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A Prospective Study of the Treatment of High-grade Histology non-Hodgkin's Lymphoma Involving the Gastrointestinal Tract

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Abstract—*Thirty-six patients presenting with stage II-IV primary gastrointestinal non-Hodgkin's lymphoma of high-grade pathology were treated in a prospective study from 1975 to 1983 with combined modality therapy. A complete response rate of 56% was obtained and the overall 5-yr survival rate was 36%. The 5-yr relapse-free survival rate of the complete remitters was 79%. Multivariate analysis revealed that the remission achieved ($P < 0.001$) and the completeness of primary surgery ($P = 0.018$) would reliably predict the duration of overall survival. The finding of diffuse histiocytic histology (Rappaport) predicted longer relapse-free survival. The majority of deaths were related to intra-abdominal complications and not to disseminated lymphoma. Gastrointestinal tract non-Hodgkin's lymphoma of high-grade pathology of all stages is curable with a combination of chemotherapy and radiotherapy following surgery to remove as much macroscopic disease as is possible.*

INTRODUCTION

NON-HODGKIN'S lymphoma (NHL) presenting primarily in extranodal tissues accounts for approximately 16-24% of all cases of NHL [1-4]. Despite the fact that the gastrointestinal (G-I) tract represents the most common site of extranodal involvement (4-12% of all NHLs) [2, 3, 5], the disease is uncommon and it is difficult for large numbers of patients to be accrued in single centres. This makes randomised, prospective, controlled trials of different treatment regimens impractical.

To date all the series concentrating on the results of treatment of patients with primary gastrointestinal lymphoma have had to rely on retrospective analysis [4, 6-15]. Inevitable problems of case selection, varying treatments and incomplete records have led to conflicting results. Different variables have been found to be associated with an unfavourable prognosis and among these have been stage IV disease [6, 7, 9, 10], bowel perforation [6, 9], older age groups [14, 16], large tumours [11, 16], inadequate primary surgery [6, 14] and involvement of the small or large intestine as opposed to the stomach [13, 14]. There is agreement from all these series that the finding of a follicular component to the histology is associated with a higher 5-yr survival rate. The majority of patients with primary G-I NHL will, however, have diffuse lymphomas and while some series have found that subdivision of these 'high-grade' histologies produces groups which are of prognostic significance [9, 16, 17], this has not been confirmed in others [7, 14, 18].

Several of these variables were included in a proposed new staging system for primary G-I NHL after a retrospective analysis of 104 cases seen at the Christie Hospital between 1950 and 1975 [6]. This system has been found to be of use by others [10] in predicting survival, but differences in treatment policies within these studies makes direct comparison of results of the management of different stages difficult. Some groups have used surgery alone for the majority of their patients [1, 3], some surgery and radio-

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therapy [9, 11, 13, 19, 20] and others have included chemotherapy [8, 12, 21]. In order to reduce some of the problems associated with interpretation of the wide variation of results using the different treatment approaches in these retrospective series, a prospective study was set up in 1975. All patients with stages II-IV 'high-grade' histology primary G-I lymphoma have been given one form of intensive induction chemotherapy followed by abdominal radiotherapy. Subsequent chemotherapy was given depending on the stage of disease at presentation. We now present the results of the first 36 patients treated up to 1983.

MATERIALS AND METHODS

Primary G-I lymphoma was defined according to the criteria of Lewin *et al.* [7] as occurring if the patient had obvious predominant alimentary tract lesions without enlargement of peripheral nodes or obvious lymphoma clinically detectable elsewhere. All patients whose G-I involvement was detected following previously diagnosed extra-abdominal lymphoma are classified as secondary cases and not included in this study. All patients originally had a biopsy-proven diagnosis of high-grade-pathology NHL using the modified Rappaport classification [22]. At the time of referral, pathological specimens were reviewed at the Christie Hospital and those patients with malignant lymphomas of diffuse histiocytic, diffuse poorly differentiated lymphocytic, diffuse mixed or diffuse undifferentiated subtype were accepted for inclusion in the trial. The histology has since been re-reviewed by one of the authors (MH) and is also grouped according to the Kiel classification (with the addition of a 'true histiocytic' category). In those cases where a diagnosis of true histiocytic lymphoma was entertained immunoperoxidase stains for alpha-1 antitrypsin and muramidase were carried out [16, 23].

