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CLINICAL TRIAL REPORT

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A weekly alternating chemotherapy regimen with low toxicity for the treatment of aggressive lymphoma

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Abstract A total of 50 consecutive adult patients with newly diagnosed aggressive non-Hodgkin's lymphoma were treated with a weekly alternating combination chemotherapy schedule, BEMOP/CA, including bleomycin, etoposide, methotrexate, vincristine, cyclophosphamide and Adriamycin. Two-thirds of the patients were over 60 years old or had stage 4 disease. Clinical remission was achieved in 56% of cases. The 3-year survival is 53% (95% confidence interval, 39–66%). The presence of B symptoms and a serum albumin value of <33 g/l at presentation were poor prognostic indicators for survival in a multivariate proportional-hazards model. Overall, the response rate and survival for this group of patients with intermediate- and high-grade lymphomas is similar to results previously reported. The BEMOP/CA treatment was brief (16 weeks) and associated with a low fatal toxicity (one early death and one late fatality from *Pneumocystis* pneumonia), and the drug costs are equivalent to those for eight cycles of CHOP.

Key words High-grade lymphoma · Weekly chemotherapy

Introduction

Two decades ago the first reports of the treatment of high-grade non-Hodgkin's lymphoma (NHL) with combination chemotherapy appeared and reported remission rates of 50–60% [1, 4]. Two-thirds of these patients remained free of disease, yielding cure rates of around one-third. In an attempt to improve upon these results, regimens were developed employing increasing numbers of cytotoxic agents and greater dose intensities. The second and third generation of chemotherapy regimens produced higher remission rates and were initially thought to produce more durable remissions. However, it has subsequently emerged that the excellent results reported from specialist centres using these non-randomised regimens may have been in part a consequence of patient selection. The South-west Oncology Group (SWOG) and Eastern Cooperative Oncology group (ECOG) randomised comparison of CHOP with three third-generation regimens failed to demonstrate an advantage of any treatment over CHOP, which was both less toxic and cheaper [5].

The BEMOP/CA schedule (bleomycin, etoposide, methotrexate, vincristine, cyclophosphamide, Adriamycin) was developed from the EMA/CO regimen used for the treatment of gestational trophoblastic tumours [11]. The aim in 1987, when the study was activated, was to improve upon the remission and survival rates achieved with CHOP by using a weekly alternating schedule, without producing the toxic deaths seen with the second- and third-generation regimens.

Patients and methods

Patients

Between October 1987 and January 1994, 50 consecutive adults (>16 years) with newly diagnosed, biopsy-proven aggressive NHL (intermediate-grade or high-grade) were treated with the weekly alternating BEMOP/CA chemotherapy schedule. Patients with HIV- or HTLV-1-related lymphomas or transformed follicular lymphoma were excluded from this analysis. There was no age restriction. The clinicopathological characteristics of the patients are shown in Table 1. Patients with stages IE, II and IIE tumours were included if they had bulky disease (a mass measuring >10 cm in diameter), B symptoms, or multiple sites of involvement; had been previously treated; or had extra-nodal involvement considered unsuitable for radiotherapy.

Staging

Pre-treatment staging investigations included a clinical examination, full blood count, biochemical profile, bone marrow aspirate and trephine, chest radiography and computed tomography (CT) scanning

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Table 1 Clinicopathological features of the patients included in this study

Characteristic	Number of patients (%)
Gender:	
M	31 (62%)
F	19 (38%)
Age:	
Mean (range)	51 (18–88) years
>60 years old	17 (34%)
Stage:	
I	4 (8%)
II	16 (32%)
III	5 (10%)
IV	25 (50%)
B symptoms	26 (52%)
"Bulk"	14 (28%)
Serum sodium (mmol/l):	
0–135	14 (28%)
≥136	36 (72%)
Serum albumin (g/l):	
0–32	13 (26%)
≥33	37 (74%)

