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A pilot study of cyclical chemotherapy with high-dose methotrexate and CHOP (MTX-CHOP) in poor-prognosis non-Hodgkin's lymphoma (NHL)

J. A. Child[1], D. L. Barnard[2], S. C. Cartwright[3], I. Lauder[4], A. V. Simmons[2], J. Stone[3], and J. Thorogood[5] for the Yorkshire Lymphoma Group (YLG)

[1] Department of Haematology, The General Infirmary, Leeds, LS1 3EX
[2] St. James's University Hospital, Leeds
[3] Regional Radiotherapy Centre, Cookridge Hospital, Leeds
[4] Department of Pathology, University of Leeds, Leeds
[5] Yorkshire Regional Cancer Organisation, Cookridge Hospital, Leeds, England

Summary. *In a pilot study of cyclical chemotherapy in patients with poor-prognosis non-Hodgkin's lymphoma (NHL), high-dose methotrexate (MTX) 1 g/m² with folinic acid rescue was given as initial treatment and then between cycles of a single-arm CHOP combination administered every 4 weeks. Of 21 patients with previously untreated or minimally treated grade 2 (high-grade) histology stage II/III/IV NHL, 13 (62%) achieved complete remission (CR); the CR rate for stage III/IV patients was 56%. Of all 25 patients with grade 2 stage II/III/IV NHL, including previously treated patients, 16 (64%) achieved CR. The median follow-up of patients who completed treatment is currently 22 months and only 1 relapse has been recorded in the CR group. Only five of 24 grade 2 patients given the initial 'test' MTX failed to show any response, and eight patients achieved partial remission (PR) as a result of this single treatment. The response to MTX-CHOP in nine patients with grade 1 (low-grade) histology NHL was poor; only two achieved CR. These findings lend support to other data which indicate a useful role for MTX in the induction chemotherapy of advanced high-grade NHL, though the optimum dosage and drug sequence have yet to be determined.*

Introduction

The treatment of non-Hodgkin's lymphoma (NHL) of unfavourable or high-grade histology improved with the introduction of combinations such as C-MOPP [6] and CHOP [11], and it has become clear that if patients achieve a true complete remission (CR) long-term survival is a possibility [7]. However, the frequency with which such chemotherapy may be given is limited by myelosuppression, and proliferation of lymphoma often occurs between cycles of treatment. In an attempt to overcome this problem a number of alternative strategies, embodying more frequent chemotherapy, have been tested. Some regimens are comparable to those used in the treatment of acute lymphoblastic leukaemia (ALL), e.g., OPAL [10] and VAP [1, 5]. In others less myelosuppressive agents are given when the bone marrow is still depressed following combination chemotherapy, as in BACOP where bleomycin is introduced between cycles of CHOP [13]. In COMLA, moderate-dose methotrexate (MTX) with folinic acid rescue is given in a cyclical regimen which includes another antimetabolite, cytosine arabinoside [18, 19]. The administration of high-dose MTX during periods of bone marrow depression is made possible by folinic acid rescue as in the M-BACOD schedule where the combination of bleomycin, cyclophosphamide, adriamycin, vincristine, and dexamethasone is followed by MTX at day 14, the cycle being repeated at 3-weekly intervals [2, 16]. The results of this mode of treatment appeared very encouraging, with a CR rate in previously untreated patients of 78% [3]. MTX also offered the further potential of prophylaxis against central nervous system involvement. Against this background and because the British National Lymphoma Investigation (BNLI) and the Yorkshire Lymphoma Group (YLG) had previously favoured CHOP, a pilot study of MTX-CHOP, in which MTX in a dose of 1 g/m² was alternated with a single-arm CHOP combination, was instigated. Because it was thought important to establish the incidence and extent of the initial response to MTX, a 'test' infusion was given as the first treatment. In addition to investigating the effects of the regimen in high-grade lymphomas, some patients with likely poor prognosis but low-grade histology have been treated. The results and analysis of this investigation are reported and their implications discussed.

