Phase I/II trial of filgrastim (r-metHuG-CSF), CEOP chemotherapy and antiretroviral therapy in HIV-related non-Hodgkin’s lymphoma

M. Newell, D. Goldstein, S. Milliken, C. Lewis, J. Hoy, B. Thomson, & D. Cooper

Summary

Background: A phase I/II trial determined the maximum tolerated dose (MTD) of CEOP for AIDS-related non-Hodgkin’s lymphoma (NHL) with concurrent filgrastim and antiretroviral therapy.

 Patients and methods: Fourteen AIDS-NHL patients, chemotherapy-naive and ECOG performance status <2 received filgrastim 1.0 μg/kg s.c. daily for 3–7 days to assess neutrophil response, followed by CEOP with filgrastim support 10 ng/kg s.c. daily, day 2–14, continued if the absolute neutrophil count (ANC) <1.2 x 10⁹/l. Two CEOP dose cohorts were used: cohort 1 (5 patients) - cyclophosphamide (C) 500 mg/m², epirubicin (E) 37.5 mg/m², vincristine (O) 2 mg and prednisolone (P) 75 mg/m² daily on days 1–5; cohort 2 (9 patients) - C 750 mg/m², E 50 mg/m², same doses of O and P. Antiretroviral therapy was maintained (zidovudine-10, ddl-3, both-l).

Results: In cohort 1, 4/5 patients received at least 3 courses of CEOP with one complete response after five cycles and four progressions. Four have died (3–21 months after entry) with 1 alive at 40 months. Dose limiting toxicity (DLT - grade IV febrile neutropenia in cycle 1) occurred in 1 patient. In cohort 2, 5/9 completed ≥5 cycles with 6 complete responses, 1 partial response and 2 progressions, 6 deaths and 3 alive at >33 months. DLT (evaluable in 8 patients) occurred in two patients. Median survival for both cohorts was 17 months. Mean relative dose intensity was >85%.

Conclusions: The dosages of CEOP in cohort 1 defined the MTD however the cohort 2 doses with filgrastim and antiretroviral therapy gave an encouraging response, acceptable toxicities and merit further study.

Key words: AIDS, antineoplastic agents, antiretroviral therapy, G-CSF, non-Hodgkin’s lymphoma

Introduction

People infected with the human immunodeficiency virus (HIV) are at high risk of development of non-Hodgkin’s lymphoma (NHL), particularly high-grade B-cell lymphomas. HIV-related NHL was first described in 1982 [1, 2] and was subsequently included in the Centre for Disease Control case definition for AIDS in 1985 [3]. In Australia up until December 1995, NHL accounted for 3.8% of all initial AIDS-defining illnesses [4], similar to other published data suggesting that the overall incidence of lymphoma amongst all persons with AIDS varies from 3% to 10% [5]. In general, development of NHL in AIDS conveys a poor prognosis with a median survival of 6–9 months due to advanced presentation, rapid clinical progression and a high incidence of extra-nodal involvement [6].

Previous studies have shown that cytotoxic chemotherapy may induce palliation of NHL, however responses are often poor, varying from 33% to 56% [6]. Poor prognostic factors include advanced immunodeficiency (as measured by a peripheral CD4+ lymphocyte count below 0.1 x 10⁹/l and the presence of prior AIDS-defining opportunistic infections), a Karnofsky performance status below 70%, the presence of primary cerebral lymphoma and immunoblastic histology [7–9].

HIV infected patients often have impaired haemopoietic function due to direct viral involvement of bone marrow stem cells and cytokine modulation [10]. As a result, cytotoxic therapy can result in an increased degree of myelosuppression compared with non AIDS-related NHL resulting in frequent treatment delays and dose reductions due to toxicity. This is compounded by the use of myelosuppressive antiretroviral agents such as zidovudine which usually need to be discontinued, with the potential for increasing viral load and subsequent worsening of immune function.

One approach to reduce the haematological toxicity associated with cytotoxic chemotherapy has been the development and use of colony stimulating factors that stimulate proliferation, differentiation and end-cell functional activation of haemopoietic cells [11]. Early trials demonstrated that HIV-associated neutropenia can be reduced with the use of the colony stimulating factor GM-CSF [12, 13] but is less commonly used in HIV malignancies as studies have shown that this agent...
may stimulate HIV replication as rises in serum p24 antigen levels have been observed. Any clinical significance of this finding is unknown [13, 14, 18].

