AIDS-related non-Hodgkin’s lymphoma in the first decade of highly active antiretroviral therapy

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Summary

Highly active antiretroviral therapy (HAART) has had a dramatic effect on the natural history of HIV disease, reducing the incidence of opportunistic infections and Kaposi’s sarcoma, and improving overall survival. Since HAART became available in 1996, the incidence of AIDS-related non-Hodgkin’s lymphoma (NHL) has fallen, and although there has been no change in the clinical features at presentation, the overall survival of patients with AIDS-related NHL has improved. Prognosis is now determined chiefly by lymphoma-associated factors similar to those in the general population (the International Prognostic Index), although serum CD4 count at lymphoma diagnosis is an additional independent prognostic factor. The management of patients with AIDS-related NHL with either infusional chemotherapy or CHOP-like regimens (cyclophosphamide, doxorubicin, vincristine and prednisolone) achieves response and survival rates approaching those observed in the general population. However, careful attention should be paid to central nervous system chemoprophylaxis, opportunistic infection prophylaxis and potential drug interactions between cytotoxic and antiretroviral therapies. In the era of HAART, the goal of therapy for these patients is now complete remission rather than palliation.

Introduction

Acquired immunodeficiency syndrome (AIDS) following infection with human immunodeficiency virus (HIV), was brought to the world’s attention in 1981 with the first case reports of Pneumocystis carinii (now known as P. jirovecii) pneumonia in homosexual men in Los Angeles.1 These reports were quickly followed by descriptions of Kaposi’s sarcoma in similar patient groups.2,3 There followed a cornucopia of opportunistic infections and isolated reports of high-grade B-cell non-Hodgkin’s lymphomas (NHL), both primary cerebral lymphomas and systemic NHL. By 1985, high-grade B-cell NHL was included along with Kaposi’s sarcoma as an AIDS-defining illness by the Centre for Disease Control (CDC) following the publication of a series of 90 homosexual men with NHL.4–8 A final AIDS-defining malignancy, invasive cervical cancer, was added as an AIDS-defining illness in 1993, although the incidence of this malignancy is not increased as dramatically in HIV-seropositive women.9 A number of other cancers occur at an increased frequency in people with HIV infection but are not AIDS-defining; these include Hodgkin’s disease, anal cancer, lung cancer10 and testicular seminoma.11 In Africa, and particularly Sub-Saharan Africa where the burden of HIV infection is the...
greatest, AIDS-related lymphoma is an increasing cause of morbidity and mortality. In these economically developing countries, the diagnosis and management of AIDS-related lymphoma presents particular challenges and problems for clinicians given the ‘environment of extreme scarcity’. These clinical challenges include access to HAART, drugs for the prevention and management of opportunistic infection, access to intravenous chemotherapy and the availability of supportive therapy required during chemotherapy such as blood transfusion.

This review deals with HIV-associated non-Hodgkin’s lymphoma and the changes that have occurred in its management in the first decade of highly active antiretroviral therapy (HAART).

Highly active antiretroviral therapy (HAART)

The introduction of highly active antiretroviral therapy (HAART) during the mid-1990s in developed market economies has altered the natural history of HIV infection, and has resulted in a fall in the incidence of both opportunistic infection and AIDS-associated malignancies.

The development of effective antiretroviral therapies commenced with the introduction of nucleoside reverse transcriptase inhibitors starting with zidovudine in 1987. Since then, three new classes of antiretroviral agents have been introduced: protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir, lopinavir, atazanavir), non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine, efavirenz) and fusion inhibitors (enfuvirtide). The introduction of the first two classes in the late 1990s led to the use of combination highly active antiretroviral treatment (HAART). HAART has had an enormous impact on the treatment of HIV in terms of overall survival, incidence of opportunistic infections and quality of life. In randomized studies HAART leads to a dramatic decline in the mortality and morbidity of HIV. However, only 1 million of the estimated 42 million people infected with HIV worldwide are receiving HAART, as the majority of affected people live in developing countries. In addition, even in the established market economies with access to medical treatment, many individuals remain undiagnosed and consequently do not receive HAART. For the commonest AIDS-defining malignancy, Kaposi’s sarcoma, HAART remains an effective therapy, although its effect on lymphoma is more controversial.

Epidemiology of AIDS-related systemic non-Hodgkin’s lymphoma in era of HAART

Given the known association between NHL and both congenital and iatrogenic immunosuppression, the documentation of an increase in the incidence of NHL in the HIV-seropositive population was not surprising. Registry linkage studies in the pre-HAART era found that the incidence of NHL in HIV-positive individuals was 60–200 times higher than in a matched HIV-negative population, and the relative risk was even greater for primary cerebral lymphomas. There has been a significant fall in the incidence of both Kaposi’s sarcoma and primary cerebral lymphoma following the introduction of HAART, which is believed to be secondary to the immune reconstitution produced by HAART. In contrast, the effects of HAART on systemic NHL are less clear, although some cohort studies suggest a modest non-significant decline in the incidence, including in the haemophilia population. An international meta-analysis of 20 cohort studies compared the incidences of systemic NHL between 1992–6 and 1997–9. There was an overall reduction in the incidence of both primary cerebral lymphoma (rate ratio 0.42) and systemic immunoblastic lymphoma (rate ratio 0.57) but not Burkitt’s lymphoma (rate ratio 1.18). A further European epidemiological study found a significant decrease in the incidence of AIDS-defining conditions from 30.7 per 100 patient years in 1994 to 2.5 per 100 patient years in 1998. However NHL as the AIDS-defining diagnosis increased from 4% to 16% during the same time period.

