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Original Paper

Centre Effect on Treatment Outcome for Patients with Untreated Acute Myelogenous Leukaemia? An Analysis of the AML 8A Study of the Leukemia Cooperative Group of the EORTC and GIMEMA

S. Keating,[1] T. de Witte,[2] S. Suciu,[1] F. Mandelli,[3] E. Damasio,[4] R. Willemze,[5] E. Morra,[6] S. Amadori,[7] M. Dardenne,[1] M.L. Vegna[3] and R.A. Zittoun[8] for the European Organization for Research and Treatment of Cancer (EORTC) Leukemia Cooperative Group and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA)*

[1]EORTC Data Center, Avenue E. Mounier, 83, Bte 11, 1200 Brussels, Belgium; [2]Department of Hematology, St Radboud University Hospital, Nijmegen, The Netherlands; [3]Department of Haematology, Università La Sapienza, Rome; [4]Department of Haematology, Ospedale San Martino, Genoa, Italy; [5]Department of Haematology, Leiden University Medical Center, Leiden, The Netherlands; [6]Department of Haematology, Ospedale Maggiore ca Granda, Milan; [7]Department of Haematology, Ospedale San Eugenio, Rome, Italy; and [8]Hôtel-Dieu, Paris, France

In the AML 8A study patients were treated with remission-induction therapy followed by one consolidation course. Patients in complete remission (CR) were randomised between autologous bone marrow transplantation (ABMT) and a second intensive consolidation course, except for those with a histocompatible sibling donor, who received allogeneic bone marrow transplantation (alloBMT). This analysis was performed to determine whether centres which only performed induction and consolidation therapy, achieved similar results as centres who also performed transplantation. 542/676 (80%) from transplantation centres and 150/194 (77%) from referring centres achieved CR, with an early death rate of 5% and 11%, respectively ($P = 0.01$). 66% of patients with a donor from transplantation centres received alloBMT in first CR compared with 57% from referring centres ($P = 0.2$). Transplantation centres randomised 64% of patients without a donor, referring centres 47% ($P = 0.04$). The full protocol treatment was completed by 275/542 (51%) and 61/150 (41%) patients, respectively ($P = 0.04$). The overall survival rate at 6 years from diagnosis was 34% and 36%, respectively ($P = 0.9$). In conclusion, the type of centre did not appear to have an influence on overall survival. The feasibility of the study was acceptable for both types of centres. The referring centres applied more selection for transplantation. Despite a more intensive second-line treatment at transplantation centres, the overall outcome remained similar to that of referring centres. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: acute myeloid leukaemia, centre effect, allogeneic bone marrow transplantation, autologous bone marrow transplantation, intensive chemotherapy, randomised clinical trials
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Correspondence to S. Keating, e-mail: skeating@worldonline.nl
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*Members of each group who participated in the study are listed in the Appendix.

INTRODUCTION

THE TREATMENT outcome for patients with acute myelogenous leukaemia (AML) is gradually improving. Many cooperative groups performing multicentre randomised trials

have reported complete remission (CR) rates ranging between 65 and 83%, and disease-free survival (DFS) rates at 5 years of 24–55% in patients less than 60 years of age [1–6]. These large randomised trials are performed by clinical research groups consisting of different types of hospitals. The results of such trials could be influenced by the diversity of centres participating. One question which arises is whether centres who do not have the facilities to perform transplantation and refer their patients for allogeneic bone marrow transplantation (alloBMT) and autologous BMT (ABMT) after performing induction and consolidation treatment themselves, achieve similar results to transplantation centres in terms of treatment outcome and feasibility. An analysis was performed within the framework of the AML 8A trial, which was conducted by the Leukemia Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) between 1986 and 1993. This multicentre, randomised phase III trial, performed at 59 different centres, assessed the value of ABMT versus a second intensive consolidation course, following induction treatment and a first common intensive consolidation course for patients with *de novo* AML. Patients with a human leucocyte antigen (HLA)-identical sibling donor were not randomised, but included in an alloBMT programme.