Table 2 The BEMOP/CA schedule for aggressive NHL

Week 1	Bleomycin, 15 IU, in 1 ml 1% lignocaine, i.m. Etoposide, 200 mg/m², i.v. Methotrexate, 50 mg/m², i.v. Vincristine, 1.4 mg/m², i.v. Folinic acid, 15 mg p.o., 24 and 36 h after methotrexate
Week 2	Cyclophosphamide, 400 mg/m², i.v. Adriamycin, 30 mg/m², i.v.
Prednisolone, 100 mg p.o., alternate days, tailing off after week 12	
Co-trimoxazole, 960 mg b.i.d. p.o., throughout 16 weeks	
Alternate weeks 1 and 2 to a total of 16 weeks	

of the thorax and abdomen. Patients did not undergo routine staging laparotomy. Restaging was undertaken at 1 month after completion of the chemotherapy, and response was assessed according to International Union Against Cancer (UICC) criteria. Patients achieving a clinical remission were subdivided into two categories according to the radiological findings. Patients with no radiological abnormally were classified as having achieved a complete remission (CR), whilst those with persistent equivocal radiological abnormalities were assigned a good partial remission (GPR). Patients failing to achieve a clinical remission but in whom the tumour was reduced by at least 50% achieved a poor partial remission (PPR).

Treatment

The drug doses and schedules for BEMOP/CA are shown in Table 2. Doses were reduced by 25–50% from the outset in elderly patients (>60 years). Similar reductions were instituted in seven patients following life-threatening infections. All patients received prophylactic co-trimoxazole. Our intent was to carry out 16 weeks of BEMOP/CA therapy. Treatment was delayed in the presence of neutropaenia (absolute neutrophil count $< 1 \times 10^9$/l) or thrombocytopaenia (platelet count $< 100 \times 10^9$/l).

Statistical methods

Survival was calculated from the 1st day of treatment until death or the date of last follow-up or until the date of relapse in the case of event-free survival calculations. Overall and event-free survival duration curves were plotted according to the method of Kaplan and Meier [7]. The log-rank method was used to test for the significance of differences in survival distributions [12], and the variables found to be significant at $P < 0.1$ were put into a stepwise Cox regression model to establish which were independently prognostic [3].

Results

Outcome of therapy

The median follow-up period was 2.4 years (range 0.2–7.5 years). Clinical remission was achieved in 26 (52%) patients [CR in 22 (44%) and GPR in 4 (8%)]. A further 14 (28%) patients attained a partial response to treatment but failed to achieve clinical remission. There was evidence of disease progression during treatment in 6 (12%) patients, and 4 (8%) patients died within 2 months of starting BEMOP/CA and were therefore not assessable for response. The 3- and 5-year survival for this cohort is 53% [95% confidence interval (CI) 39–66%) and 50% (95% CI 36–64%), respectively. The event-free survival at 3 and 5 years is 55% (95% CI 41–68%) and 50% (95% CI 35–65%), respectively. The patients' performance status at presentation was not recorded prospectively and, hence, cannot be analysed; however, serum sodium and albumin levels served as surrogate values for performance status. The age at presentation, stage, presence of bulk and serum sodium level did not influence survival in the multivariate regression model. Only a serum albumin value of <32 g/l ($P = 0.0001$) and the presence of B symptoms ($P = 0.01$) were independent adverse prognostic features. In all, 36 (72%) patients received at least 12 weeks of the schedule, although only 7 patients received the full 16 weeks without delays or reductions in the doses given.

Toxicity

Ten patients died before therapy could be completed: six of progressive lymphoma and four from other causes [3 cardiac deaths, 1 gastro-intestinal bleed and tuberculosis (TB)]. One patient died of acute heart failure after only 2 weeks of BEMOP/CA. Two more cardiac deaths occurred on treatment after the 6th and 7th week of BEMOP/CA in patients whose lymphomas were responding clinically, and one of these patients was found to have extensive coronary artery disease at post-mortem examination. The patient who died of a gastrointestinal bleed and active TB after the 7th week of BEMOP/CA had no active lymphoma at laparotomy. One toxic death due to *Pneumocystis* pneumonia (PCP) developed at 1 month after completion of 16 weeks of BEMOP/CA in an HIV-negative man who was in complete remission. This gives a final toxic death rate of

2/50 (4%) as the 3 cardiac deaths were probably unrelated to the chemotherapy treatment.

In all, 11 patients relapsed and died of lymphoma. A further two deaths occurred due to causes other than progressive or recurrent disease. One patient died of second primary metastatic colorectal cancer at more than 2 years after completion of the chemotherapy. The other patient died of a respiratory viral infection following autologous bone marrow transplantation whilst in second remission.

Overall, 11 (22%) patients had a leucocyte nadir count below 1×10^9/l at some time during the course of the treatment. The mean white cell count (WCC) nadir for all 50 patients was 2.1×10^9/l. Thrombocytopaenia (total platelet count $<100 \times 10^9$/l) developed in 7/50 (14%) patients. All patients developed alopecia and the majority experienced some degree of nausea, although this was generally well controlled. Less than half the patients (40%) developed mucositis of WHO grade 3/4. Infections requiring antibiotic therapy occurred in approximately one-third of all patients (30%).

