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Prednisolone, Cytosine Arabinoside, Lomustine (CCNU), Etoposide and Thioguanine (PACET) Combination Chemotherapy for Relapsed or Refractory Non-Hodgkin Lymphoma

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27 patients with relapsed/refractory non-Hodgkin lymphoma (NHL) received combination chemotherapy with prednisolone, cytosine arabinoside, lomustine (CCNU), etoposide and thioguanine (PACET). 25 patients are evaluable for response. 7 (26%) obtained a complete response and one (4%) a partial response. The median survival for the entire group was 6 months. 2 patients are currently alive without disease, 1 of whom has received further therapy. The regimen was intensely myelosuppressive, but was well tolerated. The complete response rate and median survival figures are comparable to previous studies of salvage therapy confirming the poor prognosis for relapsed NHL and emphasising the need for prospective randomised studies.
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INTRODUCTION

AT LEAST 30 to 50% of patients with intermediate or high-grade non-Hodgkin lymphoma (NHL) will either fail to achieve a complete remission, or will relapse after first-line therapy [1]. Most patients with low-grade NHL will relapse following initial therapy, whether treated with single agents or combination chemotherapy [2].

Patients with intermediate or high-grade NHL have a very poor outlook with salvage chemotherapy. Reported median survivals are around only 6–9 months with long-term survival in only 10–20% of patients [3–5]. Although the time course for patients with low-grade NHL is longer, most will eventually die of their disease.

High-dose therapy with autologous bone marrow transplantation (ABMT) is now widely used for relapsed NHL. Long-term disease-free survival rates of 30–40% have been reported for selected patients thus treated [6–8].

One of the major limitations of high-dose therapy with ABMT has been that only a small proportion of relapsing patients are eligible for such treatment, because of age, poor performance status, marrow infiltration at relapse or unresponsive disease. We devised a salvage regimen based on the BACT [carmustine (BCNU), cytosine arabinoside, cyclophosphamide and 6-thioguanine] regimen [8]. At the time this study was initiated, BACT had been used successfully with ABMT in relapsed NHL. Three major modifications of the regimen were undertaken:

Lomustine (CCNU) was substituted for BCNU to allow oral administration; etoposide was added in view of its reported high single-agent activity in NHL [9], and doses were modified to allow it to be given without bone marrow transplantation. However, since each patient was expected to receive three cycles of this regimen, the total doses received were comparable with those in BACT.

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PATIENTS AND METHODS

Patients with relapsed non-Hodgkin's lymphoma were entered into this prospective study between November 1985 and December 1989. The following patients were eligible: aged 16–70 years; histologically documented relapse of NHL or relapse/progression of NHL in a site of previously histologically documented disease (biopsy-proven relapse was mandatory for all patients with previous low-grade NHL in view of the possibility of histological transformation); previous treatment with at least one anthracycline-based combination chemotherapy regimen; and normal values for renal, hepatic and bone marrow function, unless the abnormality was directly attributable to lymphoma.

During the early part of this study, all patients with relapsed NHL were entered on this protocol, since ABMT was not routinely used. From June 1986, ABMT was introduced and subsequent patients were those ineligible for ABMT. Standard staging techniques were used, and pathological material classified according to the Working Formulation.

Patients relapsing more than 6 months after their previous chemotherapy regimen received 1 cycle of CHOP (see Table 1) prior to entry onto the study. Only those patients with an objective response were considered eligible. Patients with primary refractory disease, and those relapsing within 6 months of their previous regimen entered the study without assessment of disease sensitivity. All patients were admitted to hospital for chemotherapy, which was as follows: prednisolone 40 mg/m^2 orally days 1–5; cytosine arabinoside 200 mg/m^2 intravenously days 1–5, given as a twice-daily bolus injection; CCNU 60 mg/m^2 orally days 1 and 2; etoposide 100 mg/m^2 intravenously days 1–5 given as a 45–60-min infusion; thioguanine 80 mg/m^2 orally days 1–5.

Table 1. Patient characteristics

		No. of patients
Total		27
Age (years)		
Median		57
Range		25–69
Male/female		14/13
Histology at relapse	SL	1
	FSC	1
	FM	1
	FLC	2
	DM	5
	DLC	12
	DLCI	3
	DSNC	1
	LL	1
Stage at relapse	I	5
	II	4
	III	5
	IV	3
Symptoms	A	17
	B	10
Bone marrow involvement		8
>10 cm disease bulk		7
Number of prior regimens	1	19
	2	6
	≥3	2
Previous regimen	CHOP	7
	CHOP/PEPA	9
	NH4	10
	Others	2
Response to previous regimen	CR	14
	PR	9
	PD	4
Median duration of previous response (range)	CR	6.5 months (1–25)
	PR	2 months (1–9)

SL = Small lymphocytic; FSC = follicular, predominantly small cleaved cell; FM = follicular mixed small and large cell; FLC = follicular, predominantly large cell; DM = diffuse mixed small and large cell; DLC = diffuse large cell; DLCI = diffuse large cell immunoblastic; DSNC = diffuse small non-cleaved cell; LL = lymphoblastic lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone [1]; CHOP/PEPA = cyclophosphamide, doxorubicin, vincristine, prednisolone, procarbazine, etoposide, prednisolone, doxorubicin [11]; NH4 = cyclophosphamide, etoposide, doxorubicin, vincristine, bleomycin, methotrexate, prednisolone [12]; CR = complete response; PR = partial response; PD = progressive disease.

No dose reductions were made for courses 1 and 2, although the third course was reduced to 3 days in most patients, depending upon their haematological tolerance.

Patients failing PACET chemotherapy were usually treated with palliative single-agent chemotherapy or radiotherapy.

