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The Treatment of Disseminated non-Hodgkin's Lymphoma of Unfavourable Histology

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Summary. *Forty-eight consecutive previously untreated adults with advanced non-Hodgkin's lymphoma (NHL) of unfavourable histological type were referred to the Department of Medical Oncology at St. Bartholomew's Hospital, London, between 1972 and 1977. They received adriamycin, vincristine, prednisolone and* L-*asparaginase (OPAL) initially, and those in whom complete remission was achieved proceeded to cranial irradiation and intrathecal methotrexate, followed by continuous oral maintenance chemotherapy comprising weekly methotrexate, cyclophosphamide, and daily 6-mercaptopurine for 3 years. Complete remission was achieved in 24 of the 48 (50%). The median duration of remission was 10 months, nine patients continuing without relapse for between 3 and 7 years. The median survival was 9 months, 12 patients being alive and disease-free (three in second remission) after between* $3^1/_2$ *and* $8^1/_2$ *years.*

The prognosis was significantly better in patients with nodal stages II and III (disease) than in those with stage IV, for both response ($P = < 0.05$*) and survival (*$P = 0.002$*). Patients in whom complete remission was achieved survived significantly longer than those in whom it was not, regardless of stage.*

These results confirm our preliminary observations with this treatment programme that a proportion of patients with stage II and III unfavourable histology NHL may be curable although the outlook for stage IV remains poor.

Introduction

In 1972 it was decided at St. Bartholomew's Hospital that all adults with advanced lymphoid malignancy other than Hodgkin's disease should receive the same therapy (OPAL) (Table 1) regardless of whether the distribution was solely nodal (stage III), nodal and extranodal but with less than 30% infiltration of the bone marrow (stage IV), or primarily extranodal with heavy infiltration of the bone marrow (acute lymphoblastic leukaemia). Preliminary results for patients with both lymphoma and leukaemia have already been published [7, 8].

Long-term follow-up (minimum 3 years) for the total cohort of patients with lymphoma is presented below, together with their classification by the methods of both Rappaport [9] and Kiel [6].

Table 1. OPAL treatment plan

Remission induction and consolidation (every 2 weeks)		CNS prophylaxis
Adriamycin	30 mg/m^2 IV	Cranial R/T 2,400 rad
Vincristine	2 mg IV	
L-Asparaginase × 14 days	10,000 U/m^2 IV	Intrathecal methotrexate 12.5 mg × 5
Prednisolone	40 mg daily PO	6-Mercaptopurine 75 mg/day PO
Allopurinol	300 mg daily PO	
Maintenance		
6-Mercaptopurine	75–150 mg/day	adjusted to maintain a total WBC 3.0 × 10^9/l, continued for 3 years
Methotrexate	30 mg/week	
Cyclophosphamide	300 mg/week	

Materials and Methods

1. Patients. Forty-eight consecutive, previously untreated, adults aged 14–75, median 48, years were referred to the Imperial Cancer Research Fund Department of Medical Oncology at St. Bartholomew's Hospital between 1972 and 1977. Clinical details are shown in Table 2.

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Table 2. Patient characteristics and response

Patients		No.	Complete remission	Survival > 3 years
Age	under 55	32	19	8
	over 55	16	5	4
Sex	M	34	18	11
	F	14	6	1
Symptoms	absent	16	9	8
	'B'	32	15	4
Stage	II	2	13	8
	III	15		
	IV	31	11	4
Histology[a]	Ib	22	14	6
	Cb	6	1	1
	LbB	6	3	2
	Lbu	5	2	2
	HGu	4	1	0
	MH	3	3	1
	DCbCc	2	0	0
	DH	32	16	7
	DU	15	8	5
	DM	1	0	0

[a] DH, diffuse histiocytic; DU, diffuse undifferentiated; DM, diffuse mixed; Ib, immunoblastic; Cb, centroblastic; LbB, lymphoblastic B type; LBu, lymphoblastic undifferentiated; HGu, high-grade unclassifiable; MH, malignant histiocytosis; DCbCc, diffuse centroblastic

2. Histological Diagnosis. The diagnosis was confirmed on a stained section of lymph node or extranodal tissue by Dr. A. G. Stansfeld.