Predictors of AIDS-related lymphoma

An analysis of a cohort of 7840 HIV-positive patients identified three factors in a multivariate analysis that were significantly associated with the development of systemic NHL: age, nadir CD4 cell count and no prior HAART. As the CD4 count falls, the development of lymphoma becomes more likely, and this may explain why there has been a decline in the incidence of NHL since the introduction of HAART. It therefore appears that the immune restoration that accompanies HAART protects against the development of HIV-related lymphoma. An update of this data using 9621 HIV-1-infected patients again found that the use of
HAART protected against NHL development. Moreover, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART was found to be as protective as protease inhibitor (PI)-based HAART, and these were significantly more protective than nucleoside analogues alone (rate ratio 0.5, 95%CI 0.4–0.7) or no antiretrovirals (p < 0.001). With regard to other possible therapeutic interventions which might prevent HIV-related NHL, in one case-control study, administration of high-dose acyclovir (> 800 mg/day), which has mild activity against Epstein Barr in vivo, for ≥1 year was associated with a significant reduction in the incidence of NHL. However, there is controversy concerning the association between serum Epstein Barr viral DNA loads and the risk of developing lymphoma.

Clinical presentation of AIDS-related non-Hodgkin’s lymphoma
Systemic AIDS-related lymphomas have a number of differences from NHL in the HIV-seronegative population, including: (i) presentation with advanced stage disease and B symptoms, (ii) extranodal, bone marrow and leptomeningeal involvement, (iii) plasmacellular differentiation and (iv) association with Epstein Barr virus (EBV). Central nervous system involvement is frequent in systemic AIDS-associated NHL. Leptomeningeal disease is present at diagnosis in 3–10%, and is significantly associated with Burkitt’s lymphoma and both bone marrow and paraspinal or parasinal involvement. The administration of intra-thecal chemotherapy is an integral part of the management of such patients.

A number of published series have compared the clinical characteristics of AIDS-related lymphomas presenting in the pre-HAART era with those presenting in the post-HAART era. In a comparison of the clinical characteristics of 99 AIDS-related NHL patients presenting prior to 1996 with 55 cases presenting between 1996–1999, there were no differences between the two groups with regard to stage at presentation, presence of B symptoms, bone marrow infiltration or performance status. A French study of 145 cases reported similar results, with no significant differences at presentation with regard to gender, stage, histology, or proportion with elevated serum lactate dehydrogenase (LDH) and extranodal disease.

Treatment of AIDS-related non-Hodgkin’s lymphoma in the era of HAART
In the 1980s, conventional chemotherapy schedules were used at full dosages for patients with better prognostic factors. However, the marked toxicity, in particular myelosuppression and the increased incidence of opportunistic infections, led to modifications of the standard lymphoma regimens. The subsequent development and introduction of haematopoetic growth factors allowed the introduction of more myelotoxic schedules. The appreciable death rate from opportunistic infections generally offset any decline in NHL-related deaths, and most centres persisted with either dose-reduced chemotherapy schedules or prognostic stratification that reserved full-dose therapy for only patients with the best prognostic factors.

With the advent of HAART, groups began combining HAART with cytotoxic chemotherapy; Table 1 summarizes the outcome for such regimens. However, initial reports either had HAART as optional therapy and did not report the number of patients on such treatment, or only had a proportion of patients on HAART. The first report of a series including patients treated with chemotherapy and HAART described an alternating weekly chemotherapy regime using bleomycin, etoposide, vincristine, methotrexate, prednisolone/cyclophosphamide, doxorubicin (BEMOP/CA) in patients with a good prognosis. Half were receiving HAART, and the overall 2-year survival rate was 46% (95%CI 27%–65%), with a 2-year lymphoma-specific survival of 59% (95%CI 27%–65%).

The feasibility of combining chemotherapy with HAART therapy was formally explored in the AIDS Malignancy Consortium 005 (AMC 005) trial, which compared CHOP chemotherapy at a reduced dose (mCHOP) or full-dose CHOP, with concomitant HAART therapy ( stavudine, lamivudine, and indinavir) being given to all patients. This was not a randomized comparative trial, but rather two successive treatment arms. They reported overall response rates for mCHOP and full-dose CHOP of 60% (95%CI 45%–75%) and 57% (95%CI 38%–77%), respectively (p = 0.79), although the complete response rate was significantly higher in the full-dose CHOP arm.
Table 1  Summary of published phase II/III trials in the post-HAART era

<table>
<thead>
<tr>
<th>Chemotherapy regimen (reference)</th>
<th>n</th>
<th>Receiving HAART</th>
<th>Complete response rate</th>
<th>Median survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose m-BACOD^40</td>
<td>98</td>
<td>Optional (No data on numbers)</td>
<td>41%</td>
<td>35 weeks (95%CI 30–45%)</td>
<td>1 year: 27% 2 year: 11%</td>
</tr>
<tr>
<td>Standard dose m-BACOD^40</td>
<td>94</td>
<td>Optional (No data on numbers)</td>
<td>52%</td>
<td>31 weeks (95%CI 22–42%)</td>
<td>1 year: 24% 2 year: 7%</td>
</tr>
<tr>
<td>BEMOP-CA^41</td>
<td>30</td>
<td>50%</td>
<td>60%</td>
<td></td>
<td>2 year: 46% (95%CI 27–65%)</td>
</tr>
<tr>
<td>CHOP^42</td>
<td>25</td>
<td>100%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mCHOP^42</td>
<td>40</td>
<td>100%</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP^44</td>
<td>17</td>
<td>100%</td>
<td>75%</td>
<td></td>
<td>2 year probability: 0.59 (95%CI 0.31–0.87)</td>
</tr>
<tr>
<td>CHOP m-BACOD</td>
<td>44</td>
<td>82%</td>
<td>52% HAART responders:</td>
<td>360 days, HAART-treated: 425 days (95%CI 241–609)</td>
<td>1 year (cumulative probability): 0.49 HAART-treated: 0.51</td>
</tr>
<tr>
<td>MA-COP-B</td>
<td></td>
<td></td>
<td>71% HAART-failed/naïve:</td>
<td></td>
<td>Virological response to HAART: 0.84</td>
</tr>
<tr>
<td>ACVB^48</td>
<td></td>
<td></td>
<td>30%</td>
<td></td>
<td>2 year: 55% 60% (at median follow-up of 53 months)</td>
</tr>
<tr>
<td>CHOP^45</td>
<td>24</td>
<td>100%</td>
<td>50%</td>
<td>NYR</td>
<td></td>
</tr>
<tr>
<td>DA-EPOCH^59</td>
<td>39</td>
<td>0%</td>
<td>74%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDE^55</td>
<td>55</td>
<td>100%</td>
<td>44% (95%CI 30–55%)</td>
<td>13.7 months (95%CI 11–not reached)</td>
<td>1 year: 57% (95%CI 43–70%) 2 year: 45% (95%; 20–58%)</td>
</tr>
<tr>
<td>CDE^56</td>
<td>46</td>
<td>100%</td>
<td>50%</td>
<td>26 months</td>
<td>2 year: 61% (95%CI 47–70%) 1 year: 58%</td>
</tr>
<tr>
<td>CHOP (Liposomal dox)^46</td>
<td>24</td>
<td>100%</td>
<td>75%</td>
<td>&gt;13.4 months</td>
<td>2 years (estimated): 64% (95%CI 52%–76%)</td>
</tr>
<tr>
<td>CDE+rituximab^65</td>
<td>74</td>
<td>76%</td>
<td>70% (95%CI 59–81%)</td>
<td></td>
<td>2 year probability: 0.59 (95%CI 0.31–0.87)</td>
</tr>
<tr>
<td>CHOP^47</td>
<td>50</td>
<td>‘Most’</td>
<td>47%</td>
<td>110 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>CHOP+rituximab^57</td>
<td>99</td>
<td>‘Most’</td>
<td>58%</td>
<td>139 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>CHOP/ACVB-P^74</td>
<td>35</td>
<td>100%</td>
<td>54%</td>
<td>22 months</td>
<td>1 year: 54% 2 year: 49%</td>
</tr>
</tbody>
</table>