Reprint requests should be addressed to J. A. Child

Patients and methods

A total of 37 patients with NHL were entered into the study. All were considered by the submitting clinicians to justify inclusion on the following grounds: high-grade histology, stage III/IV disease or stage II disease that was either bulky and/or showed extranodal involvement; or low-grade histology disease that was advanced or aggressive and had a poor prognosis according to clinical assessment. The protocol required that patients should be under 75 years of age and show no evidence of renal dysfunction (serum creatinine < 140 μmol/l). Two patients were excluded from analysis because of inadequate data and one because of revised diagnosis.

Staging. Standard staging procedures comprised diagnostic biopsy of nodal or extranodal tissue, bone marrow aspiration and trephine, and combinations of ultrasonic echography, lymphography, and computerised axial tomography. Those patients. If all the grade 2 histology patients in our series are considered together the incidence of CR was 16 of 25 (64%).

Histopathology. All histopathological material was reviewed by the Yorkshire Lymphoma Panel and also, in the majority of cases, by the BNLI panel. The histopathological categories

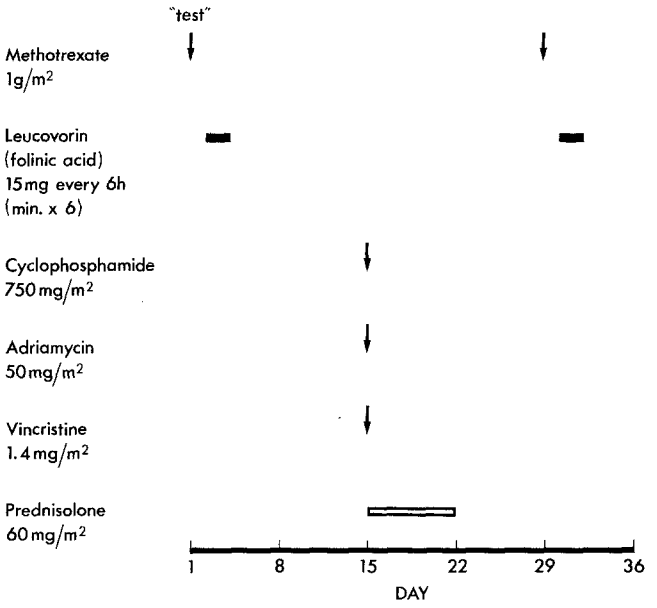

Fig. 1. Time sequence and drug dosages of the MTX-CHOP regimen. Leucovorin and prednisolone are given PO, the other agents IV. A complete cycle spans 4 weeks

were those of the BNLI classification, in which high-grade lymphomas are referred to as grade 2 and low-grade lymphomas as grade 1 [9].

Drug regimen. The drug sequence is shown in Fig. 1. Chemotherapy was given every 2 weeks unless myelosuppression dictated otherwise. Initially, it was intended to start CHOP 1 week after the 'test' MTX to minimise the delay in instituting the combination chemotherapy. However, early experience in three of five patients suggested that this could result in unacceptable severe myelosuppression, and for the remainder of the study a 2-week interval between the 'test' MTX and CHOP was adopted. Sodium bicarbonate was given to maintain urine alkalinity, the dosage being 1–3 g t.d.s. on the day before each MTX infusion, the day of infusion, and for 2 days subsequently. If there were doubts as to the state of hydration patients were admitted for treatment and pre-hydration, but the majority of patients were considered to maintain a good oral fluid intake and were treated on a day-case basis. Following the MTX infusion in 500 ml saline over 4 h a further 500 ml saline was given over 2 h. Folinic acid (Leucovorin) was started 24 h after the MTX infusion was completed in a dose of 15 mg q.d.s. PO to a minimum of six doses. The dose modifications advised for CHOP were as follows: WBC 2–4,0 $\times 10^9$/l and/or platelets 50–100 $\times 10^9$/l, 50% doses of cyclophosphamide and adriamycin, 100% doses of other drugs; WBC $< 2 \times 10^9$/l and/or platelets $< 50 \times 10^9$/l, postponement of treatment or, if such abnormalities persisted, vincristine, and prednisolone alone. Because MTX with folinic acid rescue was unlikely to cause appreciable myelosuppression, rigid dose reduction of MTX was not incorporated in the study. The occurrence of severe toxicity attributable to MTX was regarded as a reason for stopping the drug and withdrawing the patient from the study. It was advised that patients of 60 years and over be given half the dose of MTX initially and that the first CHOP be modified (to cyclophosphamide 500 mg/m^2, adriamycin 40 mg/m^2) so that the initial tolerance/toxicity could be assessed. A centralised assay for MTX blood levels (EMIT) was available. MTX levels $> 5 \times 10^{-6}$ at 24 h were an indication for additional folinic acid rescue.

