Eur J Cancer Clin Oncol, Vol. 23, No. 9, pp. 1379–1384, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

Combination Chemotherapy Including Epirubicin for the Management of Non-Hodgkin's Lymphoma

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Abstract—*One hundred patients with untreated non-Hodgkin's lymphoma were entered in a prospective randomized study in South and West Wales designed to assess the value of the anthracycline antibiotic, epirubicin (4'-epidoxorubicin), in their management. Patients with low grade histology and progressive disease were randomized to receive either epirubicin, vincristine and prednisolone (EVP) or cyclophosphamide, vincristine and prednisolone (CVP). The response rate of* 81% *in patients receiving EVP with complete remission rate of* 52% *were similar to a response rate of* 88% *and complete remission rate of* 58% *for patients receiving CVP. No difference was observed in survival between the two groups.*

Patients with high grade lymphoma were randomized to receive either cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, epirubicin, vincristine and prednisolone (CEOP). The response rate was 71% *for CHOP and* 84% *for CEOP. The complete remission rates were* 46% *for CHOP and* 61% *for CEOP.*

The cardiotoxicity of the two anthracyclines were monitored closely in 45 *patients using measurements of systolic time intervals. Patients receiving epirubicin tolerated higher dose per course and higher total cumulative dose with less evidence of compromised left ventricular function than patients receiving doxorubicin.*

Epirubicin is an effective agent when used in combination chemotherapy in both low grade and high grade lymphoma with less toxicity than doxorubicin.

INTRODUCTION

EPIRUBICIN (4'-epidoxorubicin) is a stereoisomer of doxorubicin (adriamycin) in which the hydroxyl group at the 4 position of the amino sugar side chain is epimerized. In pre-clinical experimental tumour systems as well as in clinical trials, epirubicin was found to be an effective anti-neoplastic agent. It has been shown to have equivalent anti-tumour activity to doxorubicin in most solid neoplasm with overall less toxicity especially cardiotoxicity [1–4]. We set out to evaluate the efficacy and toxicity of epirubicin in a randomized trial in untreated patients with non-Hodgkin's lymphoma.

PATIENTS AND METHODS

Patients considered eligible for the study were newly diagnosed untreated patients with non-Hodgkin's lymphoma regardless of age. The histopathology of the lymphomas was based on the subdivisions adopted by the British Lymphoma Pathology Group [5] which are adaptable to those used in the Kiel classification [6]. For therapeutic purposes low grade lymphomas comprised the small lymphocytic lymphomas with or without plasma-cytoid features, and follicular lymphomas of predominantly small cell (centrocytic) and mixed cell types. Tumours which were grouped as being of intermediate grade malignancy were follicular lymphomas of predominantly large cell (centroblastic) type, diffuse intermediate (centrocytic) lymphomas and diffuse mixed small and large cell lymphomas (diffuse centrocytic/centroblastic). Intermediate grade lymphomas were treated as high grade lymphomas in patients under 60 years of age and as low grade lymphomas in older patients. High grade lymphomas included lymphoblastic and other large cell lymphomas (centroblastic, immunoblastic, true histiocytic and undifferentiated or unclassifiable).

We adopted a comprehensive clinical staging procedure in each of our patients to try to ensure

Accepted 11 May 1987.
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Supported by a grant from the Leukaemia Research Appeal for Wales.

uniformity and accuracy. Local and systemic symptoms and details of the site and the size of the disease were documented on notification sheets, which were specifically designed to assist computer analysis. Apart from the full blood count, including platelet count, E.S.R., 12 channel blood chemistry analysis, serum immunoglobulin assays, all patients had bone marrow and trephine biopsies. C.S.F. examination was carried out on all patients with high grade lymphoma at presentation, and in patients with low grade lymphoma who were under the age of 30. The radiological investigations included a chest X-ray, lymphangiogram or CT scan, while other radiological investigations, e.g. barium meal, were carried out if there were any indication of gastrointestinal tract involvement. Eight of our patients underwent laparotomy which was done to obtain histological diagnosis and not for staging purposes.