ACVB, Adriamycin, cyclophosphamide, vinblatine and bleomycin; ACVB-P, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisolone; BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone; BEMOP-CA, bleomycin, etoposide, vincristine, methotrexate, prednisolone/cyclophosphamide, doxorubicin; CDE, cyclophosphamide, doxorubicin, etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; COP-B, cyclophosphamide, oncovin, prednisolone, bleomycin; DA-EPOCH, dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin; m-BACOD, modified BACOD; m-CHOP, Modified CHOP; MA-COP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin.

(48%, as compared to 30% in mCHOP). No long-term outcome data have been reported for this group of patients. There were no significant differences in grade 3 and 4 toxicities observed in the two groups. Furthermore, HIV viral loads declined and CD4 counts increased significantly despite the concurrent use of chemotherapy, and only one opportunistic infection was reported during the trial and its follow-up period, in contrast with previous trials.\textsuperscript{40,43}

These data were supported by a further study which looked at the effect of HAART on the response to treatment and survival in patients with HIV-associated NHL treated with CHOP...
chemotherapy, using historical controls. This revealed that patients treated with CHOP plus HAART had a higher response rate than those treated with CHOP alone (75% vs. 34%; \( p = 0.003 \)). The median overall survival for those treated with CHOP alone was 7 months (range 3–10.8 months), whereas the median time was not reached in the HAART plus CHOP group (\( p = 0.0015 \)). Under multivariate analysis, HAART treatment was an independent prognostic factor for complete response and overall survival.\(^4^4\)

The authors therefore suggested that the addition of HAART to CHOP might improve the efficacy of chemotherapy, and appeared to be safe and effective. Other studies involving CHOP given with HAART have reported response rates of 47–75%, with median survival of up to 27 months and overall survival of 58% and 55% being reported at 1 and 2 years, respectively.\(^4^5^–^4^7\) The substitution of liposome-encapsulated doxorubicin for conventional doxorubicin in the CHOP regimen does not appear to affect the efficacy of this treatment.\(^4^6\)

A prospective observational study of 44 patients included 34 treated with CHOP and the remaining 10 with either m-BACOD, modified m-BACOD, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin (MA-COP-B) or adriamycin, cyclophosphamide, vinblastine, and bleomycin (ACVB). Eight patients in this cohort did not take HAART. The study reported a complete response in 52% of patients, with a complete response more frequently seen in those who had a virological response to HAART (70% as opposed to 30% in non-responders: OR 5.67, 95%CI 1.54–20.78). Multivariate analysis revealed that virological response to HAART was the only variable associated with tumour response (OR 6.36, 95%CI 1.56–25.81).\(^4^8\) This finding could be related to the fact that those who had a virological response received a significantly higher dose intensity of chemotherapy, compared to those who did not respond to HAART, due to the possible improvement in haematopoiesis given the inhibition of HIV. This enabled a greater dose density of chemotherapy to be delivered, which is a known factor in the outcome of NHL. The estimated overall survival for all patients was 360 days (95%CI 81–639), with a 1 year cumulative survival probability of 0.49; however, in the HAART-treated patients, estimated overall survival was 425 days (95%CI 241–609), with a 1 year cumulative probability of 0.51, increasing to 0.78 in those with a virological response to HAART.\(^4^8\)

### Infusional chemotherapy: the CDE regimen

Preclinical data suggested that infusional schedules of cytotoxic agents might have a therapeutic advantage,\(^4^9\) and this is supported by clinical data such as the response of chemotherapy refractory multiple myeloma to infusional doxorubicin and vincristine,\(^5^0\) and the higher response rates seen in small-cell lung cancer with 5-day infusions of etoposide, as compared with a one-day regimen of the same dose.\(^5^1\) Two infusional chemotherapy regimens have been investigated in AIDS-related NHL, namely: cyclophosphamide, doxorubicin and etoposide (CDE) administered as a 96-h continuous infusion, and cyclophosphamide, doxorubicin, etoposide, vincristine and prednisolone (EPOCH), which will be discussed later. CDE was first found to be highly active and capable of producing durable remissions in HIV-related NHL in a small pre-HAART era study, in which CDE was administered to 12 HIV-seropositive and two HTLV-1-seropositive patients, with a complete response rate of 71% and a partial response rate of 21%. Median survival was estimated at 17.4 months, with 7 of the 12 HIV-positive patients alive and disease-free at a median follow-up of 15 months.\(^5^2\) A subsequent report of 25 patients with AIDS-related lymphomas treated with CDE plus didanosine produced a complete response rate of 58% (95%CI 38–78%) and a median survival of 18.4 months; this was seen as a major advance in the treatment of HIV related NHL.\(^5^3\) The same schedule combined with saquinavir produced similar results, although there was more mucositis with the protease inhibitor.\(^5^4\) A multicentre phase II trial of infusional CDE plus concurrent HAART produced far less impressive results than the earlier trials, with a reported complete response rate of 45% (95%CI 35–55%) and 2-year survival of 44% (95%CI 33–53%).\(^5^5\) A comparison of patients treated with CDE revealed improved overall survival with the concurrent use of HAART as compared to those in the pre-HAART group, namely those patients treated with didanosine (\( p = 0.039 \)). Complete response rates of 50%, with a 2-year survival of 61% and median survival of 26 months, have been reported by others using this regimen.\(^5^6\)

