1083-8791/06/1203-0006$32.00/0
doi:10.1016/j.bbmt.2005.10.019

The Outcome of Sibling and Unrelated Donor Allogeneic Stem Cell Transplantation in Adult Patients with Acute Myeloid Leukemia in First Remission Who Were Initially Refractory to First Induction Chemotherapy

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Received July 18, 2005; accepted October 24, 2005

ABSTRACT

The optimal management of patients with initially refractory acute myeloid leukemia is unknown. We analyzed the outcomes of 68 adult patients (median age, 37 years) with acute myeloid leukemia in first complete remission with initially refractory disease who were treated with matched sibling (n = 44) or unrelated donor (n = 22) stem cell transplantation or who received transplants from other donors (n = 2). Thirty-one patients took 2 courses of chemotherapy to achieve first complete remission, a further 31 took 3 courses, and 6 patients took 4 or 5 courses. Ten patients (15%) had adverse cytogenetics. Patients were mainly conditioned with cyclophosphamide and total body irradiation (87%). Four patients (6%) did not engraft by day 28; 2 of these engrafted at 47 and 60 days. Grades II to IV and III/IV acute graft-versus-host disease (GVHD) were seen in 34% and 14% of patients, respectively. Chronic GVHD was seen in 50% of patients. The estimated actuarial disease-free and overall survivals were 34% and 37%, respectively, at 4 years. The performance status of survivors is good; 82% of patients have Karnofsky scores of 90 to 100. On multivariate analysis, overall and disease-free survival were associated with adverse cytogenetics (P = .055 and .023). Approximately one third of patients survived 4 years after allogeneic stem cell transplantation for initially refractory acute myeloid leukemia in first complete remission: relapse and treatment-related mortality were the major causes of treatment failure. Further studies are needed to determine the optimal conditioning regimens and GVHD prophylaxis.

KEY WORDS

Allogeneic stem cell transplantation • Sibling donor • Unrelated donor • Acute myeloid leukemia • First induction chemotherapy refractory

INTRODUCTION

The role of allogeneic stem cell transplantation (SCT) in the management of adults with acute myeloid leukemia (AML) in first complete remission (CR1) is uncertain. Prospective trials using biological randomization show statistically significantly superior disease-free survival in allografted patients compared with those receiving best alternative therapy, but they do not show significantly improved overall survival [1,2]. However, patients with poor-risk cytogenetics do seem to have a superior outcome with a matched sibling allograft [3].

The Medical Research Council trials performed over the last 10 years have done much to help us stratify risk in adults with AML. Although there are some disagreements about which cytogenetic abnormalities confer an adverse prognosis, there is widespread agreement that the response to first-line chemotherapy is of immense prognostic significance [4]. The AML 10 and AML 12 studies found that patients with ≥15% blasts after the first course of chemotherapy have a low chance of prolonged disease-free survival with further chemotherapy alone and have suggested that these patients be regarded as high risk and candidates for sibling allografts or unrelated donor allografts if they lack a matched sibling donor [4-6]. The outcome of this therapeutic strategy is, however, unclear, and it seems likely that patients refractory to chemotherapy will also have a relatively poor outcome after high-dose chemoradiotherapy and a possible immunologic graft-versus-leukemia effect, although this is uncertain.

By using data retrospectively collected by the British Society of Blood and Marrow Transplantation Registry and additional data obtained by reference to patient records from the submitting transplant centers, we performed a national study of patients who had more than 15% blasts after the first course of chemotherapy but then subsequently achieved a CR and patients who took more than 2 courses of chemotherapy to achieve a CR. We described the toxicities of these allogeneic transplantations and analyzed the factors associated with a successful outcome.