The aim of this analysis was to assess whether transplantation centres, having more sophisticated facilities for the treatment of AML, achieved a higher overall survival rate than referring centres, who treated patients for induction and consolidation treatment, but transferred their patients to transplantation centres for alloBMT and ABMT. Another point of interest was to determine whether there was a difference in the selection of patients for the various treatments and whether these treatments were feasible for both types of centres. It could then be determined whether multicentre trials should be performed by all types of centres or whether they should be limited to selected hospitals, with more advanced facilities.

PATIENTS AND METHODS

Study design

The AML 8A study was a randomised prospective phase III study conducted from November 1986 to December 1993 at 59 European centres. This analysis was performed in October 1998.

Entry criteria

Patients with untreated newly diagnosed AML, between 10 and 45 years of age, with no blast crisis of chronic myeloid leukaemia and no leukaemias supervening after other myeloproliferative diseases or myelodysplastic disorders of more than 6 months duration. Patients with severe heart, renal, hepatic or neurological concomitant diseases were excluded from registration. Patients were subsequently treated according to the AML 8A protocol of the EORTC/GIMEMA. All patients were informed of the treatment and the involved risks, and gave their formal consent according to the local customs.

Methods

Transplantation centres were those centres who had the facilities to perform transplantation themselves, autologous and/or allogeneic. Referring centres were centres who performed induction and consolidation (first and second) courses treatment themselves and thereafter referred the patients for transplantation to transplantation centres. Six of the 29 referring centres were able to perform ABMT themselves, but referred patients for alloBMT.

Patients were registered at diagnosis and induction treatment was subsequently given. The induction regimen consisted of daunorubicin: 45 mg/m^2 on days 1, 2 and 3, intravenous (i.v.) push injection; cytarabine: 200 mg/m^2 continuous i.v. infusion each day from day 1 to day 7. Patients entering a complete response (CR) after one or two courses of the induction regimen received a first intensive consolidation course, 4 weeks after the beginning of the (last) induction course. This intensive consolidation consisted of: cytarabine 1000 mg/m^2 by a 2-h i.v. infusion, every 12 h for 6 days and of amsacrine 120 mg/m^2 i.v. on days 5, 6 and 7. The dose of cytarabine was lowered to 500 mg/m^2 after the first year of the study due to severe gastrointestinal toxicity. CR was confirmed by blood and bone marrow examination 3 weeks after the end of this consolidation course. At that time, in case of HLA-A and -B identical sibling(s), mixed lymphocyte culture was performed, followed eventually by alloBMT. Patients not selected for alloBMT with confirmed CR, had to be randomised for either a second intensive consolidation or ABMT.

Patients randomised for a second intensive consolidation course, received high-dose cytarabine 2000 mg/m^2 over 2-h i.v. infusion, every 12 h on days 1–4 and daunorubicin 45 mg/m^2/day on days 5, 6 and 7. No haematopoietic growth factor was used.

Statistical analysis

The duration of survival corresponds to the time from diagnosis to the date of death. For patients who achieved CR, the duration of survival corresponds to the time from the date of CR to the date of death. DFS was calculated from the date of CR until the date of first relapse or date of death in first CR. Actuarial curves were calculated according to the Kaplan–Meier technique. The differences between curves were tested for statistical significance using the two-tailed log rank test [7]. Characteristics of patient groups, CR rate, resistance rate, death rate, as well as toxicities and the amount of supportive care given were compared using the χ^2 test for categorical values. For ordered variables the Wilcoxon test was used [7]. The feasibility of transplantation in the two types of centres was compared by using the χ^2 test stratified by the availability of a donor, by whether the patients were randomised or not, and the randomised treatment arm.

The main end-points for the comparison of the two types of centres were the feasibility of the transplantation and especially the duration of survival. Several other end-points were considered, ranging from the occurrence of grade 3–4 toxicities to the amount of supportive care given, and also the donor availability. However, statistical comparisons were not performed systematically, in order not to inflate the overall probability of type I (false-positive error). When the number of patients was quite low, or when important imbalances were observed between the two centre groups, no P values were calculated either.

