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A randomized trial of two types of adjuvant chemotherapy in radiotherapy-treated patients with clinical stages I and II high-grade non-Hodgkin's lymphoma

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Summary. This paper reports the 8-year results of comparing the use of two types of adjuvant chemotherapy following involved field radiotherapy for clinical stages I and II high-grade non-Hodgkin's lymphoma. Twenty-four patients received 6 weeks of VAP plus 2 years of oral maintenance chemotherapy, and 30 had six cycles of CMOPP. Four patients were not in complete remission at completion of i. v. chemotherapy (CR rate 91%). Ten patients (18.5%) have relapsed (VAP/M = 5; CMOPP = 5), with only two of these remaining alive, both of them being disease free. There have been three deaths from intercurrent causes, one from malignant melanoma and the other two from myocardial infarction. The relapse-free survivals at 2, 5 and 8 years were 80%, 76% & 76% respectively. The overall survivals at the same time points were 86%, 72% & 68%. There were no significant differences in either relapse-free or overall survival for either of the two treatment groups. The shorter period of weekly intravenous chemotherapy (VAP/M) was better tolerated than 36 weeks of CMOPP, and the former appears to produce equivalent results.

Introduction

Radiation therapy (RT) alone is inadequate therapy for clinical stages (CS) I and II high-grade non-Hodgkin's lymphoma (NHL). The freedom from recurrence varies from 0% to 40% at 5 years for clinically staged patients with diffuse histology, and only 26%–59% remain alive (Table 1). Even in patients with CS-I disease a relapse rate of 33%–50% is disappointingly high following local therapy alone [2, 4, 8, 10, 12, 13, 19, 23]. Nonrandomized studies do suggest that pathological staging with laparotomy may improve the results, with only 22%–38% having relapsed at 2 years [6, 9, 13, 24, 25]. However, as many as 10%–25% of patients may develop progressive systemic disease during the period of the laparotomy and radiotherapy [1, 11, 12]. This, together with the fact that a high proportion of these patients are elderly, makes laparotomy a substantial undertaking. As a result, chemotherapy (CT) has been given as an adjuvant to RT with apparent improvement in the relapse-free survival (RFS) and probably the overall survival [1, 12, 13, 18, 20, 25]. There are no reports of randomized studies to determine the most effective type of adjuvant CT or indeed the optimum intensity and duration of treatment required to effect a cure. In 1976 the Manchester Lymphoma Group initiated a programme of localized RT with a randomization to one of two types of adjuvant CT for patients with CS-I and -II high-grade NHL. One arm consisted of six weeks of weekly intravenous CT followed by 2 years of oral maintenance (VAP/M) and the other of six cycles of CMOPP given over a period of 36 weeks.

Table 1. The results of radiation therapy in clinical stages-I and -II diffuse-histology non-Hodgkin's lymphoma treated by radiation therapy alone

References	Number of patients	Freedom from recurrence (5 years) %	Survival (5 years) %
Fuller et al. [6]	152	–	26
Peckham et al. [19]	30	–	50
Helman et al. [9]	65	0	50
Reddy et al. [20]	67	40	55
Chen et al. [54]	58	37	59
Mauch et al. [14]*	28	35	45

* Six-year figures

Patients and methods

Patients between the ages of 16 and 70 years with a histologically confirmed and centrally reviewed diagnosis of NHL of the following Rappaport groups were considered eligible; diffuse histiocytic (DH), diffuse poorly differentiated lymphocytic (DPDL), lymphoblastic (LB), diffuse mixed (DM) and diffuse undifferentiated (DU). Prior to this analysis all the histological sections had been reviewed by one of us (MH). The Rappaport grouping was checked and the slides were also classified in the Kiel system. Patients who had had a previous malignancy or a serious concurrent medical illness which would preclude the use of CT were excluded from the study.

