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# EMOP/CA Chemotherapy for the Treatment of Aggressive Non-Hodgkin's Lymphomas

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**Abstract**—*From October* 1983 *to June* 1987, 32 *patients with aggressive non-Hodgkin's lymphomas (diffuse centroblastic, lymphoblastic and Burkitt type) were treated with the weekly alternating EMOP/CA schedule, total duration* 12 *weeks. There were six bulky stage II, nine stage III and* 17 *stage IV patients, median age* 54 *years (range* 19–75). *The complete remission rate was* 59% (95% *confidence limits* 40–76%) *and the partial remission rate* 28% *providing an overall response rate of* 87%. *With a median follow up time of* 33 *months (range* 18–56) *the relapse-free survival of those patients achieving a complete remission is* 52% *and the overall survival for the* 32 *patients treated is* 27%. *The CR rate for patients with stage IV disease was* 47% *and for those with stage II and III disease was* 73% *of whom* 81% *remain in remission. EMOP/CA chemotherapy produces acceptable results in stage II and III aggressive non-Hodgkin's lymphomas but is inadequate therapy for stage IV disease.*

## INTRODUCTION

THIS study of weekly alternating chemotherapy for the treatment of advanced aggressive non-Hodgkin's lymphomas was activated in 1983. The chemotherapy was based on the EMA/CO schedule which had been developed for the treatment of choriocarcinoma. In this programme the interval between alternating courses was reduced to 7 days in an effort to prevent the regrowth of tumour which occurred between more conventional 21-day cycles [1]. This approach proved highly successful with significantly increased complete remission and survival rates [2]. High grade lymphomas have similar rapid growth rate characteristics to choriocarcinoma and thus the aim of the present study was to test an analogous treatment programme in their management.

EMOP/CA differed from EMA/CO in two respects. Firstly the actinomycin-D was replaced by Adriamycin® and secondly prednisolone was added and was administered in an alternate day schedule in an effort to minimize side-effects.

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## PATIENTS AND METHODS

Patients included in the study had biopsy proven diffuse centroblastic, immunoblastic, lymphoblastic or Burkitt type lymphomas (Kiel) and had had no prior chemotherapy. All patients had stage II bulky, stage III or stage IV disease. Stage II bulky was defined as a mass >10 cm or extensive lesions. All patients were aged 75 years or less and had a WHO performance status of 0, 1 or 2. Pre-treatment investigations included CT scans of thorax and abdomen, bone marrow aspirate and trephine biopsy, chest X-ray, fbc, and biochemical profile. Patients with bulky disease were treated with radiation to sites of previous bulk at the completion of chemotherapy.

Response was assessed according to UICC criteria 4 weeks after the completion of chemotherapy. Duration of survival was measured from the start of chemotherapy and survival curves were calculated by the method of Kaplan and Meier [3].

*Chemotherapy Programme*

| | |
|---|---|
| Etoposide 200 mg/m$^2$ | i.v. weeks 1, 3, 5, 7, 9, 11 |
| Methotrexate* 50 mg/m$^2$ | i.v. weeks 1, 3, 5, 7, 9, 11 |
| Vincristine 1.4 mg/m$^2$ | i.v. weeks 1, 3, 5, 7, 9, 11 |

| | |
|---|---|
| Cyclophosphamide 400 mg/m$^2$ | i.v. weeks 2, 4, 6, 8, 10, 12 |
| Adriamycin® 20 mg/m$^2$ | i.v. weeks 2, 4, 6, 8, 10, 12 |
| Prednisolone 100 mg | oral on alternate days reducing over the final 2 weeks. |

*Folinic acid 15 mg oral at 24 and 36 h given if oral mucositis occurred.

## RESULTS

From October 1983 to June 1987 32 patients were entered into the study. The median age of these patients was 54 years (range 19–75) and at the start of chemotherapy six had bulky stage II, nine stage III and 17 stage IV disease. Dominant site of tumour was nodal in 22 cases, CNS in one, GIT in one and other extranodal in eight. Liver involvement was present in five patients, CNS in one and bone marrow in three. Patient characteristics are shown in Table 1.

Of the 32 patients entered in the study, 19 (59%) (95% confidence limits 40–76%) achieved a complete remission (CR) and nine (28%) a partial remission (PR). Eight of 17 patients (47%) with stage IV disease entered complete remission but seven of these (87%) subsequently relapsed. The CR rate in the group of patients with stage II or III disease was 73% and 81% of these remain in remission. Four patients had progressive disease on treatment.

Complete remissions occurred in 14 of 22 (64%) patients with dominant nodal disease and in five of nine (56%) with dominant extra-nodal disease. The one patient who presented with CNS involvement developed progressive tumour on treatment despite weekly intrathecal methotrexate. Complete remissions were noted in two of three patients with marrow involvement and three of five with liver involvement. Nine patients received radiotherapy to sites of previous bulk at the completion of chemotherapy.

*Table 1. Patient characteristics*

| | |
|---|---|
| Male | 19 (60%) |
| Female | 13 (40%) |
| B symptoms | 13 (40%) |
| Age: | |
| 19–39 | 6 (18%) |
| 48–59 | 18 (56%) |
| 60–75 | 8 (25%) |
| Histological sub-type: | |
| diffuse centroblastic | 28 |
| lymphoblastic | 3 |
| Burkitt type | 1 |
| Stage II bulky | 6 (18%) |
| III | 9 (28%) |
| IV | 17 (53%) |

### *Survival*

With a median follow up of 33 months (range 18–56 months) the median survival for all patients is 18 months (Fig. 1) and for those obtaining a complete remission is 30 months. Of the 19 patients who obtained a CR, nine (47%) have relapsed and of these two are alive with disease. The remaining 10 (52%) remain alive and in continuing remission (Fig. 2). Relapse by stage is shown in Table 2.

