

Autologous Bone Marrow Transplantation for High-Grade Lymphoid Malignancy Using Melphalan/Irradiation Conditioning Without Marrow Purging or Cryopreservation

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We report the safety and efficacy of 34 consecutive autologous bone marrow transplant (ABMT) procedures performed in adult patients with high-grade lymphoid malignancy after remission induction therapy. Fifteen patients with acute lymphoblastic leukemia (ALL) and six with high-grade non-Hodgkin's lymphoma (NHL) received pretransplant conditioning with intravenous (IV) melphalan and fractionated total body irradiation (TBI). Thirteen other patients with NHL were conditioned with melphalan alone, having previously received local involved field radiotherapy. Unmanipulated non-cryopreserved autologous marrow was reinfused within 48 hours of harvesting. Engraftment occurred in all patients with medians of 10 days of neutropenia (neutrophils $<0.5 \times 10^9/L$), 4-day platelet transfusion requirement, 3 U packed RBC transfusion, and 18 days in hospital posttransplant. There were no procedure-related deaths. Actuarial disease-free survival in the 13 patients with ALL receiving autotransplant early in first remission is 48% with a median

follow-up of 3 years. Two other ALL patients who had autotransplants after a period of maintenance therapy also remain in complete remission (CR). These results compare favorably with our 34% disease-free survival (DFS) in 15 allogeneic ALL transplant patients and 21% DFS in 19 patients on standard maintenance after a common induction schedule. No relapses have occurred in the 17 NHL patients transplanted in remission (median follow-up 2 years), but the two NHL patients who developed recurrent disease before ABMT died of progressive disease after temporary responses. We conclude that this method of ABMT results in rapid reengraftment with lack of toxicity and that the conditioning treatment used shows good efficacy against disease. It is applicable in high-grade lymphoid malignancy in first remission, and our results call into question the need for marrow purging in ALL and NHL patients transplanted in first remission.

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RESULTS OF treatment of high-grade lymphoid malignancies have improved in recent years with more intensive chemotherapeutic regimens. Dose tolerance, limited by myelotoxicity, can be extended by autologous marrow rescue. This approach has been used successfully in first remission in adult acute lymphoblastic leukemia (ALL)^{1,2} and in poor-risk non-Hodgkin's lymphoma (NHL).^{3,5}

In the Northern region of England in 1983, the observed poor survival prospects for adults with ALL treated with conventional chemotherapy⁶ led to a policy of offering patients in remission after initial induction aged less than 55 years a bone marrow transplant (BMT) procedure in first complete remission (CR1). All patients aged between 15 and 55 years who elected to have transplantation received autologous BMT (ABMT) except those aged less than 45 years with an HLA-identical sibling who were offered allogeneic BMT in CR1 in preference to autotransplant. Melphalan, in addition to total body irradiation (TBI), was chosen for preconditioning for ABMT because its short half-life avoided the necessity for marrow cryopreservation facilities, which were not then locally available. No attempt was made to "purge" the marrow of potential residual disease. The improved survival prospects afforded by these transplantation options (autologous or allogeneic) in ALL as compared with conventional maintenance chemotherapy were reported in preliminary form previously.¹

Lack of toxicity in the ALL ABMT patients led to a similar approach in a group of adults with high-grade NHL who entered CR but who had poor prognostic features at diagnosis. Before ABMT, they were treated on a standard induction protocol with six cycles of either methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, and

prednisolone (M-BACOP) or M-BACOP alternating with prednisolone, etoposide, vindesine, and chlorambucil (PEEC) as part of a randomized trial of induction therapy (NHL-III, Scotland and Newcastle Lymphoma Group, SNLG).⁷ Patients who had features suggestive of a risk of CNS relapse were preconditioned with melphalan and TBI as were ALL patients. Those with localized bulky extranodal disease received local radiotherapy before conditioning with melphalan alone at the same dosage.

We wished to assess the toxicity and the effects on survival of this method of ABMT in these groups of high-risk lymphoma patients and continue the comparison between autotransplant in ALL with use of allogeneic transplant and standard maintenance in CR1.

