM 2 years post-BMT were also not significantly different. When comparing patients transplanted within 8 weeks of achieving complete remission to all patients transplanted after 8 weeks of CR, the differences in DFS and TRM do reach a significant level (DFS, $P = 0.003$, TRM, $P = 0.005$). The DFS (31%) was shorter in those patients who were allografted within 8 weeks after achieving CR. Among the 13 patients in this group, three relapses were reported and six deaths in CR. The group of patients transplanted within 8 weeks of achieving CR included a higher percentage (46%) of late responders in comparison to those transplanted more than 8 weeks after achieving CR (26% late responders).

Age

The DFS at 3 years after BMT was 70% for patients younger than 26 years. This was longer than the DFS of 59% of patients between 26 and 35 years of age or 55% of patients older than 35 years of age, but the differences were not significant (Table 2). The relapse risks of the three different age groups were also not significantly different. Patients between 36 and 45 years of age had a higher TRM at 3 years than younger patients (36–45 years, 33%; 26–35 years, 18%; ⩽25 years, 13%; $P = 0.02$). For the older patient group the risk of dying per time-unit in first CR is 2.87 times higher than that of patients less than 26 years of age.

Cytogenetic data

Patients were categorized according to cytogenetic abnormalities.[16] Good prognostic cytogenetic abnormalities were considered to be t(8;21), t(15;17) and inv16. Patients with normal metaphases and –Y were considered to have an intermediate prognosis. Poor prognostic cytogenetic abnormalities were trisomy 8, 5q–, monosomy 5 and 7 and all other cytogenetic abnormalities, including complex abnormalities. Analysis of cytogenetics at diagnosis was performed in 61 patients allografted in first CR. Among these patients, 11 relapses have been reported and 17 patients died in first CR. There was a trend to a higher relapse risk at 3 years for patients with poor prognostic cytogenetic abnormalities, compared to good and intermediate groups (poor, 43%; intermediate, 21%; and good, 8%), but due to the low number of relapses observed this difference only reached borderline significance ($P = 0.06$). The TRM at 2 years was similar in the three groups (good, 26%; intermediate, 32%; poor, 33% at 3 years, $P = 0.98$) (Table 2).

WBC

The WBC ($\times 10^9$/l) at diagnosis appeared to be not only of prognostic value (see Table 2) for the duration of remission ($P = 0.07$), but also for the TRM ($P = 0.03$). There was a strong relationship between the WBC and DFS ($P = 0.005$), ie the higher the WBC, the worse the prognosis at 3 years (<10, 74%; 10–49, 54%; ⩾50, 47%). In a bivariate analysis, the prognostic importance of the WBC was tested according to the number of courses of remission-induction treatment needed to achieve CR. The WBC remained an independent prognostic factor for TRM ($P = 0.03$) and DFS ($P = 0.01$).

FAB classification

The FAB classification, when evaluating each subgroup separately, had no significant predictive value for outcome post-BMT in this analysis (Table 2). When comparing FAB M4 and M5 *vs* the other FAB subgroups no significant difference was found in terms of DFS, TRM or relapse risk. Thirteen events occurred among the 60 patients with M4

Table 2 Prognostic factor analysis for patients who have been allografted in first CR