Clinical staging included a full history and physical examination, full blood count and ESR, biochemical profile (including liver function tests) and a bone-marrow aspirate with trephine biopsy from a single site. Radiology included a chest roentgenogram and an abdominopelvic

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Table 2. Adjuvant chemotherapy used for clinical stages-I and -II high-grade non-Hodgkin's lymphoma

CMOPP	VAP
Vincristine 2 mg i.v. days 1 and 8	Induction: vincristine 2 mg i.v. weekly × 6
Cyclophosphamide 650 mg/m² i.v. days 1 and 8	Adriamycin 50 mg/m² i.v. every 2 weeks × 3
Procarbazine 100 mg/m² p.o. daily, days 1 – 14	Prednisolone 40 mg p.o. daily for 6 weeks
Prednisolone 40 mg p.o. daily, 1 – 14	
	Oral maintenance for 2 years: 6-Mercaptopurine 50 mg/m² p.o. daily
	Methotrexate 10 mg/m² p.o. weekly
	Cyclophosphamide 200 mg/m² p.o. weekly

CAT scan in all cases. Appropriate radioisotopic investigations were performed where clinically indicated. Only patients who remained CS-IA, -IB, -IIA or -IIB (all ± E) after staging were entered into the study. Patients with CS-IAE disease of Waldeyer's ring were not included in this study since it was our experience that this group do very well with RT alone. Similarly, patients with pathological stages-I and -II gastrointestinal tract NHL were not included since they were the subject of a separate study [22]. The RT was given to the site of disease with an adequate margin at a dose of 30 GY fractionated over 3 weeks using megavoltage. Randomization was performed by the department of medical statistics at completion of staging and stratification was by clinical stage. All patients were randomized whether they achieved a complete remission (CR) with RT or not. CT was commenced 1 month after completion of RT, and details of the dose/schedules are given in Table 2. Each cycle of CMOPP was given over 2 weeks followed by a 4-week rest period, to a total of six cycles. VAP induction was given over the first 6 weeks and then oral maintenance continued for a total of 2 years.

If during VAP, or when the next cycle of CMOPP was due, the white blood count (WBC) was below 3×10^9/l or the platelet count below 100×10^9/l the CT was delayed until recovery to these levels, with review at weekly intervals. If there was a delay of more than 3 weeks, adjuvant CT was abandoned, or oral maintenance commenced in the VAP group. During oral maintenance the doses of drugs were adjusted to keep the WBC between 2.5 and 3.0 $\times 10^9$/l. CR was defined as complete disappearance of all evidence of disease, with a return to normal of all previously abnormal investigations and a return to normal health of the patient. Duration of remission was measured from the start of radiotherapy to relapse and survival from the date of starting treatment to death. Survival and relapse-free survival (RFS) were plotted by the method of Kaplan and Meier.

Results

This trial was activated at the beginning of 1976 and closed in July 1985. The median follow-up is therefore 4.5 years. There was a steady accrual of patients during the course of the study. Fifty-four patients were entered (VAP/M = 24; CMOPP = 30) and their characteristics are given in Table 3. There were no statistically significant differences in the distribution of patient characteristics between the two treatment groups.

One patient was not available for assessment of response. He presented with postnasal space lymphoma associated with cranial nerve palsies. Although an ear, nose and throat examination at the end of CT showed no evidence of NHL, he continued to have cranial nerve palsies and could not, therefore, be classified as CR; he does not appear in the overall CR figures. However, for the purposes of plotting RFS, this patient has been regarded as being relapse free at the end of CT and appears in Figs 1 and 2.

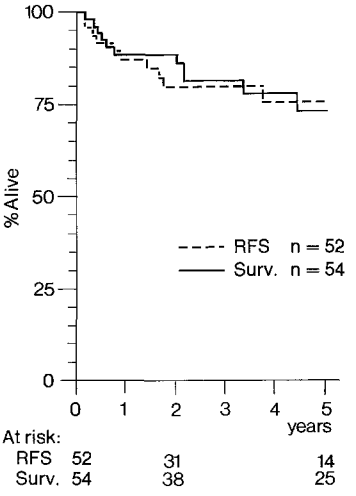

Fig. 1. The overall survival and relapse-free survival (RFS) curves for 54 patients with clinical stages-I and -II high-grade non-Hodgkin's lymphoma treated with local radiotherapy (RT) and adjuvant chemotherapy (CT). The RFS curve includes 49 patients who were in complete remission (CR) after both RT and CT plus two others who were in CR after RT but who progressed during adjuvant CT