Filgrastim (r-metHu G-CSF) is a colony-stimulating factor with selectivity for the neutrophil lineage. It has a well-defined clinical profile in the treatment of both solid tumours and haematological malignancies and been shown to reduce the severity and duration of neutropenia resulting from cytotoxic chemotherapy [15–17]. Additionally, filgrastim does not appear to stimulate HIV replication [18].

A previous study in HIV seropositive patients with NHL attending two of the hospitals participating in this study using a modified CEOP regimen (cyclophosphamide 750 mg/m², epirubicin 50 mg/m², vincristine 2 mg and prednisolone 100 mg daily × 5, given every 3 weeks) reported a response of 72% with acceptable toxicities. However, colony stimulating factors were not used in this study and antiretroviral therapy was discontinued prior to commencement of chemotherapy [19].

The rationale behind the present study was that concurrent treatment with filgrastim and cytotoxic chemotherapy may result in fewer treatment delays from haematological toxicity and an increased dose intensity of chemotherapy and permit the continuation of potentially myelosuppressive antiretroviral therapy throughout the treatment period. Such strategies may both promote improved responses and allow the maintenance of immune function, therefore reducing the incidence of opportunistic infections and further AIDS-related conditions.

The aims of this study were to determine the maximum tolerated dose (MTD) of CEOP chemotherapy that can be given with filgrastim support and whether antiretroviral therapy can be given concurrently with this regimen.

Patients and methods

This was an open, non-randomised dose escalation study. HIV infected patients with a confirmed diagnosis of non-Hodgkin's lymphoma were recruited from three Australian teaching hospitals during 1991–1994 (St. Vincent's and Prince Henry Hospitals, Sydney; Fairfield Infectious Diseases Hospital, Melbourne). The protocol and consent form and any subsequent amendments to these were approved by each hospital's Research Ethics Committee and informed consent was obtained from each patient.

HIV seropositive patients with a histologically confirmed diagnosis of NHL were eligible for the trial with additional inclusion criteria - written informed consent obtained, ECOG performance status 0–2, current treatment with one or more licensed antiretroviral agents (zidovudine, didanosine or zalcitabine). Laboratory exclusion criteria were: primary cerebral lymphoma, prior chemotherapy, the total neutrophil count needed to be >1.2 \times 10^9/L and ALT or AST <5 \times upper limit of normal. Prior to receiving the first cycle of chemotherapy, all patients received daily subcutaneous injections of filgrastim 1.0 \mu g/kg for at least three days with daily measurement of absolute neutrophil count. This was continued either up to a maximum of seven days or when a total neutrophil count of 10.0 \times 10^9/L had been achieved on two consecutive occasions at least 24 hours apart, whichever occurred first. This was to determine the bone marrow response to filgrastim prior to chemotherapy and identify patients likely to benefit from filgrastim. Only those patients with a total neutrophil count of at least 1.2 \times 10^9/L after 3 days were permitted to proceed to the first cycle of chemotherapy. If this was not achieved, those patients were withdrawn from the study.

CEOP chemotherapy was administered every three weeks up to a maximum of 2 cycles beyond complete remission. During each cycle of chemotherapy, daily filgrastim support commenced on the second day of the chemotherapy cycle and continued at a dose of 10 \mu g/kg by subcutaneous injection for at least 14 days; this dose was chosen as it was felt to be effective at a period of time when a range of filgrastim doses was used. Filgrastim was discontinued for that cycle after day 14 if the ANC on 2 consecutive occasions was greater than 10.0 \times 10^9/L, the second determination being after day 14. Following discontinuation, filgrastim was restarted at 5 \mu g/kg/day if the ANC decreased again to below 2.0 \times 10^9/L. In the event of bone marrow toxicity, the dose of filgrastim was reduced to 5 \mu g/kg/day once the expected neutrophil nadir had been reached. For the next cycle, the dose of filgrastim remained at 10 \mu g/kg/day with reduction if necessary.

Intended CEOP chemotherapy involved the use of three cohorts of escalating doses (see Table 1), commencing with recruitment of four patients into the lowest dose cohort. Higher dose cohorts were successively opened if no patients experienced any dose limiting toxicity (DLT) in that cohort, as defined by the occurrence in cycle 1 of grade IV febrile neutropenia or grade III/IV mucositis or this was felt to be clinically significant in this patient population.