The patients were staged according to the Ann Arbor classification and the system proposed by our own group [6]. All had blood taken for routine haematological and biochemical investigation and all had bone marrow examination, chest X-rays and CT scans of the lower chest and abdomen. Whenever possible, the patients also underwent barium studies of the G-I tract to determine the extent of residual disease, and jejunal biopsies to look for evidence of gluten-sensitive enteropathy.

Thirty-six patients with stages II-IV high-grade-histology NHL primarily involving the G-I tract were entered into the study between 1975 and 1983. All had undergone surgery at outside hospitals but detailed operation notes were available. The surgery was termed 'adequate' if the major detectable sites of macroscopic disease involving the bowel and local nodal masses had been removed. The patient characteristics are shown in Table 1 and a breakdown of histology in Table 2.

Table 1. Patient characteristics

	No.
Total	36
Sex	
Male	23
Female	13
Age in yr (median)	56
Stage (Ann Arbor)	
IIEA	6
IIEB	11
IIIB	1
IVA	4
IVB	14
Stage (Blackledge *et al.*)	
2A	6
2B	6
2C	3
3	3
4	18
Liver involved	9
Bone marrow involved	6
Lung parenchyma involved	3
Site	
Stomach	17
Small intestine	14
Large intestine	5

Table 2. Histology

Classification	Subgroup	No.
Rappaport	diffuse histocytic	22
	diffuse poorly differentiated lymphocytic	11
	unclassified	3
Kiel	centroblastic	5
	centrocytic	2
	diffuse centroblastic/centrocytic	6
	immunoblastic	6
	lymphoblastic	3
	true histiocytic	8
	unclassified	6
Working Formulation	ML, diffuse, large cell	5
	ML, diffuse, small cleaved cell	5
	ML, diffuse, mixed small and large cell	6
	ML, diffuse, large cell, immunoblastic	6
	ML, lymphoblastic	3
	ML, histiocytic	8
	ML, unclassifiable	3

Response was assessed by standard criteria, a complete remission being defined as the disappearance of all known disease (after all previously abnormal investigations had been repeated), and a partial remission as a 50% or more decrease in the sum of the products of perpendicular diameters of measurable lesions, lasting for more than 4 weeks. Progression of disease was defined as the appearance of new lesions or an increase of greater than 25% in the sum of products of perpendicular diameters of measurable lesions lasting more than 4 weeks. Static disease amounted to neither a 25% increase nor a 50% decrease in the size of measurable lesions.

All patients were previously untreated with chemotherapy or radiotherapy prior to entry to the study. The treatment, following staging procedures, involved remission induction chemotherapy over 6 weeks using vincristine 2 mg weekly, adriamycin 50 mg/m^2 every 2 weeks and prednisolone 40 mg daily (VAP). Abdominal radiotherapy (using large fields at a dose of 2500 to 3500 cGy fractionated over 3–4 weeks) was then given followed by further chemotherapy. Patients with stage II disease received oral cyclophosphamide 200 mg weekly, methotrexate 20 mg/m^2 weekly and 6-mercaptopurine 50 mg/m^2 daily — all given for 2 yr. Patients with stages III and IV disease received three 3-weekly courses of i.v. cyclophosphamide 1 g/m^2 after VAP before commencing the same oral therapy for 2 yr as those with stage II disease.

The patients were followed up at regular intervals in the clinic and the median follow up for the total patient group was 67 months.