RESULTS

This analysis included 870 patients less than 46 years of age, who were eligible and evaluable. The median follow-up

for these patients was 7.9 years (range 1–11 years). The 28 transplantation centres contributed 676 patients (78%) and the 29 referring centres 194 patients (22%). The median number of patients at transplantation centres was 22 (range 4–61) and at referring centres 5 (range 1–19). GIMEMA centres contributed 62% of the patients from transplantation centres and 77% of the patients from referring centres. The patient characteristics were similar in both transplantation and referring centres (Table 1). Cytogenetic examinations were performed more often at transplantation centres (35% versus 17%). Cytogenetic abnormalities with good risk features were t(8;21), t(15;17) and inv 16. 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, like complex abnormalities. The distribution of these risk groups was similar for the patients, for whom cytogenetic examination was performed. The overall survival rate at 6 years from diagnosis was 34% for patients from transplantation centres and 36% ($P=0.9$) for those from referring centres (Figure 1).

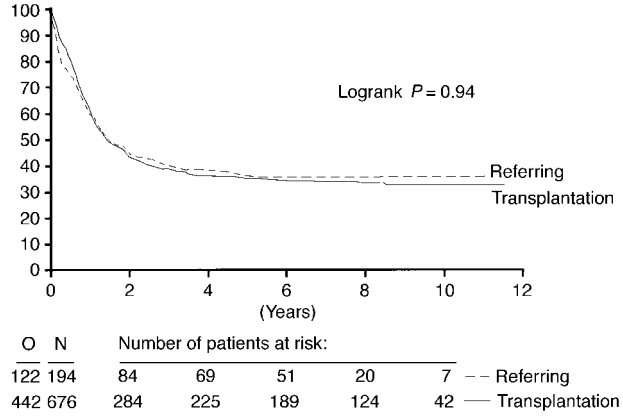

Figure 1. Overall survival from diagnosis by type of centre. N, number of patients; O, observed number of deaths.

The results of remission-induction therapy are summarised in Table 2. The overall CR rate after the first induction course was significantly higher at transplantation centres (57% versus 46%; $P=0.01$). After the second induction course, the overall CR rate was not significantly different (68% and 63%, respectively). The lower CR rate in referring centres was due to a significantly higher death rate (11% versus 5%; $P=0.01$). The majority of patients received the full dose of chemotherapy (Table 3): 89% of patients from transplantation centres and 94% of patients from referring centres for the first induction, 80 and 90%, respectively, for the second induction. There were no significant differences in the occurrence of toxicities. Patients from transplantation centres received more transfusions during the first induction course: a median number of 30 versus 19 units of platelets ($P<0.0001$) and 9 versus 8 units of red blood cells ($P=0.02$). This more intensive transfusion practice could not be related to a longer duration of cytopenia.

Patients in first complete remission (Figure 2)

A total of 585 patients achieved a CR after one or two courses of induction treatment, 462 (68%) from transplantation centres and 123 (63%) from referring centres. Another

Table 1. *Patient characteristics according to type of centre*

Characteristic	Transplantation centres *n* (%)	Referring centres *n* (%)
Number of pts	676	194
Median age (range)	32 (11–45) years	31 (12–45) years
Sex (M/F)	345/331	100/94
Median WBC (range)	15.3 (0.1–500)	21.2 (0.4–360)
FAB-classification (%)		
M1	105 (16)	37 (19)
M2	238 (35)	54 (28)
M3	41 (6)	15 (8)
M4	101 (15)	31 (16)
M4e	34 (5)	9 (5)
M5	124 (18)	38 (20)
M6	23 (3)	8 (4)
M7	3 (<1)	0 (0)
Unknown	7 (1)	2 (1)
Cytogenetic study performed (%)*	239 (35)	33 (17)
Abnormalities (%)		
Good risk	46 (19)	10 (30)
Intermediate risk	103 (43)	12 (36)
Poor risk	90 (38)	11 (33)
Performance status		
Normal	114 (17)	37 (19)
Ambulatory	320 (47)	83 (43)
Bed <50%	180 (27)	64 (33)
Bed >50%	46 (7)	8 (4)
Completely disabled	8 (1)	2 (1)
Unknown	8 (1)	0 (0)

*P value <0.0001. WBC, white blood cell count $\times 10^9$/l; FAB, French-American-British.