Variable	*n*	*Relapse risk*				*TRM*				*DFS*			
		O	*Est (%)*	*s.e. (%)*	*P value*	*O*	*Est (%)*	*s.e. (%)*	*P value*	*O*	*Est (%)*	*s.e. (%)*	*P value*
CR achieved													
1 induction	122	15	16	3.8		24	21	3.8		39	67	4.4	
>1 induction	47	15	40	8.1	0.001	11	27	7.4	0.44	26	44	7.4	0.006
Time to CR (weeks):													
0–4	100	13	17	4.4		19	20	4.2		32	66	4.9	
5–9	49	10	26	7.2	0.01	11	23	6.0	0.38	21	57	7.1	0.02
≥10	20	7	41	11.9		5	33	13.1		12	39	11.1	
Interval CR and BMT (weeks):													
0.6–7	13	3	42	18.6		6	47	14.1		9	31	12.8	
8–15	81	15	23	5.2	0.22	16	22	4.9	0.15	31	61	5.6	0.06
16–23	55	9	21	6.3		8	16	5.2		17	67	6.7	
≥24	20	3	20	10.3		5	25	9.7		8	60	11.0	
Age (years):													
≤25	43	7	19	6.4		5	13	5.7		12	70	7.2	
26–35	67	15	28	6.2	0.87	12	18	4.8	0.02	27	59	6.1	0.11
36–45	59	8	19	6.1		18	33	6.4		26	55	6.6	
Cytogenetic group:													
Good	16	1	8	7.4		4	26	11.0		5	69	11.6	
Intermediate	26	4	21	9.7	0.06	8	32	9.5	0.98	12	53	9.9	0.22
Poor	19	6	43	13.7		5	33	12.5		11	38	11.7	
WBC ($\times 10^9$/l):													
0–9	68	9	16	5.0		8	13	4.2		17	74	5.6	
10–49	67	13	25	6.1	0.07	17	27	5.8	0.03	30	54	6.2	0.005
≥50	34	8	33	9.6		9	30	8.6		17	47	8.9	
FAB:													
M1	24	3	15	8.1		5	22	8.9		8	66	9.8	
M2	70	14	26	6.0		14	22	5.2		28	58	6.1	
M3	9	0	0	—	0.52[a]	1	11	10.5	0.83[a]	1	89	10.5	0.66[a]
M4	34	6	28	10.1		9	26	7.6		15	53	9.2	
M5	26	7	31	9.7		4	19	8.8		11	56	10.0	
M6	3	0	0	—		1	33	27.2		1	67	27.2	
Total	169	30	23	3.7		35	22	3.4		65	60	3.9	

N = total number of patients; O = observed number of 'events'; Est = actuarial estimation at 3 years; s.e. = standard error of the estimate; P-value = given by the logrank test (for linear trend, in case of ordered variables); DFS = disease-free survival (probability to remain alive and disease-free); TRM = treatment-related mortality (the estimate and standard error are taken at 2 years post-BMT as all deaths in CR occur during the first 2 years. The estimate and standard error will not change after this time and therefore the timepoint at 2 years is more accurate)
[a]The *P* value for FAB classification is given, but as there are so many subgroups being compared, the chance of the *P* value being significant is extremely small

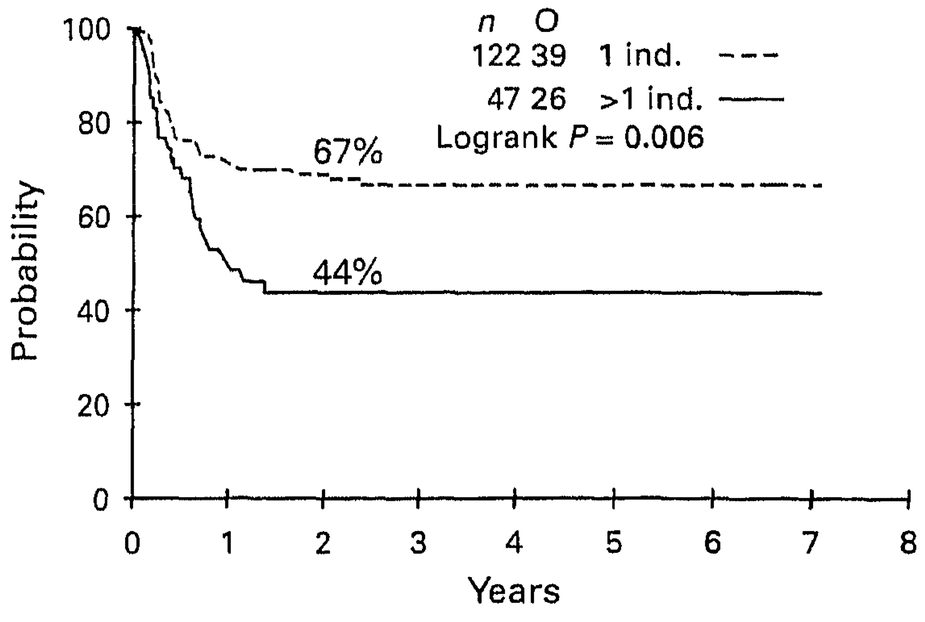

Figure 2 DFS from BMT by number of courses to reach CR. *n* = number of patients; O = observed number of 'events' (ie relapses or deaths in first CR); disease-free survival = probability of remaining alive in first CR; 1 ind = 1 induction course needed to reach CR; >1 ind = >1 induction course needed to reach CR.

