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A COOPERATIVE STUDY OF EPIRUBICIN WITH CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE (CEOP) IN NON-HODGKIN'S LYMPHOMA

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ABSTRACT

Background. **The purpose of our cooperative trial was to investigate whether epirubicin (EPI) at 90 mg/m² in a CHOP-like combination (called CEOP) could increase complete response (CR) and survival rates in non-Hodgkin lymphoma (NHL) patients while maintaining a tolerable degree of toxicity.**

Methods. **Between September 1986 and July 1992, 218 patients from 12 Centers in Lombardy entered the study. The inclusion criteria were: a histological diagnosis of intermediate or diffuse large cell (DLC) NHL and no previous radio-chemotherapy. The patients in stages IA and IIA (both intermediate and DLC) received four CEOP courses followed by local/regional radiotherapy; those with intermediate NHL in stages IB, IIB, III A and B and IV A and B received six CEOP courses and, if they achieved CR, three further courses as consolidation.**

Results. **Among the 160 evaluable patients, CR was observed in 90% of the subjects with DLC-NHL (stages IA and IIA) and in 59% of those with intermediate-grade NHL (all clinical stages). If the clinical stages are considered separately, the CR rates were 92% for stages IA, IIA and 53% for stages IB, IIB, III A and B, IV A and B. Relapses occurred in 20% of the patients treated with four CEOP courses plus radiotherapy and in 31% of those who received nine CEOP courses because of the advanced stage of their disease. As of May 1994, the median follow-up was 42 months. If all of the patients are considered together, the 7-year overall survival (OS) probability was 64% and the 7-year disease-free survival (DFS) probability 67%. In comparison with stages III/IV, the patients in stages I-II had better DFS (7-year chance 77% vs 56%, $p<0.03$). Hematological toxicity was acceptable, and a delay in the administration of CEOP chemotherapy was required in only three patients. No life-threatening infections were recorded.**

Conclusions. **Our cooperative study of the use of the CEOP combination in NHL patients shows that response rates and the length of DFS are equal to the best results obtained with CHOP and more intensive programs, although further confirmation must be provided by means of a longer follow-up and a more careful analysis of prognostic factors according to the recently proposed international index. In our experience, an EPI dose of 90 mg/m² has negligible toxicity (particularly on bone marrow), even in elderly patients. These findings are interesting since it is well known that myelotoxicity is the principal limiting factor for the majority of anthracycline-containing regimens used in the treatment of potentially curable NHL.**

Key words: anthracycline, epirubicin, non-Hodgkin lymphoma, chemotherapy, myelotoxicity

A significant improvement in the overall (OS) and disease-free survival (DFS) of non-Hodgkin lymphoma (NHL) patients was observed when doxorubicin (DX) was added to combinations of other active agents.[1,2] The Southwest Oncology Group has recently published a randomized study showing no difference in response rates, time to treatment failure or OS between the first generation CHOP regimen (consisting of DX, cyclophosphamide, vin-

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cristine, prednisone) and other more intensive chemotherapy programs that are associated with greater toxicity and higher treatment-related mortality.[3] The search for new agents, in particular from among the family of anthracycline compounds, currently represents an alternative approach for improving the outcome of NHL offered by the classical CHOP regimen and for minimizing the risk of early and long-term iatrogenic mortality.

Over the past ten years, the results of a limited number of studies involving small series of NHL patients have indicated that epirubicin (EPI) may be an effective substitute for DX in the achievement of complete response.[4-9] In all of these trials EPI has been compared to the parent compound on an equimolar rather than an equimyelotoxic basis.[10] However, since the conceptual evolution of dose-intensity in the therapy of cancer suggests the use of a more appropriate anthracycline dosage, we report here the results obtained in NHL patients using a CHOP-like regimen (called CEOP) in which EPI 90 mg/m^2 replaced DX as the primary active component. Preliminary data from this study have already been reported briefly.[11,12]

Materials and Methods

Between September 1986 and July 1992, 218 previously untreated NHL patients from 12 Centers in Lombardy (Italy) entered the study. The inclusion criteria were: a histological diagnosis of intermediate (Working Formulation: D-E-F) or diffuse large cell (DLC) (Working Formulation: G-H) NHL; no previous chemo/radiotherapy; the absence of any cardiac contraindications to an anthracycline-containing regimen; and normal renal and hepatic function. Patients with DLC-NHL in clinical stages IB, IIB, III A/B, IV A/B were not included in this analysis because they were treated with ProMACE CytaBOM as already reported.[13]

Preliminary evaluation included a medical history, a physical examination, CBC and differential, routine laboratory tests, chest X-ray and ECG. Stage was defined according to the Ann Arbor criteria, and any mass exceeding 8 cm in diameter or a mediastinal adenopathy of more than ⅓ the maximum thoracic diameter was considered evidence of bulky disease. The clinical staging procedures included lymphangiography and/or abdominal CT scan, bilateral posterior iliac bone marrow biopsy and laparascopy with multiple hepatosplenic biopsies.

