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Weekly alternating combination chemotherapy for good prognosis AIDS-related lymphoma

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Abstract

Early studies reported that the major adverse prognostic factors in AIDS-related non-Hodgkin's lymphoma (ARL) are low CD4 cell count, prior AIDS defining diagnosis and poor performance status. Since 1989 we have adopted a prognosis-stratified approach for ARL. In this study, we identified a group of good prognosis patients. These patients with one or no adverse prognostic factors were treated with alternating weekly chemotherapy using the bleomycin, etoposide, vincristine, methotrexate, prednisolone/cyclophosphamide, doxorubicin (BEMOP/CA) schedule (Bower M, Block C, Gulliford T, *et al. Cancer Chemother Pharmacol* 1995, **38**, 106–109). Modifications to the regimen with the aim of reducing toxicity were a briefer duration (12 weeks) and the addition of prophylaxis against pneumocystis and mycobacteria. Intrathecal methotrexate was administrated fortnightly to patients with Burkitt's histology, meningeal involvement or base of skull disease. 30 patients were treated, including 5 with prior AIDS, 3 with ECOG status 3 and 1 with CD4 $< 100/\mu l$. The mean age was 40 (range 22–60 years), the median CD4 cell count at ARL diagnosis was $262/\mu l$ (range $44–588/\mu l$). The International non-Hodgkin's lymphoma (NHL) prognostic factors project classifications were low risk 8 (maximum 5.4 years) (27%), low–intermediate risk 6 (20%), high–intermediate risk 11 (37%) and high risk 5 (17%). The median follow-up was 2.1 years. 3 patients withdrew from treatment within 2 weeks due to toxicity, 2 patients died within 2 weeks of starting chemotherapy. The major toxicity was myelosuppression with 14 patients developing grade 4 neutropenia. The 2-year overall survival rate is 46% (95% confidence interval (CI) = 27–65%), and lymphoma-specific survival at 2 years is 59% (95% CI: 40–78%). For selected patients with good prognosis ARL 12 weeks BEMOP/CA therapy produces good overall survival at 2 years.

Keywords: AIDS; Chemotherapy; HIV; Non-Hodgkin's lymphoma

1. Introduction

High grade B-cell non-Hodgkin's lymphoma (NHL) has been included as an AIDS defining diagnosis since 1985 and this diagnosis is 60 times more common in HIV-seropositive patients than in the general population. NHL accounts for 3% of AIDS defining diagnoses in Europe and an estimated 5–10% of patients will develop NHL at some time during their illness. The incidence of AIDS-related lymphoma (ARL) rises with progressive immunosuppression and hence is becoming more common as HIV-infected people live longer owing to better antiretroviral therapy and both prophylaxis and management of opportunistic infections [1].

ARL is an aggressive B-cell lymphoma of intermediate or high grade. The commonest histological types of systemic NHL are diffuse large cell, immunoblastic and Burkitt's lymphoma. The majority of patients present with advanced stage, B symptoms and/or extranodal disease and these factors are therefore less discriminatory regarding prognosis. Data from early retrospective studies in ARL suggests that the most influential prognostic factors relate to the severity of immunosuppression rather than lymphoma-related factors. Thus CD4 count, the presence or absence of a prior AIDS defining diagnosis and the patient's performance status have been found to be the most important predictors of outcome [2,3]. However, more recent

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prospective data, such as that provided by a recent AIDS Clinical Trials Group (ACTG) study [4] suggests that the prognostic variables in ARL closely resemble those in the International Prognostic Index for non-HIV associated NHL [5].

In most centres, the treatment of ARL is stratified according to prognosis. The median survival of patients with adverse prognostic factors is 3–6 months and these patients are best managed with palliative intent with low toxicity chemotherapy or radiotherapy with the aim of maintaining their quality of life. Patients in the better prognostic group may be treated with conventional combination chemotherapy for NHL with the aim of cure. However, because of the underlying immunodeficiency, poor bone marrow reserves due to HIV myelodysplasia and concomitant use of myelosuppressive agents such as zidovudine, many patients develop opportunistic infections, neutropenic sepsis or persisting neutropenia leading to chemotherapy delays and hence suboptimal treatment. Unfortunately, many published series reporting on the treatment of the latter group of patients vary in their selection criteria with respect to the definition of a good prognosis group, making comparison between treatment regimens difficult. Broadly speaking, it appears that the median survival of these patients is 7–9 months with 10–20% exhibiting disease-free survival for 2 years [1]. It has also become evident that dose-intensive regimens are associated with high degrees of toxicity without any survival benefit over standard dose schedules. Indeed, there is now a suggestion that by reducing the intensity of a standard-dose regimen it is possible to reduce haematological toxicity without affecting overall or disease-free survival [6].