Statistical analysis

A list of the variables that were included in the following analyses is given in Table 3. Survival curves were plotted according to the method of Kaplan and Meier [24] and tests for differences in survival distributions were based on the log rank test [25]. Cox's proportional hazards model [26] was used to determine the most significant variables that were related to survival. A stepwise logistic regression procedure was used to determine combinations of patient characteristics important in predicting complete remission.

Table 3. Variables studied

Age
Clinical stage
Karnofsky performance status
Site of G-I involvement
Histology (Kiel and Rappaport)
Liver involvement
Bone marrow involvement
Individual liver enzyme levels
Serum LDH
Presence of bulk disease (tumour mass > 5 cm)
Adequacy of surgery
Remission achieved

RESULTS

Response to therapy

Of the 36 patients treated, 20 (56%) achieved a complete remission. A further seven patients (19%) achieved a partial response, giving an overall response rate of 75%. Statistical analysis revealed that the only variable to predict which patients would achieve a complete remission was the presenting Karnofsky performance status (KP), with higher values giving a greater likelihood of achieving a CR.

Survival

The overall survival of the patient group (as measured from the first day of chemotherapy) is shown in Fig. 1. The median survival was 10 months and the 5-yr survival rate was 36%. The majority of deaths (67%) occurred in the first 6 months and only three patients died beyond 1 yr.

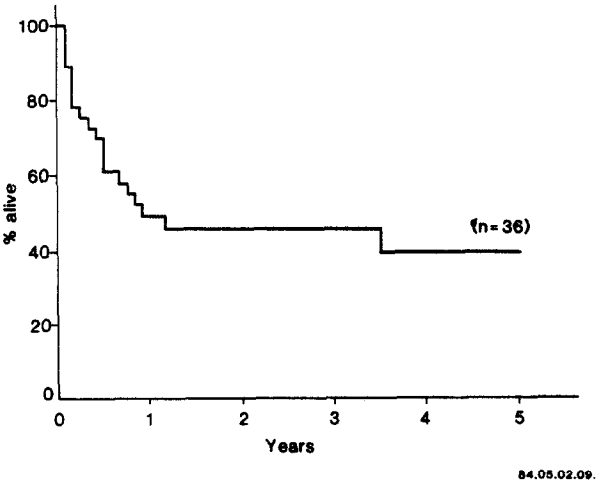

Fig. 1. Overall survival of patient group.

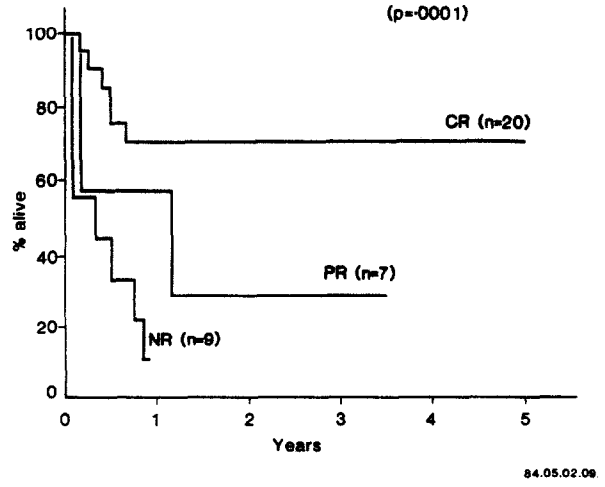

Fig. 2. Survival according to remission achieved.

Survival curves were plotted and compared using the log rank method for factors which were of possible prognostic importance. The most significant of these was whether a complete response was achieved ($P = 0.0001$) (Fig. 2). The median survival of the complete responders was 6 yr, only one late death having occurred in this group beyond 8 months. This patient, with previous coeliac disease, was treated for diffuse histiocytic NHL involving the small intestine in 1976 and was admitted to a regional surgical unit with symptoms of intestinal obstruction in 1983. A central abdominal mass was palpable and was attributed to recurrent lymphoma. Unfortunately the patient died and no post mortem was performed. On the balance of probability she has been classified in this study as having died from recurrent G-I lymphoma.

