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Combination Chemotherapy for Advanced Non-Hodgkin's Lymphoma of Unfavourable Histology

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Summary. *Thirty previously untreated adults with diffuse histiocytic and diffuse undifferentiated lymphoma were treated with a combination of adriamycin, vincristine, prednisolone, and* L-*asparaginase. Complete remission was achieved in 11 out of 12 cases with stage III and 7 out of 18 cases with stage IV disease ($P < 0.005$). Bone marrow infiltration, clinical central nervous system involvement, and massive intra-abdominal disease all influenced the prognosis adversely. Complete remission was followed by cranial irradiation and intrathecal methotrexate, and maintained with weekly cyclophosphamide and methotrexate and daily 6-mercaptopurine. The duration of remission was significantly longer for patients with stage III disease (the median of which has not been reached), than for patients with stage IV disease ($P = 0.007$). Survival was significantly longer for patients in whom complete remission was achieved than for those in whom it was not ($P = 0.001$), and also for patients with stage III than for those with stage IV disease ($P = 0.02$).*

Introduction

The Rappaport classification of the non-Hodgkin's lymphoma (NHL) [15] has been shown repeatedly to be an accurate prognostic guide, patients with advanced diffuse histiocytic and diffuse undifferentiated lymphoma until recently having an anticipated median survival of approximately 6 months [11].

There is continuing dispute, however, concerning the scientific accuracy of this classification, particularly regarding the true nature of so-called histiocytic lymphoma. Evidence from several sources now suggests that this is usually a tumour of lymphoid origin [4, 12] and as such possibly closely related to acute leukaemia of lymphoid origin.

Therefore, from November 1972 adults with stage III and IV diffuse histiocytic (DH) and diffuse undifferentiated (DU) lymphoma referred to the Department of Medical Oncology at St. Bartholomew's Hospital were entered on to the treatment programme being used for adults with acute lymphoblastic leukaemia (ALL) so that the clinical course of patients with both ALL and advanced NHL of unfavourable histology might be followed in a prospective manner. The results of the first 51 patients with ALL have recently been reported [13] and we now present the results of the first 30 patients with DH and DU lymphoma.

Materials and Methods

1. Treatment Programme

Details of this have already been published [13] and will not be repeated here. The programme is represented schematically in Table 1. At the outset of the study the interval between courses of vincristine and adriamycin was 1 week. This interval was extended to a minimum of 2 weeks (but rarely exceeded 3) because considerable cytopenia was observed following the second injection in cases of leukaemia entered on to the treatment programme.

2. Staging

All patients were staged according to a modification of the Ann Arbor classification used for Hodgkin's disease. It was modified as follows:

a) Lymphangiography was not routinely performed in patients with clinical evidence of disease on both sides of the diaphragm.

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Table 1. Details of treatment programme

1. Remission induction and consolidation

Drug	Adm.	Dose	Intervals of treatment
Adriamycin	i.v.	30 mg/m^2	Days 0, 14, 28, 42 approx.
Vincristine	i.v.	1.4 mg/m^2 (max. 2 mg)	Days 0, 14, 28, 42 approx.
Prednisolone	p.o.	40 mg	Daily
Asparaginase	i.v.	10,000 IU/m^2	Days 0–14
Allopurinol	p.o.	200 mg tid	Daily

First assessment 1 week after fourth course of V + A; if disease persists, two further courses at 2-week intervals and reassessment 1 week after sixth injection

2. CNS treatment

Craniospinal irradiation (2400 rads) given in 20 fractions and concomitant intrathecal chemotherapy: i.t. methotrexate 12.5 mg × 5 doses followed by i.t. cytosine arabinoside 50 mg × 5 doses all given over 4 weeks

3. CNS prophylaxis

Cranial irradiation (2400 rads) given in 20 fractions and concomitant intrathecal methotrexate 12.5 mg × 5 doses given over 3 weeks (in latter part of study, i.t. methotrexate begun during remission induction) provided platelets greater than 50 × 10^9/litre