In this study, we have identified a group of good prognosis patients with ARL, based on their degree of immunosuppression and performance status. These patients have been treated with curative intent using a modified alternating weekly combination chemotherapy schedule — bleomycin, etoposide, vincristine, methotrexate, prednisolone/cyclophosphamide, doxorubicin (BEMOP/CA). This regimen has the advantage of allowing the adjustment of doses of individual drugs on a weekly basis in accordance with specific toxicities as well as the theoretical advantage of employing non-cross-resistant cytotoxic agents.

2. Patients and methods

Since 1989 we have adopted a prognosis-stratified approach for patients with newly diagnosed ARL. Patients with one or no adverse prognostic factor (prior AIDS defining illness, ECOG performance status >2, CD4 cell count $<100/\mu l$) are treated with curative intent. Between 1989 and 1998, 141 patients have had a diagnosis of ARL and 66 (47%) were in the good prognosis group. During this period, 26 patients were enrolled onto a UK AIDS Oncology Group study of PACE-BOM (prednisolone, doxorubicin, cyclophosphamide, etoposide/bleomycin, vincristine, methotrexate) between 1991 and 1994, whilst 7 were treated with radiotherapy alone for stage 1A disease and 3 patients received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy. 30 patients were treated with alternating weekly chemotherapy with curative intent using the BEMOP/CA schedule [7]. The treatment schedule involved alternating weeks of treatment. Week one therapy was bleomycin 15 IU intramuscularly (i.m.), etoposide 200 mg/m^2 intravenously (i.v.), vincristine 1.4 mg/m^2 and methotrexate 50 mg/m^2 followed by folinic acid rescue (15 mg orally (p.o.) 24 and 36 h later). The second week treatment was cyclophosphamide 400 mg/m^2 i.v. and doxorubicin 30 mg/m^2 i.v. In addition, patients received prednisolone 50 mg p.o. on alternate days tailing off after the eighth week. Modifications to the regimen compared with that originally used for non-HIV-associated aggressive non-Hodgkin's lymphoma were a briefer duration (12 weeks compared with 16 weeks in immunocompetent patients) and the addition of mycobacterial prophylaxis (isoniazid 300 mg once a day and pyridoxine 10 mg once a day) as well as pneumocystis prophylaxis (co-trimoxazole 960 mg once a day). Intrathecal methotrexate was administrated fortnightly to patients with Burkitt's histology, meningeal involvement or base of skull disease. Granulocyte-colony stimulating factor (G-CSF) was not routinely administered with this regimen although it was given as secondary prophylaxis to patients whose neutrophil count fell below 0.5×10^9/l.

2.1. Statistical methods

Survival was calculated from the day of diagnosis until death or 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 [8]. The log rank method was used to test for the significance of differences in survival distributions [9]. Comparison of variables between groups was by chi-squared test for nominal variables.

3. Results

3.1. Patient characteristics

30 patients with good prognosis ARL were treated including 5 patients with prior AIDS defining diagnoses, 3 with ECOG performance status 3 and 1 with CD4 cell count at ARL diagnosis of $<100/\mu l$. The median age at ARL diagnosis was 40 years (range: 22–60 years) and all

but 3 were men. 26 patients were homosexual men including 1 who was also an intravenous drug user (IVDU), 2 heterosexual African women, 1 woman was an IVDU and the mode of transmission for 1 man was unknown. The stages of ARL were stage I (5), stage II (3), stage III (3), stage IV (19) and 24 (80%) had B symptoms. The International NHL prognostic factors project classifications [5] were low risk 8 (27%), low–intermediate risk 6 (20%), high–intermediate risk 11 (37%) and high risk 5 (17%). The clinicopathological features of the cohort are listed in Table 1. At ARL diagnosis 15/30 (50%) were receiving antiretroviral therapy, 10 with protease inhibitor-based regimens, 3 with combinations of reverse transcriptase inhibitors and 2 with zidovudine monotherapy.