Table 2. Results of remission-induction therapy according to type of centre

	Transplantation centres ($n=676$) n (%)	Referring centres ($n=194$) n (%)	P value
Induction 1:			
CR	382 (57)	89 (46)	0.01
PR/resistant disease	259 (38)	86 (44)	0.2
Death*	33 (5)	17 (9)	0.06
Induction 1 and 2:			
CR	462 (68)	123 (63)	0.2
PR/resistant disease	175 (26)	49 (25)	0.9
Death*	36 (5)	21 (11)	0.01
Induction 1, 2 and salvage:			
CR	542 (80)	150 (77)	0.4

*Death during induction treatment or in the hypoplastic phase following induction treatment. CR, complete remission; PR, partial remission.

107 patients, 80 (12%) and 27 (14%), respectively, achieved a CR after salvage therapy. The first intensive consolidation course was given, after the achievement of CR with induction therapy, to 432/462 (94%) patients from transplantation centres and to 119/123 (97%) patients from referring centres. The full dose of chemotherapy was given to 81% and 89% of patients, respectively (Table 3), the dose of cytarabine being 1 g/m^2 every 12 h for 6 days before 1988 and 500 mg/m^2 every 12 h for 6 days from 1988 onwards. There was a trend for more grade 3 and 4 haemorrhages in patients from referring centres (9% versus 5%; $P=0.09$). Patients from transplantation centres received more platelet transfusions: 20 versus 10 units ($P=0.0008$). However, this could not be related to a longer duration of thrombocytopenia. At the end of the first consolidation course, 413/432 (96%) and 111/119 (93%) patients were alive and in CR.

HLA-typing

Transplantation centres performed HLA-typing in 483/542 (89%) patients in CR, whilst referring centres typed 122/150 (81%) patients in CR (Figure 2). HLA-typing was not performed in 38 (7%) and 16 (11%) patients, respectively, and information on HLA-typing was not available for 21 (4%) and 12 (8%) patients, respectively. A HLA-identical sibling donor was found in 196 (41%) of the 483 patients from transplantation centres who were HLA-typed. Even more HLA-identical siblings were found in patients from referring centres: 67/122 (55%); $P=0.004$. Results of HLA-typing remained unknown for 4 patients. The average number of children in families of patients from transplantation centres was 3.5 compared with 4.1 for those from referring centres ($P=0.007$). The overall survival rate at 6 years from CR for HLA-typed patients was 45% for patients from transplantation centres versus 52% for those from referring centres (Figure 3). The DFS rate at 6 years from CR was 37% and 45%, respectively ($P=0.12$, stratified by donor availability).

Patients with a donor

AlloBMT was performed during first CR in 129/196 patients (66%) with a donor from transplantation centres and

Table 3. Toxicities and supportive care given during remission-induction and consolidation treatment according to type of centre

	Induction 1		Induction 2		Consolidation 1		Consolidation 2	
	Transplantation	Referring	Transplantation	Referring	Transplantation	Referring	Transplantation	Referring
Number of patients	676	194	117	40	432	119	71	15
Infection (grade 3 or 4) n pts (%)	124 (18)	39 (20)	15 (13)	6 (15)	78 (18)	28 (24)	12 (17)	5 (33)
Haemorrhage (grade 3 or 4) n pts (%)	43 (6)	14 (7)	2 (2)	1 (3)	20 (5)	11 (9)	1 (1)	1 (7)
Median number of days:								
Fever	6	7	4	4	4	5	3	5
Antibiotics i.v.	17	17	10	10	12	10	12	11
Hospital admission	30	30	29	28	30	28	28	27
Median number of units:								
Platelet transfusions	30	19	15	12	20	10	20	18
Red blood cell transfusions	9	8	6	4	5	5	4	4
Median number of days to:								
$\geq 1.0\times10^9$/1 neutrophils	19	19	19	19	19	19	23	20
$\geq 100\times10^9$/1 platelets	18	18	18	16	21	20	28	23
% Patients who received full dose of:								
Daunorubicin	95	97	88	95	na	na	90	87
Cytarabine	93	95	86	95	88	92	87	93
Amsacrine	na	na	na	na	86	92	na	na

na, not applicable; i.v., intravenous.