PATIENTS AND METHODS

Patient Identification and Definition

To be eligible for inclusion in the study, the patient had to have had an allograft for AML in CR1 and to have satisfied 1 of the following criteria: (1) >15% blasts present after the first course of chemotherapy and (2) ≥3 courses of chemotherapy to achieve CR1. The British Society of Blood and Marrow Transplantation database records the number of courses of chemotherapy required to achieve CR. All patients with ≥3 courses were included on the study. All patients who required 2 courses of chemotherapy to achieve a CR were analyzed further, and centers were asked to list the patients who had >15% blasts present after the first course of chemotherapy. Initially 103 patients were identified in 18 centers before the blast count after course 1 was ascertained. One center had 3 patients in this group, but none had >15% blasts after course 1. Two centers (n = 7) declined participation; 15 centers contributed patients to the study. The standard definition of CR was used: <5% blasts with evidence of count recovery and resolution of organomegaly, but no duration was specified because these patients proceeded to transplantation rapidly.

The following hospitals contributed patients: University College (n = 14), Royal Free Hospital (n = 13), Nottingham City Hospital (n = 12), Royal Liverpool Hospital (n = 7), Bristol Children's Hospital (n = 5), Addenbrooke's Hospital (n = 4), John Radcliffe Hospital (n = 3), Royal Marsden Hospital (n = 2), St. James' Leeds (n = 2), St. James' Dublin, Belfast City Hospital, St. George's Hospital, Leicester Royal Infirmary, King's College Hospital, and the Christie Manchester (n = 1 patient each).

Demographic Data

The following demographic and transplantation data were collected: age, sex, age of donor, cytomegalovirus status of donor and recipient, conditioning regimen, use of in vivo or ex vivo T-cell depletion, salvage therapy, cytogenetic abnormalities, dose of total body irradiation (TBI), and number of fractions. Posttransplantation data were collected with regard to extramedullary toxicity, use of high-dose antifungal therapy, acute and chronic graft-versus-host disease (GVHD), time to relapse, patient remission status at last follow-up, and patient Karnofsky score at last follow-up. The time to engraftment was the first of 3 days in which the neutrophil count was $\geq 0.5 \times 10^9$/L.

Statistical Analysis

The study aimed to examine the following major end points: survival, disease-free survival, transplant-related mortality, incidence of grade II to IV acute and chronic GVHD, and cause of death. Survival, disease-free survival, relapse rate, transplant-related mortality, and chronic GVHD were assessed by Kaplan-Meier survival analysis. Factors that influenced overall and disease-free survival, transplant-related mortality, and relapse rate were assessed. All relevant clinical factors were put into the models to determine whether they affected the chance of survival. Cox proportional hazard regression models were used for overall and disease-free survival, whereas cumulative incidence analysis was used for competing risk models of transplant-related mortality and relapse rate. The factors assessed for effect included patient sex and age, donor age, female donor to male recipient, French-American-British (FAB) type, adverse cytogenetics, type of donor (related or unrelated; matched or mismatched), time from diagnosis to transplantation, number of courses of chemotherapy to achieve CR, source of stem cells (bone marrow or peripheral blood), fractions of TBI conditioning, dose of TBI, acute or chronic GVHD prophylaxis, and T-cell depletion. The R software package was used for all statistical analyses described [7].

Factors that were significant ($P < .05$) in univariate models of overall or disease-free survival were

Table 1. *Clinical Characteristics of Patients and Details of Transplantation*

Variable	Data
Male	38
Female	30
Age at transplantation (y)	36 (17.8-59.8)
FAB classification	
M0	7
M1	10
M2	21
M3	5
M4	9
M5	6
M6	4
M7	2
Unknown	2
Cytogenetics	
Normal	27
Abnormal	28
Failed	4
Unknown/not done	9
Chromosome 5 abnormality	1
Chromosome 7 abnormalities	4
Chromosome 5 and 7 abnormalities	1
Complex abnormalities	3
Complex abnormalities + chromosome 5 abnormal	1
Last chemotherapy before transplantation	
Fludarabine, Ara-C, G-CSF	11
Fludarabine, Ara-C	4
Fludarabine, Ara-C, G-CSF, idarubicin	13
Mitoxantrone, Ara-C	9
Ara-C, daunorubicin, etoposide	6
Amsacrine, Ara-C, etoposide	5
Daunorubicin, Ara-C, thioguanine	8
Other	4
None	1
Unknown	7
Number of courses of chemotherapy to CR	
2	31
3	31
4	3
5	3
Median diagnosis to transplantation interval (d)	188 (70-471)
Female donor/male recipient	11
Stem cell source	
Marrow	48
Peripheral blood	20
Donor type	
Matched sibling	44
Unrelated donor	22
Mismatched sibling	1
Syngeneic	1
TBI	
None	11
Single fraction	16
12-13 Gy	4
13-14 Gy	5
14.4 Gy*	32
Cyclophosphamide/TBI†	57
Busulphan/cyclophosphamide	4
Busulphan/melphalan	1
Fludarabine/melphalan	5
Fludarabine/busulphan	1
Additional GVHD prophylaxis‡	
Cyclosporine, no methotrexate	15
Cyclosporine/methotrexate	32
Methotrexate, no cyclosporine	3
In vivo or ex vivo T-cell depletion	29
Intravenous monoclonal antibodies	22
Alemtuzumab "in the bag"	7
CD34 selection	5

