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Intensive Combination Chemotherapy with Vincristine, Adriamycin and Prednisolone (VAP) in the Treatment of Diffuse Histology Non-Hodgkin's Lymphoma

(A Report of 89 Cases with Extensive Disease from the Manchester Lymphoma Group)

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Abstract—*Eighty-nine patients with extensive, diffuse histology non-Hodgkin's lymphoma were treated with an intensive* 6-week *course of chemotherapy (vincristine, adriamycin and prednisone). Radiotherapy was given to sites of bulk disease and to complete remission whenever possible, and low dose oral maintenance chemotherapy was given for* 2 yr *to those patients in remission.*

Complete remissions were seen in 61% *of patients, with* 81% *of patients with stage II abdominal disease achieving a complete remission. Fewer patients with bone marrow involvement and liver function abnormalities achieved a remission.*

Survival was influenced by remission status (P = 0.001), *raised AST* (P = 0.001), *lymphopenia* (P = 0.001) *and 'B' symptoms* (P = 0.046). *Prolonged relapse free survival was seen in more patients with diffuse histiocytic lymphoma than DPDL lymphoma* (P = 0.048), *and in those patients who received radiotherapy* (P = 0.0013). *VAP appears to be an effective regime in the management of diffuse lymphoma with low toxicity.*

INTRODUCTION

THE INTRODUCTION of intensive, intermittent combination chemotherapy has resulted in considerable improvement in the outlook of patients with diffuse histology non-Hodgkin's lymphoma of unfavourable grade [1]. Using single agent chemotherapy for diffuse histiocytic lymphoma, the complete remission rate was only 5% [2] but this has been improved to 47–70% in several studies involving intermittent combination chemotherapy [3–7]. The more successful combinations include adriamycin, vincristine, cyclophosphamide and prednisolone. The median survival of patients with diffuse histiocytic lymphoma has been improved from less than 1 yr to over 18 months and approximately one third of patients are long term relapse free survivors [8]. The importance of achieving a complete remission has been stressed and those patients with diffuse histiocytic lymphoma who achieve a carefully documented complete remission have a low incidence of relapse and a good prospect of prolonged relapse free survival [9].

Chemotherapy for diffuse poorly differentiated lymphocytic lymphoma has been less successful in terms of prolonged relapse free survival and even with the latest combinations, these patients tend to have a continuing relapse pattern with a high incidence of

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relapse after 2 yr and no evidence of long relapse free survival [10, 11].

The approach using intermittent combination chemotherapy is attended by a considerable number of patients relapsing between courses of chemotherapy before achieving a complete remission and although some patients with diffuse histology lymphoma achieve prolonged survival, the overall median survival is not satisfactory. In January 1975, the Manchester Lymphoma Group addressed this problem by using a more continuous, weekly chemotherapy similar to that used in acute lymphoblastic leukaemia (ALL) for rapid remission induction in an attempt to avoid the early failures seen between intermittent courses of chemotherapy. The short, weekly remission induction programme using vincristine, adriamycin and prednisolone with a total dose of adriamycin of only 150 mg/m^2 was designed to improve the rapidity and number of patients achieving a complete remission and reduce the toxicity seen with more prolonged high dose combined chemotherapy given at 2–4 weekly intervals. This approach was first used in a series of patients treated at St. Bartholomew's Hospital, London, by one of the authors of this paper (DC) [12]. The St. Bartholomew's Hospital regime involved vincristine, adriamycin, prednisolone and L-asparaginase (OPAL) but the L-asparaginase was omitted from the present regime and the schedule of adriamycin changed to reduce toxicity. In addition, local radiotherapy was given to areas of residual or previously bulky disease in an attempt to reduce the relapse rate in these areas. Subsequent chemotherapy involved a 2 yr oral treatment with cyclophosphamide, methotrexate and 6-mercaptopurine.

It is the purpose of this paper to report the results of treating 89 patients with diffuse histology lymphoma using this protocol in a single centre.

MATERIALS AND METHODS

Patient characteristics

Patients with biopsy proven diagnosis of diffuse histology non-Hodgkin's lymphoma seen at the Christie Hospital, Manchester, in the Department of Medical Oncology and Radiotherapy by members of the Manchester Lymphoma Group were admitted to this study. All histological specimens were reviewed and classified according to Rappaport [13]. The histological types acceptable for inclusion were diffuse poorly differentiated lymphocytic (DPDL), diffuse histiocytic (DH), diffuse mixed lymphocytic histiocytic (DM) and diffuse undifferentiated (DU) lymphoma. Patients who were stage III or IV (Ann Arbor classification) [14] were entered into the study. Patients with massive stage II abdominal disease (lymph node masses >10 cm) or who had gastrointestinal lymphoma with extensive intra-abdominal nodal involvement were also included. All patients were above 15 yr of age.

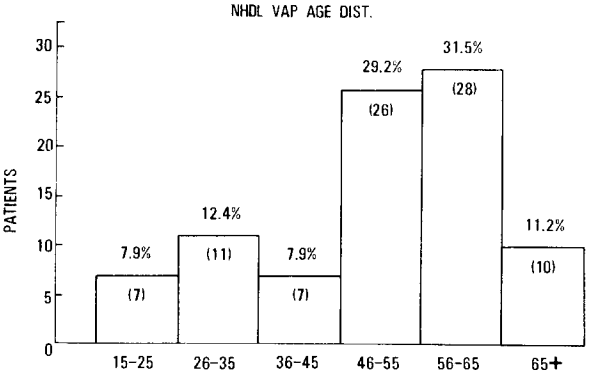

Fig. 1. Bar chart showing the distribution of age by decades. More than 70% of patients were older than 45 yr.