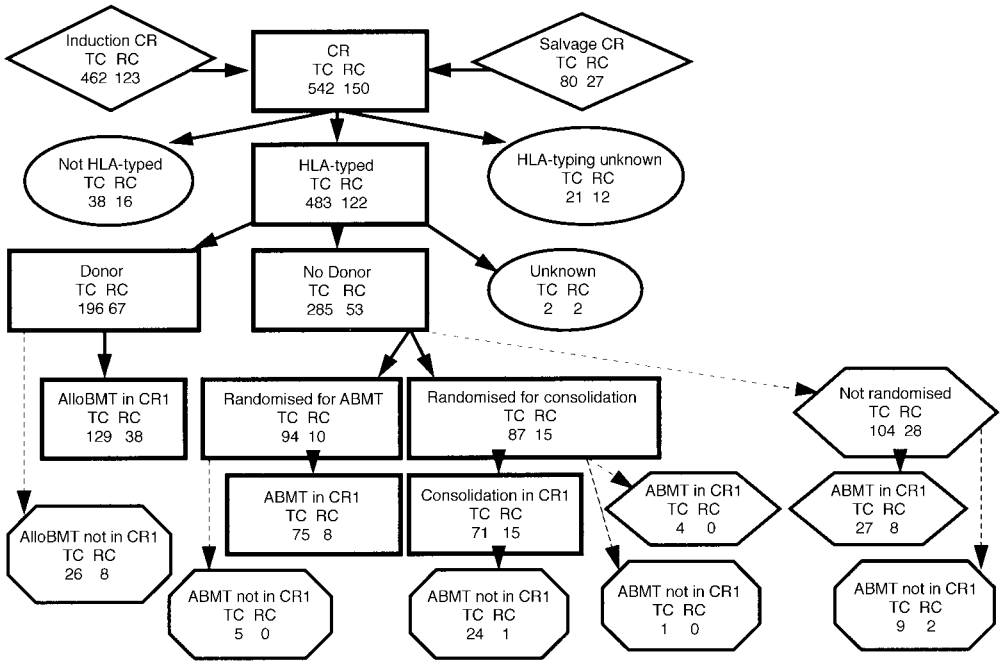

Figure 2. Overview of treatment given to patients in CR (complete remission) by type of centre. Double-lined boxes indicate treatment given according to the protocol; dashed lines indicate treatment given outside of protocol. TC, transplantation centre; RC, referring centre. ABMT, autologous bone marrow transplantation; AlloBMT, allogeneic bone marrow transplantation.

in 38/67 patients (57%) from referring centres (Table 4). All 38 patients from 19 referring centres were transferred to nine transplantation centres for this treatment. The median time from CR to alloBMT was longer ($P = 0.1$) for patients from transplantation than those from referring centres, 109 days (range 4–338 days) and 95 days (range 11–469 days), respectively. Out of the 67 patients from transplantation centres who did not receive alloBMT in first CR, 26 (39%) received alloBMT at a later stage of the disease, 13 patients during relapse and 13 in second CR. At referring centres this occurred in 8/29 (28%) patients, 2 patients during relapse and 6 in second CR. The crude death rate in CR after alloBMT was 19% for patients from transplantation centres and 15% for those from referring centres. At 6 years from CR the DFS rate for patients with a donor was 45% for patients from both types of centres and the overall survival rate was 50% for patients from transplantation centres and 51% for patients from referring centres.

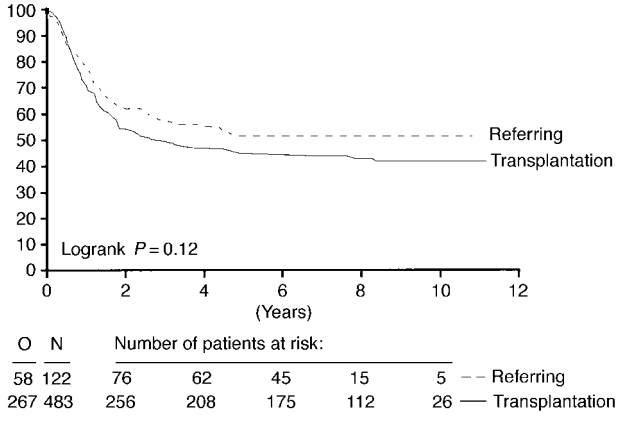

Figure 3. Overall survival from CR for HLA-typed patients by type of centre. N, number of patients; O, observed number of deaths.