MATERIALS AND METHODS

Patients

ABMT was performed between January 1984 and December 1988 in 15 patients with ALL in CR1 and 19 patients with NHL: 16 in CR1, 1 in CR2, and 2 in whom planned transplantation in CR1 was preempted by recurrence of disease before the procedure.

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Median age for all patients was 30 years (range 18 to 58 years). Patient details are shown in Tables 1 and 2. Patients with ALL who received allogeneic transplant (15) and standard maintenance (19) are also discussed for comparison.

The diagnosis of ALL was based on Romanowsky-stained smears of blood and BM, cytochemical staining including periodic acid-Schiff (PAS) and Sudan black reactions, and immunologic studies (Table 3). No cases were associated with antibody to HTLV-1 or HIV.

ALL Details of Patient Population and Selection of Therapy

From October 1982, a multidrug schedule for therapy in ALL patients aged more than 15 years was introduced in the Northeastern region of the UK. Designated NE ALL III, this is a 28-week induction and consolidation protocol described in detail previously.^{3,6} In our previous publications,^{2,3} we indicated that this therapy was used for all patients who were able to receive an aggressive protocol in our region, which has a population of 3.3 million. Between October 1982 and June 1988, the number of unselected patients aged more than 15 years with ALL was 100. Twenty were excluded from the protocol and treated with palliative therapy only because of advanced age or death occurring within the first week of diagnosis. Of those receiving NE ALL III, 16 died in the first month or did not obtain remission. Nine patients either died in remission or developed recurrent leukemia before the end of the 28-week schedule. Three patients were resistant to standard induction and achieved remission with a regimen of cytosine arabinoside 1 g/m² twice daily for 3 days plus mitoxantrone, 12 mg/m² IV daily for three days (two courses). Thus, 55 patients reached the end of the 28-week schedule in established remission and were considered for secondary therapy at that time. Six patients were aged more than 55 years and were not considered for transplant. They received standard maintenance therapy but are not considered further in this study as it relates only to patients aged less than 55 years. The remaining 49 patients were allocated to the various forms of therapy as described below.

Group I: NE ALL III plus standard maintenance (<55 years) 6 mercaptopurine [(6MP) and methotrexate] (19). From October 1982 to January 1984, all patients who were in CR at 28 weeks who did not have an allogeneic donor received standard maintenance

with daily oral 6MP 100 mg/m² (maximum 150 mg) and weekly oral methotrexate 15 mg/m² (maximum 20 mg) for 100 weeks. From 1984 to 1986 patients aged less than 30 years with WBC more than 50 × 10⁹/L who had a "common" ALL phenotype continued on this schedule; ie, "good-risk" patients were kept on the standard maintenance. From 1986 to 1988 standard maintenance was used only for those patients aged more than 55 years because allogeneic or autologous transplant was offered to all patients aged less than 55 years and none of the patients refused these options.

Group II: NE ALL III plus allogeneic transplant (15). From March 1983, patients with ALL aged more than 15 and less than 45 years underwent tissue typing against their siblings and all those who had fully matched HLA-identical donors (16) were offered allogeneic transplant in CR1. Only one patient (patient 7) who had an allogeneic donor preferred to have an autotransplant. The remaining 15 patients proceeded with this option. By chance, the median age of this group was substantially lower than that of patients in groups I and III, but they self-selected on the basis of tissue typing alone.

Group III: NE ALL III plus autologous transplant with melphalan and TBI (13). Owing to the observed high relapse rate in poor-risk patients on NE ALL III and standard maintenance in 1983 who were aged more than 30 years with WBC more than 50 × 10⁹/L, the melphalan/TBI autotransplant was introduced as an alternative consolidation with standard maintenance between 1984 and 1986 for such patients. Because of the lack of toxicity of this method, it was subsequently offered to all patients who did not have an allogeneic donor who were aged more than 15 and less than 55 years from 1986 to 1988 regardless of risk features. No one offered an ABMT refused the procedure. We were able to perform ABMT on all patients fulfilling the criteria, and there was no problem of transplant delay owing to lack of marrow cellularity. The median time from diagnosis to autotransplant was 7.0 months (range 6 to 12 months).