Table 1. Distribution of stage and histology in patient populations

	Histology				
	D.P.D.L.	D.H.L.	D.M.	D.U.	Total
2 Abd.	9	8	0	0	17
3	4	7	0	2	13
Stage 4	28	20	6	5	59
Total	41	35	6	7	89

D.P.D.L.—diffuse poorly differentiated lymphocytic.
D.H.—diffuse histiocytic.
D.M.—diffuse mixed lymphocytic–histiocytic.
D.U.—diffuse indifferentiated.

Ninety-two patients entered the study between January 1975 and December 1978. Three patients were excluded because they died before any treatment was given, leaving a total of 89 patients for analysis. No patient who had received previous chemotherapy was eligible for the study but five patients who had previously been treated with a single course of local radiotherapy were included.

The ages ranged from 18 to 71 yr and the distribution is shown in Fig. 1. Forty-six of the patients were male and 43 female. The distribution for stage and histology of the patients is shown in Table 1. Forty-three patients

(48%) had evidence of systemic ('B') symptoms (fever, sweats or a >10% body weight loss). Sixty-five patients (73%) had predominantly nodal disease and 24 (27%) had extradonal disease as the main presenting clinical feature. Of the latter, 17 had gastrointestinal, three had testicular, and four had skin involvement. In the patients presenting with stage II abdominal disease, 11 of 17 (65%) had involvement of the gastrointestinal tract proven at diagnostic laparotomy.

All patients in this series with extranodal disease also had evidence of nodal or widely disseminated disease. Diagnosis was made by lymph node biopsy in 65 patients, extranodal biopsy in 12 patients and by lymph node and extranodal biopsy in 12 patients. The bone marrow was involved in 19 out of 41 patients (46%) with DPDL and nine out of 35 patients (26%) with DH histology. Only two out of six patients with DM and one out of seven patients with DU lymphoma had bone marrow involvement.

Staging

Staging investigations included a full blood count, ESR, tests for haemolysis and bone marrow examination with a marrow aspirate and a Jamshidi needle trephine. Any patient with diffuse infiltration of more than 30% lymphoblasts in the bone marrow aspirate was considered to have acute lymphoblastic leukaemia and excluded from the study. Bone marrow involvement was defined as a >30% infiltration by lymphoid cells noted in the aspirate or patchy infiltration on bone marrow trephine. Although surface marker studies were frequently carried out on the peripheral blood and marrow specimens the results were not taken into account in this staging analysis. Liver function tests were routinely carried out but liver biopsy was only undertaken if the bone marrow was negative and the liver function normal or equivocal. An examination of the cerebrospinal fluid (CSF) was carried out before treatment started. All patients had a chest x-ray, plain abdominal film and a soft tissue lateral of the post nasal space. Patients with symptoms suggesting bone or soft tissue disease had x-rays of the involved area. Lymphography was not routinely performed except in those patients who were clinically stage II above the diaphragm. From September 1976 all patients had abdominal computed tomography performed using a previously published standard technique [15]. Laparotomy and laparoscopy were not used routinely but 20 patients had a laparotomy to establish the diagnosis of lymphoma.

Treatment

All patients received an initial 6-week course of combined chemotherapy using vincristine, adriamycin and prednisolone (VAP) (see Fig. 2). If bone marrow toxicity occured with the white blood count falling below 3000/μl or the platelet count below 100,000/μl, treatment was delayed 1 week before continuing at full dose. Full doses were given to patients with continuing bone marrow infiltration in spite of low blood counts. A minimum of 6 weeks treatment was given to each patient. At the end of 6 weeks the dose of prednisolone was gradually tailed to zero over 7 days and restaging was carried out. This included clinical examination, full blood count, bone marrow aspirate and trephine, liver function tests, chest x-ray and abdominal computed tomography. The CSF examination was repeated and any other investigations which had been abnormal before treatment were also repeated.

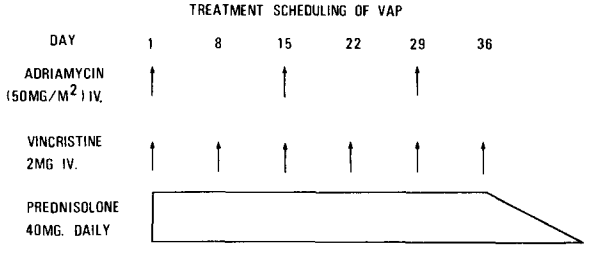

Fig. 2. Diagram of the treatment schedule for remission induction. Whenever possible the treatment was postponed for 1 week *rather than reducing the dose.*

If the patients had achieved a complete remission following VAP, radiotherapy was given to previous sites of bulky disease, provided this did not involve irradiating more than 50% of the active marrow. Bulk disease was defined as >5 cm nodal disease. A dose of radiotherapy of 2500 rad (25 Gy) in eight fractions over 10 days or its equivalent were given using megavoltage radiotherapy. If a partial remission was achieved with residual disease only apparent in one or two sites, then radiotherapy was given in an attempt to complete remission.