4. Maintenance

p.o. daily 6-mercaptopurine 75 mg/day begun at CR
p.o. weekly cyclophosphamide 300 mg/week on same day, begun when CNS therapy finished
p.o. weekly methotrexate 30 mg/week on same day, begun when CNS therapy finished
Doses adjusted to maintain total WBC at 3 × 10^9/litre

NB Allopurinol always stopped before 6-mercaptopurine begun

b) Laparotomy was not performed as a routine procedure.

c) Liver biopsy was only performed in cases who had not been advanced to stage IV by other investigations (usually bone marrow biopsy).

Bone marrow aspirate and needle biopsy were performed in all cases. For the purpose of reporting this study an arbitrary distinction was drawn between lymphoma and leukaemia. As discussed in a previous paper [13], patients with greater than 30% infiltration of the bone marrow with blast cells were classed as having leukaemia and excluded from this analysis.

The cerebrospinal fluid (CSF) was not examined at presentation unless there was a clinical indication.

Extensive extranodal spread within the abdomen was diagnosed as stage IV involvement (as opposed to II_E).

3. Restaging

Lymphangiography and bone marrow biopsy were performed on patients in whom clinical remission was achieved. Repeat biopsies of other extranodal sites, i.e., bone, were not performed routinely. A cytocentrifuge preparation of the CSF was examined prior to central nervous system (CNS) therapy in all cases.

4. Definitions

Complete Remission (CR). Normal performance status associated with neither clinical nor radiological evidence of disease, a normal bone marrow and CSF.

Partial Remission (PR). Reasonable performance status associated with at least 50% reduction in tumour mass but definite residual disease. There were only two partial remitters and for the purpose of this study they have been analysed with the failures as nonremitters.

Failure (F). Reasonable or poor performance status associated with less than 50% reduction in tumour mass.

Remission Duration. Time in months from CR to diagnosis of relapse.

Survival. Time in months from presentation to death.

5. Calculations

Survival curves and graphs were developed by standard life table formulae [1], and statistical significance was detrmined by the Wilcoxan tests modified to deal with life table data by Gehan [9]. X^2 with Yates correction was used to test significance in a 2 × 2 table.

6. Patients

Thirty previously untreated adults with biopsy proven NHL of unfavourable histology and presumed poor prognosis were entered on to the treatment programme between December 1972 and May 1976. All patients were evaluable. The clinical details are shown in Tables 2 and 3.

Table 2. Clinicopathological details of responders

No.	Age	Sex	Histology	Stage	Extranodal site	Courses of V + A	Duration of response (months)	Survival (months)
1	30	M	DH	III	–	6	40+	42+
2	42	M	DH	III	–	6	30+	31+
3	23	M	DH	III	–	6	18+	21+
4	56	F	DH	III	–	4	16	31+
5	52	F	DH	III	–	6	15+	19+
6	57	M	DH	III	–	4	16+	18+
7	60	F	DH	III	–	6	13	38+
8	16	M	DH	III	–	6	11	15
9	53	M	DH	III	–	4	6	14
10	53	M	DH	III	–	4	4	52+
11	16	M	DU	III	–	6	13+	15+
12	42	F	DH	IV	Ovary, abd.	4	2	6
13	45	M	DH	IV	Bone	6	6	23
14	41	M	DH	IV	Subcutaneous tissue, skin	4	7	9
15	41	M	DH	IV	BM	6	4	20+
16	48	M	DH	IV	BM	6	6	17
17	16	M	DH	IV	BM, CNS	6	12	14
18	21	M	DU	IV	BM, abd.	6	6	18