Duration of remission

A total of 26 patients achieved a clinical remission and 15 (58%) remain alive in remission. Ten patients suffered a relapse (seven of whom died) and one died of PCP whilst in remission. All the relapses occurred in the 1st year after diagnosis except one, which was diagnosed after 4 years of remission.

Discussion

The 56% clinical remission rate achieved with this regimen compares with similar rates achieved in other trials, although the series presented herein included many patients with adverse features; 70% of the patients were over 60 years old, had stage 4 disease or had a serum albumin level below 33 g/l at presentation.

Studies with original first-generation regimens such as C-MOPP conducted by the NCI [4] and CHOP conducted by the SWOG [9] have produced CR rates of 40–55% with 30–35% long-term survivors. A 10- to 15-year follow-up has revealed few late relapses. Second-generation combinations (ProMACE-MOPP, M-BACOD, COP/BLAM) have initially produced higher CR rates/survival. However, longer follow-up periods revealed late relapses in all of these studies. Finally, third-generation regimens were developed (m-BACOD, ProMACE-CytaBOM, MACOP-B) that achieved even better CR rates and overall survival. These non-randomised trials of third-generation protocols generally enrolled selected patients. Four randomised comparisons of CHOP against second- and third-generation regimens have been published, including the large SWOG/ECOG study [2, 5, 6, 10]. None has demonstrated a survival advantage over CHOP for any of these treatments. The 3-year overall survival rate of 53% compares with the values published by the SWOG/ECOG for 3-year overall survival of 50% (ProMACE-CytaBOM, MACOP-B), 52% (BACOD) and 54% (CHOP) [5].

In our series, only two deaths (one from second primary tumour and one from relapsed lymphoma) and one relapse occurred at more than 2 years after completion of the treatment. The toxic death rate in this series is reported as 4%, although three further deaths occurred from cardiac causes probably unrelated to the therapy. By comparison the fatal toxicity rates found in the SWOG/ECOG trial were 1% for CHOP, 3% for ProMACE-CytaBOM, 5% for m-BACOD and 6% for MACOP-B [5]. However, few other trials have achieved such low toxic death rates.

The infection rate with BEMOP/CA was 30%, and 22% of the patients developed leucopaenia. This is not greatly different from the grade 4 toxicity observed in the SWOG/ECOG trial, which was 31% (CHOP), 29% (ProMACE-CytaBOM), 43% (MACOP-B) and 54% (m-BACOD) [5]. Most combination regimens for high-grade lymphoma that include methotrexate induce mucositis. The regimen described herein produced mucositis in 40% of patients and this was the major toxicity.

The cost of the drugs used in this regimen, including the steroids and co-trimoxazole for the full 16-week course [calculated for a body surface area (BSA) of 1.8 m^2] is currently £1571.84, which compares with £1519.96 for eight cycles of CHOP as used in the SWOG/ECOG trial. The cost of anti-emetics has not been included in these estimates as the anti-emetic requirements vary widely between individual patients, although most patients recently treated wtih BEMOP/CA have been prescribed 5-hydroxytryptamine$_3$ (5HT3) inhibitors to control emesis. The treatment is given as an outpatient regimen and the reasonably low infection rate has reduced in-patient episodes and, hence, costs.

The duration of BEMOP/CA is only 16 weeks as compared with 24 weeks for standard CHOP treatment, and other groups have also attempted to reduce the duration of chemotherapy [13]. The North West Thames Ovary Group has demonstrated in a prospective randomised trial that prolonged carboplatin treatment is no more effective than five cycles followed by irradiation [8]. Similarly, in small-cell lung cancer, prolonged chemotherapy produced no improvement in survival and led to greater toxicity and expense [14]. The ability to treat patients for a shorter period with the same efficacy and short-term toxicity may in addition prove to be of benefit in terms of the late complications of therapy, including second malignancies.

Overall, BEMOP/CA achieves remission and survival rates similar to those obtained with other chemotherapy regimens in patients with aggressive non-Hodgkin's lymphoma. BEMOP/CA is less toxic than most second- and third-generation regimens and yields a low treatment-related death rate and a low infection rate. It has the potential advantage over CHOP of being a weekly treatment, which allows rapid modification of the doses if side effects are experienced, and this may account for the low toxicity experienced. These benefits warrant a randomised comparison of BEMOP/CA and CHOP.

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