3.2. Meningeal disease

Meningeal treatment was given to 10 patients (3 Burkitt's, 3 meningeal disease at presentation, 4 base of skull involvement). Of these patients treated with prophylactic intrathecal methotrexate, 2 developed meningeal relapse, one man with stage 3B Burkitt's lymphoma (BL) who was successfully salvaged with cranial radiotherapy and a woman with stage 4B BL who although the cerebrospinal fluid (CSF) was acellular at presentation did have Epstein–Barr virus (EBV) detected at presentation in the CSF by polymerase chain reaction (PCR). In total, 4 patients relapsed with meningeal disease including the aforementioned. The other 2 patients had not received prophylaxis: 1 had stage 4A diffuse large cell lymphoma and relapsed 6 months after diagnosis and 1 with stage 4B immunoblastic lymphoma relapsed 1.2 years after diagnosis of ARL.

3.3. Response to BEMOP/CA

The median follow-up was 2.1 years (maximum 5.4 years). 3 patients withdrew from treatment within 2 weeks of starting, 2 on account of toxicity (both neutropenic sepsis) and 1 due to patient preference. 2 patients died within 2 weeks of starting chemotherapy (1 of pulmonary embolus on the same day as the first dose of chemotherapy, 1 of gastrointestinal perforation secondary to ileal ARL). 25 patients were evaluable for response and 15 (60%) achieved a complete remission and a further 8 (32%) had partial responses.

Table 1
Clinicopathological features at presentation

	n (%)
Prior AIDS	5 (17)
ECOG performance status >2	3 (10)
CD4 <100 cells/μl	1 (3)
Stage III/IV	22 (73)
B symptoms	24 (80)
Hyponatraemia (serum sodium <135 mmol/l)	7 (23)
Hypoalbuminaemia (serum albumin <30 g/l)	17 (57)
Raised serum LDH	20 (65)
Bone marrow infiltration by NHL	4 (13)
Meningeal involvement at presentation	3 (10)
Burkitt's lymphoma	3 (10)
Diffuse large cell (DLC) lymphoma	19 (63)
Immunoblastic lymphoma	8 (27)

DLC, diffuse large cell; LDH, lactate dehydrogenase.

3.4. Overall survival and relapse

Two years overall survival for the cohort is 46% (95% CI = 27–65%) (Fig. 1). If patients who die of other AIDS-related causes are censored, the lymphoma specfic survival at 2 years is 59% (95% CI: 40–78%). In total, 8 patients have relapsed including 4 with meningeal relapse as mentioned above. The median time to relapse was 5 months (range 2–14 months). All the patients who relapsed, except 1, have died of progressive ARL.

3.5. Toxicities

The major toxicity of this regimen was haematological and 14 patients developed grade 4 neutropenia, including all 4 who had marrow infiltration at diagnosis. In addition, 2 patients developed grade 4 thrombocytopenia. The major haematological toxicity observed exceeds that seen with this regimen when used in the HIV-seronegative population and may be due to the very high frequency of HIV-associated myelodysplasia observed on bone marrow examination in this cohort (67%). The frequency of grade 4 neutropenia was no higher amongst patients on antiretrovirals than those not on antiretrovirals ($\chi^2 = 0.76$ $P = 0.86$) or amongst those receiving protease inhibitors ($\chi^2 = 1.3$ $P = 0.71$). 3 patients developed mucositis during their treatment, but this was severe grade 3 in only 1 case. 5 patients developed opportunistic infections during the course of their chemotherapy (1 cytomegalovirus retinitis reactivation, 2 peri-anal herpes simplex, 1 giardiasis, 1 cryptosporidiosis).

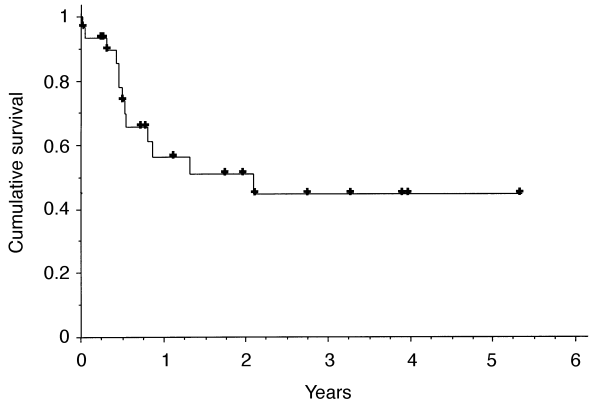

Fig. 1. Kaplan–Meier overall survival duration curve.

