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Alternating six-drug combination chemotherapy induction for intermediate and high-grade non-Hodgkin's lymphoma

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Summary. 31 patients with intermediate and high-grade non-Hodgkin lymphomas were treated by a six-drug alternating regime comprising four cycles of 200 mg/m^2 i.v. methotrexate on days 8, 15, 28 and 35, 50 mg/m^2 i.v. Adriamycin on day 1, 40 mg/m^2 oral prednisolone on days 1–7 and 21–27, 120 mg/m^2 i.v. etoposide on days 21–23, 600 mg/m^2 i.v. cyclophosphamide on day 21 and 1.4 mg/m^2 i.v. vincristine on day 1 (MAPECO). In all, 3 patients had stage I disease, 12 stage II, 6 stage III and 10 stage IV. Of 28 evaluable patients, 19 were complete responders (68%) and 9 were partial responders (32%); at 2 years, the actuarial relapse-free survival of the 19 patients achieving complete remission is 80%, and 5 patients remain in complete remission at 3 years. This is a preliminary report of an effective intensive regime with acceptable toxicity.

Introduction

The use of intensive combination chemotherapy has greatly improved the outlook in non-Hodgkin's lymphoma with unfavourable histology. A number of earlier four- and five-drug regimes, most of which comprised an alkylating agent, a vinca alkaloid and a steroid with the addition of doxorubicin, have been reviewed by Longo and De Vita [11], and achieved prolonged disease-free intervals in about 30% of patients. More intensive regimes incorporating high-dose protocols such as COMLA [7], sequential use of multiple-drug combinations including ProMACE-MOPP [5] and M-BACOD [16, 17], high-dose continuous regimes such as MACOP-B [10], and late intensification chemotherapy [2] are being evaluated. Higher response rates are seen in most of these series, but the follow-up is inadequate to determine whether the disease-free intervals are more prolonged than those achieved with less intensive regimes.

The present regime (MAPECO) involves six drugs given in an alternating sequence, incorporates mid-cycle methotrexate at an intermediate dose to minimise mid-cycle relapse [17], and integrates etoposide into first-line chemotherapy based on encouraging phase II data [19]. This report presents the response and toxicity data on patients with lymphoma classified as intermediate and high-grade by the NCI Working Formulation [14].

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Patients and methods

Since 1983, 31 consecutive patients with a median age of 49 years have been treated in the Cancer Research Campaign Department of Radiation Oncology at Clatterbridge Hospital by the MAPECO regime shown in Table 1. No patient had received prior chemotherapy. All histology slides were reviewed by one pathologist (J. N.), and the tumours were initially categorised according to the Kiel classification as shown in Table 2, along with the Working Formulation equivalents. This was done primarily on the basis of morphological criteria; however, in case of ambiguity, immunostaining was carried out, contributing extra information in five cases. Fresh tissue was used if possible [12], but in many cases paraffin blocks were the only material available; sections were studied using MB2, a pan-B-cell antibody, UCHL1, a pan-T-cell antibody, and leucocyte common antibody where relevant [15].

Patients with lymphoblastic lymphoma were given prophylactic cranial irradiation and five injections of intrathecal methotrexate on the completion of induction chemotherapy. Two patients with this histological type were given maintenance therapy for 12 months, including 1 mg/m^2 i.v. vincristine every 28 days, 75 mg/m^2 oral mercaptopurine daily and 5 mg/m^2 oral methotrexate on days 1–5 every 28 days. One patient was diagnosed as having skin lymphoma of low histological grade, originally treated by radiotherapy; at later presentation with stage IV disease in the bowel, lymph nodes and bone marrow he was considered to have transformed in view of the rate of disease progression.