Group IV: NE ALL III plus maintenance plus ABMT (2). One patient received NE ALL III, cranial irradiation, and 100 full weeks of maintenance. This patient then requested an autotransplant procedure that had just become available. An additional patient who underwent cranial irradiation had ABMT delayed as a result and continued on maintenance therapy until 6 weeks before

Table 1. ALL ABMT Patients

Case No.	Age/Sex	Induction Treatment	Time From Diagnosis to ABMT (mo)	Days of Neutropenia <0.5 × 10 ⁹ /L	Days of Platelet Transfusion	Units of Blood Transfusion	Days in Hospital	Outcome
1	45/F	NE ALL III + DCF	9	12	2	0	17	R d 822, D
2	51/M	NE ALL III	11	12	1	3	23	A/W d, 1,532+
3	48/F	NE ALL III	12	19	18	7	24	A/W d 1,142+
4	18/M	NE ALL III	8	9	5	2	21	R d 432, D
5	32/F	NE ALL III	6	10	6	2	18	R d 184, D
6	34/F	NE ALL III	7	9	3	2	21	R d 180, D
7	39/M	NE ALL III	6	10	3	0	18	A/W d, 1073+
8	39/M	NE ALL III	6	13	6	0	21	R d 97, D
9	18/M	NE ALL III + Cy/MTZ	6	8	38	21	53	R d 145, D
10	18/M	NE ALL III	7	11	4	6	20	A/W d 943+
11	24/F	NE ALL III	8	25	10	4	18	A/W d 425+
12	30/M	NE ALL III	6	15	6	10	19	A/W d 351+
13	19/M	NE ALL III	9	14	5	2	25	A/W d 291+
14	21/M	NE ALL III	23	10	7	7	22	A/W d 1,551+
15	18/F	NE ALL III	34	9	7	19	19	A/W d 1,278+

Patients 14 and 15 who were transplanted after maintenance therapy are not included in the survival figure for the autotransplant group. Survival is calculated from transplant date for each patient.

Abbreviations: DCF, deoxycoformicin; Cy/MTZ, high-dose cytarabine and mitoxantrone; A/W, alive and well; d, days posttransplant; R, relapse; D, died.

Table 2. NHL ABMT Patients

Case No.	Age/ Sex	Diagnostic Histology	State at Diagnosis	Site(s) of Disease	Status at ABMT	Conditioning	Time From Diagnosis to ABMT	Days of Neutropenia <0.5 × 10 ⁹ /L	Days of Platelet Transfusion	Units of Blood Transfusion	Days in Hospital	Outcome
1	50/M	Lymphoblastic	IIIB	Neck/Med	CR1	M/TBI	9	7	3	3	18	A/W d 1,698+
2	58/M	Diff C/blast (previous HD)	IIIAS	Med/abdomen	CR1	M	9	3	1	2	13	D d 1,200 ca lung
3	30/M	Lymphoblastic	IIIB	Med/abdomen	CR1	M/TBI	8	5	10	4	20	A/W d 1,346+
4	45/F	Diff C/blast	IIIEA	Thyroid/Med/abdomen	CR1	M	6	11	10	4	26	A/W d 1,318+
5	44/M	Lymphoblastic	IVB	Med/abdomen/bone marrow	CR2	M/TBI	6	10	1	0	18	A/W d 1,162+
6	29/M	Diff C/blast	IIIB	Med/abdomen	CR1	M/TBI	7	8	3	0	17	A/W d 1,121+
7	43/M	Lymphoblastic	IE	CNS	CR1	M	8	11	2	0	18	A/W d 1,094+
8	26/F	Diff C/blast	IVAE	Pelvis	CR1	M	12	7	1	2	18	A/W d 984+
9	24/F	Diff C/blast	IVB	Abdomen (bowel/liver)	CR1	M	9	8	1	2	14	A/W d 951+
10	24/F	Diff C/blast	IIE	Abdomen (bowel)	CR1	M	8	7	2	0	15	A/W d 923+
11	25/M	Diff C/blast	IIAE	Med	CR1	M	11	14	8	0	20	A/W d 540+
12	48/M	Immunoblastic	IVB	Abdomen/marrow	Rel	M/TBI	8	8	2	4	15	D d 70
13	41/M	Diff C/blast	IVB	Med/lung	CR1	M	8	8	1	0	15	A/W d 457+
14	47/M	Diff C/blast	IIIA	Med/abdomen	CR1	M	14	19	8	0	19	A/W d 443+
15	30/M	Diff C/blast	IIAE	Abdomen (bowel)	CR1	M	11	13	4	2	19	A/W d 414+
16	54/M	Diff C/blast (previous thyroid ca)	IE	Med	CR1	M	13	14	3	2	18	A/W d 400+
17	21/M	Diff C/blast	IIB	Med	CR1	M	9	15	5	4	20	A/W d 373+
18	43/M	C/cytic/C/blast	IVA	Med/abdomen	CR2	M	6	12	3	4	18	A/W d 329+
19	24/M	Lymphoblastic	IVB	Abdomen (bowel)	Rel	M/TBI	6	12	5	3	24	D d 30