The patients in stages IA and IIA (both intermediate and DLC histological types) received four CEOP courses followed by local/regional radiotherapy; those with intermediate NHL in stages IB, IIB, III A and B and IV A and B received six CEOP courses and, if they achieved complete remission (CR), three further courses as consolidation. Patients in progressive disease after three CEOP courses or in partial remission (PR) after six courses were considered off study. The CEOP regimen included cyclophosphamide 750 mg/m^2 i.v. on day 1, EPI 90 mg/m^2 i.v. on day 1, vincristine 1.5 mg/m^2 (2 mg total dose) i.v. on day 1 and prednisone 100 mg p.o. on days 1-5. The courses were administered every 21 days utilizing an appropriate dose reduction scale according to WBC, platelet, bilirubin and creatinine values; if the platelet and WBC counts were less than 100×10^9/L and 3.5×10^9/L, respectively, chemotherapy was postponed for seven days. No growth factors were used to shorten the duration of iatrogenic neutropenia.

CR, PR, no response (NR) and relapses were assessed according to conventional criteria, as reported in a previous paper.[13] Both hematological and extrahematological toxicity were graded according to the WHO system; the highest grade of a toxic event observed during the CEOP courses was recorded. The probability of DFS was calculated from the date of CR until the first signs of relapse or the date of the last avalaible follow-up examination. The duration of OS was measured from the beginning of treatment until death or until the date of the last available follow-up. All types of death were considered as events. Both the DFS and OS curves were calculated using Kaplan and Meier's life tables method.

Results

Fifty-eight of the 218 patients were considered unevaluable for various reasons: 26 received the CEOP regimen as adjuvant therapy

Table 1. Characteristics of 160 patients treated with CEOP regimen.

Age (median)	12-78 years (56)	
	n° patients	*%*
Age > 60 years	66	41.3
Sex (M/F)	92/68	57.5/42.5
Diffuse large cell (WF: G-H)	31	19.4
Intermediate grade (WF: D-E-F)	129	80.6
Stages I A-II A	50	31.3
intermediate grade	19	11.9
DLC	31	19.4
Stages I-II B; III-IV A/B	110	68.7
Bone marrow infiltration	54	33.8
Performance status (median)	90%	

after surgery, 11 were affected by gastric NHL in early stages did not receive chemotherapy, 21 were considered off study for treatment refusal or protocol violations. The clinical characteristics of the 160 evaluable patients are summarized in Table 1: their median age was 56, with 41% of them being over 60 years; the majority of the patients were affected by intermediate-grade NHL in an advanced stage of disease.

The response rates are summarized in Table 2. A CR was observed in 90% of the patients with DLC-NHL (stages IA and IIA) and in 59% of those with intermediate-grade NHL (all clinical stages). If the clinical stages are considered separately, the CR rates were 92% for stages IA, IIA and 53% for stages IB, IIB, III A and B, IV A and B. PR rates were higher in patients with intermediate grade histology (35%) and advanced disease (40%). Few cases were classified as NR.

Table 2. Response rates in 160 patients treated with CEOP. Relapses after CR were recorded after a median follow-up of 42 months.

	CR	*PR*	*NR*	*relapses*
Intermediate grade (WF: D-E-F)	76 (59%)	45 (35%)	8 (6%)	–
Diffuse large cell (WF: G-H)	28 (90%)	2 (7%)	1 (3%)	–
Stages IA-IIA (4 CEOP+RT)	46 (92%)	3 (6%)	1 (2%)	9 (20%)
Stages IB-IIB; III-IV A/B (6 CEOP)	58 (53%)	44 (40%)	8 (7%)	18 (31%)

As of May 1994, the median follow-up was 42 months (range 2-92). Relapses (Table 2) had occurred in 20% of the patients treated with four CEOP courses plus radiotherapy and in 31% of those who had received nine CEOP courses because of the advanced stage of their disease. If all of the patients are considered together, the 7-year OS chance was 64% and the 7-year DFS chance 67%. As shown in Figure 1, compared with stages III/IV, the patients in stages I-II had better DFS (7-year chance 77% vs 56%, $p<0.03$). On the contrary, no significant differences in either OS or DFS were found when the curves were calculated by age (< vs. > 60 years), performance status, the presence of B symptoms, histologic subtype, bone marrow involvement or LDH level.