Chemotherapy

'Low grade' lymphoma. Patients with generalized symptomatic or progressive low grade lymphomas were randomized to receive either a combination of vincristine (1.5 mg/m^2 on day 1), cyclophosphamide (400 mg/m^2 orally for 5 days) and prednisolone (60 mg/m^2 orally for 5 days) or a combination of epirubicin, vincristine and prednisolone, where oral cyclophosphamide was substituted by a single dose of epirubicin (60 mg/m^2 given intravenously on day 1) the doses of vincristine and prednisolone were unaltered. Courses were given at 3 weekly intervals to a total of eight courses. Patients were then assessed regarding their remission status. Complete remission (CR) was defined as the complete disappearance of disease and loss of all systemic manifestations, as well as the reversal of all previously abnormal investigations. Partial remission (PR) was defined as the disappearance of at least 50% of known disease with the loss of the systemic manifestations and no response (NR) was anything less than partial remission.

'High grade' lymphoma. Patients with clinical stage III or IV high grade lymphoma or intermediate grade lymphoma in patients less than 60 years of age, were given combination chemotherapy regardless of whether they were symptomatic or not. Patients were randomized to receive either a combination of cyclophosphamide (750 mg/m^2 i.v. day 1) doxorubicin (50 mg/m^2 day 1) vincristine (1.5 g/m^2 i.v. day 1) and prednisolone (60 mg/m^2 orally days 1–5) (CHOP); or cyclophosphamide, epirubicin, vincristine and prednisolone (CEOP) where epirubicin at a dose of 60 mg/m^2 was substituted for doxorubicin and no changes were made to the other three drugs. Eight courses of treatment were given at 3-weekly intervals and the patients were then formally re-assessed. The response criteria were the same as for the low grade lymphomas.

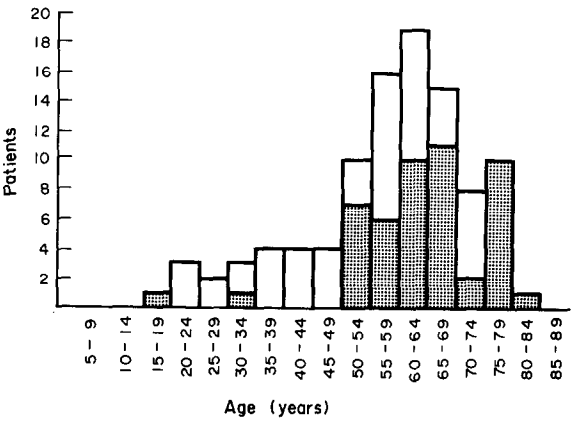

Fig. 1. Age distribution of all histological types. Open areas: 'high-grade' lymphoma, shaded areas: 'low-grade' lymphoma.

Cardiotoxicity study.

All patients had their cardiovascular status assessed by history, clinical examination, E.C.G. and chest X-ray. None of the patients studied had radiotherapy to the mediastinum or the precordium.

Regular measurements of left ventricular systolic time intervals were carried out in 45 patients receiving the anthracycline antibiotics. The pre-ejection period and left ventricular ejection time were measured using a multi-channel photographic system by simultaneous recording of the electrocardiogram, photocardiogram and carotid pulse tracing as described previously [7]. These measurements were carried out prior to, and 2 weeks after, each course of chemotherapy. An increase in the ratio of the pre-ejection period to the left ventricular ejection time of more than 0.08 above the ratio before treatment with the anthracycline, was considered as indication of cardiac damage [7, 8]. The anthracycline antibiotics were stopped if patients continued to show progressive increase in ratio. Life table analysis of survival and other statistical measurements were carried out as described previously [9].