Abbreviations: Med, mediastinum; A/W, alive and well; d, days posttransplant; D, died; HD, Hodgkin's disease; Diff C/blast, diffuse centroblastic; C/cytic/C/blast, centrocytic centroblastic; TBI, total body irradiation.

Table 3. ALL Patient Characteristics and Survival Rates

Group	Sex	Median Age (y)/(range)	Immunologic Phenotype	Actuarial Relapse-Free Survival 3 y From Transplant (%)
I, Standard maintenance (19)	13 F	32 (14-54)	T	5
	6 M		Common	21
			Null	10
II, Allograft (15)	4 F	19 (15-40)	T	5
	11 M		Common	34
			Null	7
III, ABMT (13)	5 F	31 (15-50)	T	4
	8 M		Common	48
			Null	6
IV, Standard maintenance and autograft (2)	1 F	18	T	1
	1 M	21	Common	Both patients alive and well

Characteristics of 49 patients with ALL aged 15 to 55 years achieving sustained remission at 28 weeks from diagnosis. The 15 patients who received allogeneic transplant (group II) received preconditioning with cyclophosphamide (60 mg/kg twice) and TBI (200 cGy six times) in 3 days with cyclosporin alone used as immunosuppression. The preconditioning for the ABMT (groups III and group IV) was melphalan/TBI (described in text). Standard maintenance was 6-mercaptopurine and methotrexate for a period of 100 weeks (group I). The late autograft in patients 14 and 15 were performed as a result of requests by patients and attending physicians. Actuarial relapse-free survivals given were calculated from the time of transplant (Table 1) and assessed for all groups at 36 months, after which no relapses have occurred in any group in this cohort.

Abbreviation: NK, not known.

autotransplant. Additional basic characteristics of the ALL groups are shown in Table 3.

NHL patients. Patients with high-grade NHL with the recognized poor-risk features of Ann Arbor stage 4 disease, bulk (> 10 cm) disease either nodal or extranodal, disease at multiple extranodal sites, NHL occurring after previous treatment for Hodgkin's disease, or risk criteria as described by Coleman et al⁸ (lymphoblastic histology with CNS or BM involvement), were autografted after remission induction treatment. All patients received melphalan conditioning. TBI was used as well in patients with features associated with a risk of CNS relapse (ie, lymphoblastic histology, multiple extranodal sites, or marrow involvement).

NHL patients had remission induced on the SNLG NHL-III protocol,⁷ except for patient 19 who received additional systemic and intrathecal treatment because of the histologic appearances of Burkitt's lymphoma. Patients were selected on the above poor-risk criteria. No patient offered autotransplant declined. For NHL patients, median time to transplant from diagnosis was 8 months (range 6 to 14 months), with remission induction chemotherapy taking 5 months, and local radiotherapy (4 weeks) preceding autotransplant in patients not receiving TBI.

