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Allogeneic Bone Marrow Transplantation for Acute Myeloid Leukemia in First Remission

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Evidence that conventional treatment (chemotherapy and/or immunotherapy) produces a substantial number of cures in acute myeloid leukaemia (AML) is lacking (Powles et al. 1980a). Thomas et al. (1977) showed that there was a proportion of long-term survivors of a group of AML patients treated with high-dose cyclophosphamide, total body irradiation (TBI) and allogeneic bone marrow transplantation (BMT).

The purpose of the study reported here is to define the place for BMT in the treatment of AML and involves a comparison of two groups of first remission patients treated either with BMT or chemoimmunotherapy. This study is an extension of the results published earlier this year (Powles et al. 1980c).

A. Patients and Methods

Since August 1977, 33 1st remission AML patients have received a BMT – 27 from HLA-identical and MLC-compatible sibling donors, two from identical twin donors and four from related mis-matched donors (three sibling and one paternal, incompatible in MLC). The outcome of the matched allografted patients has been compared with the simultaneous group of 33 patients with AML in first remission, who lacking a suitable donor did not receive a transplant and were maintained on chemotherapy and immunotherapy.

Patients details are shown in Table 1. Remission was induced by various regimes using cytosine arabinoside, thioguanine and anthracycline-daunorubicin alone or with adriamycin, or rubidazone. Consolidation with the same three agents or with thioguanine and cytosine arabinoside followed. Twenty of the transplanted patients had their remission induction given elsewhere and were referred to our unit when in remission. Those patients who did not receive a transplant were given maintenance chemotherapy consisting of courses of cytosine arabinoside (10 mg/kg as 24 h intravenous infusion) followed by daunorubicin (1.5 mg/kg intravenously), given at intervals of 2, 4, 6, 8, 10 and 12 weeks after consolidation for a total period of 42 weeks (Powles et al. 1979), or 3 day courses of cytosine arabinoside (1.5 mg/kg sub-cutaneously, 12 hourly) and 6-thioguanine (80 mg orally, 12 hourly) given every 3 weeks for 27 weeks. In addition they received continuous weekly immunotherapy consisting of subcutaneous injections of irradiated myeloblasts and intradermal BCG.

Table 1. Details of patients studied

	Allografted (27)	Non-transplanted (33)
M:F	14:13	14:19
Age-mean (range)	24.8 (8–46)	29.4 (3–47)
Diagnosis: M1	3	2
M2	4	14
M3	1	1
M4	14	14
M5	1	2
M6	4	0
Time to CR-median (range)	10.6 weeks (2–53)	7.7 weeks (3–17)

Patients with a suitable donor received a transplant as soon as practicable after achieving remission. They were conditioned according to the Seattle schedule with high-dose cyclophosphamide (60 mg/kg intravenously for two doses) followed by total body irradiation (1,000 rad mean midline dose given from a cobalt source at 2.5 rad/min). No anti-leukaemic chemotherapy was given after transplantation except low-dose methotrexate (Mtx) for six patients to prevent graft versus host disease. Subsequently, Cyclosporin A (CSA) was used instead of Mtx for 21 patients (Powles et al. 1980b). Patients were nursed in cubicles with filtered positive pressure ventilation, received sterile food and non-absorbable anti-microbials as gut decontamination. Systemic antibiotics and platelet transfusions were given as indicated. No patient required granulocyte transfusions. They were discharged from hospital after marrow reconstitution, 3 to 4 weeks after transplantation.

B. Results

Actuarial analysis of complete remission duration is shown in Figure 1. Of the 33 patients treated with chemo-immunotherapy 20 have relapsed with a median remission duration of 12 months compared with four of the matched allografted patients. This difference is highly significant ($P<0.001$) using the log-rank test.