### Treatment of HIV-associated NHL with omission of HAART

The omission of HAART for the duration of chemotherapy for HIV-related NHL was examined in a trial involving a dose-adjusted chemotherapy.
Role of rituximab in the treatment of HIV-associated NHL

Rituximab is a chimeric monoclonal antibody directed against CD20 (B1), a B-cell-specific cell-surface molecule that is involved in B cell activation and differentiation, and that is present on mature B-cells and nearly all B-cell lymphomas. Studies in immunocompetent patients with diffuse large B-cell lymphoma (DLBCL) have shown improved outcome in those receiving rituximab. Following these studies, and since 60–70% of HIV-related NHL are DLBCL, the addition of rituximab to chemotherapy has been investigated in a number of trials. The AMC Trial 010 found no significant difference between rituximab plus CHOP (R-CHOP) vs. CHOP alone for either complete response rates (57% vs. 47%; \( p = 0.147 \)) or overall survival (139 weeks vs. 110 weeks; \( p = 0.76 \)). The addition of rituximab to CDE in a Phase I/II trial involving 29 patients found a complete response rate of 86% and a partial response in a further 4%. Actuarial survival at 2 years was 80%, with median overall survival not reached at a median follow-up of 9 months. A subsequent pooled analysis of three prospective phase II trials involving 79 patients found a complete response of 70% (95%CI 58–81%) and an overall survival of 64% (95%CI 52–76%). It therefore appears that the addition of rituximab could enhance the efficacy of CDE, but there remain concerns over additional toxicity.

Interaction between HAART and chemotherapy

Both NNRTIs and PIs are extensively metabolized by the cytochrome P450 system, so there is the potential for competitive drug interactions when they are administered concomitantly with other drugs metabolized through this pathway. PIs can modify the metabolism of cytotoxic drugs by inhibiting the CYP3A4 enzyme. A pharmacokinetic study of modified-dose and full-dose CHOP given with HAART (which consisted of stavudine, lamivudine and indinavir) revealed that the clearance of cyclophosphamide was reduced. This is consistent with an effect of indinavir. In contrast, no effect of mCHOP or CHOP on indinavir levels was observed. Another potential interaction occurs because PIs are substrates and inhibitors of the drug transporter P-glycoprotein, an efflux pump that transports a wide range of structurally unrelated drugs such as PIs and anthracyclines. Other published studies have confirmed interactions between PI containing HAART and chemotherapy. For example, CDE combined with the PI saquinavir resulted in 67% of patients developing mucositis, while this only occurred in 12% when CDE was administered with the nucleoside analogue didanosine. In addition, neutrophil counts 10 and 14 days after CDE chemotherapy were significantly lower in patients receiving PIs as compared to non-PI HAART regimens. The reduced hepatic metabolism of cyclophosphamide and doxorubicin due to inhibition of P450, and/or the increased...
intracellular concentration of cytotoxic agents as a result of inhibition of P-glycoprotein\textsuperscript{70,71} by PIs, probably account for the increased incidence of neutropenia seen with this group of anti-retrovirals. Despite the increase neutropenia, there is no observed increase in response with PI-based HAART, suggesting that there is no significant dose-response gradient, even if there is a significant dose-toxicity relationship.\textsuperscript{56} Thus consideration should be given where possible to the use of non-PI-based HAART in patients receiving chemotherapy for HIV-related NHL, particularly since data indicate that NNRTI-based therapy is as potent and provides durable virological control.

Within the setting of high-dose chemotherapy, the pharmacokinetic effects and potential clinical ramifications of the concomitant administration of HAART need particular attention and consideration.

Certain other anti-retrovirals are best avoided in combination with chemotherapy, such as zidovudine, which significantly adds to the myelo-suppression of chemotherapy, and didanosine, which may worsen the peripheral neuropathy caused by taxanes and vinca alkaloids.

### CD4 cell dynamics, viral load and chemotherapy

The effect of chemotherapy on CD4 count and plasma HIV viral load has been investigated in some clinical trials. The results reported vary: some studies have found an increase in the CD4 count on treatment (e.g. from a median baseline value of 138 (CHOP) and 122 (mCHOP) cells/mm\textsuperscript{3} to a median of 216 cells/mm\textsuperscript{3} after treatment\textsuperscript{42}), but two other trials of chemotherapy alone found a decrease in CD4 cell count with treatment, with a mean change between commencement and completion of $-47$ cells/mm\textsuperscript{3}\textsuperscript{48} and a 50% decrease in another.\textsuperscript{72}

With regard to viral load, two trials found significant decreases (from a median baseline of 29,000 copies/ml to a median of 500 copies/ml\textsuperscript{42} and a change of $-1.61 \log_{10}$ copies/ml\textsuperscript{46}) by the time of completion of chemotherapy. In the CHOP and mCHOP trial, there were no differences in the CD4 and VL dynamics between the two chemotherapy arms.\textsuperscript{42} With DA-EPOCH where HAART is discontinued, the viral load increased a median of 0.83 $\log_{10}$ (range $-0.28$ to 4.12 $\log_{10}$), while the CD4 count decreased by a median of 189 cells/mm\textsuperscript{3} (range $+19$ to $-973$) by the sixth cycle of treatment.\textsuperscript{59}