Autotransplantation Procedure

Bilateral check BM aspirates and trephines were obtained from the posterior iliac crests to confirm remission and adequate cellularity 2 to 4 weeks before ABMT. At ABMT, patients were anesthetized and received 2,000 IU sodium heparin IV. BM was harvested from the posterior iliac crests into acid citrate dextrose anticoagulant in standard blood transfusion collection packs, to yield a median nucleated cell dose of 2.9×10^9 /kg recipient weight (range 1.9 to 5.5 kg), and stored at 4°C. Storage for 48 hours under these conditions does not affect CFU-GM growth in culture (G.H. Jackson, unpublished observations, 1990). Conditioning proceeded with melphalan 3 mg/kg body weight by IV infusion immediately

Table 4. ABMT: Details of Engraftment

Conditioning	Melphalan/TBI	Melphalan Alone
Days of neutropenia ($<0.5 \times 10^9/L$)	10 (5-25)	11 (3-19)
Days of platelet transfusion	5 (1-38)	3 (1-10)
Days in hospital posttransplant	20 (15-53)	18 (13-26)

Comparison of reengraftment after melphalan/TBI conditioning as compared with melphalan alone. Numbers are median numbers of days, with ranges in parentheses.

after drug reconstitution and from a light-protected container to avoid loss of efficacy owing to rapid hydrolysis of the drug.

Patients receiving TBI received a total dose of 1,050 cGy in three fractions of 350 cGy in 36 hours at a dose rate of 25 cGy/min. The unmanipulated stored marrow was reinfused within 48 hours of harvesting.

Supportive Care

Patients were nursed in single rooms and received standard supportive care during hematologic recovery. They received platelet transfusions as well to maintain the platelet count above $20 \times 10^9/L$. All cellular blood products for transfusion were irradiated and were cytomegalovirus (CMV)-antibody negative.

RESULTS

Hematologic Reconstitution

Marrow reengraftment occurred rapidly in all patients except ALL patient 9, who had prolonged thrombocytopenia. He alone had received high-dose cytarabine and mitozantrone (Cy/MTZ), before ABMT conditioning. Median number of days of neutropenia ($<0.5 \times 10^9/L$) was 10 (range 3 to 25 days). Patients required transfusion of platelet concentrates on a median of four occasions (range 1 to 38) and received a median of 3 U (range 0 to 10 U) packed RBC. Reengraftment rates between patients receiving melphalan/TBI and those receiving melphalan alone (Table 4) were not different.

Other Toxicity

Mild oral mucositis was common in patients receiving TBI in addition to melphalan. Twelve of 21 patients in the melphalan/TBI group and 5 of 13 in the melphalan-alone group required IV antibiotics for pyrexial episodes during the transplant admission. No patient had renal failure or interstitial pneumonitis. Patients spent a median of 18 days

(range 15 to 53 days) posttransplant in the hospital. There were no procedure-related deaths.

Effect on Disease

Actuarial DFS after autotransplant (calculated from time of transplant) for patients with ALL is 48% with a median follow-up of 2.5 years from time of transplant (Fig 1) (Table 3). This increases to 57% if the two patients transplanted after maintenance therapy are included. Failure in this group resulted entirely from leukemic relapse. In the other comparable groups (Table 3) DFS for the allograft group was 34%; leukemic relapse and pulmonary toxicity (interstitial pneumonitis and CMV pneumonitis) were responsible for the deaths. No deaths resulted from graft-v-host disease. The DFS for the standard maintenance group was 21% (Fig 1), with leukemic relapse accounting for all the failures.

Figure 2 shows the relapse-free survival data for the NHL patients. No relapses have occurred in the 17 NHL patients transplanted in CR (curve 1, median follow-up 2 years). One patient, a smoker, died 3 years posttransplant with squamous carcinoma of the lung and without evidence of lymphoma recurrence. This event is responsible for the step in survival curves 1 and 2 at day 1,200 (Fig 2). Curve 2 (Fig 2) relates to all 19 transplanted NHL patients, including the two patients who relapsed before ABMT, both of whom died of progressive disease after transient responses.