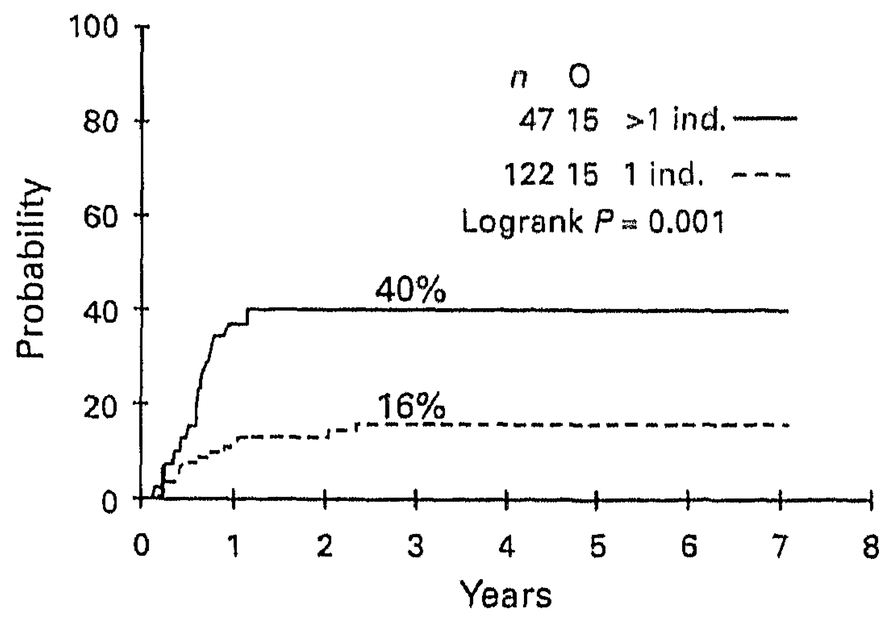

Figure 3 Cumulative relapse risk from BMT by number of courses to reach CR. *n* = number of patients; O = observed number of relapses; 1 ind = 1 induction course needed to reach CR; >1 ind = >1 induction course needed to reach CR.

or M5 sub-types and 21 events among the 109 patients with other FAB sub-types.

Treatment-related factors

Several factors which were treatment-related were investigated for exploratory purposes. These factors were not standardized in the protocol and were left to the discretion of the clinician. The results given were descriptive and no conclusions can be drawn from them; they call for confirmation by randomized trials.

Conditioning regimen

Patients received cyclophosphamide either in combination with total body irradiation (TBI) or busulfan. The TBI could be given as a single fraction or fractionated over 2 or 3 days. Fifty-six patients received the regimen containing busulfan and 105 were given TBI. Twenty patients received TBI in one fraction, 45 received TBI in two or three fractions and 40 patients received TBI in more than three fractions. The remaining eight patients received a different conditioning regimen using several types of chemotherapy. The relapse risk at 3 years ranged from 32% for TBI given in a single fraction to 12% for TBI in more than three fractions and was 26% for patients receiving busulfan. The TRM at 2 years varied from 40% for TBI given in a single fraction to 18% for TBI given in two or three fractions and was 15% for patients receiving busulfan. The DFS at 3 years was 41% for TBI given in a single fraction, 63% when given in two or three fractions, 70% for TBI given in more than three fractions and was 63% for the patients receiving busulfan.

Prevention of GVHD

Nineteen patients received no form of treatment for the prevention of GVHD, 62 patients received cyclosporin A alone and 85 patients received a combination of cyclosporin A and methotrexate. The remaining three patients received other treatments for the prevention of GVHD. The relapse risk at 3 years ranged from 17% for the combination of cyclosporin A and methotrexate to 28% for cyclosporin A alone. The TRM at 2 years varied from 16 to 29% and the DFS at 3 years from 52 to 69%.

T cell depletion

Twenty-eight of the allografts were treated with T cell depletion. The relapse risk at 3 years was 37% for these allografts compared to 20% for non-T cell depleted allografts. The TRM at 2 years was 30 and 21% respectively, the DFS at 3 years 44 and 64% respectively.