Table 3. Clinicopathological details of non-responders

No.	Age	Sex	Histology	Stage	Extranodal site	Courses V + A	Survival
1	55	F	DH	III	–	6	6
2	61	F	DH	IV	Abd.	2	1
3	47	M	DH	IV	Abd.	5	1
4	49	F	DH	IV	BM	3	3
5	60	F	DH	IV	BM, CNS	4	3
6	48	M	DH	IV	BM, pleura, CNS	5	17
7	36	M	DH (B)	IV	Bone, CNS	4	3
8	52	M	DU	IV	Abd.	2	1
9	59	M	DU	IV	Abd., liver	2	18+
10	23	F	DU	IV	Abd., BM, CNS	6	8
11	20	M	DU (B)	IV	Abd., BM, CNS	4	1
12	30	M	DU (B)	IV	BM, CNS	2	1

1. Extranodal disease
   a) Bone marrow involvement (BM) was diagnosed on aspirate or needle trephine
   b) Extensive involvement outside lymph nodes (abd.), not necessarily arising from the gastrointestinal tract, was considered stage IV disease
   c) Central nervous system involvement (CNS) was diagnosed on the basis of clinical signs associated with abnormal cells or the cerebrospinal fluid on all occasions. It was present either at presentation or occurred during attempted induction
2. Partial remission was achieved in Nos. 6 and 9

Results

1. Response to Therapy

CR was achieved in 18 out of 30 (60%) cases, and PR in two out of 30 (7%). Four cycles of vincristine and adriamycin were required in six, and six cycles in the remaining 12. Increasing the interval between the cycles of vincristine plus adriamycin did not influence the CR rate. The CR rate was significantly higher in patients with stage III than stage IV disease ($P = 0.005$) regardless of the extranodal site of involvement (Table 4). It was lowest in patients with massive abdominal disease (two of eight), CNS involvement (associated with bone marrow involvement in six cases) (one of seven) and DU lymphoma (two of eight). All three cases of DU lympho-

Table 4a. Complete remission rate. Influence of stage

Stage	No.	C. R.	Fail	C. R. Rate	%
III	12	11	1	11/12	92
IV	18	7	11	7/18	39
Total	30	18	12	18/30	60

Table 4b. Extranodal site involvement influence of prognostic factors on complete remission rate

	Involved	Not involved	Total	*P*
Any extranodal site	7/18	11/12[a]	18/30	0.005
Bone marrow	4/10	14/20	18/30	n.s.
CSF	1/7	17/23	18/30	0.01
Abdomen	2/8	16/22	18/30	< 0.05

[a] Stage III

Table 5. Association between bone marrow involvement and central nervous system involvement in DH and DU

Stage	No.	CNS involved		
		at presentation	at relapse	total
III	12	0	1[a]	0
IV BM−	8	1	1	2
IB BM+	10	7	2	9
Total	30	8	4	12

[a] Associated with BM relapse

ma of Burkitt's type had CNS involvement and in none of them was CR achieved, (These have been reported elsewhere [3]). The strong correlation between CNS infiltration and bone marrow involvement is shown in Table 5. The only patient with CNS involvement at presentation in whom CR was achieved received therapeutic as opposed to prophylactic CNS therapy. This resulted in the resolution of papilloedema and clearance of blasts from the CSF. No *asymptomatic* cases of central nervous involvement were detected.