DISCUSSION

Most institutions reporting use of ABMT in adult ALL and high-risk lymphoma use cyclophosphamide \pm busulfan \pm TBI conditioning as well as marrow cryopreservation and, sometimes, purging techniques. Melphalan is an alternative conditioning agent, and its short 1/2 life avoids the necessity for cryopreservation. Melphalan conditioning, however, has been associated with a reported high toxicity: melphalan/TBI was compared with cyclophosphamide/TBI in a study of allogeneic BMT for AML.⁹ Results suggested a greater antileukemic effect for melphalan but toxicity in the melphalan arm was very high, with renal failure accounting for most of the excess deaths. Our results indicate that melphalan/TBI conditioning itself is well tolerated and lend support to the suggestion of those investigators⁹ that another mechanism, eg, interaction between melphalan

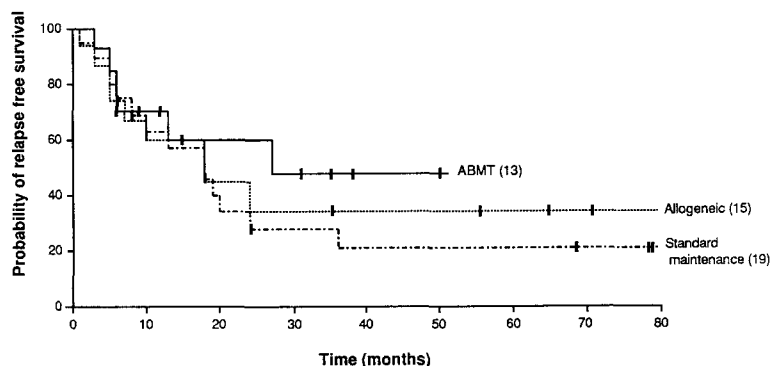


Fig 1. Adult ALL actuarial disease-free survival curves: ABMT, allogeneic, standard maintenance. These curves show the relative survival from the time of transplant in the allogeneic and autologous groups. The curves for standard maintenance start from the time of completion of the 6-month induction schedule. The plateau at which percentage survival figures are given was calculated at 36 months for each curve. A chi-square test of patients who received autotransplant v patients who had standard maintenance does not currently show a statistically significant difference ($P = .35$).

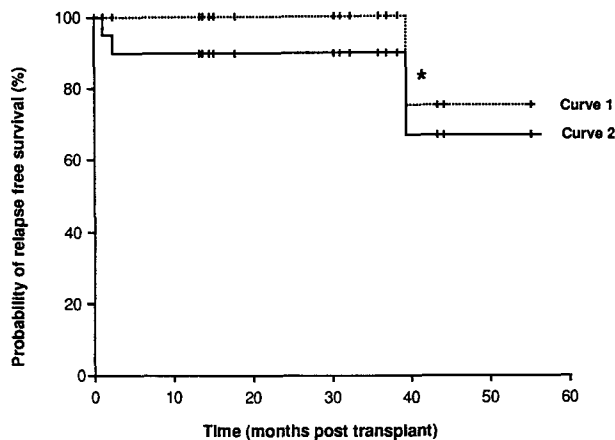


Fig 2. Actuarial disease-free survival for NHL patients following ABMT. NHL patients. Kaplan-Meier actuarial relapse-free survival curves. Curve 1 relates to patients autografted in CR1. Curve 2 includes the two patients who were relapsing at the time of autotransplant (described in text). The decrease at 39 months (*) resulted from a death from an unrelated lung carcinoma that was not censored.

and cyclosporin, may have been responsible for the toxicity in their allograft study. No significant changes in serum creatinine concentration were observed posttransplantation in our patients. Hematologic reconstitution, and in particular recovery of platelet counts in our patients was more rapid than that reported with cryopreserved marrow,¹⁰ even with use of recombinant growth factors.¹¹

The lack of toxicity in our autografted patients with ALL gives this group the best overall survival, although the incidence of relapse is higher than that of the allografted group. This difference in early morbidity and mortality between the two types of transplantation was noted previously in a larger comparative study of 91 patients with high risk ALL,¹² although as in our study the question of the significance of the difference in outcome between the two groups is not statistically answered.