For those trials that reported either a decrease in CD4 or increase in viral load, some information is available on recovery times. With concomitant HAART, a normalization of CD4 count occurred within 1 month,\textsuperscript{72} while the drop reported by Antinori\textsuperscript{48} had recovered to greater than baseline when re-measured at 6 months post chemotherapy ($+25$ cells/mm\textsuperscript{3}, $p = 0.19$) and was significantly higher by 9 months ($+131$ cells/mm\textsuperscript{3}, $p = 0.001$).\textsuperscript{48}

With DA-EPOCH, the viral load returned to baseline levels at 3 months, but CD4+ cells took 6–12 months to recovery to baseline values.\textsuperscript{59}

Only one trial that combined chemotherapy and rituximab has described CD4 and viral load changes. It showed a small drop in the median CD4 count between baseline and 1 month post-treatment, from 161/mm\textsuperscript{3} to 108/mm\textsuperscript{3}. Viral load, which was detectable in 40% of patients at start of treatment, became undetectable in all patients a month after completing treatment.\textsuperscript{65}

The maintenance of virological response with the administration of both R-CDE and CHOP chemotherapy has been confirmed by others,\textsuperscript{73} in this study, 68% and 84%, respectively, of patients maintained a virological response while receiving chemotherapy.\textsuperscript{73} HIV genotype and virtual phenotype analysis was carried out on all those patients who suffered virological failure. While different mutations were present in the reverse transcriptase and protease genes, there were no significant changes in the resistance profiles in the majority of non-responders, suggesting that chemotherapy does not significantly increase the occurrence of new resistance patterns.\textsuperscript{73}

The possible relationship between response to HAART and response to chemotherapy was investigated in a univariate analysis of R-CDE. A detectable viral load at the completion of treatment was associated with significantly increased risks of treatment failure (HR 1.97, 95%CI 0.99–3.91, $p = 0.03$) and death (HR 2.39, 95%CI 1.10–5.18, $p = 0.03$).\textsuperscript{65} In a separate multivariate analysis, virological response was the only factor associated with tumour response.\textsuperscript{48} In contrast, Little and colleges found tumour responses in the face of worsening viral and immunological parameters,\textsuperscript{59} and Levine found no relationship between virological control and response to chemotherapy, although relapses tended to occur more frequently in those without virological control.\textsuperscript{46}

### CNS involvement

The high rate of leptomeningeal disease at presentation, which may be asymptomatic, has resulted in the widespread use of staging lumbar punctures and prophylactic intrathecal chemotherapy for patients...
considered to be at high risk of relapse from the cerebrospinal fluid results. Based on published data from 12 studies in the post-HAART era, only two of which were prospective or randomized (Table 1), information regarding the rate of CNS disease is somewhat variable (Table 2). Some trials did not formally report the rate of CNS involvement at the time of initiation of systemic treatment, even though lumbar puncture was reported as being part of the initial assessment, and one formally excluded any patient with meningeal disease. In the seven studies where the rate of CNS involvement was reported, it varied between 0% and 20%. With regard to CNS relapse during treatment, the data are again highly variable and often no formal report or comment is made (Table 2). In the publications where data on CNS relapse was reported, it varied between 3% and 13%; the number of patients in these studies varying between 24 and 198. One study that compared patients in the pre-and post-HAART era reported a 4% rate of meningeal involvement, but did not comment on any difference between the pre- and post-HAART groups. Two additional reports that compared patients in the pre-and post-HAART eras made no comment on CNS involvement.

Table 2 Summary of details of CNS involvement and relapse reported in trials involving systemic treatment for AIDS related non-Hodgkin’s lymphoma in the post-HAART era

<table>
<thead>
<tr>
<th>Chemotherapy regimen (reference)</th>
<th>CNS involvement at commencement of treatment</th>
<th>Details of CNS relapse during treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose m-BACOD vs. standard dose m-BACOD, BEMOP-CA</td>
<td>6/198 (3%)</td>
<td>On treatment 6 (3%) developed meningeal relapse, no details given</td>
</tr>
<tr>
<td>MCHOP and CHOP</td>
<td>3/30 (10%)</td>
<td>In total 4 developed meningeal recurrence: 2 receiving prophylactic IT MTX, 2 not</td>
</tr>
<tr>
<td>CHOP (pre- and post-HAART eras)</td>
<td>Patients with meningeal involvement excluded from trial</td>
<td>No details on CNS relapse in the 27% of those who developed progressive disease</td>
</tr>
<tr>
<td>m-BACOD, MA-COP-B, ACVB, CHOP</td>
<td>No comment</td>
<td>No comment</td>
</tr>
<tr>
<td>DA-EPOCH</td>
<td>Lumbar puncture performed routinely. 93% had extranodal disease</td>
<td>Two developed CNS disease during treatment</td>
</tr>
<tr>
<td>CDE (pre- and post-HAART eras)</td>
<td>Meningeal involvement at commencement of treatment in 4/98 (4%)</td>
<td>Those with Burkitt lymphoma who died had CNS disease (57% of Burkitt’s cases had CNS disease)</td>
</tr>
<tr>
<td>CDE</td>
<td>No comment</td>
<td>CNS treatment-related complications in 3/5 patients who died in remission</td>
</tr>
<tr>
<td>CHOP</td>
<td>Lumbar puncture performed routinely. No comment.</td>
<td>No comment</td>
</tr>
<tr>
<td>CDE, CHOP (liposomal dox)</td>
<td>9/35 (20%)</td>
<td>No comment</td>
</tr>
<tr>
<td>CDE</td>
<td>0/24</td>
<td>2/18 CR relapsed with CNS disease, all having received prophylactic IT therapy.</td>
</tr>
<tr>
<td>CHOP vs. CHOP+rituximab</td>
<td>Lumbar puncture performed routinely.</td>
<td>No comment</td>
</tr>
<tr>
<td>CHOP vs. ACVBP</td>
<td>No comment</td>
<td>No comment</td>
</tr>
<tr>
<td>CDE + Rituximab</td>
<td>3/74 (4%)</td>
<td>No comment</td>
</tr>
</tbody>
</table>