Toxicity of PACET was recorded according to the WHO toxicity scale. Response was assessed 1 month after the completion of chemotherapy or at the time of disease progression, if soooner. Standard response criteria were used.

Actuarial survival curves were constructed according to the method of Kaplan and Meier [10]. Duration of survival was calculated from the date of commencement of PACET to the date of death or the last follow-up. Failure-free survival was calculated from the date of commencement of PACET to the date of death from disease or treatment-related toxicity, relapse, disease progression or last follow-up.

RESULTS

27 patients were entered onto this protocol. Their characteristics are shown in Table 1.

5 patients had stage I disease at the time of relapse but were not considered eligible for salvage radiotherapy alone, either because of disease bulk, previous radiotherapy or previous widespread systemic disease.

The 27 patients received a total of 54 cycles of PACET (one cycle—11 patients; two cycles—5 patients; three cycles—11 patients), 43 of which were of 5 days duration, and 11 of which were 3-day cycles.

Response

2 patients suffered toxic deaths and are inevaluable for response, but are evaluable for toxicity and survival.

An overall response rate of 30% was achieved. 6 of the 7 patients achieving a complete response (CR) to PACET, had also achieved a CR to their previous chemotherapy regimen and 5 of these had had responses of >6 months duration. Both patients whose disease had transformed histology achieved CR to PACET. 1 patient with progressive disease on the previous therapy achieved a short-lived (2 month) CR to PACET. For all 7 patients, the median duration of CR was 6 months (range 2–54+).

Survival

The actuarial failure-free survival is shown in Fig. 1. The median survival for the entire group is 6 months. The actuarial overall survival is 15% at 48 months, and the failure-free survival is 7% at 48 months.

1 patient, who failed to respond to two cycles of PACET, took his own life 6 weeks after completing the second cycle. Widespread lymphoma was present at autopsy.

2 patients are currently disease-free. One of these is the patient with high-grade histology, who had low-dose local radiotherapy to a site of local relapse following two cycles of PACET. Only 1 patient is currently alive and disease-free solely due to the study chemotherapy. This patient had follicular large cell lymphoma, with a previous CR of 22 months duration.

Toxicity

The major toxicity of this regimen was myelosuppression, which was severe. Mild (WHO grade 2) nausea and vomiting

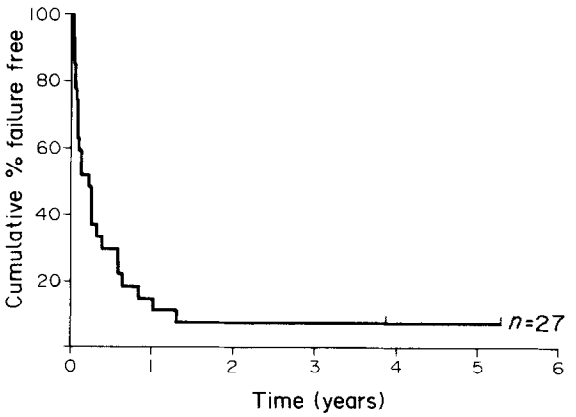

Fig. 1. Actuarial failure-free survival.

were frequent, but not dose limiting. All patients suffered WHO grade 4 neutropenia with at least one cycle of therapy and all but one required antibiotics. All required platelet support with at least one cycle of treatment.

Two toxic deaths occurred. One was due to presumed sepsis in a neutropenic patient after one cycle of PACET. The second was secondary to acute gastrointestinal haemorrhage following one cycle. No evidence of disease was found at necropsy in this patient.

DISCUSSION

These results confirm the reported poor prognosis for patients with non-Hodgkin's lymphoma who fail anthracycline-based chemotherapy [3–5]. The overall response rate of 30% in our series is disappointing. In the MD Anderson study of IMVP-16 (ifosfamide, methotrexate, etoposide) an overall response rate of 62% was achieved [3]. The patient group in this study was similar to ours, but with a small number of patients with Hodgkin's disease, and a higher proportion of patients with low-grade histology. However, despite the higher overall response rate, the CR rate in this study is similar to ours (35 vs. 26%), and the survival appears to be comparable.

The use of MIME (methyl-gag, ifosfamide, methotrexate, etoposide) in 208 patients with relapsed or refractory NHL of all histologies produced an overall response rate of 84%, but a CR rate of only 24% [4]. The actuarial overall survival for patients in this study was comparable to ours (24% at 3 years) and of the complete responders, over half had relapsed at the time of the report, although the median duration of CR was considerably longer than in our patients, at 15 months. High-dose cytosine arabinoside has been combined with cisplatin in view of the reported *in vitro* synergism of these two agents [13], to produce the DHAP regimen [14]. In the first 83 patients with relapsed/refractory NHL treated on this regimen, the CR rate was only 34%. The median survival for DHAP-treated patients was 7 months, and the median time to treatment failure for CR to DHAP was 15 months.

The median survival for patients treated with PACET in this study is comparable with previous reports of salvage therapies used in NHL.

Although PACET proved to be intensely myelosuppressive, the toxic death rate was low (7%). The regimen was otherwise well tolerated. Apart from the two toxic deaths, no patients discontinued therapy because of unacceptable toxicity. Therapy was most commonly discontinued because of disease progression. Salvage therapy for relapsed and refractory NHL remains a major challenge. A number of studies of high-dose therapy with ABMT have been published. Most of these report long-term survival in 20–40% of patients, particularly when only those patients whose disease was still sensitive to "conventional" chemotherapy are considered. However, these studies include highly selected patients not comparable to those reported here. Many of those with poor prognostic features (marrow involvement, age over 60 years, poor performance status) are excluded from such studies. Prospective randomised studies comparing ABMT with other salvage regimens are urgently needed. One such study, the PARMA international protocol [15] is currently in progress and results are awaited with interest.

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