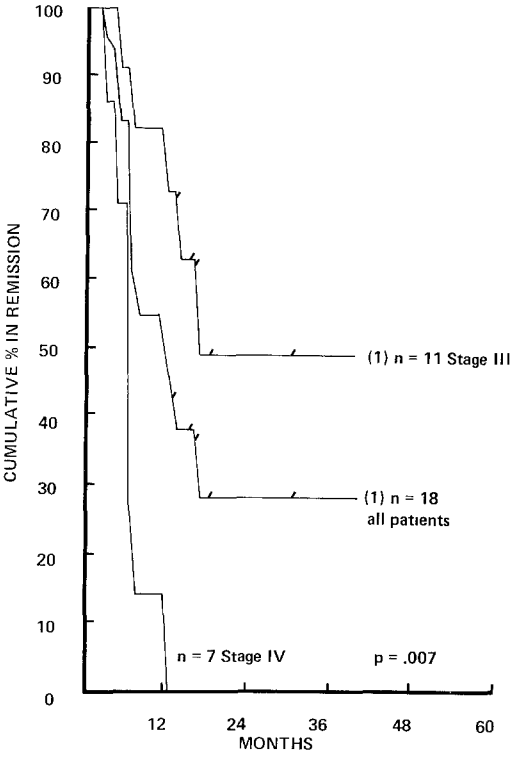

Fig. 1. Complete remission duration (influence of stage)

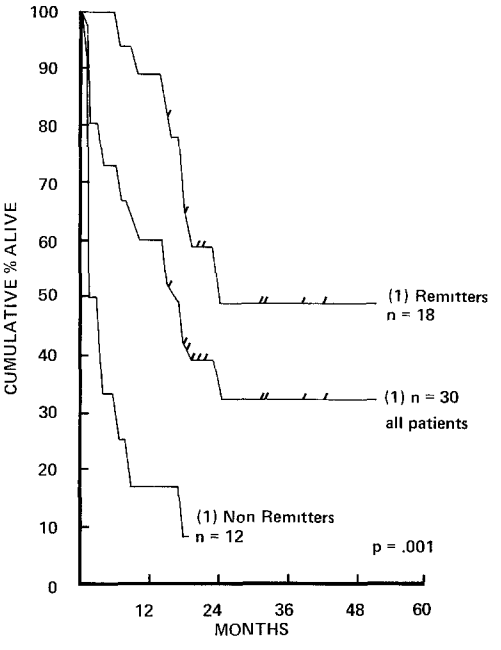

Fig. 2. Survival (influence of response to therapy)

2. *Duration of Remission*

Twelve out of 18 patients in whom CR was achieved have relapsed and the median duration of CR was 12 months. Five out of 11 stage III patients have relapsed and the remainder continue in CR between 13 and 41 months. All seven stage IV patients have relapsed by 13 months. The predicted median duration of CR for stage III patients is 17 months and is significantly longer than that for stage IV patients, 6.5 months ($P = 0.007$) (Fig. 1). Bone marrow relapse has occurred to date in five patients (four with previous bone marrow disease and

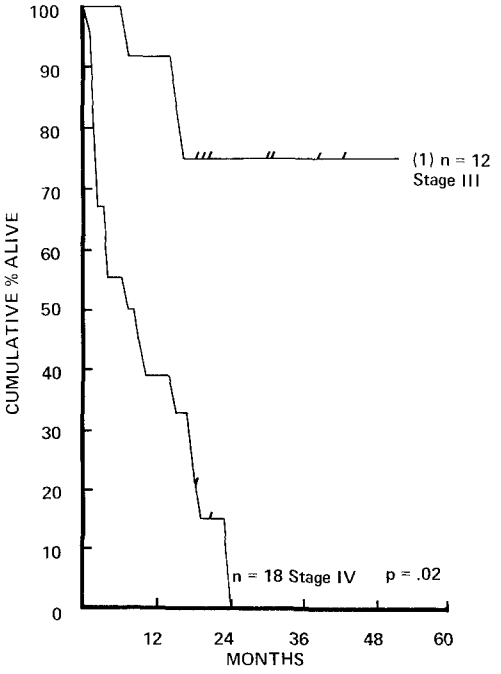

Fig. 3. Survival of remitters (influence of stage)

one previously stage III), and was associated with or followed by CNS relapse in three out of five.

3. Survival

Nineteen out of 30 patients have died, the remainder being alive between 15 and 52 months. The median survival of all patients was 16 months.

Only eight out of 18 patients in whom CR was achieved have died and the remainder are alive between 15 and 52 months. The predicted median survival of these 18 patients is 24 months, which is significantly longer than those in whom CR was not achieved ($P = 0.001$), 11 of whom have died, one remaining alive at 18 months (Fig. 2).