Patients in whom the CSF was abnormal with lymphoma cells seen using the cytocentrifuge received cranial irradiation [3000 rad (30 Gy) in 16 fractions over 21 days and five intrathecal injections of methotrexate (8 mg/m^2) given during the course of radiotherapy]. This was followed by five twice weekly intrathecal injections of cytosine arabinoside (50 mg). Defined extra-dural deposits were also irradiated. Central nervous system prophylaxis was not used in this study.

Patients who achieved a complete or good partial remission following the above were eligible for two years 'maintenance' chemotherapy using:

6-Mercaptopurine tablets
50 mg/m^2 daily
Methotrexate tablets
20 mg/m^2 weekly
Cyclophosphamide tablets
200 mg/m^2 weekly

During this period a full blood count was carried out at 3-weekly intervals and the doses of maintenance chemotherapy adjusted to keep the white blood count 3000–3500/μl.

A major remission assessment was carried out every 6 months for the first 2 yr and then annually with full haematological, bone marrow aspirate and trephine, CSF and radiological examinations. Abdominal computed tomograms were routinely carried out from September 1976.

Remission status

Complete remssion was defined as the disappearance of all known disease with a return to normal of all clinical, haematological, biochemical and radiological features.

A good partial remission was considered to have occurred if there was a $>90\%$ resolution of visible disease, minimal marrow infiltration or slightly raised liver enzymes in a symptom free patient.

A poor partial remission consisted of a $>90\%$ but $>50\%$ disease regression.

Analysis

Patient data was stored on a computer using programs developed in the Department of Medical Statistics and Medical Oncology at the Christie Hospital. Analysis of the data was performed using programs by R. Swindell (Department of Medical Statistics) and actuarial survival curves plotted using the Log Rank method [16]. Multivariate analysis of factors influencing survival using Cox's Regression method was carried out by M. Palmer [17].

RESULTS

Remission induction

The overall complete remission rate in the group of 89 patients was 61% with a further 28% achieving a good partial remission with very little apparent disease remaining. Fourteen (82%) of patients with stage II disease involving the abdomen, eight (62%) stage III patients and 32 (54%) stage IV patients achieved a complete remission.

A lower remission rate occurred in patients with liver abnormalities; patients without evidence of liver abnormality (normal size on palpation and normal liver function tests) had a complete remission rate of 65% (31/48) whereas patients with unequivocally abnormal liver function (50% elevation of serum alkaline phosphatase with associated liver enzyme abnormalities) or a positive liver biopsy had a complete remission rate of only 48% (12/25). This difference did not reach the conventional limit for statistical significance. There were 16 patients with liver function tests in the equivocal range and 11 of these achieved a complete remission (69%).

Several other prognostic factors were assessed in relation to achievement of complete remission. Of 31 patients with evidence of bone marrow involvement, 14 (45%) achieved a complete remission compared with 40/58 patients with a normal bone marrow (69%). This difference was not statistically significant ($P=0.07$). No other haematological parameter influenced the complete remission rate and there was no significant influence of the site of initial disease. There was no significant differences between histological subtypes in relation to complete remission rate. Of 41 patients with DPDL lymphoma, 25 (61%) achieved a complete remission compared with 22/35 patients (63%) with DH lymphoma.

An extended course of VAP beyond 6 weeks (up to 10 weeks), was given to four patients with good partial remission but although further regression was noted in three of these patients, only one patient achieved a complete remission with this further therapy.

Local radiotherapy to residual masses completed the remission in four of the 54 complete remitters. One patient only achieved his complete remission during 'maintainance' chemotherapy.

Toxicity of remission induction therapy

The weekly programme of combination chemotherapy was generally well tolerated, 84% of the patients received 80% or more of the scheduled total dose of VAP. No patient received less than 65% of the scheduled total dose. Thirty one patients (35%) had some haematological toxicity (WBC $<3000/\mu$l, platelets $<100{,}000/\mu$l). No patient without marrow involvement had severe myelosuppression (WBC $<1000/\mu$l). The adriamycin

injections were postponed or not given on 30 occasions in 17 patients. Fifty-nine patients experienced other side effects including mild nausea and vomiting (50 patients), slight weakness or paraesthesiae (27 patients) and colitis (2 patients). Herpes zoster infections occurred in five patients and other severe infections occurred in 11 patients (seven with bacterial septicaemia, and five with broncho-pneumonia). Three patients died with broncho-pneumonia in complete remission at the end of remission induction and one patient died of progressive pulmonary fibrosis. All patients had either partial or total alopecia.

Survival and relapse free survival

The actuarial survival curve for all 89 patients is shown in Fig. 3. The median survival was approximately 2 yr with a follow up time of four to 53 months (median 29). The median survival for those patients with stage III/IV disease was 18 months with an actuarial 3 yr survival rate of approximately 35%. Several prognostic factors for survival and relapse free survival were identified.