Duration of treatment. In the event of unacceptable toxicity or lack of response after two cycles of MTX-CHOP following the initial test MTX, further treatment was not given. Patients responding to treatment continued to a minimum of six cycles of MTX-CHOP, not including the initial test MTX, with the aim of giving three complete cycles after the achievement of CR.

Assessment of response and statistical method. Patients were assessed clinically at each (usually fortnightly) visit. Re-investigation to confirm remission depended upon the original findings, but it was required that information as to response be obtained following the initial test MTX and also, particularly, after two further complete cycles of MTX-CHOP (this was considered to represent a point at which adequate treatment had been given in assessing early response to the cyclical regimen). In assessment, the following criteria were adopted: complete remission (CR), clinically disease-free and all initially abnormal tests attributable to lymphoma normal (on repeat investigation as appropriate) for more than 1 month; partial remission (PR), at least 50% reduction in the product of the two largest perpendicular diameters of all measurable lesions for more than 1 month; minor response (MR), objective evidence of response but measurably less than for PR, with no evidence of disease progression; no response (NR), lack of any objective change or progressive disease. Remission duration was calculated from the date of full re-assessment and establishment of CR to the first documentation of recurrent disease. Survival was calculated from the first day of therapy to death or the most recent follow-up.

Patient characteristics. The age, sex, histopathological diagnosis, and grade, the stage with indication of extranodal sites involved and prior treatment, if any, are presented in Table 1. The age ranges were: grade 2, 15–74 (median 50) years; grade 1, 46–72 (median 60) years. Twenty-eight patients had received no treatment or minimal treatment [low-dose local radiotherapy (RT) in three cases and a single dose of bleomycin in one]. Of the four previously extensively treated patients with grade-2 disease, three had received only RT. Additional treatment, following MTX-CHOP as per protocol, was given to one young patient (case 1) with T-cell lymphoblastic NHL: he was given formal CNS prophylaxis with cranial irradiation and then 9 months' UKALL maintenance chemotherapy.

Results

Response to treatment was analysed according to histopathological grade and stage of disease. Table 1 shows the overall results.

Grade 2, previously untreated or minimally treated patients (cases 1–21)

Of 18 patients with stage III/IV disease, 10 (56%) achieved CR and four PR. All patients who achieved CR are alive at 3–28 months and all are still in CR (1 patient, case 14, relapsed but went into CR again on re-treatment with MTX-CHOP). Of the eight patients who did not achieve CR, six are now dead.