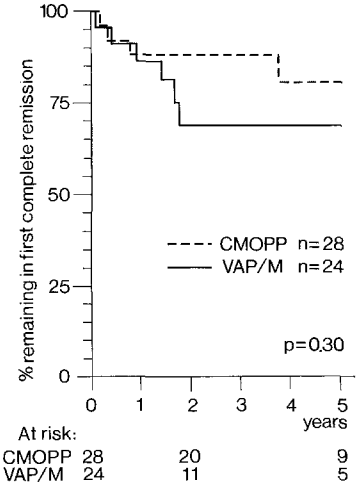

Fig. 2. The relapse-free survival curves for patients with clinical stages-I and -II high-grade non-Hodgkin's lymphoma treated with local radiotherapy followed by either CMOPP or VAP/M adjuvant chemotherapy

Table 3. The pre-treatment characteristics together with complete remission (CR) rate, relapse frequency and the likelihood of dying for patients with CS-I and -II high-grade non-Hodgkin's lymphoma (NHL)

Characteristics		Number (%)	Number with CR (%)	Number relapsed (%)	Number dead of NHL (%)	Number dead – all causes (%)
Overall		54	49* (91)	10 (20)	10 (20)	13 (24)
Adjuvant chemotherapy:	VAP/M	24	23 (96)	5 (22)	5 (21)	7 (29)
	CMOPP	30	26 (87)	5 (19)	5 (17)	6 (20)
Sex	Male	27	23 (85)	5 (22)	6 (22)	9 (33)
	Female	27	26 (96)	5 (19)	4 (15)	4 (15)
Karnofsky status (%)	Median = 90% (range 70–90)					
Age (years)	≤46	23	22 (96)	4 (18)	4 (17)	5 (22)
	>46	31	27 (87)	6 (22)	6 (19)	8 (26)
Bulk ≥5 cm	Yes	25	22 (88)	4 (18)	4 (16)	6 (24)
	No	29	27 (93)	6 (21)	6 (21)	7 (24)
B symptoms	Yes	4	4 (100)	1 (25)	1 (25)	1 (25)
	No	50	45 (90)	9 (20)	9 (18)	12 (24)
Stage	I	27	26 (96)	5 (19)	4 (15)	5 (19)
	II	27	23 (85)	5 (22)	6 (22)	8 (30)
Histology (Rappaport)	DPDL	17	16 (94)	4 (25)	4 (24)	6 (35)
	DH	25	22 (88)	4 (18)	4 (16)	5 (20)
	rest (LB, DM, DU)	12	11 (92)	2 (18)	2 (17)	2 (17)
Histology (Kiel)	CB/CC	14	14 (100)	4 (29)	3 (21)	4 (29)
	CB	8	8 (100)	0 (0)	0 (0)	0 (0)
	IB	17	13 (76)	3 (23)	3 (18)	5 (29)
	Rest	15	14 (93)	3 (21)	4 (27)	5 (33)
Tonsillar involvement = 5						
Above diaphragm = 49						
Skin involvement = 1						

DPDL, Diffuse poorly diffentiated lymphocytic; *DH*, diffuse histiocytic; *LB*, lymphoblastic; *DM*, diffuse mixed lymphocytic/histiocytic; *DU*, diffuse undifferentiated; *CB/CC*, centroblastic/centrocytic diffuse; *CB*, centroblastic; *IB*, immunoblastic

* Two patients further achieved an apparent CR with RT but relapsed during adjuvant CT.