Patients without a donor

The overall survival rate at 6 years from CR for all patients without a donor was 41% for those from transplantation centres compared with 52% for those from referring centres ($P = 0.2$). The DFS rate at 6 years from CR was 31% and 45%, respectively ($P = 0.2$). Transplantation and referring centres randomised 181/285 (64%) and 25/53 (47%) patients, respectively ($P = 0.04$). The median time from CR to randomisation was 52 days for transplantation centres, and 44 days for referring centres ($P = 0.06$).

Patients randomised for a second intensive consolidation course

Out of 87 patients from transplantation centres who were randomised for a second consolidation course, 71 (82%) patients received it compared with all (100%) of the 15 patients from referring centres who were randomised in this treatment arm. The full dose of chemotherapy was given to 82 and 87% of patients. A trend was observed for more grade 3 and 4 infections in referring centres (33 versus 17% in transplantation centres), but there were no further differences in the occurrence of toxicities and the amount of supportive care given was similar (Table 3). The median duration from CR to the start of the second consolidation course was 69 days (range 41–165 days) for patients from transplantation centres versus 54 days (range 41–167 days) for those from referring centres ($P = 0.0003$). Out of 42 patients from transplantation centres who relapsed after the second consolidation course, 24 (57%) patients received ABMT, compared with only 1/10 (10%) patients from referring centres ($P = 0.02$). 4 patients from transplantation centres did not receive the second consolidation course but received an ABMT in first CR. Another patient who did not receive the

Table 4. Overview of transplantations performed (alloBMT for patients with a donor, ABMT for patients without a donor) by centre type

	Donor		No donor							
	All		All		Randomised consolidation 2		Randomised ABMT		Not randomised	
	TC	RC	TC	RC	TC	RC	TC	RC	TC	RC
HLA-typed patients	196	67	285	53	87	15	94	10	104	28
BMT in CR1 (%)	129 (66)	38 (57)	106 (37)	16 (30)	4	0	75	8	27	8
BMT not in CR1 (%)	26 (13)	8 (12)	39 (14)	3 (6)	25	1	5	0	9	2
BMT total (%)	155 (79)	46 (69)	145 (51)	19 (36)	29	1	80	8	36	10

TC, transplantation centre; RC, referring centre; HLA, human leucocyte antigen; BMT, bone marrow transplantation; alloBMT, allogeneic BMT; ABMT, autologous BMT; CR1, first complete remission.

second consolidation course received ABMT after relapse. The crude death rate in CR after the second consolidation course was 5% for patients from transplantation centres and 7% for those from referring centres. The DFS at 6 years from CR was 32% for patients from transplantation centres and 27% for those from referring centres. The overall survival rate was 51 and 33%, respectively.

Patients randomised for ABMT

Out of 94 patients from transplantation centres who were randomised for ABMT, 75 (80%) patients received it, as did 8/10 (80%) patients from referring centres (Table 4). 5 patients from four referring centres receiving ABMT were transferred to three transplantation centres. The ABMTs for the other 3 patients from three referring centres were performed at the referring centre. The median time from CR to ABMT was 96 days (range 48–344 days) and 79 days (range 63–157 days), respectively ($P = 0.3$). Out of the 19 patients from transplantation centres who did not receive ABMT in first CR, 5 (26%) received ABMT after relapse. Neither of the 2 patients at referring centres who relapsed received an ABMT at a later stage.

The crude death rate in CR after ABMT was 11% for patients from transplantation centres and no patients from referring centres died in CR. The DFS rate at 6 years from CR was 43 and 70%, respectively. The overall survival rate at 6 years from CR was 50 and 80%, respectively.