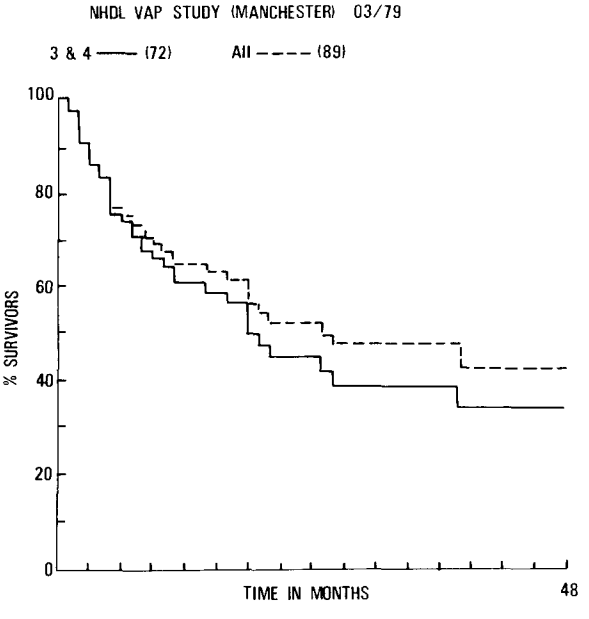

Fig. 3. Survival curve showing the survival of the whole population, with the survival of stage III/IV patients also shown. Although the median survival is only 18 months, 40% of patients can expect a survival of greater than 4 yr.

Histology. The histological subtype did not significantly influence overall survival ($P=0.07$, Fig. 4) although the median survival for patients with DPDL lymphoma was only 18 months compared with more than four years in the case of DH lymphoma. This feature is reflected in the longer relapse free

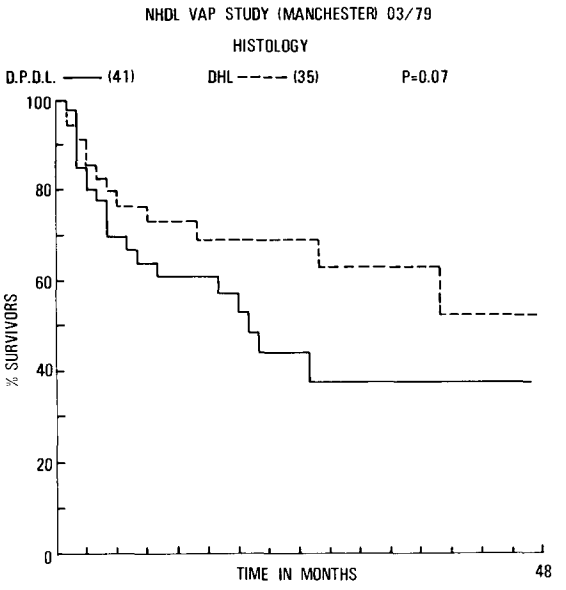

Fig. 4. Survival curve showing the influence of histology. The DPDL lymphoma group show a continuing relapse pattern.

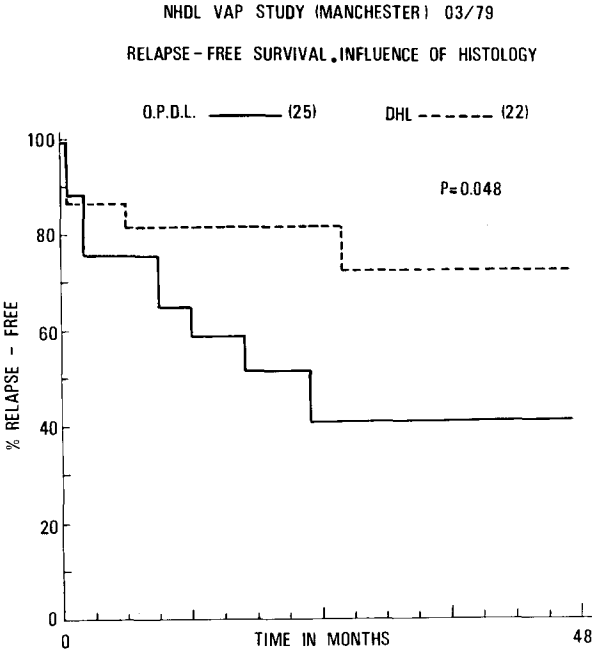

Fig. 5. Relapse free survival curve showing the influence of histology. Prolonged remissions are seen in the diffuse histiocytic lymphoma group.

survival in patients with DH lymphoma achieving a complete remission compared with that for patients with DPDL lymphoma ($P=0.048$, Fig. 5). Of 22 patients with DH lymphoma who achieved a complete remission, only five had died of their disease and there is an actuarial relapse free survival of 72% at 4 yr.

Patients with DPDL lymphoma showed a continuing relapse pattern and 11 of the 25 patients achieving a complete remission have

relapsed within 2 yr. There were only six patients with DM lymphoma and seven patients with DU lymphoma. The number of patients in these subtypes were too small for proper analysis in relation to survival.

Stage. The survival by stage is given in Fig. 6. The 17 patients with stage II disease involving the abdomen have done particularly well with an actuarial 3-yr survival of 80%. Fourteen of the 17 patients achieved a complete remission and only two have relapsed. One patient with DPDL lymphoma relapsed at 2 months and one with DH lymphoma relapsed at 26 months. In patients with abdominal stage II disease there was no significant difference in survival or relapse free survival between those with and without gastrointestinal involvement. Patients with significant 'B' symptoms (>10% body weight loss or fever) at presentation had a poorer survival than patients without these symptoms (Fig. 7).

This difference in survival was related to the stage of the patients and no significant difference was seen in the patients with stage IV disease ($P=0.24$).

As with remission induction, the presence of liver abnormalities was of considerable prognostic significance in terms of survival and relapse free survival. A raised serum aspartate aminotransferase (AST) or serum alkaline phosphatase and a reduced albumin were all of adverse prognostic significance. The most significant of these features was the AST ($P=0.0001$).