Ara-C indicates cytosine arabinoside; G-CSF, granulocyte colony-stimulating factor.

*Of the 32 patients who received 14.4 Gy, 8 received this in 6 fractions and 24 in 8 fractions.

†Of the 57 patients received additional agents: melphalan 1, thiotepa 5, fludarabine 2, busulphan 3, and other/unknown 3.

‡Eight patients received additional steroids as GVHD prophylaxis: cyclosporin A (CsA) alone 3, methotrexate (MTX) alone 2, and CsA + MTX 3.

included in a multivariate Cox model. The median follow-up of survivors was 4.1 years (range, 1-14.4 years).

RESULTS

Patient and Transplant Characteristics

Sixty-eight patients underwent transplantation in 15 centers from 1989 to 2003. Their pretransplantation clinical characteristics are shown in Table 1. Two patients had secondary AML. Intermediate- to high-dose cytosine arabinoside–containing regimens were most frequently used to obtain remissions. Twenty-two patients had unrelated donors (32%), 44 received stem cells from matched sibling donors (65%), and 2 received syngeneic and mismatched related transplants. Because of the prolonged time period during which patients underwent transplantation and differing institutional policies regarding acceptable matches, the degree of matching of the unrelated donors varied. All patients had serologic class I typing and molecular class II typing, and 8 (36%) of 22 were mismatched. The median time from diagnosis to transplantation was 188 days (range, 70-471 days). Fifty-seven patients (84%) had TBI-containing conditioning; 32 had 14.4 Gy (24 in 8 fractions in 4 days and 8 in 6 fractions in 3 days), and 16 had single-fraction TBI with a median dose of 7.5 Gy (range, 6.84-10.0 Gy). The remaining 9 patients received 11 to 13 Gy of TBI.

Engraftment

Engraftment data were available in 64 evaluable patients. Two patients (3%) did not engraft; 1 had an unrelated donor, and the other had a sibling donor. Two additional patients (sibling donors) engrafted at days 47 and 60; we have classified these patients as having primary graft failure, and, therefore, 6% of patients did not engraft. The median time to engraftment was 15 days (range, 10-29 days). The time to engraftment is unknown in 15 patients. The median

Table 2. *Major Transplantation Outcomes*

Variable	Data
Acute GVHD (66 evaluable)	
No GVHD	21 (32%)
Grade I	23 (35%)
Grade II-IV	22 (33%)
Grade III-IV	9 (14%)
Chronic GVHD (54 evaluable)	25 (50%)
Relapse	20
Relapse rate at 5 y	31% (95% CI, 19%-42%)
Median time to relapse (d)	172 (94-540)
Alive	25 (37%; 95% CI, 26%-51%)
Karnofsky score at last follow-up (2 patients not evaluated)	
13	
90	5
80	3
70	1

times to unsustained platelet counts of 20 and 50 $\times$ 10^9/L were 21 and 24 days, respectively (Table 2).