Table 1. Patient characteristics and results of MTX-CHOP therapy

Patient			Histology	Grade	Stage	Extranodal sites	Prior therapy	Response (CR duration in months)	Survival from test MTX in months	
No.	Age	Sex								
1	19	M	LPD (T cell)	2	IV	B.m.		CR (> 24)	> 26	
2	18	M	LPD (T cell)	2	IV	B.m.		CR (> 1)	> 3	
3	62	M	MSL/ULC	2	IV	B.m/liver		MR	3	†
4	59	F	MSL/ULC	2	IVE	Skin		PR	8	†
5	61	M	MSL/ULC	2	IV	B.m.		MR	< 1	†
6	40	M	ULC	2	IV	B.m.		CR (> 21)	> 23	
7	51	M	ULC	2	IV	B.m.		CR (> 21)	> 22	
8	74	M	ULC	2	IV	B.m.	Local RT	NR	1	†
9	50	M	ULC	2	IV	B.m.		NR	6	†
10	29	M	ULC	2	IV	Liver		PR	> 5	
11	59	M	ULC	2	IV	Bone		CR (> 10)	> 11	
12	59	M	ULC	2	IIIE	Stomach		PR	> 11	
13	34	F	ULC	2	III		Local RT	PR	2	
14	16	M	ULC	2	III			CR (10)	> 28	
15	40	M	ULC	2	III		Local RT	CR (> 21)	> 26	
16	55	M	ULC	2	III			CR (> 7)	> 9	
17	57	M	ULC	2	III			CR (> 7)	> 8	
18	71	F	ULC	2	III			CR (> 20)	> 23	
19	33	M	LPD	2	IIE	Sft. tiss.		CR (> 13)	> 14	
20	22	F	ULC	2	II			CR (> 8)	> 9	
21	63	F	HC (MP)	2	IIE	Jejunum	Bleo 10 mg	CR (> 31)	> 44	
22	36	F	LPD	2	IV	B.m.	CHOP × 6	PR	21	†
23	40	M	ULC	2	IV	B.m.	RT	CR (> 22)	> 24	
24	15	F	LPD	2	IIIE	Nerve rt.	RT	CR (> 20)	> 28	
25	65	F	MSL/ULC	2	II		RT	CR (> 27)	> 27	
26	46	M	FCMSL	1	IV	B.m/liver		CR (> 19)	> 22	
27	67	M	FCMSL	1	IV	B.m/liver		NR	< 1	†
28	72	M	LID	1	IV	B.m.		MR	< 1	†
29	60	M	LID	1	IV	B.m.		MR	> 17*	
30	60	M	LID	1	IV	B.m.		NR	< 1	†
31	64	M	LID	1	III			CR (> 7)	> 9	
32	69	M	LID	1	IV			PR	8*	†
33	48	F	FCS	1	IV	Lung	RT, CLB, COP	MR	4	†
34	57	M	LID	1	III		CHOP, BACOP	PR	5	†

LPD, lymphocytic poorly differentiated; MSL/ULC, mixed small lymphoid and undifferentiated large cell; UCL, undifferentiated large cell; FCS, follicle cell, small; FCMSL, follicle cell, mixed small and large; LID, lymphocytic intermediate differentiation; HC (MP), histiocytic cell (mononuclear phagocytic); B.m., bone marrow; Sft. tiss., soft tissue; Bleo, bleomycin; CLB, chlorambucil; RT, radiotherapy; † death; * given alternative therapy at two months

Considered by stage, CR was recorded in five of 11 stage IV and five of seven stage III patients. The three patients with stage II disease all achieved CR and are alive at 44, 14, and 9 months after starting treatment. The CR rate including stage II disease was 13 of 21 (62%).

Response to 'test' MTX (Table 2). Based on the clinicians' assessment of accessible lesions, four of the 18 stage III/IV patients were judged to have achieved PR and a further nine patients were considered to have shown responses less than PR (MR); five patients were unresponsive. One of two stage II patients achieved PR.

Response to two cycles of MTX-CHOP (following the 'test' MTX). Of the 14 stage III/IV patients who went on to receive two cycles of MTX-CHOP, five had achieved CR and eight PR at the subsequent assessment. Four patients in this principal group did not receive two cycles of MTX-CHOP following the test MTX: there were two early deaths, one disease-related and drug-related (see *Toxicity*); the other two were considered by the clinicians to have unresponsive disease and were taken off study. The ultimate remission rate for stage III/IV patients who received ⩾ two cycles of MTX-CHOP was 10 of 14 (71%).

Grade 2, previously treated patients (cases 22–25)

In this small sub-set, three patients achieved CR and remain in remission at 20–27 months.

Grade 2, overall responses. When all patients with grade 2 stage III/IV disease are considered, the CR rate was 12 of 21 (57%) and of all grade 2 patients, regardless of stage and prior treatment status, 16 of 25 (64%) achieved CR. Eight of 24 patients achieved PR following the initial test MTX (Table 2).

The median follow-up of patients who completed treatment is currently 22 months and neither the median duration of CR nor median survival has yet been reached. None of the patients has developed CNS involvement during the period of observation to date.