This remained significant even if only the patients with stage IV disease were considered ($P=0.0001$).

Other liver function tests including serum gamma glutamyl transpeptidase, alanine leucine transaminase and lactic dehydrogenase and the bromsulphthalein excretion test were of unreliable prognostic significance in terms of overall survival or relapse free survival.

A palpable spleen at presentation did not affect overall survival or relapse free survival.

Haematological abnormalities. In the overall group there was a difference in survival between those patients with and without bone marrow disease; however, this difference was eliminated if the stage II patients with abdominal involvement were excluded from the analysis. The initial blood lymphocyte count proved to be a significant prognostic factor with lymphopenia patients (<1000 lymphocytes/μl) having an unfavourable prognosis ($P=0.0001$, Fig. 8). A lymphocytosis or morphological evidence of blood involvement was uncommon in this series and there were insufficient patients to assess the effect of this on survival or relapse free survival. The level of haemoglobin, platelet count and erythrocyte sedimentation rate were not of significant prognostic importance. There were only three patients presenting with evidence of haemolysis and two with severe neutropenia.

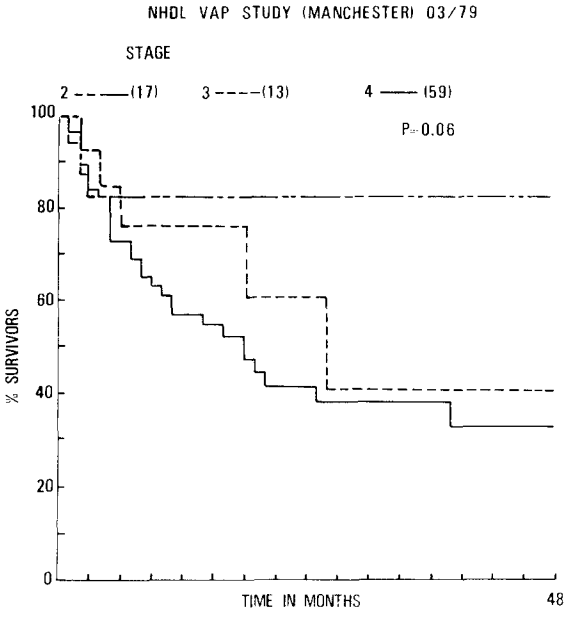

Fig. 6. Survival curve showing the influence of stage. Stage II patients (with massive abdominal disease) have a particularly good survival.

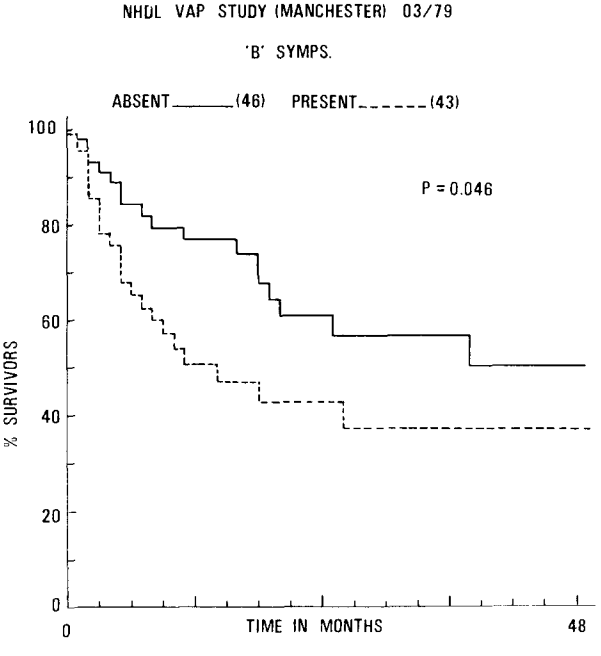

Fig. 7. Survival curve showing the influence of 'B' symptoms. This difference was not seen if only stage IV patients were considered.

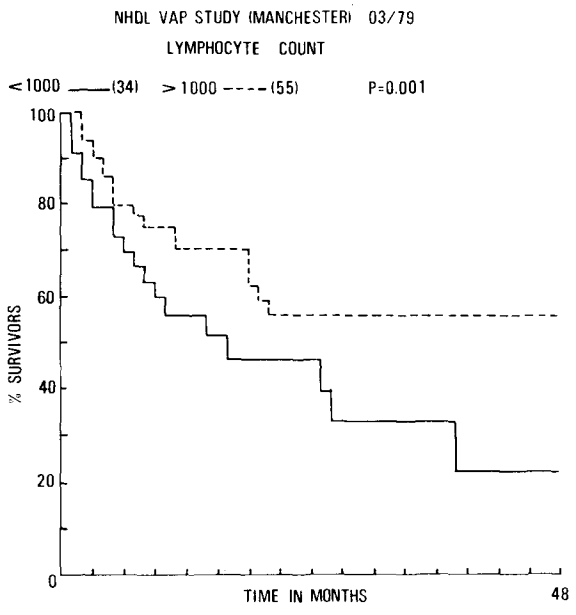

Fig. 8. Survival curve showing the influence of a lymphopenia. Several of the lymphopenic patients died early in complete remission of infection.