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In the pre-HAART era, some trials made no comment on CNS involvement, while Sparano reported no CNS involvement at initiation of therapy in 12 patients treated with infusional CDE; however 2/6 patients receiving intrathecal methotrexate developed meningeal disease after the second cycle of treatment. An 8% rate of meningeal involvement at initiation of therapy was reported in a subsequent group of 25 patients treated with the same regime and didanosine. Updated results from both these papers were subsequently included in a review of CNS involvement in 62 patients treated with infusional CDE. In this review of patients with HIV-related NHL treated using CDE between 1990 and 1996, 13 patients (21%) presented with or developed CNS involvement; five of these had meningeal involvement and six had parenchymal disease. Furthermore, in this series, two patients (7%) receiving prophylactic intrathecal chemotherapy developed meningeal disease. At presentation, five patients (8%) had CNS involvement, of whom four had clinical signs or symptoms, three had positive CSF cytology, and two of the latter also had parenchymal brain involvement on radiology. Of the three patients with meningeal involvement, two (67%) had a complete response and survived for a year. On follow-up, only one was alive at 68 months from diagnosis.

In contrast, of the 57 patients without clinical, radiological or CSF evidence of lymphomatous involvement, 26 (46%) did not meet the criteria for CNS prophylaxis, and none developed an isolated meningeal recurrence, although four developed parenchymal disease. Thirty-one patients (54%) met the criteria for CNS prophylaxis, three of whom refused it. Of the eight CNS recurrences, four met CNS prophylaxis criteria. One refused, two received intrathecal methotrexate and one intrathecal cytarabine. Of these four patients, two developed cytology-proved meningeal disease within 3 months of diagnosis (both were receiving prophylaxis with methotrexate) and the other two developed presumed parenchymal disease at 7 months, both having failed to achieve a complete response with CDE. In the two meningeal recurrences, CSF cytology cleared after continued IT methotrexate and whole-brain radiotherapy, and both achieved complete response. The other four recurrences, who did not meet CNS prophylaxis criteria, developed parenchymal brain recurrence with no evidence of meningeal disease. Of the two meningeal recurrences, one subsequently died of pneumonia at 50 months; the other was alive and disease-free at 48 months. Of the six who developed parenchymal disease, all died of systemic NHL (n = 5) or a CNS recurrence (n = 1), with a median survival of 7.5 months (range 7–21 months).

In an analysis of a prospective database, 18/176 patients with ARL had leptomeningeal involvement. In this cohort, Burkitt lymphoma histology and paraspinal or paranasal disease were associated with leptomeningeal disease, but (unlike other series) bone-marrow involvement was not. Overall survival was not significantly affected by leptomeningeal involvement at presentation. Of 21 high-risk patients given prophylactic intrathecal chemotherapy, only four (19%) developed meningeal disease. Thus the prophylactic administration of intrathecal chemotherapy to patients with risk factors but without meningeal disease at presentation prevented meningeal relapse in 81%. Given that the data was collected over a period that spans both the pre- and post-HAART era, the results could now vary in the post-HAART era. Based on the available data, it is difficult to make a direct comparison of the rate of CNS disease between pre- and post-HAART eras, but there does not appear to be any great change in the frequency or nature of the CNS disease.

**Prophylactic management of the CNS**

All the published trials involved staging lumbar puncture and some form of CNS prophylaxis, but CNS prophylaxis protocols have varied widely, both in terms of which patient groups receive prophylaxis, and in terms of the drugs used and the frequency of administration. In some trials all patients received prophylaxis, others limited prophylaxis to patients at high risk (such as those with Burkitt’s histology); and in one trial, it was limited to the last 17 patients entering the trial. In terms of drugs and frequency, this varied from 2-weekly intrathecal methotrexate to intrathecal methotrexate, cytarabine and hydrocortisone with each cycle of CHOP. In some multicentre trials, recommendations were made for CNS prophylaxis but it was ultimately left to the discretion of the local investigators (Table 3). Clinical experience has also resulted in evolution of the prophylactic regimen used, with a move away from whole-brain radiotherapy in responders, the use of cytarabine rather than methotrexate in one US centre, and the use of intrathecal liposomal cytarabine.