With regard to the efficacy of our conditioning regime, the relapse-free survival of our ALL patients compares favorably with the latest reported European Bone Marrow Transplant Group¹³ and the International Bone Marrow Transplant Registry¹⁴ for ALL patients autografted in CR1.

Our results are similar to those of a recently reported series of 21 ALL patients receiving ABMT in CR1 with purged marrow² in which the actuarial relapse-free survival was 65% with a median follow-up of only 16 months. Our series is the largest reported from a single center using unpurged ABMT in CR1 and suggests that the case for purging has yet to be proven.

In NHL, the potential value of high-dose therapy followed by ABMT in patients with advanced disease has been reported.^{15,16} The observation of a more favorable outcome in "sensitive" as compared with "resistant" relapse¹⁷ prompted transplantation in CR1 in a series of patients perceived to be at high risk of relapse on conventional therapy using criteria similar to those identified by Coleman et al.⁸ A reluctance to undertake high-dose therapy with BM rescue in CR1 has been expressed,¹⁸ however, because of procedure-related mortality rates of approximately 20% in the larger reported series performed in advanced disease^{16,17} and the difficulty of proving efficacy in patients in CR1 whose outlook is in any case more favorable than that of patients with advanced disease. The relapse-free survival data for our NHL patients suggest a useful efficacy. Proof of that efficacy will require a controlled study and longer follow-up. We have shown, however, that this is a safe approach which merits further study in such patients. We consider that this approach using modest dose intensity can be used when attempting to eradicate minimal residual disease and believe that this philosophy should encourage further investigation of this relatively "gentle" form of autotransplant in CR1 rather than using the very high doses of conditioning required for transplants at a later stage of disease.

We conclude that ABMT using melphalan with or without TBI conditioning is a well-tolerated procedure that can be performed safely without the need to cryopreserve marrow. It appears to have a useful efficacy in high-grade lymphoid malignancy in first remission. This form of ABMT in ALL has allowed completion of therapy in a shorter time and led to improved quality of life for the recipients. A trend toward improved duration of disease-free survival is not statistically significant at present. More patients and a larger follow-up will be required to prove whether overall survival will be improved.

REFERENCES

- Proctor SJ, Hamilton PJ, Taylor P, Carey P, Hargrave S, Evans RGB, Summerfield G, Finney R, Saunders P, Goff D, Reid MM: A comparative study of combination chemotherapy versus marrow transplant in first remission in adult acute lymphoblastic leukaemia. *Br J Haematol* 69:35, 1988
- Simonsson B, Burnett AK, Prentice HG, Hann IH, Bremer MK, Gibson B, Grob JP, Lonnerholm G, Morrison A, Smedmyr B, Todd A, Oberg G, Gilmore M, Campana D, Totterman T: Autologous bone marrow transplantation with monoclonal antibody purged marrow for high risk acute lymphoblastic leukaemia. *Leukemia* 3:631, 1989
- Philip T, Hartmann O, Biron P, Cahn JY, Pein F, Bordigoni P, Souillet G, Lasset C, Chauvin F: High dose therapy and autologous bone marrow transplantation in partial remission after first line induction therapy for diffuse non-Hodgkin's lymphoma. *J Clin Oncol* 6:1118, 1988
- Gulati SC, Shank B, Black P, Yapp J, Koziner B, Straus D, Filippa D, Kempin S, Castro-Malaspina H, Cunningham I, Berman E, Coleman M, Langleben A, Colvin OM, Fuks Z, O'Reilly R, Clarkson B: Autologous bone marrow transplantation for patients with poor prognosis lymphoma. *J Clin Oncol* 6:1303, 1988
- Milpied N, Ifram N, Kuentz M, Maraninchi D, Colombat P, Blaise D, Harousseau JL: Bone marrow transplantation for adult poor prognosis lymphoblastic lymphoma in first complete remission. *Br J Haematol* 73:82, 1989
- Proctor SJ, Taylor P, Thompson RB, Finney R, Reid MM, Hamilton PJ, Saunders PJ, Fail B, Dickinson A, Paul B, Qureshi M, Tinegate H, Lennard A, Stainsby D, Goff D, Kay L, Cartner R, Mamood A, Condie P, Collins A, Abela M, Renwick L, Walker W,