The occurrence of one episode of DLT necessitated the recruitment of an additional patient into that cohort and opening of the higher cohort if no additional DLT occurred. Within each cohort, it was intended that the occurrence of two or more events of DLT in cycle 1 defined the previous dosing level as the MTD of CEOP chemotherapy. Any occurrence of DLT or a nadir platelet count less than 25 \times 10^9/L with bleeding necessitated a 25% dose reduction of cyclophosphamide and epirubicin for the next and subsequent cycles. Treatment was delayed for one week if the total neutrophil count was less than 1.2 \times 10^9/L or the platelet count was less than 90 \times 10^9/L at the time of commencement of the next cycle. Patients were withdrawn from the study if no neutrophil recovery subsequently occurred.

Patients with positive CSF cytology were scheduled to receive intrathecal cytotoxic therapy every second day, consisting of methotrexate 12 mg alternating with cytosine arabinoside 60 mg. This was continued for six treatments beyond clearing of positive CSF cytology. Patients without lymphomatous CSF involvement were given intrathecal methotrexate 12 mg weekly for 4 weeks as CNS prophylaxis, at the discretion of the investigator. Baseline antiretroviral therapy was continued and monitored throughout the study. Prophylaxis for Pneumocystis carinii pneumonia as candidiasis was commenced or pre-existing prophylaxis regimens were maintained.

Patients were evaluated for adverse events before each cycle of chemotherapy. A complete assessment of all previously abnormal sites of disease was performed to evaluate response after the first 3 cycles.

Table 1. CEOP dosing cohorts.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide (C)</td>
<td>Day 1</td>
<td>500 mg/m²</td>
<td>750 mg/m²</td>
<td>1000 mg/m²</td>
</tr>
<tr>
<td>Epirubicin (E)</td>
<td>Day 1</td>
<td>37.5 mg/m²</td>
<td>50 mg/m²</td>
<td>62.5 mg/m²</td>
</tr>
<tr>
<td>Vincristine (O)</td>
<td>Day 1</td>
<td>2 mg</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Prednisolone (P)</td>
<td>Day 1-5</td>
<td>75 mg/m²</td>
<td>75 mg/m²</td>
<td>75 mg/m²</td>
</tr>
</tbody>
</table>
chemotherapy cycles and every 2 cycles thereafter. A complete response was defined as the complete disappearance of all measurable disease together with a negative abdominal CT scan, chest X-ray, bone marrow and CSF, persisting for one month after the negative results were obtained. A partial response was defined as a 50% decrease in the sum of the products of all measurable sites of disease performed by calculating the product of two perpendicular diameters together with the absence of development of new lesions or increase in the size of any known lesions.

Safety evaluation involved determination of peripheral full blood count with differential, urea, electrolytes, liver function tests, CD4+ lymphocyte count, serum p24 antigen, serum (β-2 microglobulin and neopterin performed at baseline and prior to each cycle of chemotherapy. A full blood count with differential was also performed every three days during each treatment cycle.

Dose intensity for each patient was calculated for each individual cycle relative to the intended dose intensity for that cycle, based on a three week cycle length [20]. Median survival was estimated using the Kaplan–Meier method [21], measured from the date of initiation of chemotherapy.

### Results

#### Baseline patient characteristics

Seventeen patients, all with sexually acquired HIV infection and histologically proven non-Hodgkin’s lymphoma were enrolled. Four patients had high grade NHL (immunoblastic or small non-cleaved type), 9 had intermediate grade lymphomas of the large cell undifferentiated type and in 4 patients the grade of NHL was unable to be classified. Twelve patients had lymphoma stage IV. The baseline patient characteristics are listed in Table 2. The two cohorts were reasonably well matched for good prognostic factors in AIDS-NHL i.e., baseline performance status, prior AIDS defining illnesses and CD4+ lymphocyte count.

#### Filgrastim treatment prior to chemotherapy

All 17 patients received filgrastim 1 μg/kg daily by subcutaneous injection for at least 3 days and up to 7 days before receiving their first cycle of CEOP. The median number of filgrastim doses was 4, median rise in neutrophil count 5.82 × 10⁹/l, median peak ANC 9.30 × 10⁹/l and median time to peak ANC was 3 days. There was no significant correlation between the extent of the neutrophil response to filgrastim and any of the baseline parameters in Table 2, duration of previous zidovudine therapy (14/17 patients) or prior PCP prophylaxis (trimethoprim/sulphamethoxazole 7/17, dapsone 3/17).