RESULTS

The first 100 consecutive patients who required chemotherapy consisted of 54 males and 46 females. The age ranged from 17 to 80 years with a mean of 56 years. The age distribution of all histological types is shown in Fig. 1. As expected the majority of patients were above the age of 50. Only two patients with low grade lymphoma were under the age of 50. Forty-seven patients receiving chemotherapy were treated as low grade lymphoma and 53 patients as high grade lymphoma. In the low grade lymphoma group, 26 patients had CVP and 21 patients had EVP. Three patients who received

Table 1. Response and survival of 56 patients treated as 'low-grade' lymphoma

Regime	No. of patients	Age (mean)	Death during induction	NR	PR	CR	Duration of CR (mean)	Survival (mean)
CVP	26	51–80 (65)	3	—	8	15	5–50+ mo (21)	4–60+ mo (29)
EVP	21	50–79 (65)	1	3	6	11	5–50+ mo (21)	1–60+ mo (30)

CVP—Cyclophosphamide, vincristine, prednisolone; EVP—epirubicin, vincristine, prednisolone; CR—complete remission; PR—partial remission; NR—'no response'; mo—months.

Table 2. Response and survival of patients treated as 'high-grade' lymphoma

Regime	No. of patients	Age (mean)	Death during induction	NR	PR	CR	Duration of CR (mean)	Survival (mean)
CHOP	24	21–70 (51)	6	1	6	11	4–51+ mo (21)	1–65+ mo (19)
CEOP	26	17–74 (52)	2	2	6	16	1–48+ mo (16)	1–54+ mo (18)

CHOP—cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP—cyclophosphamide, epirubicin, vincristine, prednisolone; CR—complete remission; PR—partial remission; NR—'no response'; mo—months.

CVP died during induction: one patient died after six courses of combination chemotherapy of ischaemic heart disease and at *post mortem* there was no evidence of lymphoma. The second patient died of pseudomonas septicaemia and the third patient died with progressive disease not responding to treatment. In the EVP group, one patient died during induction with septicaemia during an episode of prolonged neutropenia. Fifteen patients in the CVP group and 11 patients in the EVP group achieved complete remission (Table 1). The duration of complete remission ranged from 5 months to more than 4 years in both groups. Eleven patients in the CVP group and nine patients in the EVP group are still in complete remission at the time of the analysis. There was no significant difference in the complete remission rate or the survival time between the two groups. In the high grade lymphoma only 50 of the 53 patients were evaluable. Twenty-four patients had CHOP and 26 patients had CEOP (Table 2). Six patients in the CHOP group died during induction, four of progressive non-responsive disease including two patients with CNS involvement and three of these patients had less than two courses of chemotherapy. Two patients died of complications which can be attributed at least partly to the chemotherapy, as one patient died with severe infection during a prolonged episode of neutropenia, and other patient died of CNS bleeding during an episode of thrombocytopenia. Two patients receiving the epirubicin containing combination died during induction, one of progressive disease and one of severe infection during an episode

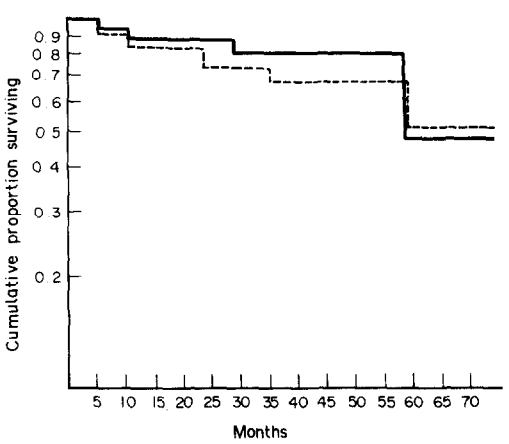

Fig. 2. Survival of patients treated as 'low-grade' lymphoma.
——— *EVP,* ----- *CVP.*

of prolonged neutropenia. Eleven patients receiving CHOP and 16 patients receiving CEOP achieved complete remission. The duration of complete remission ranged from 4 months to more than 4 years in the CHOP arm and 1 month to over 4 years in the CEOP arm. Seven patients in the CHOP group and 11 patients in the CEOP group are still in complete remisson. There was no significant difference between the two arms of the treatment, for complete remission rate of survival (Fig. 3).