Remission status. The influence of remission status following initial induction therapy on survival was highly significant ($P=0.001$, Fig. 9). The actuarial survival curve for the 54 patients achieving a complete remission shows a median survival of more than 4 yr. Patients achieving a good partial remission with more than 90% resolution of known disease but evidence of persisting small amounts of disease had a median survival of only 20 months. Those patients within the poor or no response categories had a median survival of 5 months and only one patient in this group was alive at 10 months.

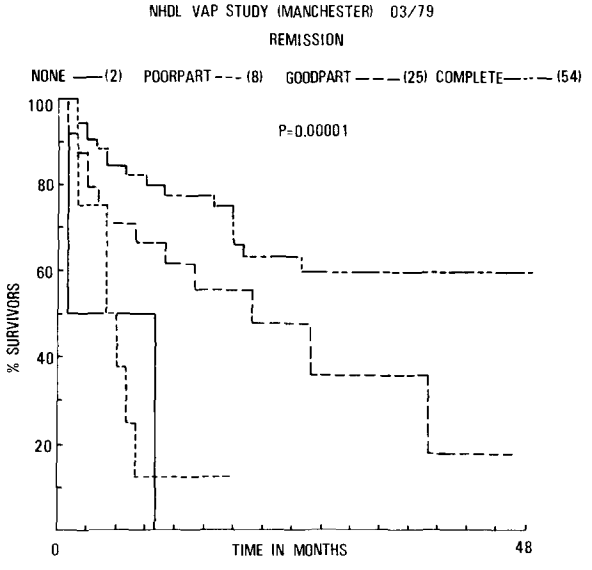

Fig. 9. Survival curve showing the influence of remission. Only those patients in complete remission have a chance of long term survival.

The age and sex of the patients did not influence survival.

Multivariate analysis was carried out using those factors which were shown to be of prognostic significance. Only two factors, AST and remission status were shown to be of independent prognostic significance.

Role of radiotherapy following remission induction. There was an overall difference in survival in favour of the groups selected for radiotherapy following remission induction (Fig. 10). This figure includes patients receiving radiotherapy for residual disease and patients achieving complete remission who received radiotherapy to sites of pre-existing bulk disease. There were 14 relapses in the group of 20 patients not irradiated and 8 out of 34 patients in the irradiated group: three of these relapses were in the irradiated area. In an analysis of the patients achieving a complete remission, the significant difference in favour of radiotherapy in both overall survival and relapse free survival was independent of initial stage and histology (Fig. 11).

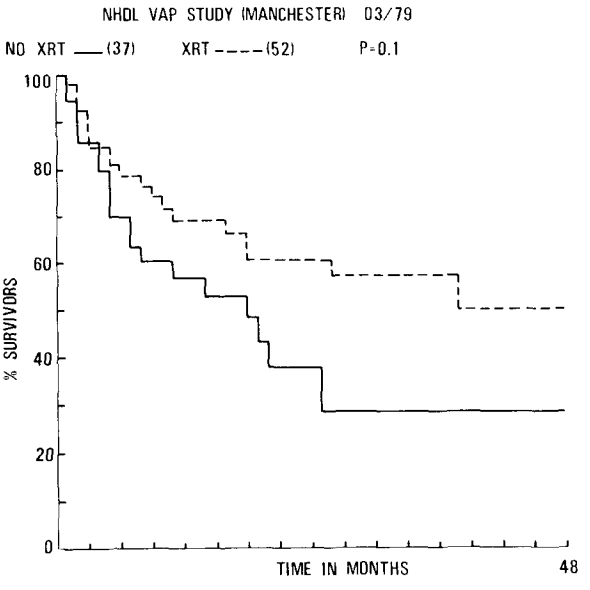

Fig. 10. Survival curve showing the influence of radiotherapy. The median survival of those patients receiving radiotherapy had not been reached at 4 yr.

Role of maintenance chemotherapy. Of the 21 patients who relapsed following the induction of complete remission, 13 occurred during the first 6 months of therapy and 20 relapsed within the first 2 yr. Maintenance treatment was generally well tolerated and with the exception of six patients who had their treatment stopped permanently because of side effects, maintenance chemotherapy was only

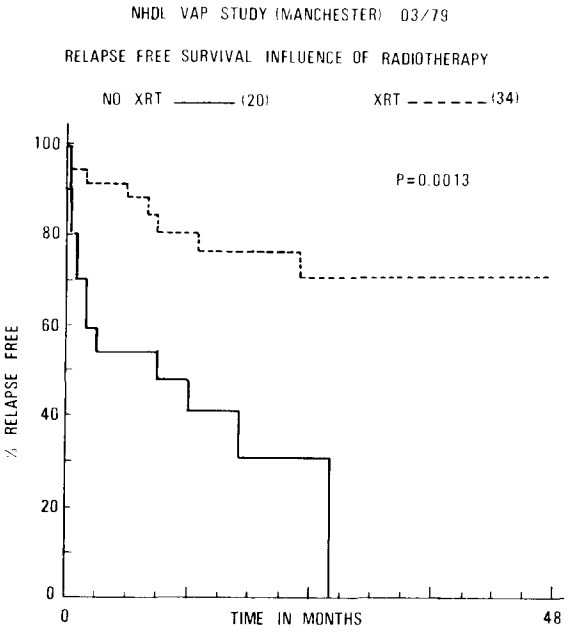

Fig. 11. Relapse free survival curve showing the influence of radiotherapy. No patient remains in remission in the no radiotherapy group.

stopped at relapse or during periods of bone marrow suppression. The majority of patients had a period of 2 months or greater when maintenance chemotherapy was not given because of bone marrow suppression. There were, however, no episodes of severe infection during maintenance chemotherapy and no infective deaths in remission, although three patients developed Herpes zoster infections.