Fourteen patients subsequently commenced CEOP chemotherapy within 48 hours of the last dose of filgrastim. Three patients at one site who received initial filgrastim did not proceed to chemotherapy on this trial as they failed to achieve a neutrophil count of 10.0 × 10⁹/l on 2 successive occasions; this was incorrectly thought to exclude them from the trial. These 3 patients were treated off-study with 3–4 cycles of CEOP chemotherapy with concurrent filgrastim but no anti-retroviral therapy. There was one complete response, one partial response and one progression.

#### Determination of cycle 1 dose limiting toxicity and maximum tolerated dose

The first five patients enrolled were treated with CEOP doses defined by cohort 1 (see Table 1). As there was only one episode of dose-limiting toxicity in the form of febrile neutropenia in cycle 1 at this dosing level, the second dose cohort was opened.

Two of the first 4 patients recruited to cohort 2 experienced DLT (febrile neutropenia) which according to the original protocol, defined cohort 1 as the MTD of CEOP. However, as all these episodes occurred at one site without any adverse outcome, it was considered desirable by the investigators to further evaluate these cohort 2 doses with a larger sample size. Thus, it was decided to amend the protocol to allow recruitment of another 5 patients to cohort 2, giving a total of 14 patients.

Of the 14 patients treated in both cohorts, 13 were evaluable for the determination of DLT in cycle 1, as one patient received a lower dose of chemotherapy in the first cycle than specified in the protocol, but received full doses for subsequent cycles. None of the additional 5 patients recruited into cohort 2 experienced dose-limiting toxicity in cycle 1, but it was felt that further dose escalation by opening the third cohort

### Table 2. Baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with CEOP</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>39</td>
</tr>
<tr>
<td>Range</td>
<td>30–61</td>
<td>27–65</td>
</tr>
<tr>
<td>CD₄ × 10⁹/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.259</td>
<td>0.382</td>
</tr>
<tr>
<td>Range</td>
<td>0–0.59</td>
<td>0–0.59</td>
</tr>
<tr>
<td>Absolute neutrophil count× 10⁹/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior to filgrastim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Range</td>
<td>1.2–4.3</td>
<td>1.5–8.6</td>
</tr>
<tr>
<td>AIDS-defining illnesses prior to NHL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (PCP)</td>
<td>1 (oesophageal candidiasis)</td>
</tr>
<tr>
<td>Baseline antiretroviral therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine 500–600 mg/day</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Didanosine 400 mg/day</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Both</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Baseline PCP prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulphamethoxazole</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Dapsone</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
was unwarranted, given the occurrence of the 2 episodes of DLT at cohort 2.

Grade IV neutropenia with fever accounted for all 3 episodes of cycle 1 DLT in both cohorts. In the cohort 1 patient, the absolute neutrophil count nadir was $0.23 \times 10^9/\text{l}$ with methicillin resistant *Staphylococcus aureus* isolated from blood cultures. In the two cohort 2 patients, the ANC nadirs were 0.01 and $0.1 \times 10^9/\text{l}$, respectively, with sterile blood cultures. Overall, including the three episodes of febrile neutropenia described above, there were 7 episodes of grade IV neutropenia occurring in the first cycle which represented 53% of all episodes of grade IV neutropenia in all cycles.

Univariate analysis revealed a significant correlation between the risk of occurrence of grade IV neutropenia in cycle 1 and the following baseline characteristics: an ECOG status of 1 or more ($P < 0.005$, Fisher’s exact test), age $>40$ years ($P < 0.01$, Mann–Whitney test) and prior prophylaxis with trimethoprim/sulphamethoxazole or dapsone for PCP ($P = 0.029$, Fisher’s exact test). However, there was no significant correlation between the occurrence of cycle 1 neutropenia and any of the other baseline characteristics listed in Table 2 including CD4+ lymphocyte count or the degree of neutrophil response to filgrastim prior to chemotherapy.

**Total chemotherapy dosing and dose intensity**

A total of 17 cycles of chemotherapy were given to 5 patients in the lower dose cohort 1 and 35 cycles in 9 patients in cohort 2. Four of the 5 patients recruited to cohort 1 and 6 of the 9 patients recruited to cohort 2 received three or more cycles of chemotherapy. One patient with lymphomatous meningitis was treated with alternating intrathecal methotrexate and cytosine arabinoside, as specified. Twelve other patients received intrathecal methotrexate as CNS prophylaxis.