### *Toxicity*

The non-hematological toxicity is shown in Table 3. Nausea and vomiting affected 81% of patients but could normally be controlled using a combination of

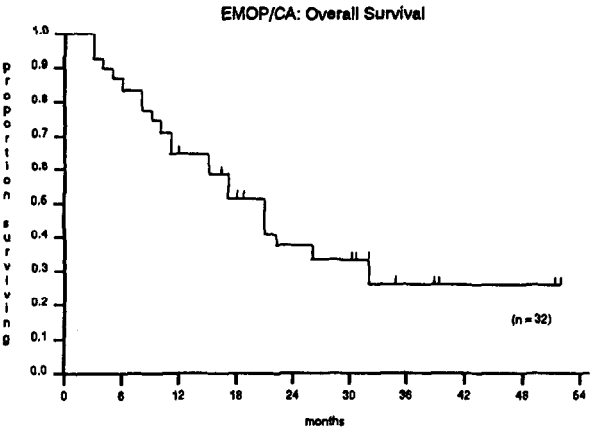


*Fig. 1. Overall survival of the 32 patients treated.*

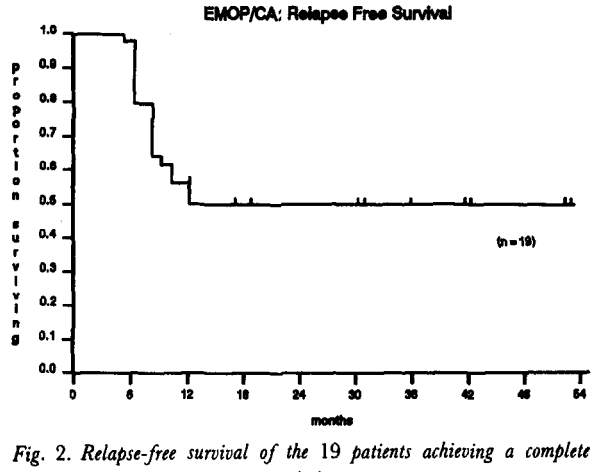


*Fig. 2. Relapse-free survival of the 19 patients achieving a complete remission.*

*Table 2. Response according to stage*

| Stage | Total | CR | Relapse from CR |
|---|---|---|---|
| II | 6 | 5 | 0 |
| III | 9 | 6 | 2 |
| IV | 17 | 8 | 7 |

*Table 3. Non-haematological toxicity*

| | WHO grade | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Mucositis | 19 | 6 | 6 | 1 |
| Nausea/vomiting | 6 | 11 | 10 | 5 |
| Alopecia | 8 | 6 | 10 | 8 |
| Neuropathy | 2 | 28 | 2 | 0 |

dexamethasone + metoclopramide and was mainly associated with the EMO week of the schedule. The other major side-effect was alopecia with grade 2–3 occurring in 56%. Mucositis requiring the addition of folinic acid occurred in 21%.

Hematological toxicity was moderate. In 34% of patients the wbc was never $<2 \times 10^9$/l at the time of retreatment and only 12% had platelet counts $<75 \times 10^9$/l at this time. Seventeen patients required treatment delays (53%) due to neutropenia, and dose reductions were made in six (18%). Intravenous antibiotics were required on four occasions for presumed septicaemia in the presence of neutropenia and oral antibiotics were used on a further five occasions. Eight patients were given blood transfusions during treatment when their hemoglobin fell below 8 g/dl.

Six patients (18%) received less than 12 weeks therapy due to toxicity. In a further four patients treatment was discontinued due to the development of progressive disease.

## DISCUSSION

This study was closed in June 1987 when it became clear that while the CR rate and survival were similar to those achieved by CHOP style chemotherapy [4, 5] they did not compare favourably with those reported for the second and third generation programmes [6–9]. A review of the chemotherapy used in these studies suggests that Adriamycin® in a dose of at least 30 mg/m$^2$ per 2 week cycle is one of the major factors in their success. This is supported by data on 'low dose' MACOP-B from O'Reilly *et al.* recently published in abstract form [10]. In this regimen the Adriamycin® was reduced to 25 mg/m$^2$ from 50/m$^2$ in standard MACOP-B resulting in a CR rate of 66% and a relapse-free survival of 39%. These results closely parallel those obtained in the current study and suggest that the poor CR rate with EMOP/CA may be due to the low dose of Adriamycin®.

A striking feature of the results with EMOP/CA was the difference according to stage of disease. Of the 15 patients presenting with stage II or III disease 11 (73%) obtained a CR and nine of these 11 patients (81%) remain in remission. This compares with a CR rate of 8/17 (47%) for stage IV patients of whom seven (87%) have relapsed. These results are in marked contrast to those reported for MACOP-B [7] where there was no difference in CR rate or survival between stage II and stage IV patients. This suggests that lower dose regimens may be adequate for patients with stage II bulky and stage III disease with the more toxic high dose intensity programmes reserved for stage IV patients.

Continuous daily prednisolone is an integral feature of most high grade lymphoma programmes but this frequently results in considerable steroid toxicity including proximal myopathy, oral candida and weight gain. In the EMOP/CA schedule the prednisolone was given on alternate days with a marked reduction in steroid-related side-effects. Although it is not known whether continuous or pulsed steroids are better in terms of anti-lymphoma activity the results using the M-BACOD [11] regimen suggest that a pulsed schedule may be equally effective.

In conclusion, EMOP/CA chemotherapy appears highly effective for stage II bulky and stage III aggressive non-Hodgkin's lymphomas but is inadequate therapy for stage IV disease.

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