Table 4. Details of patients with clinical stages-I and -II high-grade non-Hodgkin's lymphoma who were not in a complete remission following local therapy (RT) and adjuvant chemotherapy (CT)

Patient	Randomization	Stage	Histology* Rappaport (Kiel)	Remission status after RT	Adjuvant CT given	Site of failure	Time to death (months)
ED	CMOPP	IIA	DH (IB)	PR	No	Abdomen	2
DH	VAP	IIA	DH (LB)	CR	Yes (4 weeks)	CNS bone marrow	5
BN	CMOPP	IA	DH (IB)	CR	Yes (½ cycle)	CNS	5
WC	CMOPP	IIA	DPDL (IB)	PR	Yes (4 cycles)	Generalised	8

* See Table 3 for abbreviations

Forty-one patients (76%) were thought to be in clinical CR after RT. Four patients other than the one who was not strictly evaluable for response were not in CR at the end of adjuvant CT. Two of these were considered to be in a clinical CR after RT but relapsed during CT. These two patients have not been included as being in CR in the evaluation of overall response but do appear in the RFS curves of Figs. 1 and 2. Details of these induction failures are given in Table 4. Thus, the overall CR rate was 49 of 54 (91%) with 23/24 (96%) being in CR after VAP and 26/30 (87%) after CMOPP. This difference was not statistically significant.

Ten patients have relapsed, five in each group. Their characteristics are given in Table 5. Only two of these remain alive. One received only two cycles of CMOPP and then refused further CT as a consequence of severe oral ulceration. He had a generalized relapse 20 months after initial diagnosis, had a second CR with VAP CT, and remains disease free 12 months later. The second presented with right groin disease and relapsed in bone (right knee).

Table 5. Details of patients with clinical stages-I and -II high-grade non-Hodgkin's lymphoma who relapsed following local radiotherapy and adjuvant chemotherapy

Patient	Randomization	Histology* Rappaport (Kiel)	Stage	Time to relapse (months)	Site of relapse	In RT area	Status	Time to last visit or death (months)
IW	CMOPP	DPDL (LB)	IA	45	Marrow + nodes	No	Dead	66
JL	VAP	DPDL (DM)	IA	22	Generalised	No	Dead	26
DH	VAP	DH (LB)	IIA	3	CNS + marrow	No	Dead	5
RW	VAP	DH (IB)	IIA	6	Generalised	No	Dead	9
BN	CMOPP	DH (IB)	IA	1	CNS	No	Dead	6
JMc	CMOPP	DPDL (CB/CC)	IA	10	Right axilla	No	Dead	40
RF	VAP	DM (CB/CC)	IIB	22	Generalised	No	Dead	26
JJ	VAP	DM (CB/CC)	IIA	13	Abdomen	No	Dead	25
PB	CMOPP	DPDL (CB/CC)	IA	17	Right femur	No	Alive	29
JMcK	CMOPP	DM (IB)	IIA	20	Generalised	No	Alive	33

* See Table 3 for abbreviations

A second CR was achieved with RT. This patient remains alive and disease free 1 year later. Three of the relapsed patients failed to receive their adjuvant CT according to the protocol. Two patients in the VAP/M group had oral maintenance stopped after 3 months because of persistent myelosuppression. The third patient was the one mentioned above who received only two cycles of CMOPP.

In the VAP/M group every patient completed the 6 weeks of VAP as per protocol, but five failed to receive the planned 2 years of oral maintenance (two no maintenance for psychological reasons; three stopped due to persistent myelosuppression after 3, 3 and 6 months). Two of these patients have relapsed. Five patients did not receive the full cycles of CMOPP, all five having declined further CT because of subjective toxicity. One of these patients has relapsed but remains alive (see above). The overall RFS is shown in Fig. 1 and the RFS by treatment in Fig. 2. The percentage of CR patients remaining relapse free at 2, 5 and 8 years is 80, 76 and 76 respectively. The patient who was not evaluable for response has subsequently relapsed and died of NHL. Thirteen patients have died (VAP/-M=7, CMOPP=6) – ten from NHL and three from intercurrent causes. One of these died from malignant melanoma which was diagnosed 43 months after he presented with NHL. Two others died from myocardial infarcts at 2 and 50 months from diagnosis of NHL. The overall survivals at 2, 5 and 8 years are 80%, 72% and 68%. The overall survival curve is shown in Fig. 1 and the survival by treatment in Fig. 3. A univariate analysis was performed to determine the effects of the patient characteristics of RFS and survival. The results of this are given in Table 3. No factor significantly affected the likelihood of attaining a CR, the DFI or overall survival. However, there were some trends within the data which may point to important prognostic information.