Forty-five of the 74 patients receiving anthracycline antibiotics had regular measurements of the systolic time intervals before starting treatment and immediately prior to each subsequent course of

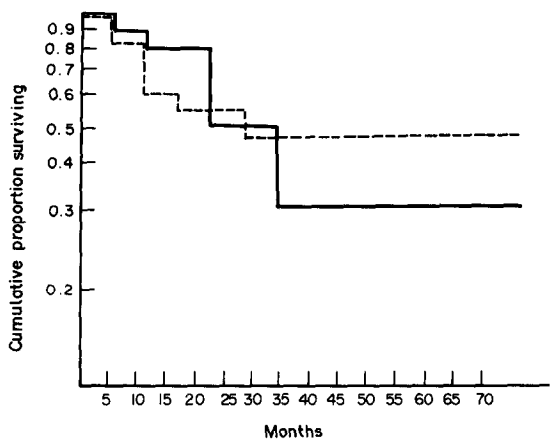

Fig. 3. Survival of patients treated as 'high-grade' lymphoma. ——— CEOP, ----- CHOP.

chemotherapy. Thirty patients received epirubicin, mean total dose 430 mg/m^2 (range 225–765 mg/m^2) and 15 patients of comparable age received doxorubicin (Table 3) with a mean total dose of 322 mg/m^2 (range 153–495 mg/m^2). Eight of the 30 patients receiving epirubicin had a total cumulative dose above 500 mg/m^2 while none of those receiving doxorubicin had a total dose exceeding 500 mg/m^2. The mean increase in ratio of PEP/LVET above that recorded prior to chemotherapy in the epirubicin group was 0.034 and 0.058 in the doxorubicin group. Six patients receiving epirubicin and five patients receiving doxurubicin showed a significant increase in this ratio. In one patient receiving doxorubicin the ratio of PEP/LVET increased progressively and no further doxorubicin was given when the ratio reached 0.64. The remaining patients continued to receive the anthracyclines with frequent checks on clinical condition and systolic intervals. All were able to complete treatment without clinical signs of heart damage and the ratio returned to normal on completion of chemotherapy. Although there was a trend suggesting that epirubicin maybe less cardiotoxic than doxorubicin, the difference failed to reach statistical significance.

DISCUSSION

Non-Hodgkin's lymphoma is not a single disease but a diverse group of diseases ranging from the very aggressive and rapidly fatal to the more indolent. One of the main problems has been in defining the histological type of these tumours, resulting in several different classifications which differ in detail although having many major features in common [10]. For the purposes of comparing drug therapy in a relatively small series it was appropriate to amalgamate several tumour sub-groups of known comparable prognosis thus avoiding the need of detailed translating between different histopathological classifications which may be necessary in investigating larger series.

The scheme devised by the British Lymphoma Pathology Group provided a suitable breakdown upon which groupings of high and low grades were superimposed, and all sections were reviewed by one histopathologist.

It is perhaps a misnomer to use the terms 'favourable histology' or 'good prognosis' for patients with low grade lymphoma as they are a group of incurable diseases. Although they are highly responsive to a variety of treatment programmes, their relapse rate remains high [11]. In our study, only two patients with low grade lymphoma were under the age of 50. This is not unexpected as the majority of patients with low grade lymphomas tend to be above that age [12]. In patients with non-progressive disease, single agent chlorambucil has been reported to be as effective as combination chemotherapy [13, 14]. However, in patients with generalized symptomatic or progressive disease, combination chemotherapy is indicated [15]. In our study, patients with generalized progressive low grade histology NHL were randomized to receive a combination of cyclophosphamide, vincristine and prednisolone (CVP) previously shown to have value in low-grade NHL [16, 17] or a combination in which epirubicin was substituted for cyclophosphamide while maintaining the same dose of vincristine and prednisolone. We found the EVP schedule easy to administer in the Out-Patient Clinic as vincristine and epirubicin were given as single injections while the patient continued to take prednisolone at home. The period of nausea and vomiting observed in our patients were limited to the first 12 to 24 h and less than that induced by cyclophosphamide given orally for 5 days. The response rate