Patients in whom CR was achieved who presented with stage III disease had a significantly longer survival than those who presented with stage IV ($P = 0.02$). Only two out of 11 stage III patients in whom CR was achieved have died, and the remainder are alive although not necessarily disease-free between 15 and 52 months. Six out of seven stage IV patients in whom CR was achieved have died with one alive with active disease at 20 months (Fig. 3).

Discussion

This treatment programme (OPAL) has resulted in a high CR rate for stage III NHL of unfavourable histology. Follow-up is not yet long enough to tell whether or not any of the patients continuing in remission have been cured, although extrapolation from the data of De Vita et al. [20] suggest this is possible. (Repeat analysis just before going to press reveals none of the patients to have relapsed.)

Table 6. Complete remission rate in adults with ALL and stage IV DH and DU treated with OPAL

Diagnosis	No.	C.R. rate	%
ALL	51	36/51	71
Stage IV DH and DU	18	7/18	39
Total	69	43/69	62

$P = 0.02$

The same programme (OPAL) is quite unsatisfactory for the treatment of stage IV disease. The CR rate is low, and the duration of CR very short. There are two likely explanations for this. The first is that the initial treatment is not intensive enough. It is reported from other centres that combinations, including cyclophosphamide, and higher doses of adriamycin have resulted in higher CR rates than we have achieved [16, 17, 18]. Cyclophosphamide has been shown to be an highly effective single agent [10], and it is possible that its inclusion in initial therapy, as opposed to maintenance, might have improved our results. The second explanation relates to the extranodal site determining stage IV involvement. Fisher et al. [6] have demonstrated that bone marrow, CNS, and massive intra-abdominal involvement carry a very poor prognosis, and the majority of our patients with stage IV disease had involvement of at least one of these sites. Increasing the intensity of systemic therapy may improve the results in patients with bone marrow involvement, but this will clearly not affect the CNS disease, and will probably not be effective in patients with massive intra-abdominal disease. An high incidence of CNS involvement has been reported by others, [5, 18] but as yet no satisfactory means of treating it has been devised. Recently much attention has been focussed on the use of high dose intravenous methotrexate. This has been shown to enter the CSF in tumoricidal doses and has been introduced (with folinic acid rescue) into the treatment of NHL [19]. Studies in childhood lymphoblastic leukaemia and NHL show that a combination of intrathecal and intravenous methotrexate, are effective when given prophylactically [7, 8], and it is possible that the latter may also be effective in NHL in adults. Massive intra-abdominal disease is frequently so bulky as to make it impossible to eradicate with combination chemotherapy. Magrath et al. [14] have reported bulk resection to be helpful in abdominal Burkitt's lymphoma, and it is possible that more exten-

sive surgery at presentation, or adjuvant radiotherapy, might be contributory.

Prospective comparison of these results with those previously reported for adults with acute lymphoid leukaemia [13] treated with identical chemotherapy reveals that stage IV DH and DU carry a worse prognosis than ALL. The CR rate was significantly lower (Table 6) and the duration of remission and survival significantly shorter ($P = 0.03$ and $P = 0.03$ respectively).

The interpretation of these differences is complicated by the fact that the two groups of patients may not be directly comparable. The group with leukaemia was younger (although within this group, age did not influence the prognosis) and there was a higher incidence of clinical CNS (although not asymptomatic CNS involvement) and massive intra-abdominal involvement in the group with lymphoma. The possibility that these differences between ALL and NHL represent a fundamental difference in cytological origin cannot be excluded. In many instances in both groups their origin from lymphocytic cells is presumed but not proven. Our data indicate however that the prognosis in generalised lymphoid malignancies of unfavourable histology is closely related to the distribution of the disease regardless of the morphological appearance of the malignant cells.

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