Male patients fared less well than their female counterparts [deaths in men 9/27 (33%), in women 4/27 (15%)] and this is due in part to the lower CR rate in the former group (85% vs 90%). Patients with stage-II disease show a trend to lower CR rates (85% vs 96%) and survival (19% deaths vs 30% deaths) than stage-I patients. With regard to histology, the Rappaport system did not discriminate groups with either a particularly good or bad CR rate or survival. The Kiel classification suggested that patients with immunoblastic histology achieve CR less readily than the other groups and that those with centroblastic morphology remain in remission.

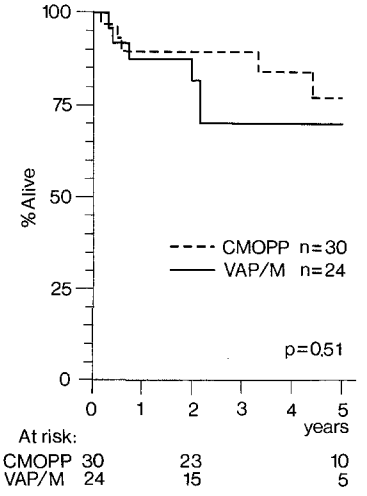

Fig. 3. The overall survival curves of 54 patients with clinical stages-I and -II high-grade non-Hodgkin's lymphoma treated with local radiotherapy followed by either CMOPP or VAP/M adjuvant chemotherapy

Discussion

In this study we have compared two types of adjuvant CT in radiotherapy-treated patients with CS-I and -II high-grade NHL. We chose the VAP/M regime because of our extensive experience with it in patients with stage -III and -IV disease [21]. Of 111 patients, 64 (68%) achieved a CR, with the median survival of CR patients not having been reached at 7 years. Of particular note was that the 5-year RFS was 66% for patients with DH-NHL compared with 29% for patients with DPDL histology. These results are comparable to those obtained with the CHOP regimen, but the former programme involved only 6 weeks of intravenous CT compared with 6–12 months of treatment usually given in the CHOP programs.

CMOPP was selected because of the encouraging results from De Vita [5] which were published at the time this protocol was being prepared. In his paper, De Vita showed that durable complete remissions could be achieved in patients with high-grade NHL for the first time.

Localized high-grade NHL is a rare disease, and it is therefore difficult to recruit sufficient numbers of patients at a single centre to make randomized trials a viable proposition. This probably accounts for the lack of randomized trials to determine which form of adjuvant chemotherapy is optimal. With only 54 patients entered into this trial to date, it is difficult to be absolutely sure that are no significant differences between these two regimes. However, they are at present equivalent both in terms of RFS and overall survival. The reason for reporting this trial now is that it represents one of the largest series of patients with localized high-grade NHL to be reported with long follow-up and is the only randomized trial to be published. This study presents useful information which should help with the design of future trials.

The overall survival of 72% at 5 years represents a substantial advance over the 26%–59% achieved with radiation therapy alone in CS-I and -II DH-NHL (Table 1). The 8-year RFS of 76% is already twice that observed with radiotherapy alone at 5 years and suggests that there will eventually be an even larger improvement in overall survival as the result of using adjuvant CT. Four trials have addressed the question of whether adjuvant CT is of benefit, and three of these have shown a significant advantage in terms of both RFS and overall survival [1, 12, 18]. In these three studies, 34 of 61 (50%) who received RT alone relapsed, compared with only ten of 63 (16%) who were given adjuvant CT.

Glatstein et al. [7] failed to demonstrate improved RFS and survival for patients given adjuvant CT. However, these patients were all laparotomy staged and received total nodal plus whole abdominal RT (where there was an abdominal presentation). There was therefore a delay of 3–4 months before patients were randomized and received adjuvant CT. This, together with the fact that the CT employed (cytosine arabinoside, adriamycin and thioguanine) has a low CR rate in advanced patients, may account for their failure to detect an advantage for adjuvant CT.