Mean dose intensity (DI) for all and the first 3 cycles, relative to the intended doses for each particular cohort is shown in Figure 1. In cohort 1 the mean DI was 89.4% of intended for the first 3 cycles and 88.3% for all cycles. In cohort 2 the mean DI was 92.6% of intended dose for the first 3 cycles and 93.9% for all cycles.

**Overall toxicity in all cycles**

Fifty-two cycles of chemotherapy administered to 14 patients were evaluable for toxicity, including the dose limiting toxicities above. The toxicities are summarised in Table 3. Altogether, there were 13 episodes of grade IV neutropenia. In 11 of these, an ANC nadir of $<0.5 \times 10^9/\text{l}$ was recorded on only one occasion during each cycle, the frequency of determination of absolute neutrophil count being every three days during each cycle. In 2 cycles in 2 separate patients, there was a longer duration of neutropenic nadir (over 2 and 4 consecutive readings, respectively). The median neutropenic nadir for all patients in each cycle is presented in Figure 2 and was not cumulative through successive cycles.

One patient experienced bone pain requiring narcotic analgesia during cycle 2, thus the filgrastim dose was halved to 5 μg/kg as required by the protocol. There were no episodes of grade III or IV mucositis. One patient in cohort 2 presented with breathlessness after his second cycle of CEOP chemotherapy. Cardiac ejection fraction was reduced at 24%, thus the epirubi-
cin was ceased and etoposide substituted for the remaining 2 cycles.

Continuation of antiretroviral therapy and PCP prophylaxis during chemotherapy

At entry, all patients were stable on antiretroviral therapy at standard doses as listed in Table 2; the majority (12/14) were on zidovudine alone. This was representative of the prescribing practice at the time of study initiation when the majority of AIDS patients were treated with zidovudine but additional antiretroviral agents were being increasingly used, alone or in combination. Twelve of the 14 treated patients were able to continue their baseline antiretroviral therapy throughout all chemotherapy cycles with no dose changes including 10/11 on zidovudine. One patient ceased zidovudine at cycle 2 due to disease progression and one voluntarily ceased didanosine at cycle 2 due to intolerance. Baseline prophylaxis for Pneumocystis carinii pneumonia was maintained (Table 2).

Effect of CEOP chemotherapy on immune function

Data concerning CD4+ lymphocyte counts before and after the complete course of chemotherapy was available for 10/14 treated patients. There was a significant decrease in median absolute CD4+ lymphocyte count (0.085 x 10^9/l, P < 0.01) which was concordant with a fall in median absolute lymphocyte count of 0.25 x 10^9/l. However no significant change in median percentage CD4+ lymphocyte count from baseline was observed (−2.0%, P = 0.1). There was no significant change in serum p24 antigen, neopterin and B-2 microglobulin during treatment. None of the patients developed any AIDS-related opportunistic infections during the period of CEOP chemotherapy and for two months after cessation of chemotherapy. Two patients developed bacterial infections (mastitis, local cellulitis) during chemotherapy but neither were related to neutropenia.

Response and survival

Seven of the 14 treated patients (50%) achieved a complete response and one achieved a partial response, giving an overall response of 57% (95% confidence intervals 28.9%–82.3%). The response was improved for the patients in cohort 2 treated with the higher doses of CEOP chemotherapy; 7/9 patients (78%) compared with only 1/5 patients (20%) in cohort 1 however this did not quite achieve statistical significance (P = 0.091, Fisher's exact test).

Of the 7 patients who had a complete response, 3 are still alive without recurrence of lymphoma (follow-up 29–33 months); all were enrolled into cohort 2. Three patients have died after having an initial complete response with subsequent relapse, the duration of response was 5, 6 and 12 months. One patient maintained a complete response and died 24 months later due to progression of HIV disease.

Six of the 14 patients did not respond to chemotherapy and were withdrawn from the study after a mean of 2.5 cycles (range 1–4 cycles). Five of these have died, one patient enrolled to cohort 1 was withdrawn and treated off-study and is still alive without recurrence with follow-up for 28 months. The median survival for all patients was 17 months (range 2–33 months).