Other factors found to reach levels of significance in predicting prolonged survival were adequate surgery ($P = 0.002$) (Fig. 3), the absence of liver involvement with lymphoma ($P = 0.005$), a presenting KP of greater than 70 ($P = 0.02$), and the histological subgroup, according to the Rappaport classification, of diffuse histiocytic lymphoma ($P = 0.02$).

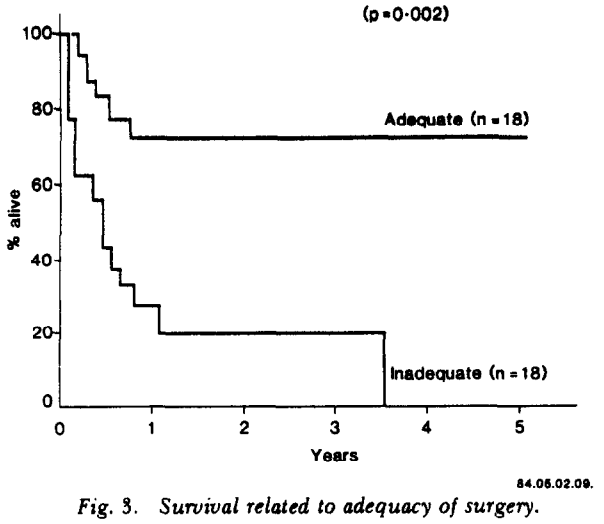

Fig. 3. Survival related to adequacy of surgery.

Several of these factors may have been interrelated, and a Cox's multivariate analysis was therefore carried out to identify which factors may be of independant significance in predicting prolonged survival. Remission status ($P < 0.001$) was again the most important variable, those achieving a complete remission surviving significantly longer than those achieving a partial response, who in turn survived significantly longer than those who did not achieve a major response. The only other variable to remain significant was the adequacy of surgery, those patients having undergone an inadequate operation surviving a shorter duration than those in whom the majority of macroscopic disease had been resected ($P = 0.018$).

Relapse-free survival

The 5-yr relapse-free survival of the 20 patients who achieved a complete remission was 79%. Only one patient (mentioned above) has relapsed beyond 4 months from the beginning of therapy. Factors were studied using log rank analysis to determine significant variables predictive of prolonged relapse-free survival and only one reached levels of significance — histological subgrouping according to the Rappaport classification. Patients with diffuse histiocytic lymphoma had a significantly longer RFS than other histological subtypes ($P = 0.03$).

Deaths

There were 21 patients who died in this study — 14 (67%) within 6 months of commencing treatment. The causes of death were: perforation (five patients), intestinal haemorrhage (six patients), haemorrhage and perforation (two patients), sudden deaths at home with histories suggestive of G-I bleeds and/or perforation (five patients), intestinal obstruction (one patient), second malignancy (one patient) and recurrent lymphoma (one patient). Three patients who died in hospital of intestinal perforation or haemorrhage during remission induction with chemotherapy had no detectable lymphoma at autopsy.

DISCUSSION

This series represents the first group of patients with primary gastrointestinal lymphoma of high-grade histology to be analysed after treatment in a prospective study using combined modality therapy. The results can be compared with those of a study of all cases of advanced stage high-grade-histology NHL [27] treated with a similar regimen at this institute and reveal almost identical complete response rates (56 vs 58%) and 5-yr survivals (36 vs 37%). Of note, however, is the shorter median survival for patients with G-I lymphoma (10 vs 20 months) but much better 5-yr relapse-free survival (79 vs 52%), reflecting the curability of this disease provided that the patients receive adequate initial therapy and careful early monitoring for complications. It is difficult to make comparisons of the results of this study with those from other series because of the differing treatments inevitable in retrospective analyses, frequent grouping of follicular and diffuse histologies and problems with inadequate staging. Most series have also included patients with stage I disease in their analyses — a group noted in the retrospective analysis from this institute [6] to have an excellent prognosis using

surgery alone and thus excluded from this study.