Table 3. Changes in ratio of pre-ejection period/left ventricular ejection time (PEP/LVET) in 45 patients receiving epirubicin or doxorubcin

Anthracycline received	No. of patients	Range of total dose (mg/m^2)	Mean increase in PEP/LVET	Patients with significant increase in PEP/LVET
Epirubicin	30	225–765 (430)	0.034	6 (20%)
Doxorubicin	15	153–495 (322)	0.058	5 (33%)

in patients receiving CVP was 88% and those receiving EVP was 81%. The complete remission rate in the CVP and EVP arms were 58% and 52% respectively. There were no statistical differences in the complete remission rate, survival or disease-free survival between the two combinations used.

In patients with high grade NHL the overall prognosis is relatively poor. Paradoxically, however, if complete remission is achieved, prolonged disease-free survival is more often possible and demonstrable than in patients with low grade lymphoma [18]. In our study patients with generalized high grade histology were randomized to chemotherapy regardless whether they were symptomatic or not. One of the most commonly used combination chemotherapy in high grade lymphoma is that containing doxorubicin, cyclophosphamide, vincristine and prednisolone (CHOP) [19–21]. It is relatively easy to use this treatment as all the drugs, apart from prednisolone, are given intravenously on day 1. We compared CHOP to CEOP where we substituted epirubicin for adriamycin to assess the efficacy and toxicity of epirubicin compard to adriamycin, particularly the cardiotoxicity aspect. Three of the six patients randomized to CHOP died before completing two courses of treatment. Two had CNS disease and one had only one course of treatment and thus perhaps inadequate therapeutic trial. Deaths related directly to chemotherapy were similar in the two arms of treatment. The response rate of 84% for CEOP compared favourably to the 71% of CHOP. When the more important complete remission rate is looked at, there is no statistical difference between the two regimes. There was also no difference in survival or disease-free survival between the two arms of treatment.

The gastrointestinal side-effects, including the nausea and vomiting, mucositis, as well as alopecia, were less in patients receiving the combination containing epirubicin. Although all patients had repeated general examination of their cardiovascular system, regular measurements of systolic time intervals was possible in only 45 patients. In our hands the measurements of the systolic time intervals have been a reliable technique in assessing anthracycline cardiotoxicity [8]. In the current study, patients receiving epirubicin had a higher dose per course and a higher total cumulative dose than patients receiving doxurubicin. Eight of 30 patients receiving epirubcin had a total cumulative dose more than 500 mg/m^2 while the highest total cumulative dose in the 15 patients studied for doxorubicin cardiotoxicity was 495 mg/m^2. One third of the patients receiving doxorubicin showed evidence of compromised left ventricular function compared to only one-fifth of those receiving epirubicin. The compromised left ventricular function was demonstrated by prolongation of the pre-ejection period shortening of the left ventricular ejection time and increased PEP/LVET ratio. Although the trend was for a smaller cardiotoxic effect of epirubicin the difference between the two groups did not reach statistical significance. The reduced cardiotoxicity of epirubicin in comparison to doxorubicin has been demonstrated before, both by histological evaluation as well as functional studies. Billingham and Torti [22], using endomyocardial biopsy, found epirubicin to be less cardiotoxic than doxorubicin. Similar conclusions were reached using radionuclide angiocardiography and echocardiography [3, 4]. The results of our study so far indicate that epirubicin is an effective agent when used in combination chemotherapy in patients with progressive low grade lymphoma. It is also effective, with perhaps a better therapeutic index than doxorubicin, in the management of patients with high grade disease.

Acknowledgements—We are indebted to Dr. D.J.B. Ashley and Dr. J. Birks for their help in the statistical analysis and to Mrs. O. White for typing the manuscript.

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