An initial comparison of these data with those obtained with radiation therapy alone in pathologically staged patients might suggest that the rigors of adjuvant CT could be avoided by the use of staging laparotomy. The RFS at 2 years is 80% in this series and lies between 62% and 78% in laparotomy-staged patients. However, the results of laparotomy staging do not include patients who are medically unfit for this procedure and also exclude the 10%–25% of patients who will develop generalised disease during the period of the laparotomy and the radiotherapy [3, 14, 15]. The inclusion of all these patients in the analysis would considerably prejudice the reported results. It is our opinion that pathological staging is an inappropriate strategy for this group of patients.

A further option which must be considered is the use of radiation treatment in CS patients, followed by a close period of observation, so that relapse would be detected at a very early stage and appropriate salvage CT given at this point. This might obviate the need to give CT to every patient with CS-I and -II high-grade NHL. This philosophy may be seen to be inappropiate on two counts. Firstly, the relapse rate of 65%–100% in CS radiotherapy-treated patients [55%–82% in patients with CS-I and -II DH-NHL (Table 3)] means that the majority of patients will eventually require systemic therapy. Secondly, the results of salvage chemotherapy may not be adequate to allow this course of action to be recommended. For example, Volkes et al. [26] reported five relapses in 31 laparotomy-staged and radiotherapy-treated patients, and only two of these achieved a CR with salvage CT. These results have been confirmed by Monfardini and colleagues [17]. It therefore seems that local RT followed by close follow-up, a strategy which has proved successful in early Hodgkin's disease, is inappropriate for patients with localized NHL.

The systemic failure of patients whilst they were undergoing localized RT led Miller and Jones [16] to use initial CT for these patients. They treated 45 patients with initial CHOP CT. Forty-four (98%) achieved a CR, and with a median follow-up time of 41 months, 38 of the patients (84%) remain continuously disease free. The overall actuarial survival for this group of patients is 93% (42 are alive). One important aspect of this study is that 17 patients required adjuvant RT. This was not given randomly. Patients who had to have dose-rate reductions in their CT or who were not in CT after three cycles of CHOP were given RT. It is important to remember that in this series two of eight patients who had bulky disease ($\geqslant$5-cm masses) and who received chemotherapy alone have relapsed compared with none of eight who had combined-modality therapy. Two other series have added confirmatory evidence that initial CT may be superior to either RT alone or RT plus adjuvant CT. Cabanillas et al. [3] reported 30 CS-I and -II patients treated with initial COP or CHOP: 88% achieved CR and 23 (85%) of the 27 patients who achieved disease-free status remain in remission. Two of the four relapses occurred in patients with bulky disease, again indicating that adjuvant RT may be important in preventing relapse in this group of patients. A retrospective review of 74 patients with stage-I and -II high-grade NHL has recently been reported by Mauch et al. [14]. Twenty-eight patients were treated with RT alone, 25 with CT alone and 21 with CT followed by local regional RT. The 6-year freedom from recurrence was 62% for patients receiving CT and 35% for those having RT alone ($P=0.006$). The 6-year survival for these patients was 75% and 45% respectively ($P=0.009$). An analysis of patients receiving CT alone versus those having additional RT showed that the 6-year freedom from recurrence and survival were 43% and 56% for the former group and 66% and 50% for the latter patients. These data support the view that adjuvant RT may be important in optimizing both RFS and survival following initial CT. However, randomized studies will be required for this assumption to be confirmed.

When this study was set up, the Rappaport histological classification of NHL was in common use. Patients with both DH and DPDL NHL were regarded as being high grade. It has subsequently been observed that patients with DPDL NHL have a continuously relapsing course, and there is a suggestion that this occurred in this study (DH: CR = 88%, relapsed = 18%; DPDL: CR = 94%, relapsed = 25%. Using a more modern classification (Kiel), the only patients who fared substantially better than the rest were those eight with centroblastic histology with no relapses and no deaths. It will be interesting to observe the results of initial CT in patients whose histology is reported in a modern histological classification.

In conclusion, the data presented above suggest that adjuvant CT after RT improves both RFS and survival compared with RT alone, but that initial CT followed by

RT to sites of bulky disease is probably optimal treatment of patients with CS-I and -II high-grade NHL.

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