Discussion

The AML 8A study of the Leukemia Cooperative Groups of the EORTC and GIMEMA was undertaken to assess prospectively the role of intensive post-consolidation chemotherapy, allogeneic and autologous bone marrow transplantation following CR in the treatment of AML. The patients registered at diagnosis represented a standard population of patients with AML. The proportion of patients who entered first CR was comparable with results of large chemotherapy trials.[4,25] In this analysis we assessed prognostic factors of patients allografted in CR1 within the framework of the AML 8A study. An allograft in first CR was performed in only 170 (63%) of the 270 patients with a histocompatible sibling. Twenty-nine patients were allografted at a later stage of the disease. This means that 74% of patients with an HLA-identical sibling donor actually received alloBMT. The remaining patients who did not receive an alloBMT had either a poor prognosis, eg toxic or early death, early relapse (18%) or refused treatment (8%).

Out of 170 patients who were transplanted in first complete remission the data were available for 169 patients. At the time of the analysis, 1 June 1995, the median follow-up from alloBMT was 3 years and 5 months (range: 3–89 months). The DFS of these 169 patients was 60% at 3 years after BMT. This is comparable to the results observed in other studies.[26] The DFS appeared significantly longer for patients who entered CR after one course of chemotherapy than for patients who needed more than one course. The relapse risk was significantly higher for these slow remitters, but the TRM was virtually identical for both groups of patients. One could expect that patients who required more chemotherapy to reach CR would respond more poorly to the intensive conditioning regimen for transplantation, resulting in a higher TRM. This did not appear to be the case. The lower DFS was due to the higher relapse risk. The actual time taken to achieve CR corresponded to the number of courses of remission-induction treatment needed to achieve CR. For this reason the majority of patients who achieved CR within 5 weeks appeared to have a longer disease-free survival than the patients who achieved CR more than 5 weeks after starting chemotherapy. The higher relapse risk in the latter group of patients was responsible for this difference. Forman *et al*[26] evaluated only 69 patients who were allografted in first complete remission. They concluded that length of remission-induction therapy had no significant influence on the survival of the patient post-transplant. In most other analyses the length of remission-induction therapy was not taken into account.[27,28] Patients transplanted shortly after achieving CR (<8 weeks) appeared to have a worse prognosis than those patients transplanted further into remission, mainly due to a higher risk of relapse and a higher transplant-related mortality. This could be due to the fact that these patients might have relapsed before the transplant, had they waited longer for the allograft. Patients transplanted within 8 weeks also needed more intensive chemotherapy to achieve CR (46% late responders). These patients did not have the opportunity to recover completely before the allograft, resulting in a higher death rate in first CR. The relapse risk and the transplant-related mortality did not decrease further when the transplant was performed more than 8 weeks after achieving CR. This suggests that at least in this study a further delay of the allograft beyond 8 weeks after entering CR did not select out a better prognostic group of patients. It is still unclear when the bone marrow transplant should take place. Randomized trials may answer this question.

The MRC, in their AML 12 trial is currently randomizing patients into four treatment procedures: four or five courses of chemotherapy or three or four courses of chemotherapy followed by allogeneic or autologous BMT.

The potentially higher antileukemic activity of allogeneic BMT is counterbalanced by a higher incidence of treatment-related toxicities, such as severe GVHD, interstitial pneumonitis, infectious complications and veno-occlusive liver disease. This analysis showed that the treatment-related mortality at 2 years was 20% overall. Patients under the age of 25 years had a TRM of 13% and patients below the age of 35 years had a TRM of 18% which compared favorably with the TRM of 33% in patients 36 to 45 years old. This indicates that the alloBMT may be deferred to a later time, after a relapse, in patients older than 35 years of age who have AML with relatively good prognostic features such as CR after one remission-induction course and favorable cytogenetic features. When the results according to number of courses to reach CR are stratified by age, early remitters in each age group still have a high TRM and low relapse risk compared to late remitters. This means that when transplanting early remitters, more should be done to decrease the treatment-related mortality. In several prospective randomized trials, such as MRC 12 at least three courses are given prior to the alloBMT. The data from this analysis suggest that one intensive consolidation course is sufficient to reduce relapse after alloBMT to 13% if CR is reached after one remission-induction course. More consolidation courses are not likely to increase DFS after alloBMT. When transplanting late remitters, treatment should be intensified in order to decrease the relapse risk post-BMT. Results from several transplant teams[28,29] do suggest that age of the patient has a significant influence on the prognosis, but this finding is not consistent, probably depending on the size of the study group, selection of the patients or the intensity of the chemotherapy prior to the allograft.[26,27]