The 5-yr survival rate for stages III and IV disease in this study was 35% and compares well with the retrospective analysis of patients treated at this centre [6]. In the latter series only 25% of patients with stages III or IV disease were alive at 5 yr (30% having a nodular/follicular pattern of histology). Of the 18 patients with diffuse histiocytic lymphoma of the G-I tract reported from the NCI [8] (treated predominantly with surgery and chemotherapy), 28% achieved a CR and only three patients were long-term survivors. In the series of 48 patients with diffuse histiocytic lymphoma from Stanford [4] (45% with stages IE and II disease) the overall CR rate was 54% and the median survival only 8 months. Several series have highlighted the disappointing survival of patients with stages III and IV disease [4, 7, 9, 10, 17, 20], with no survivors beyond 1 [9] and 2 yr [7] in two series. In our study there was no significant difference in survival according to the stage at presentation. The numbers of patients in each staging subgroup of the system proposed by our group [6] were small and a larger series would be needed to confirm its value as a prognostic variable using combined modality therapy.

All studies of primary G-I lymphoma have shown longer median survival and higher 5-yr survival rates in patients with histologies showing the presence of a nodular or follicular component. There has also been evidence to show a better survival and tendency for more localised disease if the presence of a plasmacytoid element is demonstrated [11, 12, 16] and up to 39% of patients with G-I lymphoma have been reported to demonstrate this [28]. Other series have suggested this element to be much less common [6, 7, 10, 16, 17, 22] and Isaacson *et al.* [23], in a series of 46 cases of primary G-I lymphoma, reported the predominant subgroup (50% of all patients) to have a histiocytic origin as evidenced by positive staining for histiocyte markers. Seo *et al.* [16] showed patients with true histiocytic lymphomas to have a much worse prognosis than those with lymphomas of B cell origin. In our series lymphoplasmacytoid elements were never demonstrated, but eight (22%) lymphomas were classified as true histiocytic. The latter group showed no difference in survival compared with other subgroups. Histological subgrouping was found to reach levels of significance on log rank analysis only for the Rappaport classification, with patients having diffuse histiocytic lymphoma surviving longer than all other groups combined, though this was not significant when multivariate analysis was carried out. As with studies of nodal lymphoma, however, the presence of diffuse histiocytic lymphoma (Rappaport) was of significance both on log rank and multivariate analysis in predicting prolonged relapse-free survival, only one patient with this disease dying after achieving a complete response. Subdivision of histologies using the Kiel classification resulted in groups which were too small, in a study of this size, to reach levels of significance in predicting survival.

Most studies have shown that the majority of G-I lymphomas involve the stomach and some have suggested that this site carries the best prognosis [13–15]. The stomach was the most common primary site in our series, but there was no difference in response or survival according to site involved.

Nearly all deaths (even though a large proportion of patients were found on investigation to have disseminated disease at the time of study entry) occurred early during therapy and were related to complications arising from the gastrointestinal tract. This contrasts with studies not employing chemotherapy, where up to 39% of patients die with extra-abdominal recurrence of disease [9, 10, 19], and is similar to the finding of the NCI series (in which most patients were given chemotherapy), with 38% of patients dying from intestinal haemorrhage or perforation. This fact, together with the statistically significant correlation of adequate surgery with prolonged overall and relapse-free survival, indicates the need to make surgeons aware of the vital role they have in removing as much involved tissue as possible. Re-referral for further surgery should always be considered before chemotherapy in patients who have inadequate operations so that the all-too-common occurrence of early massive intestinal haemorrhage or perforation is avoided. Too often the patient is a victim of the efficacy of chemotherapy and dies as a result of complications at the site of resolved lymphoma.

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