The wide variation in the published CNS prophylaxis protocols reflects the lack of trial data in this area of management of ARL: given the small number in the trials and the lack of head-to-head...
Table 3 Summary of CNS management and prophylactic regimens used during chemotherapy for AIDS-related non-Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Chemotherapy regimen (reference)</th>
<th>CNS management</th>
<th>Prophylactic regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose m-BACOD vs. standard dose m-BACOD</td>
<td>Prophylaxis: 50 mg IT cytarabine day 1, 8, 15, and 22 for 1st cycle 1 for all patients</td>
<td>GM-CSF 5 µg/kg/day on days 4–13 of chemotherapy; extended beyond 13 days during episodes of febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td>Treatment: WBRT 200 cGy (Total dose 2400 cGy) Cytarabine 50 mg IT three times per week until CSF cytology clear and then monthly for one year</td>
<td>Mycobacteria: isoniazid 300 mg daily, pyridoxine 10 mg daily</td>
</tr>
<tr>
<td>BEMOP-CA</td>
<td>IT methotrexate 2-weekly to patients with Burkitt’s histology, meningeal involvement or base of skull disease</td>
<td>PCP: cotrimoxazole 960 mg daily</td>
</tr>
<tr>
<td>MCHOP</td>
<td>At investigators’ discretion; however recommendation made of prophylactic 50 mg IT cytarabine weekly for first 4 weeks</td>
<td>G-CSF: neutrophils &lt;0.05 × 10^9/l</td>
</tr>
<tr>
<td>CHOP</td>
<td>All patients: 12 mg IT methotrexate, 30 mg IT cytarabine and 20 mg IT hydrocortisone during each cycle</td>
<td>nG-CSF: G-CSF 300 µg/day if &lt;70 kg or 480 µg/day if &gt;70 kg; days 4–13 for each cycle if chemotherapy delayed by 1 week or after febrile neutropenia</td>
</tr>
<tr>
<td>CHOP</td>
<td>All patients received intrathecal prophylaxis. No other details</td>
<td>CHOP: G-CSF 300 µg/day if &lt;70 kg or 480 µg/day &gt;70 kg, days 4–13 for each cycle. Both arms: allopurinol 600 mg daily 1 then 300 mg daily for first week of treatment.</td>
</tr>
<tr>
<td>m-BACOD</td>
<td>Anti-bacterial: ciprofloxacin</td>
<td>PCP: cotrimoxazole 3 x/week, or aerosolized pentamidine</td>
</tr>
<tr>
<td>MA-COP-B</td>
<td>Anti-herpetic: acyclovir</td>
<td>Toxoplasma: pirimetamine</td>
</tr>
<tr>
<td>ACVB</td>
<td>G-CSF: as primary prophylaxis during chemotherapy</td>
<td>PCP: cotrimoxazole 3 x/week or aerosolized pentamidine</td>
</tr>
<tr>
<td>CHOP</td>
<td>Prophylaxis: 12 mg IT methotrexate on day 1</td>
<td>PCP: cotrimoxazole 3 x/week or inhaled pentamidine 300 mg monthly</td>
</tr>
<tr>
<td>DA-EPOCH</td>
<td>Prophylaxis: Last 17 patients, 12 mg IT methotrexate days 1 and 5 from cycle 3–6</td>
<td>GM-CSF: Primary or secondary prophylaxis to two patients</td>
</tr>
<tr>
<td></td>
<td>Treatment: IT or intraventricular methotrexate or methotrexate/cytarabine/prednisolone twice weekly for 2 weeks beyond negative cytology, for a minimum of 4 weeks, then once weekly for 6 weeks. Patients who did not respond to MTX received cytarabine. Cranial radiotherapy used as clinically indicated in chemotherapy failure</td>
<td>G-CSF: 55 patients ‘in agreement with protocol guidelines’</td>
</tr>
<tr>
<td></td>
<td>Mycobacteria: if CD4 &lt;100/mm³</td>
<td>PCP: during treatment and post treatment until CD4 count &gt;200/mm³</td>
</tr>
<tr>
<td>CDE</td>
<td>Prophylaxis: All patients with small non-cleaved-cell lymphoma or bone marrow involvement. 50 mg IT cytarabine, day 1 and 4 of cycles 1 and 2</td>
<td>G-CSF: filgrastim 5 µg/kg/day from day 6 until neutrophil count &gt;5000 µl</td>
</tr>
<tr>
<td></td>
<td>PCP: cotrimoxazole 3 x/week</td>
<td>(continued)</td>
</tr>
</tbody>
</table>
comparisons, it is difficult to make a recommendation based on the published protocols within these trials. With regard to the treatment of CNS involvement with NHL, this again varied, but generally involved whole-brain radiotherapy and intrathecal chemotherapy, which was given for up to a year from cytological clearance, to intrathecal chemotherapy alone, with cranial irradiation reserved for when chemotherapy failed.59

Table 3

<table>
<thead>
<tr>
<th>Chemotherapy regimen (reference)</th>
<th>CNS management</th>
<th>Prophylactic regimen</th>
</tr>
</thead>
</table>
| Treatment (if CSF cytology positive): Whole-brain radiotherapy 24 Gy in 12 fractions plus 50 mg IT cytarabine alternating with methotrexate 10 mg/m² to maximum 15 mg, 3x/week until CSF cytology clear on two consecutive occasions and then twice weekly for 2 weeks, then weekly for 4 weeks, then monthly for 6 months | Fungal: fluconazole 100 mg/day<br>Optional: fifabutin if CD4 < 75 µg/ml<br>Ciprofloxacin OD from day 6 until neutrophil recovery.<br>G-CSF: filgrastim 5 µg/kg/day, no sooner than 24 h post-chemotherapy, until neutrophil count >10,000 µl. Resumed if neutrophils <1500 µg prior to next cycle. | CDE56  
Prophylaxis: four planned doses of 50 mg IT cytarabine |
| CHOP46 | Prophylaxis: 12 mg IT methotrexate day 1 of each cycle. If Burkitt’s lymphoma or bone marrow involvement: 50 mg IT cytarabine, day 1 and 4 of cycles 1 and 2 | PCP: cotrimoxazole 960 mg daily<br>Mycobacteria: azithromycin 1250 mg once a week.  
Anti-fungal: 200 mg itraconazole daily, or 50 mg fluconazole daily  
G-CSF: 300 mcg starting 24 h post chemotherapy until neutrophil count >1.5 × 10⁹/l  
G-CSF: Erythropoetin  
Anti-infectives  
PCP prophylaxis |  
| CDE+rituximab65 | Prophylaxis: At local investigators discretion. However, recommended for patients with small non-cleaved histology, bone-marrow, paranasal or testicular involvement or epidural disease. This generally involved either 4-weekly IT cytarabine or 4 IT methotrexate treatments. Treatment: IT cytarabine for those with active meningeal lymphoma and whole-brain radiotherapy recommended for those with neurological signs and symptoms | PCP: cotrimoxazole 3x/week  
Anti-fungal: fluconazole 100 mg/day  
G-CSF: filgrastim 5 µg/kg/day starting day 6 post-chemotherapy until neutrophil recovery (not defined)  
PCP: cotrimoxizole or inhaled pentamidine |  
| CHOP vs. CHOP + rituximab47 | Prophylaxis: routinely performed with IT MTX | No details |  

CSF, cerebrospinal fluid; CNS, central nervous system; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gy, Grays; IT, intrathecal; MTX, methotrexate; PCP, Pneumocystis carinii pneumonia; WRBT, whole-brain radiotherapy.