Cytogenetic results according to the Keating criteria seem to show a correlation with the relapse risk (8% at 3 years for the good prognostic group and 43% for the poor prognostic group), but too few patients have been karyotyped in this study and therefore, probably due to low statistical power, the observed trend was of borderline significance.

Our results confirm that the white blood cell count at diagnosis is a prognostic factor for disease-free survival, as described by Bostrom *et al,*[27] who evaluated 39 patients with AML who were allografted in first complete remission. In our analysis, a high WBC at diagnosis was a poor prognostic factor for patients with AML allografted in first CR. This was also seen in the overall analysis of the AML 8A study.[20]

In contrast to data of the European Bone Marrow Transplantation Registry[13] and also of Bostrom *et al,*[27] our results showed no increase in relapse risk for patients with FAB M4 or M5. Nor was there any significant difference in disease-free survival, when comparing all FAB subtypes. However, only nine patients in our analysis had FAB subtype M3, as these patients were usually treated with all-*trans* retinoic acid (ATRA) and chemotherapy protocols. FAB subtype M3 is prognostically favorable. This might explain the fact that no difference in DFS was found between the remaining FAB subtypes.

Treatment-related factors such as conditioning regimen might influence the survival parameters post-BMT. Ringdén *et al*[30] randomized 167 patients with leukemia, receiving marrow transplants from HLA-identical donors, between cyclophosphamide with either busulfan or total body irradiation (TBI) as conditioning regimen. They found a higher treatment-related mortality in patients with advanced disease treated with busulfan, but no difference concerning the relapse risk post-BMT. Other investigators have reported retrospective evaluations on single *vs* fractionated TBI,[19,26] but no significant differences in treatment outcome were detected. In this analysis, as in the overall analysis of the AML 8A study,[20] no significant differences between the various conditioning regimens were found. However, such treatments were left to the discretion of the local investigators, which means that such analyses are subject to bias, and one should not draw any conclusions from them.

Chao *et al*[31] randomized 150 patients with hematological malignancies being allografted with genotypically histocompatible bone marrow between treatment with either a combination of cyclosporine, methotrexate and prednisone or cyclosporine with prednisone alone. They found the combination including methotrexate to be more effective in the prevention of acute GVHD of grades II to IV, than the combination of cyclosporine and prednisone. In the overall analysis of the AML 8A study an almost significant difference in terms of DFS was found in favor of the combination cyclosporine and methotrexate *vs* cyclosporine alone, but here no prednisone was given. In this analysis no significant differences in the treatment for the prevention of GVHD were found. Once again, these treatments were left to the discretion of the local investigator, so no conclusions can be drawn from them.

In our series, a relative low number of relapses has been observed: 30 in total. For this reason a limited number of factors have been considered in this analysis, in order to maintain the false-positive error at an acceptable level. On the other hand, a low number of events implies that only very important prognostic factors may be detected, as the statistical power is only sufficiently high for such factors to yield significant or almost significant results (eg WBC, cytogenetics). Confidence intervals were also quite large due to the low number of events, but other series may reinforce the findings. The uncertainty of results may be due to the heterogeneity of 'treatment-related factors', which may influence the generalizability of our results to other series, where the treatment modalities (GVHD prevention etc) were different, or had been used differently. Our results came from transplantation teams (participating in the AML 8A study) of the EORTC LCG and GIMEMA, which may be a representative sample of transplant centers in Europe. There is definitely a strong need to implement the methods of randomized trials in the field of BMT, in order to evaluate properly important questions including TBI *vs* no TBI, the number of fractions in which to deliver TBI and T cell depletion or not.

AlloBMT is a treatment where only a minority of patients may benefit. In this series 30% of the patients had an

HLA-identical sibling donor. Sixty percent of these patients were actually allografted. This means that only 18% of patients were allografted and 11% of patients are long-term disease-free survivors after alloBMT.