Graft-versus-Host Disease

Sixty-six patients were evaluable for acute GVHD. Twenty-two patients (34%) experienced grade II to IV GVHD, and 9 (14%) experienced grade III or IV. It is interesting to note that 8 of the 9 patients with severe acute GVHD received stem cells from matched sibling donors. Of these 9 patients, 3 survived, and all had grade III acute GVHD. However, 23 patients (35%) had grade I GVHD, and this means that 45 patients had some acute GVHD.

Fifty-four patients survived to day 100 and were assessable for chronic GVHD. Twenty-five patients (50% at 2 years; 95% confidence interval [CI], 33%-62%; 13 matched siblings, 11 unrelated, and 1 mismatched sibling) had chronic GVHD. The median time to development of chronic GVHD was 121 days (range, 100-410 days), and in 14 patients it was from continuing acute GVHD.

Toxicity/Death

In total, 43 patients have died: 26 (38%) of transplant-related causes. Two patients died of secondary malignancy, 1 of metastatic rectal cancer, and the other of pulmonary adenocarcinoma. One patient died of Guillain-Barré syndrome. This patient's death was classified as transplant related. Four patients (6%) had documented veno-occlusive disease. Seventeen patients received high-dose systemic antifungal therapy, but information is not available concerning how many patients had definite or probable invasive fungal infection, and data are not available concerning a third of the patients. The causes of death are shown in Table 3. GVHD, infection, and pulmonary deaths were the most common causes of transplant-related death.

Table 3. *Causes of Death*

Variable	Data
Acute myeloid leukemia	17
Graft-versus-host disease	5
Pneumonitis/diffuse alveolar damage	7
Infection*	10
Secondary malignancy	2
Other†	2
Total	43

*Infections: viral 3, fungal 1, multiple pathogens 4.
†Hemorrhage 1, Guillain-Barré syndrome 1.

Relapse

Twenty patients have relapsed, and the cumulative incidence of relapse (treating transplant-related mortality as a competing risk) at 4 years was 31% (95% CI, 19%-42%). Two patients are alive in a subsequent remission lasting 8 months and 7.5 years. The median time to relapse was 172 days (range, 94-540 days). Of the 20 patients who relapsed, 7 received palliative treatment only, and the therapy of 4 patients is unknown. Five patients had chemotherapy only, 1 had gemtuzamab, and 3 had donor lymphocyte infusion. The patient who received gemtuzamab and 1 of the patients who received donor lymphocyte infusion survive in CR2.

Survival and Current Status

Twenty-five patients (37%) survive, and all but 1 are in CR, although 2 patients are in CR2. The performance status of survivors is good: 18 patients have a Karnofsky score of 90 or 100. Estimated actuarial probabilities of overall and disease-free survival are shown in Figures 1 and 2. The median overall and

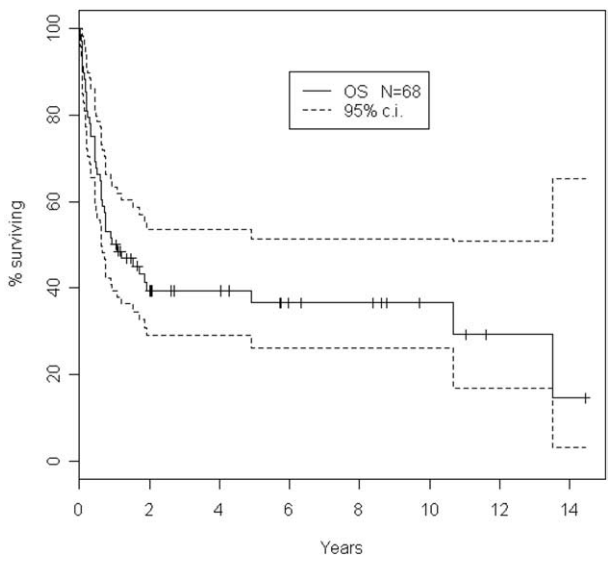

Figure 1. Probability (%) of overall survival (OS) in years. Tick marks indicate surviving patients. Dotted lines indicate 95% confidence intervals.