All of the 160 patients were evaluated for toxicity, which was recorded on the basis of the highest WHO grade observed during the four or nine CEOP courses. Hematological toxicity (Table 3) was acceptable, with grade 4 leukopenia and thrombocytopenia being recorded in three and two patients, respectively.

Furthermore, toxicity was grade 0 for hemoglobin in 61.3%, for WBC in 61.3% and for platelets in 94.2% of cases. The administration of CEOP chemotherapy was delayed for seven days in only three patients. No life-threatening infections were recorded and only seven patients suffered from grade 3 infections. No treatment-related deaths were reported.

Table 3. Hematological toxicity recorded in 160 patients treated with CEOP regimen.

WHO grade	*0*	*1*	*2*	*3*	*4*
Hb	98 (61.3%)	43 (27.1%)	18 (11.0%)	1 (0.6%)	–
WBC	98 (61.3%)	30 (19.0%)	19 (11.6%)	10 (6.4%)	3 (1.7%)
PLT	150 (94.2%)	5 (2.8%)	1 (0.6%)	2 (1.1%)	2 (1.1%)

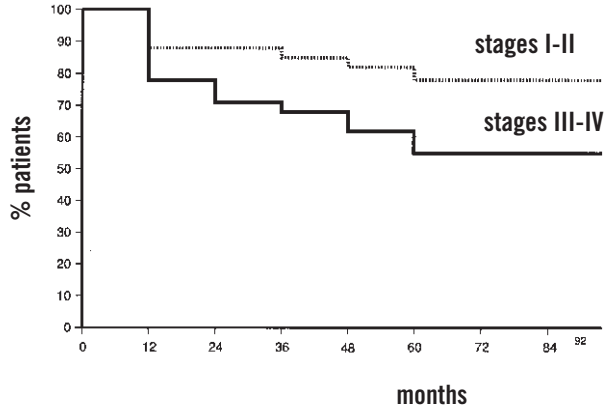

Figure 1. Probability of disease-free survival by stages in patients who achieved CR with CEOP regimen.

None of the patients experienced any type of grade 4 non-hematological toxicity (Table 4). Alopecia and low-grade nausea/vomiting were the most common complaints. Symptoms attributable to mucositis or vincristine neurotoxicity were reported quite infrequently. Reversible cardiac arrhythmias (tachycardia or premature atrial beats) were rarely registered 24-48 hours after EPI administration; moreover, none of the patients showed any clinical signs of congestive heart failure.

Discussion

Over the past ten years, EPI has been used extensively in the treatment of the most important human malignancies;[10] however, only a few studies have been published concerning its use in NHL, and these have usually been limited to small series of patients.[4-9] In randomized trials,[4,7] EPI has replaced DX at almost equimolar doses of 50-75 mg/m^2 in combination regimens, especially CHOP. These studies have shown that, in terms of tumor response and survival, the results obtained with EPI are similar to those observed for the parent compound. Furthermore, authors have generally underlined the fact that non-hematological and bone marrow toxicity is less frequent and less severe in patients receiving EPI rather than DX protocols.

On the basis of these data and the emerging concept of dose-intensity, the purpose of our cooperative trial was to investigate whether a higher dose of EPI (90 mg/m^2) in a CHOP-like combination could increase complete response and survival rates in NHL patients while maintaining a tolerable degree of toxicity.

The protocol used in this cooperative study differentiated the patients in clinical stages IA and IIA from those with B symptoms and/or advanced disease. The patients in the initial stages, the majority of whom had DLC-NHL (31/50), were treated with four CEOP courses and local/regional radiotherapy. The CR rate in this group was 90%, similar to what is reported in subjects with the same characteristics treated with DX-containing regimens; furthermore, our study confirms that relatively short courses of CEOP chemotherapy followed by irradiation are much more effective in improving the probability of cure for stages I-II DLC-NHL than radiotherapy alone.[14-18]

The majority of our patients were affected by intermediate grade NHL with B symptoms and/or advanced disease. After six CEOP courses, these patients had a CR rate of 53%, which is near the maximum of the range (40-60%) obtainable with CHOP in unselected groups of patients.[2,3,15,17,19,20] It is important to underline the fact that, in our study, the CEOP responses were measured in a cooperative setting and that the median age of the patients (56 years) was similar to that reported for a number of CHOP trials.[20]

Since long-term follow-up is important when comparing the therapeutic efficacy of different regimens, it must be said that our experience with CEOP is still relatively brief. Although the DFS probability of all of our CEOP-treated

patients is more than 60%, the median follow-up is several years shorter than that reported for CHOP by SWOG.[19,20] However, if it is true that patients in continuous CR for two years have an approximately 70-90% likelihood of cure,[20] our CEOP regimen seems to offer NHL patients optimal chances.