Discussion

This prospective dose escalation study aimed to determine the maximum tolerated dose of CEOP chemotherapy with concurrent filgrastim support for the treatment of AIDS-related non-Hodgkin's lymphoma and secondarily to assess whether antiretroviral therapy can be given concurrently with CEOP and filgrastim in this patient population. Although the criteria for dose escalation of CEOP and subsequent determination of the MTD were based on the DLT for the first chemotherapy cycle, the study aimed to evaluate the tolerability of the regimen throughout all cycles.

Overall, the tolerability of our regimen was acceptable. Grade IV neutropenia was the major toxicity, occurring in 24% of cohort 1 cycles and 26% of cohort 2 cycles. Interestingly, the higher doses used in cohort 2 did not lead to an increase in incidence of grade IV neutropenia despite similar prognostic factors. More than half of the episodes of grade IV neutropenia (7/13) occurred in the first cycle. Statistically significant risk factors for the occurrence of cycle 1 grade IV neutropenia were an ECOG status greater than 0, prior chemoprophylaxis for PCP and age over 40 years. This suggests that patients with one or more of these risk factors should be meticulously monitored during the first chemotherapy cycle, with dose reductions if considered necessary. Beyond cycle 1, there was a slight increase in the median neutrophil nadir despite maintenance of dose intensity of >85% for all cycles, nevertheless close haematological monitoring throughout all cycles of chemotherapy should be undertaken.

The increase in neutrophil count in response to daily administration of filgrastim before chemotherapy demonstrated that marrow responsiveness is not compromised in this patient population. We could not identify any baseline prognostic factors which could predict a failure of response to filgrastim.

Earlier studies on the treatment of AIDS-related NHL using a variety of combination chemotherapy regimens, some with concurrent zidovudine but without haemopoietic growth factor support reported complete responses of 33%–63% and median survivals of between 4 and 11 months [6, 22, 23]. Subsequent studies examined the impact of growth factor support without concurrent zidovudine use. In a phase I trial reported by Walsh of 17 patients treated with m-BACOD with GM-CSF, no dose limiting toxicity occurred in 8
patients who received standard doses of m-BACOD [24]. In a randomised study by Kaplan, 30 patients were treated with standard CHOP and half of these with GM-CSF. A higher mean neutrophil nadir and decrease in febrile neutropenia, hospitalisations, treatment delays and dose reductions occurred with those treated with GM-CSF on days 4 to 13 compared with both those treated with GM-CSF on days 1–10 and the control group. There was no significant difference in complete response and median survival [14].

Tirelli reported 37 patients treated with intensive LNH84 or CHVmP/VCR-BLM chemotherapy; 19 patients without filgrastim and 18 patients with filgrastim 5 µg/kg from day 2 to 13. In the filgrastim treated group, there was significant reduction in the severity of neutropenic nadir, the mean duration of hospitalisation due to toxicity and the mean duration of treatment delays but no significant difference in overall response or the incidence of mucositis or sepsis [25].

Concurrent treatment with chemotherapy, GM-CSF and zidovudine has been reported in 2 studies. Hahn et al. reported a study of 14 patients treated with cyclophosphamide, etoposide, doxorubicin, vincristine, methotrexate and cytarabine in conjunction with GM-CSF 10 µg/kg/day and concurrent zidovudine. Of 10 evaluable patients, 4 achieved a complete response; however 8 required dose reductions and/or delay due to haematological toxicity [27]. Gabarre et al. treated 32 patients using intensive induction chemotherapy LNH 84 with GM-CSF 5 µg/kg/day and zidovudine 5 mg/kg/day. The complete response was 50% with no significant reduction in haematological toxicities [28].

Recently, Kaplan reported a large randomised study of 188 patients, one arm receiving standard doses of m-BACOD and concurrent GM-CSF, the other arm received reduced doses of m-BACOD with GM-CSF support if needed. The first group had an increased incidence of grade IV neutropenia (36% of cycles vs. 22%) but response, time to progression and median survival was similar in the two arms [26]. No concurrent use of antiretroviral therapy occurred in this study. These studies suggest that growth factor support has only a marginal impact on response and when used in conjunction with zidovudine does not significantly reduce haematological toxicity. However our encouraging results using CEOP, filgrastim and concurrent antiretroviral therapy may be due to several factors. The use of filgrastim may be a factor in our ability to sustain higher chemotherapy doses as all but one of the above studies used GM-CSF for haematological support. This is supported by two comparative studies of G-CSF v. GM-CSF in non-HIV malignancies (lymphoma and breast cancer) which reported a faster neutrophil recovery in the G-CSF treated group in one study and reduced duration of neutropenia and fewer hospitalisations in the other [29, 30]. Our choice of the CEOP regimen may also be a factor. Our experience of this regimen in AIDS-NHL has shown that it is well tolerated in this patient population and may optimise delivery of cyclophosphamide and anthracycline [19]. This is supported by 3 studies in non-HIV lymphoma which showed CEOP to have equivalent efficacy but reduced toxicity when compared to CHOP [31–33]. Also, the other studies in AIDS-NHL have mainly used third generation chemotherapy regimens which have been shown by Fisher to have no superiority to CHOP in the treatment of non-HIV lymphoma [34].