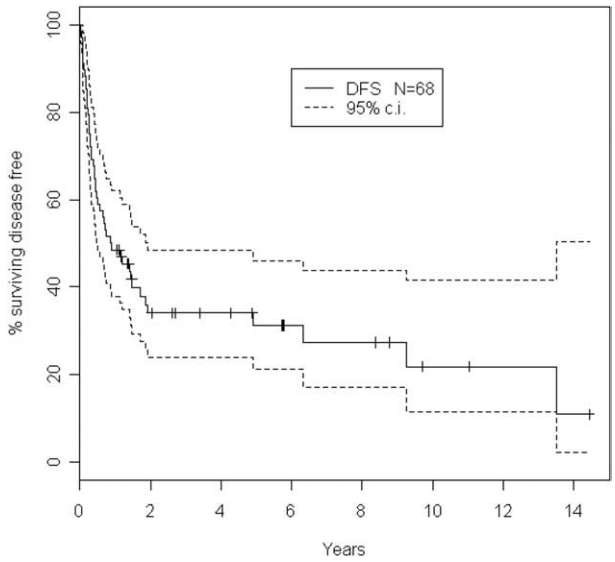

Figure 2. Probability (%) of disease-free survival (DFS) in years.

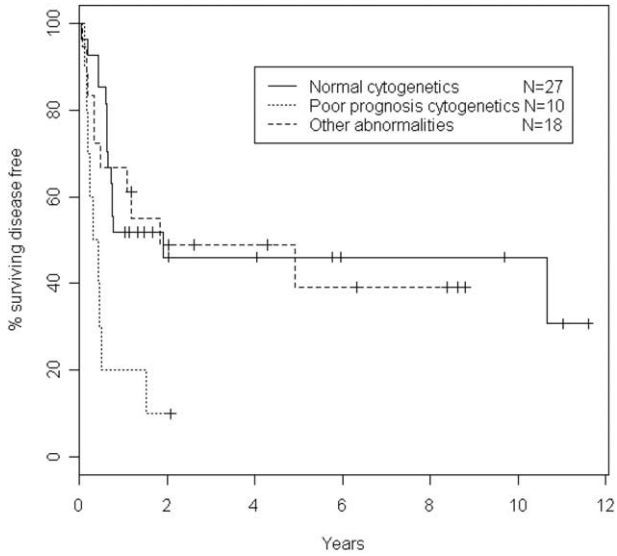

Figure 4. Probability of disease-free survival (%) in years according to cytogenetics.

disease-free survivals are 12 months (95% CI, 7 months to 6 years 4 months) and 10.6 months (95% CI, 5 months to 1 year 11 months), respectively. Estimated actuarial survival at 4 years is 39%, and disease-free survival is 34% (Figures 1 and 2). Although there is no clear plateau to the survival curve, the 3 events at 5 years or later are transplant-related deaths (1 of them metastatic rectal carcinoma), and there were no relapses after 18 months after transplantation.

Univariate and Multivariate Analysis of Factors Predictive of Relapse and Survival

Ten of 22 unrelated donor recipients survive, compared with 15 of 44 sibling allograft recipients (not significant). Only 1 of 7 patients with mismatched unrelated donors survives, but because of small numbers and the lack of uniform typing, these data should be treated with caution. The overall survival at 1 year is 67% for matched and 29% for mismatched unrelated donor recipients ($P = .15$). Of the 6 patients with mismatched donors, 3 died of relapse, and 3 had transplant-related deaths.

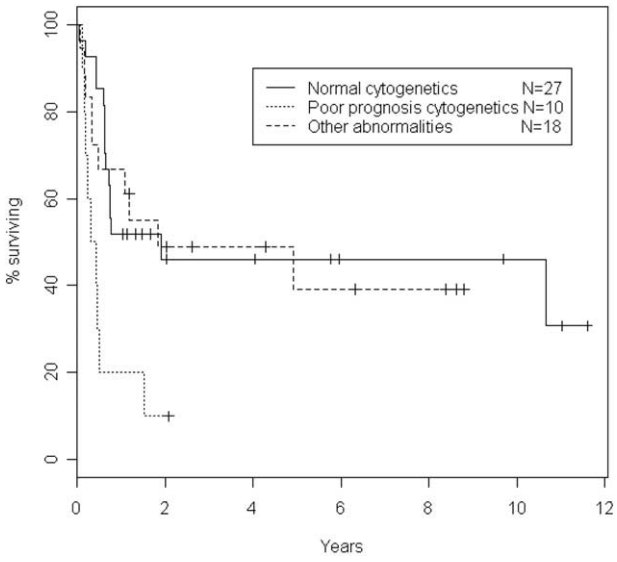

Figure 3. Probability (%) of overall survival in years according to cytogenetics.