Twelve of the 33 chemo-immunotherapy patients have died (11 of relapse and one of infection while in remission) with a median survival of 21 months from date of complete remission. There have been five deaths in the 27 matched allografted patients, one of relapse, four of GVHD with or without pneumonitis, (two of these patients received methotrexate prophylaxis and one only a short course of CSA). Actuarial analysis of survival from complete remission of these two groups (Fig. 2) shows that while there is not at present a statistically significant difference between them, at no time do the transplanted patients fare worse and they have a 75% 3 year actuarial survival compared with 45% for the chemoimmunotherapy patients.

Survival from graft date is shown in Figure 3. Nineteen (70%) matched allografted patients remain alive in continuous remission compared with 12 (33%) of chemoimmunotherapy patients ($P=<0.01$).

The syngeneic and mis-matched allografts received the same conditioning regimen and supportive care. The mis-matched allografts all received prolonged CSA as prophylaxis against GVHD. Their outcome is shown in Table 2.

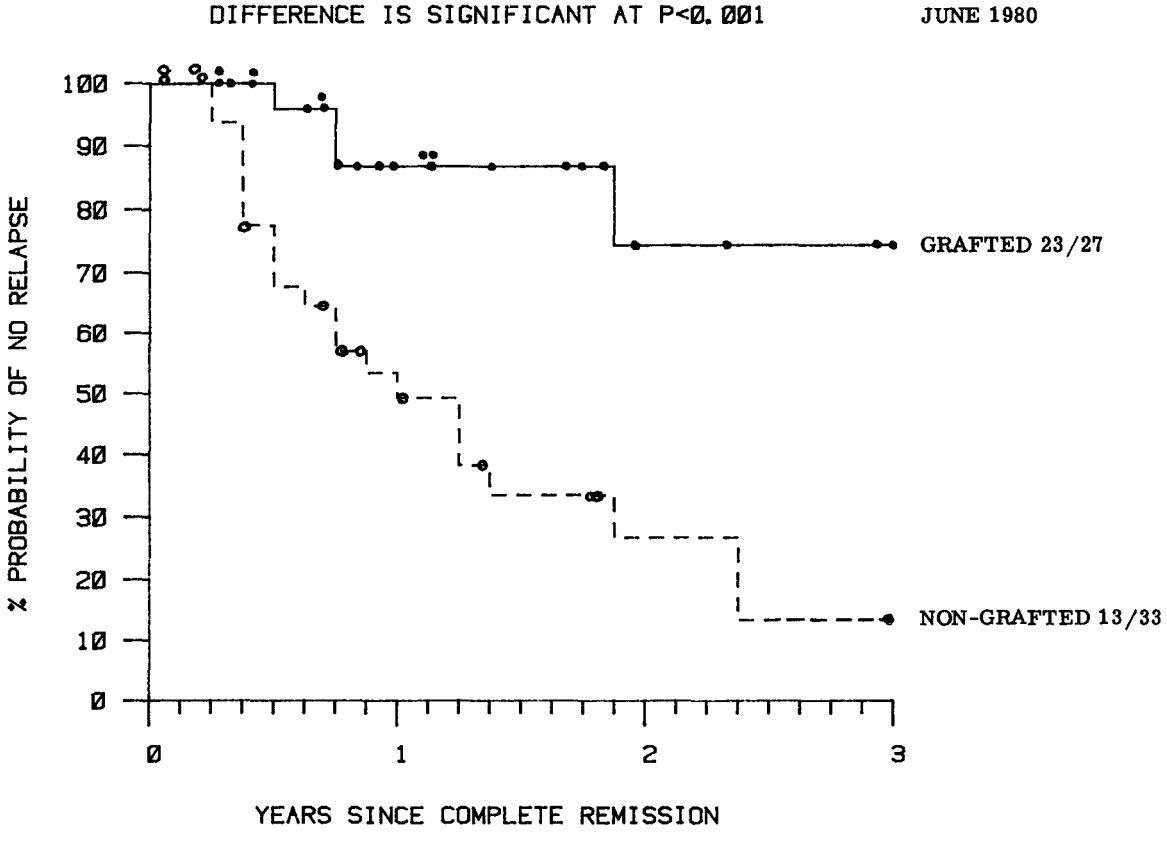

Fig. 1. Actuarial life table analysis of complete remission duration

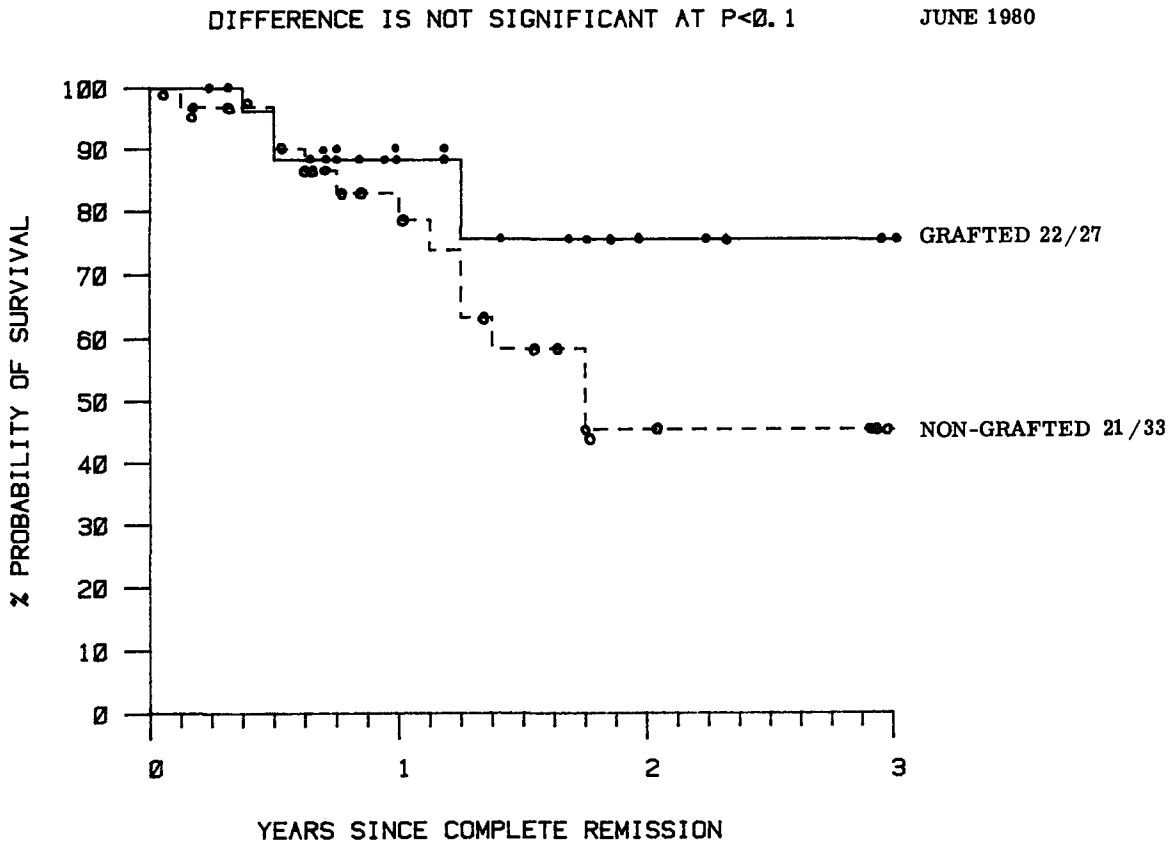

Fig. 2. Actuarial life table analysis of survival from complete remission date

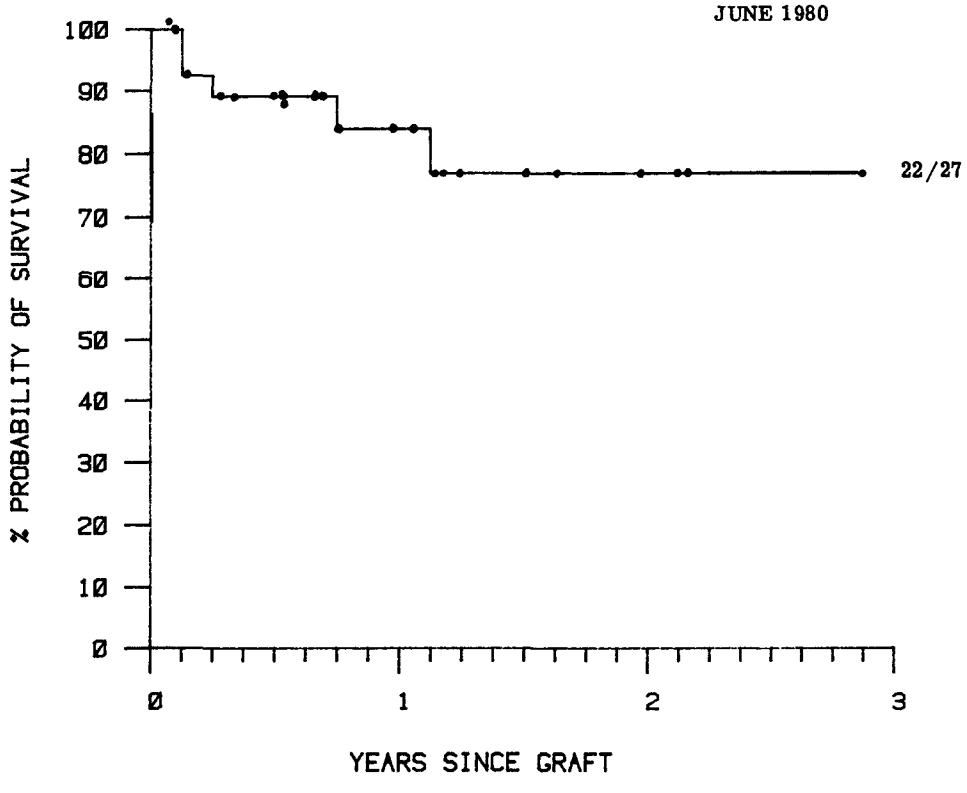

Fig. 3. Actuarial life table analysis of survival from transplant date

	No.	Recurrent Leukaemia		Other deaths
		Total	Died	
Matched allograft:				
CSA prophylaxis	21	3 (14%)	1	2 GVHD
Mtx prophylaxis	6	1 (17%)	0	2 GVHD
Mis-matched allograft	4	1	1	1 pulmonary oedema
Syngeneic graft	2	1	1	0

Table 2. Outcome of patients transplanted for AML in first remission

C. Discussion and Conclusions

The results show clearly that allogeneic BMT significantly reduces the risk of relapse in AML in first remission compared with conventional chemoimmunotherapy, although it is too early to state what the long-term (greater than 2 years) remission rate may be.

The transplanted patients at no time fare worse than the non-transplanted controls, despite four deaths from GVHD. With the greatly reduced mortality from GVHD in patients on long-term CSA (Powles et al. 1980b) this may be a much less severe problem in future. Of the 21 patients with AML in first remission who received CSA after matched allografts 20 received the drug for a period of at least 4 months (Powles et al. 1980b) and 18 are alive and 16 (80%) free from leukaemia.

Cyclosporin A does not seem to influence the relapse rate after transplantation when compared with methotrexate; so far only 3 of the 21 matched patients on CSA have had recurrent leukaemia (Table 2).

We feel that patients under the age of 45 with AML in a first remission who have a suitable donor should be offered as an alternative to chemoimmunotherapy a bone marrow transplant, but at present this should only be done in a suitably experienced centre.

References

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