Although this study did not aim to determine response and survival as a primary objective, it is encouraging to note that our overall complete response of 50% is comparable with other published studies and 3 of the seven patients who achieved a complete response are still alive after a minimum follow-up of 29 months. However, the small numbers of patients in our study preclude any firm conclusions as to the influence of the doses used in our study on response and survival in AIDS-related non-Hodgkin's lymphoma, which would require a much larger study.

The ability to maintain antiretroviral therapy during CEOP was an important finding in our study, shown by the absence of any relationship between zidovudine usage and the DLT of CEOP. A previous study has demonstrated that up to 50% of complete responders to treatment of NHL die of opportunistic infections [22]. This emphasises the need for continuing antiviral therapy during and after chemotherapy, especially as there have been recent advances in suppression of HIV replication using combination antiretroviral therapy. Although there was a significant fall in the absolute CD4+ lymphocyte count during chemotherapy, there was a parallel decrease in total lymphocyte count (median decrease 0.25 x 10^9/l) and the percentage CD4+ lymphocyte count did not significantly change. This suggests the reduction in CD4+ lymphocyte count was a consequence of generalised lymphopenia secondary to CEOP and not a result of viral activation or some CD4+ lymphocyte specific toxicity. This is supported by the absence of significant increases in HIV p24 antigen levels and the non-occurrence of further opportunistic infections during the study period. Lymphopenia secondary to cytotoxic therapy is also a well described phenomenon in the setting of non-HIV malignancies [35]. HIV quantitative viral load determination was not available when this trial was performed and this area merits further study to further define the effect of chemotherapy on immune function in HIV infection.

In this study the MTD of the CEOP regimen with concurrent antiretroviral therapy and filgrastim support was defined according to the protocol by the cohort 1 doses; however, the doses of CEOP used in cohort 2 had an acceptable incidence of grade IV neutropenia, no grade III or IV mucositis, a low occurrence of thrombocytopenia and gave an encouraging response and median survival. The addition of filgrastim allowed these doses to continue at a mean relative dose intensity of over 85% and permitted the continuation...
of antiretroviral therapy. As our study used a well-tolerated outpatient chemotherapy regimen with a potentially more active neutrophil growth factor compared with most of the previously published studies, our results suggest that the CEOP doses used in cohort 2 with concurrent antiretroviral therapy and filgrastim merit further study in large phase II and III trials in AIDS-related non-Hodgkin’s lymphoma, despite the previous negative data on the influence of dose on response to mBACOD in the absence of antiretroviral therapy. This may identify whether maintenance of dose intensity using the CEOP regimen with filgrastim together with concurrent antiretroviral therapy may significantly alter survival in this disease.

Acknowledgments

This study was supported by a grant from AMGEN Inc.

The National Centre in HIV Epidemiology and Clinical Research is supported by the Australian National Council on AIDS through the Commonwealth AIDS Research Grants Committee.

The authors would like to acknowledge the following individuals for their contributions to this study: Geraldine Dolan, Suzanne Ryan and Anne Sarr for assistance with patient follow-up and data management, Matthew Law for statistical advice and Dr Andrew Grulich and Prof. J. Kaldor for advice with the manuscript.

References

21. Mamounas EP, Anderson S, Wickerham DL et al. The efficacy of recombinant human granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in permitting the administration of higher doses of cyclophospha-


Received 27 August 1996; accepted 16 October 1996.

Correspondence to:
Mark Newell, MD
National Centre in HIV Epidemiology and Clinical Research
University of New South Wales
2nd floor, 376 Victoria St.
Darlinghurst, Sydney 2010 NSW
Australia