As in the majority of studies, this cooperative trial included subsets of heterogeneous patients with standard and poor prognostic features. Although the real importance of a number of clinical characteristics is still under investigation, a predictive international index[21] has recently been proposed in order to identify patients at low or high risk of relapse. In our analysis, only the distinction between localized (stages I and II) and advanced disease (stages III and IV) was associated with different outcomes. However, no significant differences in either OS or DFS were found when the curves were compared by age (< vs > 60 years), performance status, the presence of B symptoms, histologic subtype, bone marrow involvement or LDH level. These findings suggest that the administration of EPI 90 mg/m^2 may minimize the prognostic role of some clinical factors, in particular age, performance status and serum LDH concentrations.

Although the therapeutic efficacy of our CEOP regimen must be confirmed by a longer follow-up, some important conclusions can be drawn about the incidence of relevant toxicities. The great majority of our patients experienced no significant hematological or non-hematological side effects, and the incidence of nausea, vomiting and alopecia was similar to that reported with other anthracycline-containing regimens. There were no cardiac effects, in terms of congestive heart failure. Contrary to what has been reported for DX,[10] there were no clinical signs of cardiotoxic synergy between EPI and radiation; equally important, the level of myelotoxicity proved to be highly tolerable and there were no episodes of life-threatening infections. This last aspect was mainly due to the mildness and short duration of myelodepression, since only three patients needed a delay in treatment. These findings are interesting since it is well known that myelotoxicity is the principal limiting factor for the majority of anthracycline-containing regimens used in the treatment of potentially curable NHL.

The use of EPI in NHL patients may therefore have some practical advantages: first, limit the tendency of physicians to modify anthracycline dosage or delay treatment (both of which may compromise the outcome by increasing the risk of developing resistant cells); second, avoid the use of growth factors which both significantly increase the cost of therapy and are in any case only recommended in certain clinical situations.[22] In our study, not even the patients over 60 years old showed any prolonged or dangerous pancytopenia. Consequently, the use of EPI in elderly NHL patients might avoid the poorer outcome due to significant dosage modifications, as already documented in CHOP-treated patients.[23]

Over the past few years second- and third-generation chemotherapy regimens based on a larger number of drugs, the alternation of non-cross-resistant agents and dose escalation have

Table 4. Non-hematological toxicities recorded in 160 patients treated with CEOP regimen.

WHO grade	*0*	*1*	*2*	*3*	*4*
Mucositis	116 (72.8%)	23 (14.5%)	16 (9.8%)	5 (2.9%)	–
Nausea/vomiting	48 (30.3%)	41 (26.0%)	51 (31.8%)	20 (12.8%)	–
Diarrhea	141 (87.9%)	11 (6.9%)	7 (4.6%)	1 (0.6%)	–
Alopecia	10 (5.8%)	6 (4.0%)	71 (44.5%)	73 (45.7%)	–
Infection	130 (80.9)	15 (93%)	8 (5.2%)	7 (4.6%)	–
Nervous system	116 (72.8%)	22 (13.9%)	18 (11.0%)	4 (2.3%)	–

all been proposed in the therapy of NHL. The early enthusiasm aroused by initial results has been partially dampened by the fact that the use of more intensive programs has been associated with a significant increase in toxicity and early mortality.[3,15,24-27] Furthermore, longer follow-ups have failed to show that more aggressive combinations are better than standard CHOP in terms of OS and DFS.[3,27,28] Given this recent evidence, the clinical development of the CEOP regimen in the treatment of patients with intermediate or DLC-NHL merits particular consideration.

In conclusion, our cooperative study on the use of the CEOP combination in NHL patients shows that response rates and the length of DFS are equal to the best results obtained with CHOP and more intensive programs, although further confirmation must be obtained by means of a longer follow-up and a more careful analysis of prognostic factors according to the recently proposed international index.[21] In our experience, an EPI dose of 90 mg/m^2 has negligible toxicity (in particular on bone marrow), even in elderly patients. Since the history of NHL treatment demonstrates that dose intensity is an important factor determining favorable outcome, it can be expected that a further increase in the dose of EPI will increase response rates with minimal toxicity. In this regard, interesting data were recently reported by Zuckerman,[29] who used an EPI dose of 180 mg/m^2 in combination regimens for treating NHL patients, most of whom were in an advanced stage of the disease.

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Appendix

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