The following factors were examined on univariate analysis to see whether they were associated with survival or relapse: type of donor, patient and donor age, time from diagnosis to transplantation, sex, poor-prognosis cytogenetics (chromosome 5 and 7 or complex abnormalities) (Figures 3 and 4), acute or chronic GVHD, number of courses of chemotherapy to achieve CR, mismatched unrelated transplant, FAB type, female donor to male recipient versus all others, bone marrow versus peripheral blood, single fractions versus fractionated, 14.4 Gy versus all other fractionated doses, cyclosporin A plus methotrexate versus all other prophylaxis, and T-cell depleted versus not (within unrelated transplant groups). The following factors affected overall survival significantly. A prolonged time from diagnosis to transplantation (>180 days) was associated with better median survival (1796 versus 225 days; $P = .034$). Associated with this was that patients who had ≥3 courses of treatment to achieve CR had a superior relapse-free survival ($P = .04$). Cytogenetics did correlate with survival. The median overall survivals of patients with abnormalities of chromosomes 5 and 7 or complex cytogenetics were compared with those of patients with other cytogenetic abnormalities or normal cytogenetics, and the differences were significant (135 versus 675 versus 698 days; $P = .017$). Disease-free survival was also significantly worse in patients with poor-risk cytogenetics ($P = .004$). Sur-

Table 4. *Multivariate Analysis*

End Point	Covariates	*P* Value
OS	Time from diagnosis to transplantation	.120
	Cytogenetics (chromosome 5/7/complex vs. rest)	.067
DFS	Time from diagnosis to transplantation	.048
	Cytogenetics (chromosome 5/7/complex vs. rest)	.023

OS indicates overall survival; DFS, disease-free survival.

vival was not significantly associated with age, FAB class, donor type, acute or chronic GVHD, donor age or sex, stem cell source, or the dose or fractionation of TBI. GVHD did not affect the chance of relapse. Fifteen patients had neither acute nor chronic GVHD; the overall survival of these patients at 2 years was 40%, similar to the outcome of all patients.

A multivariate analysis was then performed of the factors significantly associated with survival and disease-free survival on univariate analysis (Table 4). Adverse cytogenetics were significantly associated with relapse and disease-free survival, and there was a trend toward it's being associated with overall survival. In the multivariate analysis, time from diagnosis was no longer associated significantly with overall survival.

DISCUSSION

It is well known that high-dose chemoradiotherapy and an immunologic graft-versus-leukemia effect can cure patients in whom standard-dose chemotherapy for AML has produced inadequate cytoreduction, but the outcome of allografting AML patients who are initially refractory to chemotherapy and then achieve CR has not been specifically described in the literature. In fact, allogeneic SCT can cure a minority of patients with completely refractory acute leukemia. Thomas et al. [8] first reported the outcome of 100 such patients nearly 30 years ago. Patients with initially refractory AML who subsequently do respond to chemotherapy potentially have a better prognosis, but little is written about these patients as a separate group.

The outcome of patients with AML with resistant disease after course 1 of chemotherapy is poor, with 22% 5-year survival from the start of course 2 [5]. In the Medical Research Council studies, patients with chemoresistant disease are grouped with patients with adverse cytogenetics into an overall poor-risk group. These studies have not shown that allogeneic bone marrow transplantation was of benefit in this poor-risk group (on a donor versus no-donor analysis), but the numbers of patients receiving an allograft were small because many relapsed early. It may be difficult to decide about the value of allograft when such a large proportion of patients in the donor group did not receive the assigned therapy [9]. There is clearly some overlap between these risk groups, but to aid clinical decision making, we thought that it would be helpful to examine the outcome of patients with chemorefractory AML separately.