The aim of this analysis was to identify factors, present at diagnosis or therapy-related, which are of prognostic importance after allogeneic bone marrow transplantation in patients, less than 46 years of age, with newly diagnosed acute myeloid leukemia. The number of courses of remission-induction treatment to achieve CR and the time taken to reach CR have a significant influence on the disease-free survival of the patient post-alloBMT. The relatively high relapse risk in patients who needed more time and chemotherapy courses to achieve CR warrants the use of a more intensified conditioning regimen prior to the allogeneic BMT. This may also apply for those patients who have poor prognostic cytogenetic abnormalities. Age was found to be a prognostic factor for treatment-related mortality. Only analysis of prospectively registered patients can evaluate treatment modalities such as allogeneic bone marrow transplantation. Prospective randomized trials are extremely useful for this approach.

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Appendix

The following centers and investigators from the EORTC Leukemia Cooperative Group participated in this study: *Austria*: Innsbruck, Universitätsklinik (J Thaler); *Belgium*: Antwerpen, University of Antwerpen (ME Peetermans); Brugge, Hôpital St Jan (A Louwagie); Bruxelles, Institut Bordet (P Stryckmans), Hôpital Saint Pierre (C Cauchie), and Hôpital Erasme (W Feremans); Verviers, Hôpital Civil (R Paulus); *Croatia*: Zagreb, Hospital Rebro (B Labar), Novosel School (B Jaksic); *France*: Paris, Hôtel-Dieu (RA Zittoun, A Vekhoff); Villejuif, Institut Gustave Roussy (M Hayat); *The Netherlands*: Eindhoven, Catharina Ziekenhuis (H Hillen); s'Hertogenbosch, Groot Ziekengasthuis (J Burghouts); Leiden, Leiden University (R Willemze); Nijmegen, St Radboud Hospital (T de Witte, P Muus); *Portugal*: Porto, San Joan (M Ribeiro); Turkey: Ankara, Ibnui Sina Hospital (MD Beksac). The following centers and investigators from the GIMEMA group participated in this study: *Italy*: Ancona, Università di Ancona (P Leoni); Avellino, Ospedale Civile (E Volpe); Bari, Univerità di Bari (V Liso); Bologna, Istituto LA Seragnoli (S Tura, G Visani, A Zaccaria); Cagliari, Ospedale Businco (G. Broccia); Catania, Ospedale Ferrarotto (E Cacciola); Catanzaro, Ospedale Pugliese (A Alberti); Cuneo, Ospedale S Croce (A Gallamini); Firenze, Università di Firenze (P Rossi Ferrini, F Leoni); Foggia, Ospedale Riuniti (M Monaco); Genova, Ospedale S Martino (E Damasio, R Cerri); Napoli, Università Federico II (B Rotoli), and Ospedale Cardarelli (R Cimino); Nuoro, Ospedale S Francesco (A Gabbas); Palermo, Ospedale Cervello (F Caronia), and Università di Palermo (A Cajozzo); Pavia, Policlinico S Matteo (C Bernasconi); Perugia, Università Clinica Medica (F Grignani), and Università Istituto di Ematologia (M Martelli); Pesaro, Ospedale S Salvatore (G Lucarelli); Pescara, Ospedale Civile (G Torlontano); Potenza, Ospedale S Carlo (F Ricciuti); Reggio Calabria, Ospedale Riuniti (F Nobile); Roma, II Università Tor Vergata (G Papa*, S Amadori), I Università La Sapienza (F Mandelli, W Arcese, and G Meloni), Università Cattolica del Sacro Cuore (B Bizzi), and Ospedale S Camillo (A De Laurenzi); San Giovanni Rotondo, Ospedale Casa Sollievo della Sofferenza (M Carotenuto); and Torino, Ospedale Maggiore S Giovanni Battista (L Resegotti), and Università di Torino (A Pileri).

Cytology committee: M Cadiou, M Bernier, G Den Ottolander, U Jehn, W Sizoo, GL Castoldi, S Fenu and V Liso.

Cytogenetic committee: A Hagemeijer, G Alimena, A Bernheim and A. Zaccaria.

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