Table 2. Response to initial test MTX infusion

	PR	MR	NR
Previously untreated, grade 2			
Stage IV	2	5	5
Stage III	2	4	
Stage II[a]	1	1	
Previously treated, grade 2			
Stage IV	2		
Stage III	1		
Stage II		1	
Previously untreated, grade 1			
Stage IV	1	2	2
Stage III	1	1	
Previously treated, grade 1			
Stage III	1		
Stage IV		1	

[a] One patient did not receive the initial MTX test infusion

Grade 1 patients (cases 26–34)

Of the nine patients with stage III/IV disease, only two achieved CR. These two patients are alive at 9 and 22 months, respectively. All but one of the other patients have died. However, five patients in this group received less than two cycles of MTX-CHOP following the test MTX: one patient previously diagnosed as having grade 2 histology was withdrawn and given alternative treatment; there were three early deaths, disease-, and drug-related, and another patient with refractory disease was taken off study. One patient who achieved PR initially continued to six courses but died of progressive disease.

Toxicity

Side-effects were broadly categorised as mild, moderate or severe.

Mild toxicity. In 12 patients mild toxicity was attributed to CHOP and took the form of nausea and vomiting immediately following treatment, mild paraesthesiae attributable to vincristine, and cytopenias not requiring dose modifications; five patients experienced mild mucositis following MTX and 1 of these also had diarrhoea.

Moderate toxicity. Three patients developed side-effects attributable to drugs in the CHOP combination; two patients had definite vincristine neuropathy and one of these also had cyclophosphamide-induced cystitis. One patient (case 26) was intolerant of adriamycin, which was omitted in subsequent therapy. Five patients had cytopenias requiring dose modification at some stage during therapy and these changes were attributable to the MTX-CHOP combination (though they may have been more a reflection of CHOP than MTX). Two patients had oral mucositis described as being of moderate severity (but responding to treatment and not necessitating omission of MTX from subsequent cycles). One patient (case 34) developed neutropenia following the initial 'test' MTX and was subsequently given half-dose MTX.

Severe toxicity. One patient (case 27) developed severe mucositis following the initial test MTX, then pancytopenia, septicaemia, and progressive renal failure. Retrospective review indicated that there had been previous minor renal and hepatic insufficiency (a previous IVP had also suggested poor excretion). Death in this case was considered to be drug-related. In three patients severe cytopenias developed following the first treatment with CHOP. In all three cases the CHOP combination had been started 1 week following the test MTX. One of these (case 5) developed septicaemia but did not present immediately, and died after the late institution of supportive therapy. The two other patients (cases 28 and 30) both had advanced grade 1 NHL with grossly infiltrated bone marrow. In each of these death was principally due to septicaemia and could be regarded as drug-related but also, in part, disease-related (reflecting impaired marrow reserve due to marrow infiltration).

Mortality during study

In addition to the four patients described above, in whom death was chemotherapy-related, a further nine patients died of disease.

Discussion

In this pilot study, 56% of patients with previously untreated or minimally treated histological grade 2, stage III/IV NHL achieved CR. In the sub-set who received a minimum of two cycles of MTX-CHOP following the test MTX, the CR rate was 71%. These findings lend some support to the concept that MTX, when given between cycles of adriamycin-containing combinations, enhances response. These patients would otherwise have received the standard double-arm 'modified' CHOP of the BNLI protocol given every 3 or 4 weeks, for which the CR rate is 39% [12]. As in the BNLI studies, there were no exclusions within histopathological grade 2. Although the majority of patients had undifferentiated large cell disease, corresponding to 'histiocytic' lymphoma in the Rappaport classification, other categories were represented. It is of particular interest that two patients (cases 1 and 2) with stage IV lymphocytic, poorly differentiated (T-cell lymphoblastic) lymphoma responded rapidly, and achieved CR.

Comparisons of the results of treatment in different series are notoriously difficult because of differences in patient selection and the criteria for defining responses, but in the largest series of patients given comparable treatment (with the M-BACOD regimen) a CR rate of 76% has been reported [3]. Patients with diffuse histiocytic and diffuse undifferentiated NHL in the Rappaport classification (excluding lymphocytic poorly differentiated) were given 3 g/m^2 MTX with cycles repeated at 21 days, whereas our patients received 1 g/m^2 and each complete cycle spanned 28 days. In an update of the M-BACOD programme, Skarin et al. [17] report an overall CR rate (to include 6 early deaths) of 72% and an overall survival reaching a plateau at 59% projected out to 5 years. Their series of 101 patients included a minority of patients with stages IE, II, and IIE disease, and some previously treated patients. If all the grade 2 histology patients in our series are considered together the incidence of CR was 16 of 25 (64%).