3. Staging Procedure. At presentation clinical examination, full blood count and routine biochemistry, plain radiography of the chest and abdomen, and bone marrow aspiration were accompanied by bone marrow trephine and lymphography, provided stage IV involvement had not already been confirmed and that the demonstration of para-aortic lymphadenopathy would alter the stage classification.

The final Ann Arbor stage as modified for NHL was assigned to the majority of patients without information from laparotomy, which was performed solely as a diagnostic procedure in 16 patients. These included 11 of the 15 patients with large abdominal masses; the remainder were classed in stage III(2) or IV(2) by virtue of disease elsewhere.

Evaluation of the response to treatment was performed 1 month after completion of therapy and comprised clinical examination with full haematological and biochemical investigation, and radiology as appropriate. Bone marrow trephine was performed in all patients in whom it had been positive at presentation. Lymphography was performed in all cases in whom complete remission (CR) was suspected, and investigation of extranodal sites involved at presentation was carried out as appropriate. Patients in whom a persistent minimal abnormality was detected on lymphography at completion of therapy were re-evaluated after a further 3 months: if the abnormality was unchanged or improved CR was then documented and the investigation was repeated at frequent intervals.

Treatment Programme. Details have been published previously [7, 8] and the programme is shown in Table 1.

Response. Patients were documented either as achieving CR or as having failed to remit, all patients with a less than complete response being included as failures. Complete remission was defined as the return to a normal state of health 1 month after the final cycle of therapy, with no radiological, haematological, or biochemical evidence of disease in sites at which it had been shown to exist at presentation.

Methods of Analysis. Survival was calculated from the date of first treatment to death and duration of first remission from the date of CR until the date of relapse as defined by follow-up monthly over the first 3 years and 2-monthly thereafter. Survival curves were developed by standard life-table analysis [1] and tests of significance by the log-rank method. Remission proportions were compared by the Chi-square method with Yates' correction.

Results

1. Response to Initial Therapy

Complete remission was achieved in 24 of 48 patients (50%) with primary induction therapy. Patient characteristics were examined for factors which independently influenced their rate of response (Tables 2–6). Those under 55 years old had a significantly higher response, 20/32 compared with 4/16 ($P = < 0.05$). In addition, the CR rate was higher for those with nodal (stages II and III, 13/17) than for those with extranodal disease (stage IV, 11/31, $P = < 0.01$). For patients with stage IV disease the only extranodal site associated with a significantly worse prognosis was the central nervous system (CNS), CR being achieved in 1/9 patients compared with 10/22 for all other sites ($P = < 0.05$).

Major abnormalities of renal or hepatic function were detected primarily in patients with stage IV disease (Table 5), and while the prognosis was not significantly worse for them than for other stage IV patients, there was a trend for those with renal failure to respond less frequently.

Twenty-four patients did not achieve CR, and of these 23 have died (Table 7). Resistant lymphoma despite an adequate trial of therapy (minimum three cycles of treatment) was encountered in 17 patients, representing 33% of the total, six of whom developed progressive CNS disease. Of these patients, 10 received alternative therapy; three responded and only one achieved a prolonged CR (which continues). The remaining 16 have died, three as a direct consequence of increasing lymphoma (superior venal obstruction 2, CNS disease 1), the others as detailed in Table 7. Seven of the 24 patients failing to achieve CR died during treatment when there was unequivocal evidence of response; all died whilst cytopenic within 3 weeks of chemotherapy. In addition, three of these patients considered resistant died cytopenic,

Table 3. Correlation between stage and histology

Stage	Histology[a]						
	Ib	Cb	LbB	Lbu	HGu	MH	DCbCc
II and III	11	2	0	1	1	2	0
IV	11	4	6	4	3	1	2

[a] Abbreviations as in Table 2

Table 4. Correlation between Kiel and Rappaport classifications[a]

	Kiel						
	Ib	Cb	LbB	Lbu	HGu	MH	DCbCc
Rappaport							
DH	21	5	–	–	3	3	1
DU	1	1	6	5	1	–	–
DM	–	–	–	–	–	–	1

[a] Abbreviations as in Table 2

Table 5. Correlation between sites of disease at presentation and response to induction therapy

Sites of disease	No.	CR	%	P
Stages II and III	17	13	76	$P < 0.1$
IV	31	11	35	
Abdominal mass	15	6	40	
Gastrointestinal	10	3	30	
Liver (Ann Arbor)	22	7	32	
Bone marrow	14	4	29	
Lung	6	2	33	
Bone	4	1	25	
CNS	9	1	1	

giving a maximum possible treatment mortality (including intercurrent disease) of 10/48 (21%) but a relevant mortality of 7/48 (15%).