Patients not randomised

Out of 104 patients from transplantation centres who were not randomised, 27 (26%) patients received ABMT in first CR compared with 8/28 (29%) patients from referring centres. 6 patients from six referring centres receiving ABMT were transferred to four transplantation centres. The ABMTs in the other 2 patients from one referring centre were performed at this referring centre. Another 9 (9%) patients from transplantation centres and 2 (7%) patients from referring centres received an ABMT after relapse.

The crude death rate in CR was 14% for patients from transplantation centres and 11% for those from referring centres. At 6 years from CR the DFS rate was 20 and 46%, respectively ($P = 0.02$). The overall survival rate at 6 years from CR was 26 and 53%, respectively ($P = 0.02$).

Patients completing the full protocol treatment

Transplantation centres performed alloBMT in first CR in 129/196 (66%) patients with a donor. Out of 285 patients without a donor 146 (51%) received their randomised treatment in first CR: 75 ABMT and 71 a second consolidation course. In total, 275/542 (51%) patients in CR received the full treatment according to the protocol. This occurred in 61/150 (41%) patients in CR from referring centres ($P = 0.04$): 38/67 (57%) patients with a donor received alloBMT in first CR and 23/53 (43%) patients without a donor received their randomised treatment in first CR—8 ABMT and 15 a second consolidation course.

DISCUSSION

The AML 8A study conducted by the EORTC Leukemia Cooperative Group in collaboration with GIMEMA was a large prospective study comparing alloBMT with ABMT and intensive consolidation chemotherapy. The study included more than 1000 patients from 59 different European centres, registered prospectively from diagnosis. The comparison of the three treatment arms was published in January 1995 [5] and showed that during first CR in AML, ABMT as well as alloBMT resulted in a longer DFS than intensive consolidation chemotherapy with high-dose cytarabine and daunorubicin.

The present analysis was undertaken to determine whether transplantation centres, having more sophisticated facilities for the treatment of AML, achieved a higher survival rate, than centres which referred their patients for transplantation. The feasibility of chemotherapy and transplantation was also evaluated. Patients who were less than 46 years of age were included, as the AML 8A study was designed for this age group, although some transplantation centres entered patients up to 60 years of age. By only including patients less than 46 years of age this centre effect was eliminated.

Transplantation centres contributed 78% of patients, referring centres 22%. Transplantation centres were mainly large centres, registering more than 20 patients in the full course of the study. The referring centres were smaller with a median number of 5 registered patients. Patients characteristics were comparable. The CR rate was initially lower for the referring centres due to a higher hypoplastic death rate. However, the overall CR rate after induction and, if necessary, salvage treatment was comparable, as was the outcome after the first consolidation course. There were no major differences in the occurrence of toxicity during induction or consolidation treatment. Transplantation centres transfused more units of platelets and red blood cells, although the haematological recovery was not longer. This was the only difference in supportive care and this did not appear to have any

consequences for the outcome of treatment. Thus, patients can be treated at referring centres with remission induction and consolidation chemotherapy and do not have to be referred at diagnosis to specialised transplantation centres for treatment.

HLA-typing was performed in the majority (85%) of patients in CR. A histocompatible sibling donor was identified more often in patients from referring centres, 55 versus 41% of HLA-typed patients. This was apparently due to the larger average family size of this group of patients. AlloBMT was performed slightly more often in patients from transplantation centres, although the time from CR to alloBMT was longer, due to delays for infection and waiting lists. Referring centres may have selected those patients for alloBMT who were in good condition immediately following the first consolidation course. More patients from transplantation centres were allografted after relapse. However, overall the treatment outcome for patients with a donor was comparable for patients from transplantation and referring centres.

Transplantation centres randomised more often between ABMT and a second intensive consolidation course than referring centres: 64 and 47% of patients. The median time from CR to randomisation was shorter for referring centres, again suggesting that these centres only randomised patients in good condition after the first consolidation course and excluding patients who took longer to recover.