Clinical details at presentation are given in Table 2. The three patients with stage I disease comprised one pa-

Table 1. Six-drug alternating regime (MAPECO)

	Days 1	8	15	21–23	28	35
Methotrexate (200 mg/m^2) i.v. (folinic acid, 15 mg × 6 at 24 h)		*	*		*	*
Adriamycin (50 mg/m^2) i.v.	*					
Vincristine (1.4 mg/m^2) i.v.	*					
Etoposide (120 mg/m^2) i.v.				***		
Cyclophosphamide (600 mg/m^2) i.v.				*		
Prednisolone (40 mg/m^2) p.o.	*******			*******		

Cycle time, 42 days

Table 2. Clinical features of 31 patients (22 men and 9 women)

Median age 48.8 years (range, 22–70 years)			
Performance status (WHO)		Grade	Patients (*n*)
		0	9
		1	15
		2	7
Pathology (Kiel)[a]			
T-zone	3 (F)	Lymphocytic	1(A)
Pleomorphic T-cell	1 (H)	Centroblastic/centrocytic	3 (F)
T-immunoblastic	3 (H)	Centroblastic diffuse	16 (G)
T-lymphoblastic	2 (I)	B-immunoblastic	1 (H)
		B-lymphoblastic	1 (I)
Disease stage		Patients (*n*)	
I		3	
II		12	
III		6	
IV		10	
Extranodal sites:	Marrow	5	
	Bowel	6	
	Liver	3	
	CNS	2	
	Bone	1	
	Other	3	
'B' sypmtoms		6 (3 stage II, 1 stage III, 2 stage IV)	

[a] Working Formulation equivalents are shown in parentheses

tient whose disease relapsed at a site adjacent to a previously irradiated field, one with primary bone lymphoma in the femur, and one with a 10-cm mesenteric mass without demonstrable bowel involvement at laparotomy. Four patients had received prior radiotherapy. Disease was staged according to the recommendations of the Ann Arbor conference [3] based on clinical data supplemented by serum biochemistry, haematology, iliac crest trephine biopsy and computerised axial tomography (CAT) of the chest and abdomen. Isotopic bone scans and lower limb lymphangiograms were carried out if clinically indicated. Response was assessed 1 month after the completion of therapy by clinical examination and appropriate radiology, including a CAT scan in every case, with repeat iliac crest trephine and CSF cytology. Survival and relapse-free survival were calculated from the date of first treatment according to the Kaplan-Meier method [1]. Patients were seen weekly while on treatment for WHO toxicity assessment, including full blood count, differential and platelet count.

Results

The 31 patients received 4 courses (21 patients), 3 courses (5 patients), 2 courses (2 patients) and 1 course (3 patients) of the 42-day cycle. Consolidation radiotherapy was given after complete remission to three patients with bulk disease at presentation that could be incorporated within one treatment field. One patient was withdrawn from the study on day 21 following an adverse reaction to etoposide during the first cycle and was treated with m-BACOD [16]. This patient, now in complete remission at 30 months, had stage IV lymphoblastic lymphoma with CNS and marrow infiltration; the data are included in the patient characteristics but not in the response or survival analysis.

Of the remaining 30 patients, 2 were not evaluable for response as they did not have measurable disease. Of the

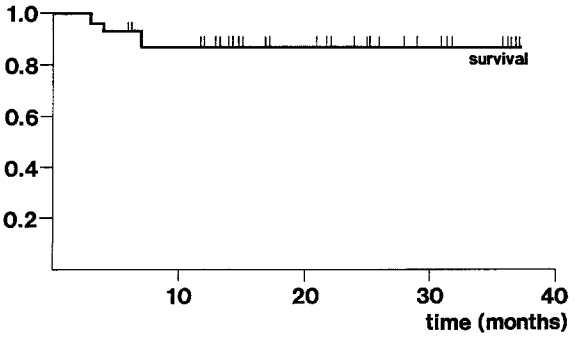

Fig. 1. Kaplan-Meier plot of survival for the 30 patients given MAPECO. Three patients in complete remission have relapsed, of whom all are alive and two are in second complete remission. One further patient progressed at 12 months after achieving a PR at 6 months and is responding to third-line chemotherapy

28 evaluable patients, 19 (68%) achieved a complete response (CR) and 9 (32%), a partial response (PR). Subsequently, three patients were converted from a PR to a CR, two by second-line chemotherapy and one by local radiotherapy to the head and neck. Four patients died, two of possible toxicity (see below) at 3 and 4 months. Two further patients with large-abdominal disease who had a PR to MAPECO but failed to respond to any subsequent treatment died at 7 months; the histological subtypes were lymphoblastic lymphoma and pleomorphic T-cell lymphoma, respectively.