2. *Duration of Remission*

Nine of 24 patients (38%) remain in CR between 3 and 7 years after entering it. The remaining 15 have relapsed, 14 within 18 months and 1 at 4 years. The median duration of remission was 9 months. Of 13 patients with stage II and III disease, six, (2 at nodal and 4 at extranodal sites; confirmed histologically in 4) have relapsed. All six were retreated and a second CR was achieved in three, two of whom remain free of disease $2^1/_2$ and $4^1/_2$ years later. Of 11 stage IV patients, 9 have relapsed, one with disease at nodal and eight with disease at extranodal sites (including four in the CNS). Histological confirmation was obtained in six, and all nine received alternative therapy. Three partial remissions were obtained, but all have subsequently relapsed. The histology at relapse was different from that at presentation in three patients, with evidence of follicular centroblastic-centrocytic lymphoma in one and diffuse centroblastic-centrocytic lymphoma in two others; all responded completely to retreatment with chlorambucil.

Twenty-one patients received full CNS prophylaxis after CR was achieved; three of them had CNS relapse, as did one of the three remaining complete remitters who did not receive prophylaxis. In all four patients the CNS relapse was secondary to a recurrence of systemic disease, and occurred from 3 to 10 months after CR had been achieved.

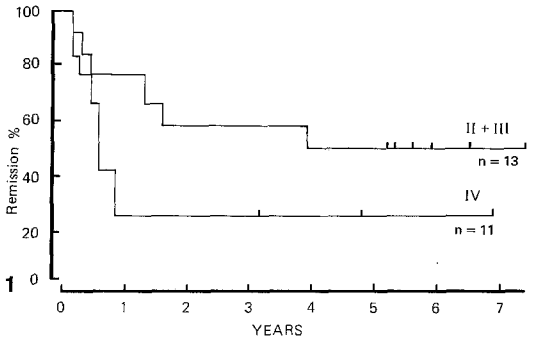
There was a trend for the duration of remission to be longer for stages II and III than for stage IV (Fig. 1), but this was not significant and no other patient characteristics were found to correlate with remission duration.

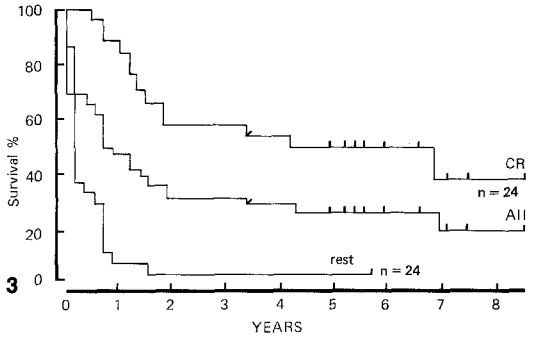
Table 6. Correlation between biochemical abnormalities and response to induction therapy

Biochemistry	No.	No. in stage IV	CR	%	P
Hypoalbuminaemia and hyperbilirubinaemia	21	16	5	24	n.s.
Stage IV normal liver	15	15	6	40	
Renal failure and hyperuricaemia	6	6	1	17	n.s.
Stage IV normal kidneys ± hyperuricaemia	25	25	10	40	

Table 7. Causes of death in patients not achieving CR

	No. of patients
Resistant lymphoma	
Disease alone	3
Infection	10
GI haemorrhage	2
Pulmonary embolus	1
	16
Responding lymphoma	
Infection	2
GI haemorrhage	1
Intracerebral haemorrhage	1
Cardiac	2
Renal	1
	7





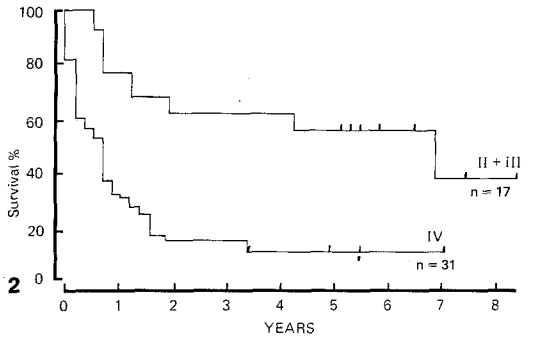


Fig. 1. Duration of remission by stage (n.s.)