The results of this pilot study, in which no patient developed CNS involvement, do not permit any firm conclusions as to possible CNS prophylaxis afforded by high-dose MTX: one patient with T-cell lymphoblastic NHL, who was considered to be at high risk for CNS involvement, was given additional formal CNS prophylaxis as for ALL. Skarin et al.

[17] record CNS relapse in only 5.4% of CR patients given M-BACOD, compared with 21% in their preceding BACOP study [14], which, however, they consider may be due in part to more effective control of systemic disease.

The present study was designed to test the initial response to MTX, of particular interest in patients previously given no chemotherapy. Of 18 patients with measurable lesions and stage III/IV disease, four were judged to have achieved PR after this single treatment, and a further nine patients showed objective responses less than PR. Only five patients were reported as showing no response at all or disease progression. This is consistent with previous data showing that high-dose MTX is effective as induction therapy [15]. Gomez et al. [8] have recently reported the results of a study in which previously untreated patients with disseminated diffuse NHL were treated with intermediate-dose MTX (180 mg/m^2 days 1 and 8) and COP in a cyclical regimen. In this study seven of 10 patients were reported as achieving CR with a median duration of 23 months. They added cyclophosphamide, giving cyclical MTX-CHOP to 13 patients who had received prior chemotherapy and reported six CR in that group (2 of these relapsing after 12 and 13 months, respectively). As in the present study, attention was paid to the initial response to MTX and decreases of more than 50% in measurable lesions were reported in six of 10 previously untreated patients and five of 11 previously treated patients. These findings, together with those in our study, demonstrate the initial effectiveness of MTX. They also suggest that it may be possible to achieve similar results with lower doses of MTX than 1 g/m^2 and certainly lower than the 3 g/m^2 of the M-BACOD schedule. It is clearly desirable to try to achieve CR as rapidly as possible and very early response should increase the likelihood of CR and hence prolonged disease-free survival.

The results of treatment of the smaller sub-sets in this study do not permit any detailed analysis, but some additional information has been obtained. Although many patients with low-grade (grade 1) NHL requiring treatment will respond to either chlorambucil or the CVP or COP combinations, advanced, aggressive disease requiring more effective therapy is well recognised. In the present study, nine patients with grade 1 histology NHL were treated with MTX-CHOP. Only two of these achieved CR. The early deaths of three patients could be attributed to gross marrow involvement and inadequate haematopoietic reserve to cope with chemotherapy. This response rate was disappointing but is in keeping with previous findings of others and the scepticism which exists as to the value of combination chemotherapy in such cases [2]. Recently Canellos et al. [4] have presented a preliminary report on the use of M-BACOD in advanced NHL with 'favourable' and intermediate-grade histology. They recorded CR in nine of 15 (60%) of patients with nodular NHL and 13 of 24 (54%) of patients with diffuse NHL. However, relapses occurred in 45% of CR patients (within a median of 26 months in the nodular group and 7 months in the diffuse group).

The toxicity of MTX-CHOP in the grade 2 histology patients was generally acceptable. The majority of patients were treated on an out-patient or day-case basis and the immediate effects of MTX were negligible in nearly all patients. More patients had CHOP-related than MTX-related toxicity, probably of lesser severity than would have been the case with double-arm CHOP. However, in a few instances death was at least partly drug-related and the importance of careful assessment of renal function prior to MTX therapy and the monitoring of blood levels after treatment are emphasised. The severe myelosuppression seen in patients with advanced grade 1 NHL where the bone marrow was grossly infiltrated suggests that this type of combination chemotherapy should probably be avoided in this category of patient. Marrow involvement in patients with grade 2 histology does not contraindicate MTX-CHOP but requires extra vigilance.

In conclusion, these findings lend support to other data which indicate a useful role for MTX as part of combination induction chemotherpy in advanced NHL with high-grade ('unfavourable') histology, though the optimum dose and drug sequence has yet to be determined. Doses less than 1 g/m^2 would probably afford inadequate CNS prophylaxis, though the case for giving high-dose MTX for this reason is debatable. It may be preferable to identify high-risk patients, e.g., younger patients and those with lymphoblastic NHL, and give formal CNS prophylaxis as in ALL.

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