Relapse within the central nervous system occurred in five patients, in four of the five patients cranial nerve palsies or signs of meningism were present. In one patient there was evidence of a spinal cord lesion with lumbar root involvement. With the exception of one patient who relapsed 10 months after presentation, within the central nervous system, the other CNS relapses occurred within the first 6 months (1, 2, 3 and 6 months).

DISCUSSION

The results of this study show that a 6-week remission induction programme of combined vincristine, adriamycin and prednisolone (using a weekly schedule) is effective and relatively free from severe toxicity. The total amount of adriamycin given was only 150 mg/m^2 in an attempt to reduce the likelihood of any long term cardiac complications in the survivors. The regime was better tolerated than schedules involving bleomycin which was introduced to reduce the possibility of tumour regrowth between cycles [5, 6].

Some of the best results in treating non-Hodgkin's lymphoma of diffuse 'unfavourable' pathology with chemotherapy have been reported from studies by the South West Oncology Group (SWOG) [7, 18]. Their best results have been obtained with regimes involving adriamycin, vincristine and prednisone (HOP) with or without cyclophosphamide and bleomycin (CHOP or CHOP-Bleo). Courses of therapy were repeated at 2–3 weekly intervals. Their remission rate in the DH group of patients was 67% and the projected one year survival was 66%. Twenty-two of 35 patients with DH lymphoma (63%) achieved a complete remission in our series using a short intensive course of chemotherapy (VAP) with five of the patients completing a remission using radiotherapy to sites of residual disease. The chemotherapy remission induction did not contain cyclophosphamide and it is of some interest in this context that the figures from the SWOG studies showed that HOP gave more complete remissions than CHOP (HOP, 70%; CHOP, 50%). Patients with DH lymphoma also had longer remission durations using HOP (median CHOP 61 weeks, HOP 101 weeks), and survival (median CHOP 44 weeks, HOP 108 weeks).

The actuarial 3 yr survival for our group of 35 patients with DH lymphoma was over 60% with a relapse free survival of more than 70% in the 22 patients achieving a complete remission. Although the complete remission rate reported for the cyclophosphamide, vincristine, procarbazine, prednisone combination (C-MOPP) and the bleomycin, adriamycin, cyclophosphamide, vincristine, prednisolone combination (BACOP) in patients with DH lymphoma was lower (46% and 47% respectively) and the median survival was only 14 months, 80% of those achieving a complete remission were still in remission at 3 yr [8, 9]. It appears that prolonged relapse free survival is possible for the majority of patients with DH lymphoma who achieve a complete remission and this is apparent in our own series for which the complete remission rate was almost two thirds.

The overall complete remission rate was reduced in patients with bone marrow involvement and abnormal liver function but this has been a finding in several studies [1, 11, 19]. In our series there was no difference in survival if only patients with stage III–IV disease were considered. This contrasts with the findings of Fisher [19] and Sullivan [20]. Fisher and co-workers found that the presence

of gastrointestinal disease adversely affected the remission rate and survival of patients with DH lymphoma. This was not confirmed in this study in which patients with gastrointestinal disease and intra-abdominal lymphadenopathy had a relatively good prognosis.

Although the number of long term survivors was similar to that seen in other studies, there were a number of early relapses within 3 months of completing VAP. It is possible that these occurred because of the short duration of the induction therapy. It was also noticeable that these relapses occurred more often in patients who had not received radiotherapy. However, since the patients were not randomly selected to receive radiotherapy, it is not possible to state whether radiotherapy was responsible for improved relapse free survival or for the reduction in the number of early relapses. The correlation between radiotherapy and improved relapse free survival was however, seen irrespective of stage and histology. Even if bone marrow infiltration was initially present, patients receiving radiotherapy to nodal sites fared better than those who did not.

The recent results of Harrison *et al.* [11]. updated by Sullivan [20], similarly suggest that radiotherapy could have a useful role following initial chemotherapy and one third of the complete remissions occurred during radiotherapy in their series. The radiotherapy given in their study included total body irradiation if the bone marrow was involved and this more aggressive approach may have contributed to the higher complete remission rate. The contribution of radiotherapy to the improved survival of this group of patients deserves further study under controlled conditions.

In common with other studies [5, 7, 12] the achievement of a complete remission was the single most important factor influencing survival. This was particularly true for the group with DH lymphoma. Careful restaging at the time of clinical complete remission is of paramount importance since any residual disease will prejudice the chance of long term survival. Whole body computed tomography has proved particularly helpful in this regard and details have been previously published by our group [15].

Although long term relapse free survival is associated with patients having DH lymphoma who achieve complete remission, patients with DPDL lymphoma have a continuing relapse pattern. The median relapse free survival was only 22 months for the latter group; a figure similar to that seen in other series [10, 11].

The results of treating patients with extensive abdominal stage II disease and gastrointestinal disease have been particularly encouraging and represent an improvement over retrospective studies [21].

The role of oral 'maintenance' chemotherapy was not evaluable in the present study but since relapses occurred in spite of this chemotherapy, alternative chemotherapy is being randomised following remission induction in our current study.