Fig. 2. Survival of all patients by stage $P = 0.002$

Fig. 3. Survival of all patients by response $P = < 0.0001$

3. Survival

Twelve patients (25%) are alive and free of disease after between $3^1/_2$ and $8^1/_2$ years, nine in first remission, two having relapsed but currently free of disease, and one who failed primary induction therapy but subsequently remitted.

Thirty-six patients have died, the median survival being 10 months. Thirty-three died within the first 2 years, and three within between 4 and 7 years, having suffered several relapses. The patient who died after 7 years had relapsed with follicular lymphoma, which then pursued an indolent course with chlorambucil treatment and never exhibited any further evidence of the original immunoblastic lymphoma.

Prolonged survival correlated closely with nodal as opposed to extranodal disease ($P = 0.002$) (Fig. 2), with 8/17 (47%) patients with stages II and III surviving longer than 3 years but only 4/31 (13%) with stage IV achieving long survival. Patients in whom CR was achieved survived significantly longer and did so for all stages ($P < 0.0001$) (Fig. 3). Other characteristics found not to correlate with survival were age, sex, 'B' symptoms, and site of extranodal disease.

4. Histology

The majority of patients had immunoblastic or diffuse histiocytic lymphoma. Within the Kiel classification several other groups are recognised, including some with malignant histiocytosis, which are called DH in the Rappaport system (Table 3). This did not lead to information of greater prognostic value, however, since neither response, duration of remission, nor survival was significantly associated with histology except for the Kiel groups centroblastic, lymphoblastic, and high-grade unclassified, which had a lower response rate in association with a higher frequency of CNS infiltration.

5. CNS Involvement

CNS lymphoma occurred in 13 patients (27%), three at presentation, six during remission induction and four at relapse. All had stage IV disease, 10 with bone marrow infiltration and two with bony cortical lesions. There was a significantly higher incidence amongst patients with stage IV lymphoblastic, centroblastic, and high-grade unclassified lymphomas (including Burkitt's) (11/21) as against stage IV immunoblastic (2/22, $P = < 0.05$). All instances of CNS infiltration occurred in the context of active systemic disease and although this was controlled by intrathecal methotrexate or cytosine arabinoside, only one CR of 10 months' duration was obtained, when of craniospinal irradiation was added to the treatment.

Discussion

The results for this group of patients, now with a minimum follow up of 3 years, confirm our initial observations that a programme comprising remission induction, cranical prophylaxis, and maintenance chemotherapy (OPAL) could be administered with a low mortality and a CR rate of 50% overall. This is comparable to the 40%–70% response obtained with several other regimens [2, 3, 9–12].

Younger patients and those with nodal disease responded considerably better than those who were older or had extranodal lymphoma. Subsequently 50% have remained in first remission for 3–8 years and are potentially cured.

Immunoblastic lymphoma was more frequently in stage II or III and this, combined with the lower incidence of CNS infiltration, made this a more favourable group amongst patients with high-grade NHL. The majority of patients presented with stage IV disease however, and often with multiple sites of involvement, so that it was not possible to differentiate response or survival by site except for those with CNS infiltration. In common with the results of other investigators [3, 11, 12] CR was achieved in 35% with stage IV only 25% of whom survive relapse-free after 3–8 years.

The poor prognosis for stage IV patients was associated with a high number of early relapses and a large number (17/31) in whom early resistance to therapy was encountered. In addition, as CNS infiltration was also associated with failure to control the systemic disease in 6/24 patients, there is an obvious need to intensify the remission induction phase. A more recent and intensive six-drug programme (A. T. Skarin, personal communication) has achieved an improved response and remission duration in stage IV patients, although CNS prophylaxis still appears to be necessary.

The value of the CNS prophylaxis as administered was obscured by the failure to control the systemic disease; however, only 3/21 who had received full treatment had a CNS relapse and in all three this was secondary to systemic relapse. Similarly, the value of maintenance was not tested; the pattern of early relapse with only one relapse following cessation of maintenance, however, unlike our experience of an identical programme in adult acute lymphoblastic leukaemia [8], suggests that there is no proven benefit from maintenance in NHL.

In conclusion, it has been possible to achieve prolonged remissions in patients with nodal disease, but new approaches are urgently required for those with stage IV extranodal involvement.

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