Evans RGB: Acute lymphoblastic leukaemia in the Northern Region of England—A study of 75 cases. *Q J Med* 57:761, 1985

7. Leonard RCF, Proctor SJ, Lucraft H, Dawson AA: Methylprednisolone, VP16, chlorambucil and vindesine (PEEC) as initial salvage therapy in non-Hodgkin's lymphoma. *Scot Med J* 33:360, 1988

8. Coleman CN, Picozzi VJ, Cox RS, McWhirter K, Weiss LM, Cohen JR, Yu KP, Rosenberg SA: Treatment of lymphoblastic lymphoma in adults. *J Clin Oncol* 4:1628, 1986

9. Helenglass G, Powles RL, McElwain TJ, Lakmani A, Milan S, Gore M, Nandi A, Zuiable A, Perren T, Forgeson G, Treleavan J, Hamilton C, Millar J: Melphalan and total body irradiation (TBI) versus cyclophosphamide and TBI as conditioning for allogeneic matched sibling bone marrow transplants for acute myeloblastic leukaemia in first remission. *Bone Marrow Transplant* 3:21, 1988

10. Hill RS, Mazza P, Amos D, Buckner CD, Appelbaum FR, Martin P, Still BJ, Sica S, Berenson R, Bensinger W, Clift RA, Stewart P, Doney K, Sanders J, Singer J, Sullivan KM, Witherpoon RP, Storb R, Livingston R, Chard R, Thomas ED: Engraftment in 86 patients with lymphoid malignancy after autologous marrow transplantation. *Bone Marrow Transplant* 4:69, 1989

11. Anderson CC, Goldstone AH, Linch DC, Jones HM, Franklin IM, Boughton BJ, Cawley JC, Richards JDM: Autologous bone marrow transplantation for patients with acute myeloid leukaemia and acute lymphoblastic leukaemia—A comparison. *Bone Marrow Transplant* 1:271, 1987

12. Kersey JH, Weisdorf D, Nesbit ME, Lebien TW, Woods WG, McGlave PB, Kim T, Vallera DA, Goldman AI, Bostrom B, Hurd D, Ramsay NKC: Comparison of autologous and allogeneic

bone marrow transplantation for treatment of high-risk refractory acute lymphoblastic leukaemia. *N Engl J Med* 317:461, 1987

13. European Group for Bone Marrow Transplantation: Working Party on Leukemia: Allogeneic bone marrow transplants of leukemia in Europe. *Lancet* 1:1379, 1988

14. Bortin MM, Horowitz MM, Gale RP: Current status of bone marrow transplantation in humans: Report from the International Bone Marrow Transplant Registry. *Nat Immun Cell Growth Regul* 7:334, 1988

15. Appelbaum FR, Sullivan KM, Buckner CD: Treatment of malignant lymphoma in 100 patients with chemotherapy, total body irradiation and marrow transplantation. *J Clin Oncol* 5:1340, 1987

16. Phillips GL, Herzig RH, Lazarus HM, Fay JW, Wolff SN, Mill WB, Lin HS, Thomas PRM, Glasgow GP, Shina DC, Herzig GP: Treatment of resistant malignant lymphoma with cyclophosphamide, total body irradiation, and transplantation of cryopreserved autologous marrow. *N Engl J Med* 310:1557, 1984

17. Philip T, Armitage JO, Spitzer G, Chauvin F, Jaggannath S, Cahn JY, Colombat P, Goldstone AH, Gorin N, Flesh M, Laport JP, Maraniachi D, Pico J, Bosly A, Anderson C, Schots R, Biron P, Cabanillas F, Dicke K: High-dose therapy and autologous marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med* 316:1493, 1987

18. Gribben JG, Vaughan Hudson B, Linch DC: The potential value of very intensive therapy with autologous bone marrow rescue in the treatment of malignant lymphomas. *Hematol Oncol* 1987