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REFERENCES

1. G. P. Bodey and V. Rodriguez, Approaches to the treatment of acute leukemia and malignant lymphoma in adults. *Semin Haemat.* **15,** 221 (1978).
2. S. E. Jones, S. A. Rosenberg, H. S. Kaplan, M. E. Kadin and R. F. Dorfman, Non-Hodgkin's lymphoma II single agent chemotherapy. *Cancer (Philad.)* **30,** 31 (1972).
3. C. A. Bagley, V. T. DeVita, C. W. Berard and G. P. Canellos, Advanced lymphosarcoma, intensive cyclical combination chemotherapy with cyclophosphamide, vincristine and prednisolone. *Ann. intern. Med.* **76,** 227 (1972).
4. G. M. McKelvey, J. A. Gottlieb, H. E. Wilson, A. Haut, R. W. Talley, R. Stephens, M. Lane, J. F. Gamble, E. E. Jones, P. N. Grozga, J. Gutterman, C. Coltman Jr. and J. E. Moon, Hydroxyldaunomycin (adriamycin) in combined chemotherapy in malignant lymphoma. *Cancer (Philad.)* **38,** 1484 (1976).
5. P. S. Schein, V. T. DeVita, S. Hubbard, B. A. Chabner, G. P. Canellos, C. Bérard and R. C. Young, Bleomycin, adriamycin, cyclophosphamide, vincristine and prednisolone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. *Ann. intern. Med.* **85,** 417 (1976).

6. A. T. Skarin, D. S. Rosenthal, W. C. Moloney and E. Frei, Combination chemotherapy of advanced non-Hodgkin lymphoma with bleomycin, adriamycin, cyclophosphamide, vincristine and prednisolone (BACOP). *Blood* **49,** 759 (1977).
7. V. Rodriguez, F. Cabanillas, M. A. Burgess, E. M. McKelvey, M. Valdivieso, G. P. Bodey and E. J. Freireich, Combination chemotherapy ("CHOP-Bleo") in advanced (non-Hodgkin) malignant lymphoma. *J. Amer. Soc. Haemat.* **49,** 325 (1977).
8. V. T. DeVita, G. P. Canellos, B. Chabner, P. Schein, S. P. Hubbard and R. C. Young, Advanced diffuse histiocytic lymphoma—a potentially curable disease. *Lancet* **i** 248 (1975).
9. P. S. Schein, B. A. Chabner, G. P. Canellos, R. C. Young, C. Bérard and V. T. DeVita, Potential for prolonged disease free survival following combination chemotherapy of non-Hodgkin's lymphoma. *Blood* **43,** 181 (1975).
10. J. K. Luce, J. F. Gamble, H. B. Wilson, R. W. Monto, B. L. Isaacs, R. L. Palmer, C. A. Coltman, Jr., J. S. Hewlett, E. A. Gehan and E. Frei, III, Combined cyclophosphamide, vincristine and prednisolone therapy of malignant lymphoma. *Cancer (Philad.)* **28,** 308 (1971).
11. D. T. Harrison, P. E. Neiman, K. Sullivan, M. Hafermann, R. H. Rudolph and A. B. Einstein, Combined modality therapy for advanced diffuse lymphocytic and hystiocytic lymphomas. *Cancer (Philad.)* **42,** 1697 (1978).
12. T. A. Lister, M. H. Cullen, R. B. Brearley, M. E. B. Beard, A. G. Stansfield, J. M. A. Whitehouse, P. F. M. Wrigley, J. M. Ford, J. S. Malpas and D. Crowther, Combination chemotherapy for advanced non-Hodgkin's lymphoma of unfavourable histology. *Cancer Chemother. Pharmacol.* **1,** 107 (1978).
13. H. Rappaport, Tumours of the haematopoietic system. In *Atlas of Tumour Pathology*, Section 3, Fasc. 8. Armed Forces Institute of Pathology, Washington D.C. (1966).
14. P. P. Carbone, H. S. Kaplan, K. Musshoff, D. W. Smithers and M. Tubiana, Report of the Committee on Hodgkin's disease staging classification. *Cancer Res.* **31,** 1860 (1971).
15. J. J. K. Best, G. Blackledge, W. St. C. Forbes, I. D. H. Todd, B. Eddleston, D. Crowther and I. Isherwood, Computed tomography of the abdomen in staging and clinical management of lymphoma. *Brit. med. J.* **2,** 1675 (1978).
16. R. Peto and J. Peto, Asymtotically efficient rank invariant test procedures. *J. roy. statist. Soc.* **135,** 185 (1971).
17. D. R. Cox, Regression models and life tables. *J. roy. statist. Soc.* **34,** 187 (1973).
18. E. M. McKelvey, CHOP-HOP combination chemotherapy in malignant lymphoma. *Proc. Amer. Soc. Clin. Oncol.* **19,** 415 (1978).
19. R. I. Fisher, V. T. DeVita, B. L. Johnson, R. Simon and R. C. Young, Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. *Amer. J. Med.* **63,** 177 (1977).
20. K. Sullivan, P. Neiman, L. V. Farewell, D. Harrison, R. Rudolph, A. Einstein and C. Bagley, Combined modality therapy in advanced diffuse non-Hodgkin's lymphoma. A two and one-half year follow-up. *Proc. Amer. Ass. Cancer Res.* **20,** 442 (1979).
21. G. Blackledge, H. Bush, O. G. Dodge and D. Crowther, A study of gastrointestinal lymphoma. *Clin. Oncol.* **5,** 209 (1979).