The actuarial relapse-free survival of the 19 patients achieving a CR was 80% at 2 years. Three patients relapsed at 7, 10 and 15 months following CR; their disease was initially staged as II, III and IV, respectively. Two showed a CR to salvage chemotherapy and are free of disease, and one patient with diffuse centroblastic lymphoma has recurrent skin nodules. Another patient achieved a stable PR with residual para-aortic lymphadenopathy after four cycles of MAPECO and developed progressive disease 6 months later. The survival of all 30 patients at a median follow-up of 21 months is shown in Fig. 1. Five patients are alive and in complete remission at >3 years.

Table 3. Toxicity profile of 30 patients given MAPECO chemotherapy

Toxicity		Patients (*n*)
Alopecia	grade III	30
Mucositis	grade II	5
	grade III	10
Dyspepsia	grade III	3
Leucocyte nadir	$<2.0\times10^9$/l	15
	$<1.0\times10^9$/l	6
Platelet nadir	$<100\times10^9$/l	6
	$<50\times10^9$/l	3
Neutropenic fever		8
Localised varicella zoster		2
Generalised measles infection		1
Transfusion required		9
Percentage of calculated dose achieved/cycle:		
	<80%	1
	80%–90%	7
	>90%	22

Diarrhoea and nephrotoxicity were not seen

The toxicity profile of the regime is presented in Table 3. In patients with mucositis, treatment was continued by increasing the folinic acid rescue to 30 mg × 6 every 6 h, and dyspepsia was reversed by a 50% reduction in the steroid dose. There were two deaths in which toxicity may have been contributory, both in patients with stage IV disease: one was a 69-year-old patient with rectal involvement who developed neutropenic fever in whom mesenteric artery thrombosis and ischaemic bowel were demonstrated at post-mortem examination. The other was a 60-year-old patient who had an undefined terminal febrile illness with a moderate neutrophil leucocytosis.

Discussion

The complete response rate in this study was comparable with those of other series involving a similar group of patients, taking into account the distribution of stage and histological sub-type [5, 7, 16, 17]. Preliminary data would suggest that these responses are durable, as 80% of the patients achieving complete remission were relapse-free at a median follow-up of 21 months. These encouraging results are not entirely due to selection of early-stage patients, as four of the six patients who progressed were classified as having stage II disease (but with a maximal tumour diameter of >10 cm). However, in general, the relationship between stage and outcome is well documented in intermediate and high-grade non-Hodgkin lymphomas [7, 9, 13, 16]. Two of the three lymphoblastic lymphomas also relapsed early [4].

The regime was well tolerated by most patients, and overnight admission was required only for social reasons or due to toxicity. Myelosuppression was most frequently seen on days 28–35 and was attributed to the etoposide, which was given in combination with an alkylating agent. One patient who was withdrawn for a suspected etoposide reaction could possibly have continued on the regime, had the infusion been given over a 4-h period. The methotrexate was given on days 7, 14, 28 and 35 in a similar manner to that in the M-BACOD regime [17] with the intention of minimising mid-cycle relapse, which was not observed in any patient. In six patients aged over 60 years, the methotrexate dose on days 14 and 35 was omitted after the first cycle as a result of WHO grade III myelosuppression due to drugs given on days 1 and 22, although $\geqslant 80\%$ of the prescribed doses were given in all but one patient. The two deaths of presumed infective cause occurred in patients over the age of 60.

This preliminary analysis demonstrates that the six-drug alternating regime MAPECO is effective yet tolerable in the treatment of intermediate and high-grade non-Hodgkin lymphomas.

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