The majority of patients who were randomised actually received the randomised treatment, both from transplantation centres and referring centres. Patients received the second intensive consolidation course 2 weeks sooner at referring centres than those at transplantation centres. All patients received the same amount of supportive care. There was a trend for more grade 3 and 4 infections at referring centres, but this did not result in a higher toxic death rate. No other differences in the occurrence of toxicity were observed. However, transplantation centres performed ABMT in more than half of the patients who relapsed after the second consolidation course compared with referring centres, who only performed ABMT in 1 patient after relapse (17%). This resulted in a higher overall survival rate for patients from transplantation centres who were randomised to receive a second intensive consolidation course.

The median time from CR to ABMT for patients randomised for ABMT was 17 days shorter for patients from referring centres. This means that patients from transplantation centres had a greater chance of relapsing before the planned ABMT. In total, 14 out of the 19 patients who did not receive ABMT in CR1 from transplantation centres, relapsed before ABMT could be given, which could explain the poorer results for patients from transplantation centres randomised for ABMT.

Results of patients without a donor who were not randomised were significantly worse for those coming from transplantation centres. The DFS and overall survival rates were lower due to the higher relapse rate of these patients. However, only 40% of these patients had achieved a CR with the first induction course compared with 64% of patients from referring centres. As these patients received intensive salvage therapy, only 49% of patients from transplantation centres received the first consolidation course compared with 79% of patients from referring centres. We can conclude that the patients from transplantation centres who were not randomised were a group of poor prognostic patients and that referring centres applied a higher selection of patients for randomisation than transplantation centres, as these patients still had a reasonable outcome even when they were not randomised.

Fifty-one per cent of all patients in CR from transplantation centres completed the full protocol treatment compared with 41% of patients in CR from referring centres. Apparently, the referring centres applied greater selection of the patients for the treatments of the protocol. Transplantation centres performed many more transplantations, alloBMT as well as ABMT, during relapse and second CR than the referring centres. However, these intensive salvage treatments did not affect the overall outcome of treatment. Greater selection of patients for transplantation in first CR by referring centres resulted in the same overall survival as performing salvage therapy in a less selected group of patients who had a higher rate of relapse.

This analysis assessed the outcome of treatment and attempted to explain any differences found using the information available in our database, such as the severities of infection and haemorrhage or the number of transfusions of blood products. However, many other factors, unknown to us, may play a role in the outcome of treatment, for example the number of beds per room, the distance between beds, the cleaning routine, the use of face masks, handwashing and so forth. In a multicentre randomised trial setting, these data are too numerous to be included and too variable to be able to analyse properly. Therefore, the data available can give an indication of the possible problems, which would warrant further investigation.

The Cancer and Leukemia Group B (CALGB) [8] found a significantly worse freedom from progression rate for patients with poor prognosis non-Hodgkin's lymphoma (NHL) treated at centres with a low accrual rate. Only a minority of these centres (27%) were CALGB transplantation approved. The major problem was that the number of patients who completed the protocol treatment was lower at these small centres, resulting in a poorer outcome. We found no difference in DFS between the two types of centres, possibly as a result of full dose chemotherapy being received in similar proportions of patients.

In conclusion, the type of centre did not influence treatment outcome of first-line treatment in the AML 8A study for untreated AML patients younger than 46 years of age. The feasibility of the study was similar in both transplantation and referring centres. The percentage of patients completing the full protocol treatment was significantly higher at the transplantation centres, but this did not translate into a better outcome, since the introduction of transplantation did not improve survival. Randomised trials should not be restricted to specialised research centres and referring centres could contribute substantially to answering randomised questions, provided that all patients have similar access to all treatment modalities. In this way the results of these trials would be more convincing and their generalisation to future patients would be guaranteed.

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APPENDIX

The following centres and investigators from the EORTC Leukemia Cooperative Group participated in this study: Austria: Innsbruck, Universitätsklinik (J. Thaler); Belgium: Antwerpen, University of Antwerpen (M.E. 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 (R.A. Zittoun and 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 and P. Muus); Portugal: Porto, San Joan (M. Ribeiro); and Turkey: Ankara, Ibnui Sina Hospital (M.D. Beksac).

The following centres 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 L.A. Seragnoli (S. Tura, G. Visani, and 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 and 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, Il 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, G.L. Castoldi, S. Fenu and V. Liso.

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