Haematology and Blood Transfusion Vol. 31
Modern Trends in Human Leukemia VII
Edited by Neth, Gallo, Greaves, and Kabisch

Ablative Therapy Supported by Autologous Bone Marrow Transplantation with In Vitro Treatment of Marrow in Patients with B-Cell Malignancy

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A. Introduction

Patients with non-Hodgkin's lymphoma who relapse almost invariably die as a consequence of the disease regardless of histological subtype [1–4]. Ablative therapy supported by autologous bone marrow transplantation (BMT) may result in durable remissions in a proportion of such patients [5–8] although this approach is limited by the high frequency of bone marrow (BM) infiltration. Nadler et al. [9] have used the B-cell-specific monoclonal antibody anti-B1 [10] and rabbit complement to deplete autologous marrow of residual, morphologically undetectable lymphoma. A study is in progress at St. Bartholomew's Hospital to evaluate the use of ablative therapy supported by such in vitro-treated autologous BM as consolidation of second or subsequent remission in patients with B-cell malignancy.

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B. Patients and Methods

I. Patients

Thirteen patients have been treated since June 1985. Clinical characteristics are shown in Table 1. Patient 6 had minimal splenomegaly at the time of treatment, the remainder had no evidence of disease by computerized tomography (CT) scan criteria and on the basis of BM morphology and phenotyping.

Table 1. Clinical characteristics

Patient	Age	Histology	Stage at presentation	Site	Remission status
1	38	Follicular	IIIA	Lymph node	3rd
2	44	Follicular	IVB	Lymph node, liver, spleen, BM	2nd
3	42	Follicular	IVB	Lymph node, pl. effn., ascites, BM	2nd
4	55	Follicular	IVB	Lymph node, lung, pl. effn., BM	2nd
5	36	Follicular	IIIB	Lymph node	2nd
6	29	Follicular	IVB	Lymph node, liver, spleen, BM	3rd
7	39	Follicular	IIA	Lymph node	2nd
8	61	Follicular	IVA	Lymph node, BM	3rd
9	26	Burkitt	IVB	Lymph node, CNS, kidney, BM	1st
10	56	Centroblastic	IVB	Lymph node, liver, spleen	2nd
11	49	Centroblastic	IVB	Lymph node, bowel	3rd
12	50	Follicular	IVA	Lymph node, BM	2nd
13	38	Follicular	IIIA	Lymph node	3rd

II. In Vitro Treatment of BM

BM was aspirated from the anterior and posterior iliac crests under general anaesthetic. The mononuclear cell fraction was treated with three cycles of anti-B1 and rabbit complement (Pel-Freez) [9] and the cells cryopreserved.

III. Therapy

Patients received cyclophosphamide, 60 mg/kg IV on days 1 and 2, followed by total body irradiation, 200 cGy bd on days 3, 4 and 5 (except for the first four patients, who received a single dose of 900 cGy on day 3). Marrow was reinfused within 24 h of completion of radiotherapy.

C. Results

I. Haemopoietic and Immunological Reconstitution

Neutrophil recovery ($>0.5 \times 10^9$/l) occurred after 25 days (mean) with a range of 15–45 days. Platelet recovery ($>20 \times 10^9$/l) occurred after 28 days (mean) with a range of 15–54 days, except in one patient with follicular lymphoma with a persistently hypocellular bone marrow who continues to require platelet transfusions at 5-month intervals. Normal numbers of B cells were detectable in the peripheral blood at 3 months. Circulating immunoglobulin M and G (IgM and IgG) levels fell to <25% of normal 2–3 months after transplantation, returning towards normal at 6 months. The ratio of T8+ve (cytotoxic/suppressor) to T4+ve (helper/inducer) cells has reversed in all patients and this abnormality has persisted for over 6 months. (Data not shown.)

II. Toxicity

Twelve patients were discharged from hospital 15–42 days after reinfusion of marrow, one died of bronchopneumonia on day 9 (Table 2).

III. Survival

Eleven patients are well without evidence of disease; the patient with B-cell acute lymphoblastic leukaemia (B-ALL) has relapsed and died.

Table 2. Haematological reconstitution

Patient	N. of cells reinfused ($\times 10^9$/l)	Days to		Complications
		Neutrophils ($=0.5 \times 10^9$/l)	Platelets ($>20 \times 10^9$/l)	
1	3.6	21	23	Fever, no organism[a]
2	0.98	28	29	Pneumonia $\times 2$[a]
3	1.7	18	25	Fever, no organism[a]
4	1.6	16	13	Fever, no organism
5	2.2	23	23	Septicaemia
6	1.3	45	45	Septicaemia[a]
7	1.9	15	15	Herpes simplex
8	0.99	42	>5m	Fever, no organism[a]
9	2.3	20	54	Fever, no organism
10	1.6	Patient died on day 9		Bronchopneumonia
11	1.3	25	35	Fever, no organism
12	1.4	25	25	Fever, no organism[a]
13	1.9	25	25	Fever, no organism

All patients lost up to10% of their body weight.
[a] Oral ulceration.

D. Conclusions

The experience to date confirms the feasibility of this approach. It remains to be established whether such intensive therapy given as consolidation prolongs remission duration.

Acknowledgements. We thank the medical and nursing staff of Annie Zunz and Dalziel Wards for their expert care and Angie Mehta for typing the manuscript. Anti-B1 was kindly supplied by Dr. Lee Nadler and subsequently by Coulter Immunology.

References

1. Sweet DL, Golomb HM, Ultmann JE, et al. (1980) Cyclophosphamide, vincristine, methotraxate with leucovorin rescue, and cytarabine (COMLA) combination sequential chemotherapy for advanced diffuse histiocytic lymphoma. Ann Intern Med 92:785
2. Skarin AT, Canellos GP, Rosenthal DS, et al. (1983) Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotraxate alternating with standard agents (M-BACOD). J Clin Oncol 1:91
3. Fisher RI, De Vita VT Jr, Hubbard SM, et al. (1983) Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann Intern Med 98:304
4. Gallagher CJ, Gregory WM, Jones AE, et al. (1986) Follicular lymphoma: prognostic factors for response and survival. J Clin Oncol (in press)
5. Appelbaum FR, Herzig GP, Ziegler JC, et al. (1978) Successful engraftment of cryopreserved autologous bone marrow in patients with malignant lymphoma. Blood 52:85
6. Appelbaum FR, Thomas ED (1983) Review of the use of marrow transplantation in the treatment of non-Hodgkin's lymphoma. J Clin Oncol 1:440
7. Philip T, Biron P, Maraninchi D, et al. (1984) Role of massive chemotherapy and autologous bone marrow transplantation in non-Hodgkin's malignant lymphoma. Lancet I:391
8. Carella AM, et al. (1984) High-dose chemotherapy and nonfrozen autologous bone marrow transplantation in relapsed advanced lymphomas or those resistant to conventional chemotherapy. Cancer 33:1382
9. Nadler LM, Botnick L, Canellos GP, et al. (1984) Anti-B1 monoclonal antibody and complement treatment in autologous bone marrow transplantation for relapsed B-cell non-Hodgkin's lymphoma. Lancet
10. Stashenko P, et al. (1980) Characterization of a human B-lymphocyte-specific antigen. J Immunol 125:1678