The overall outcome of patients who have allografts for AML in CR1 is good, with 70% prolonged survival in patients with matched siblings [9] and approximately 50% in those who have unrelated donor allografts for high-risk AML in CR1 [10,11,12]. This study shows that, on a national multicenter basis, approximately one third of patients with poorly responsive AML who do subsequently achieve CR can survive 4 years after sibling or unrelated donor transplantation. We were unable to collect detailed quality-of-life data, but Karnofsky scores at last follow-up suggest that the performance status of survivors is good. The median follow-up of the patients in this series is >4 years, but 7 patients have not reached 2 years after transplantation and are still at high risk of relapse.

The patients with poor-risk cytogenetics had a significantly poorer survival on multivariate analysis. It is of interest that acute and chronic GVHD did not affect survival in this series and did not influence the risk of relapse. This is in marked contrast with some recent series [13]. The encouraging survival in patients without acute or chronic GVHD suggests that it may be reasonable to use transplantation protocols that avoid GVHD in sicker patients, who would not tolerate this complication well. The outcome of sibling and unrelated donor transplantations was not significantly different, and this study shows that unrelated donor SCT, if a donor can be identified in time (Marks et al., unpublished data), can result in a significant proportion of survivors. The outcome of patients with mismatched unrelated donors may be less good, but because the typing was not uniform in this multicenter retrospective study and because numbers were small, this should be interpreted with caution.

More than 50% of patients with primary resistant AML may achieve a CR with salvage chemotherapy [14]. However, after the first course of chemotherapy, many do not completely recover their blood counts, and the persistent severe neutropenia may be associated with considerable morbidity, thus making some of these patients worse candidates for a subsequent allograft. The major single reason for treatment failure in this series was relapse, but transplant-related mortality was also significant. Only 5 patients in our series had reduced-intensity conditioning transplantations, and 2 survive. These numbers are insufficient to determine whether this approach warrants further investigation, but given the poor condition of many patients with initially refractory AML, it is likely that less toxic regimens

will be explored further in the future. There are no reduced-intensity conditioning studies specifically devoted to patients with initially refractory AML in CR, but it may be possible to extrapolate from other patients with high-risk AML. More intense reduced-intensity conditioning regimens may be associated with better progression-free survival [15] but have more toxicity. The approach is feasible in older, infirm patients, and medium-term survival can be achieved [16]. This study [16] found that patients with GVHD had less disease progression; this differs from our study. There are few published data with alemtuzumab-containing regimens for AML.

Clearly this study has significant limitations if one is using these data to decide whether to recommend allogeneic SCT to these patients. However, the practicalities of performing a randomized study make it unlikely that one will be performed. A degree of selection bias will be present in this series because fitter patients are more likely to undergo transplantation. In addition, we lack data about FLT3 mutations and whether they affected outcome [6]. Furthermore, we are unable to comment definitively as to whether mismatching between unrelated donors and recipients affects outcome, because the technology of typing has evolved over the study time period.

In summary, although there are no randomized head-to-head comparisons of allografting versus continued chemotherapy in patients with initially refractory AML in CR, it seems reasonable to continue a policy of offering an allograft in first remission. Matched unrelated donors are acceptable if no sibling donor is available. The results seem less good if the unrelated donor is mismatched or if there are adverse cytogenetics. Further investigations should explore whether we can harness a graft-versus-leukemia effect with less transplant-related toxicity. This approach may increase the number of patients who are eligible for a potentially curative procedure.

UNCITED REFERENCES

This section comprises references that occur in the reference list but not in the body of the text. Please position each reference in the text or delete it. Any references not dealt with will be retained in this section:[10].

ACKNOWLEDGMENTS

The Leukaemia Research Fund provided support for this work (grant no. 03/100; D.I.M.). We would like to thank all the data managers and transplant physicians of the participating centers for providing data and responding to numerous additional data requests. This work was performed on behalf of the Clinical Trials Committee of the British Society of Blood and Marrow Transplantation.

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