4. Discussion

Over recent years there has been significant progress in the treatment of HIV infection, with antiretroviral therapy in particular having improved markedly. With the consequent improvement in patient's immune status and CD4 cell counts it might be expected that the results of therapy for ARL will more closely resemble those for NHL patients not associated with HIV. We have shown in this study that using parameters that relate to patient's immune function allows the identification of a good prognosis group of patients to receive potentially curative cytotoxic treatment. Indeed, the results that we have obtained for response rates and overall survival are at least as good as, if not better than, most previously reported series [1], although the selection criteria in previous series were often less stringent than ours. Furthermore, in our series there were relatively few CNS relapses. This we attribute to the routine administration of intrathecal chemotherapy prophylaxis to patients adjudged to be at high risk of meningeal relapse which prevented CNS relapse in 80% patients given CNS prophylaxis.

Early experience with the management of ARL with conventional lymphoma chemotherapy schedules yielded disappointing survival durations and considerable toxicity. One approach to these initial findings, which was pursued in Europe was to use the more intensive LNH-84 schedule in good risk patients. This led to a complete response rate of 63% in 141 selected good risk patients with a median CD4 cell count of 227/μl. However, the median survival was only 9 months [10]. Following the early disappointing results observed with higher dose cytotoxic regimens in ARL, an alternative approach was adopted in North America where studies with reduced dose chemotherapy were conducted. In the only published randomised study in ARL which was run by the ACTG, patients were assigned to receive either standard dose mBACOD chemotherapy with granulocyte-macrophage colony stimulating factor (GM-CSF) support or reduced dose mBACOD with GM-CSF reserved for neutropenia. No significant differences were found in response rates (41–52%), response duration, time to progression and disease-free or overall survival (7.2–8.1 months) between the two groups [6]. In our study, we have reduced the duration of the BEMOP/CA schedule compared with that received by patients with NHL not associated with HIV. Although this reduction does not seem to have been detrimental to the efficacy of the regimen, it failed to prevent a marked degree of haematological toxicity which may have been exacerbated by the high frequency of underlying HIV-associated myelodysplasia. However, the haematological toxicity was no worse in patients concurrently receiving highly active antiretroviral therapy (HAART). This observation is in contrast to reports from other groups using CHOP chemotherapy for ARL [11].

Weekly alternating chemotherapy regimens such as BEMOP/CA appear to be a very satisfactory way of administering chemotherapy to patients with ARL, as they allow regular adjustments of dosages based upon specific toxicities. However, recent reports have focused on the role of infusional chemotherapy as an alternative in this group of patients [12]. The combination of cyclophosphamide, doxorubicin and etoposide (CDE) has been administered as a 96-h continuous infusion for up to 6 courses at 4-weekly intervals, together with granulocyte-colony stimulating factor (G-CSF) and didanosine. Initial reports in a selected group of 25 patients with a median CD4 count of 117/μl, produced an impressive median survival of 18.4 months (range: 1–>24 months) [13]. More recently this schedule has been used in conjunction with protease inhibitor-based HAART therapy with similar results although more mucositis was documented [14]. Whether the impressive survival with CDE reflects a schedule which truly produces more durable responses on account of the steroid sparing or infusional schedule, or alternatively is due to recent improvements in the overall management of HIV disease remains to be seen.

Two-thirds of the patients were treated in the pre-HAART era and our study has shown that using a risk-stratified approach to the management of ARL a good response rate and overall survival can be achieved for carefully selected patients. The response rate of 60% and the median survival in excess of 24 months for good risk patients treated with BEMOP/CA compares favourably with other reported series including the CDE data. However, a note of caution should be added. It is not possible to determine whether this improved clinical outcome is the result of an improved chemotherapy regimen or if this merely represents the expected outcome in a group of patients with good immune function who are treated with effective antiretroviral therapy. Whether similar results can be achieved for poor risk patients following the developments in antiretroviral therapy remains to be seen.

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