Prophylactic management of opportunistic infection and neutropenia

The administration of cytotoxic chemotherapy to both immunocompetent and immunocompromised patients results in a decline in CD4 cell counts. In light of this, prophylaxis to prevent opportunistic infections in HIV-seropositive patients is particularly
important. It is well established that prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) should commence when the CD4 cell count falls below 200/mm$^3$, and against *Mycobacterium avium* complex when it falls below 50/mm$^3$. However, many consider immediate concurrent PCP prophylaxis regardless of the CD4+ count as the standard of care for individuals commencing chemotherapy for AIDS-related lymphoma, given the potential rapid effects of chemotherapy on CD4+ lymphocyte count, and this has been the strategy adopted in many of the AIDS-related lymphoma trials.

The dramatic and prolonged T-cell depletion following the administration of the EPOCH regimen was demonstrated for patients receiving chemotherapy in the pre-HAART era. As discussed above, the concomitant use of chemotherapy and HAART ameliorates this decline in CD4 count. To prevent opportunistic infections, most of the published trials have involved prophylaxis and again this has varied widely, but has generally included PCP prophylaxis, with the inclusion of anti-mycobacterial, anti-fungal, anti-herpetic and anti-bacterial prophylaxis in some trials.

In addition to the risk of opportunistic infections, neutropenia and neutropenic sepsis can be life-threatening and are a danger with many chemotherapy regimens in the immunocompetent population. However, in those with AIDS-related NHL, in addition to the myelotoxicity of cytotoxic chemotherapy, there are a number of issues which result in a particularly poor haematological reserves. These include: (i) HIV infection, which itself is associated with tri-lineage abnormalities of haematopoiesis; (ii) increased frequency of bone marrow involvement in ARL; and (iii) the use of PI-based HAART. In light of this, granulocyte or granulocyte-macrophage colony stimulating factor (G-CSF or GM-CSF) has been incorporated into many of the chemotherapy regimes, but again the exact circumstances under which they have been used have varied from trial to trial (Table 3). G-CSF is the preferred agent, given that GM-CSF has the potential risk of enhancing HIV replication macrophages.

**Toxicity associated with chemotherapy**

In a prospective study, low CD4 count was associated with increased risk of bacterial infection in HIV-seropositive patients, and others have reported that a CD4 count of <450/mm$^3$ is an independent risk factor for febrile neutropenia and early death from infection in patients receiving chemotherapy.

The addition of rituximab to infusional CDE may increase the risk of life-threatening infections, with 14% of patients developing opportunistic infections and 8% of patients deaths attributable to treatment-related infections in a pooled analysis of three trials. Similarly, a significantly higher rate of deaths from treatment-related infections was seen when CHOP was combined with rituximab, compared to CHOP alone (14% vs. 2%; $p=0.035$). There was also a trend to more neutropenia in the R-CHOP arm ($p=0.11$). This increase in infections may be in part related to the effect of rituximab on mature B cells, which also express CD20, resulting in depletion and further immunosuppression in a group of patients already immunocompromised by HIV. This is borne out by a report of persistent panhypogammaglobulinaemia after R-CHOP treatment, with IgM, IgG and IgA levels being undetectable or below normal limits for over 3 years. Data on immunoglobulin levels from the AMC010 trial appear to support this initial observation, with severe hypogammaglobulinemia only seen in the R-CHOP group. The increased risk of death from infection with R-CHOP is probably due to a combination of impaired innate immunity, with diminished neutrophil-mediated immunity and reduced adaptive T- and B-cell function.

Data from clinical trials suggest that concurrent HAART with cytotoxic chemotherapy can have a bone-marrow-sparing effect. Concurrent treatment with the nucleoside analogue didanosine has been reported to blunt the myelosuppression of infusional-CDE chemotherapy. In the AMC005 trial of CHOP combined with HAART, 25% of patients receiving mCHOP and 13% of patients receiving CHOP developed grade 3 or higher neutropenia, and only one patient (1.6%) in the study (receiving mCHOP) developed febrile neutropenia. This degree of myelosuppression in AMC005 contrasts sharply with that reported in the pre-HAART era trial ACTG 142. In this study, 69% of patients receiving SD m-BACOD developed grade 4 neutropenia, and 8% developed febrile neutropenia. The reduced myelotoxicity reported in AMC005 suggests that the concurrent use of HAART may be important for the administration of full dosages of chemotherapy with less myelosuppression.

The improved survival since the introduction of HAART and the preservation of immune function suggests that the combination of chemotherapy with HAART is an important step forward in the management of AIDS-related lymphomas. However, there appear to be both toxicity-related and...
pharmacokinetic drawbacks to the concomitant administration of chemotherapy and HAART, although they may have a beneficial sparing effect on the bone marrow.

Outcomes in the era of HAART

Improvements in outcome have been reported for those treated in the post-HAART era. An analysis by the Eastern Cooperative Oncology Group of the outcome of patients treated with infusional-CDE chemotherapy in the pre- and post-HAART era found that the median survival (8.2 vs. 17.8 months), and the 1-year survival rate (48% vs. 55%) were superior for those treated in the post-HAART era.52 A further study showed an improvement in the survival of patients treated for HIV-related NHL treated in the post-HAART era, with an increase in median survival from 3 to 16 months.88 In addition, the complete remission rates for regimens using the combination of chemotherapy and HAART are 48–92% and the published 2-year overall survivals are 48–60%.42,45,74,89 These response rates and survival duration statistics are starting to approach those seen in the general population with advanced-stage high-grade lymphoma. Indeed, whereas the prognostic factors for survival in the pre-HAART era were predominantly immunological (prior AIDS-defining illness and CD4 cell count), in a more recent analysis, prognostic factors in AIDS-related lymphoma closely resembled those for the general population, with the international prognostic index (IPI) being an equally valuable guide in both groups.90 A recent study of prognostic factors in the post-HAART era confirms that an accurate scoring system can be based on the IPI rating and CD4 cell count alone.91 The goal of therapy is now clearly complete remission, not palliation. However, in some series there has been no change in the lymphoma response rates, and the improvements in survival duration may be related to reduced deaths from opportunistic infections amongst patients who achieve durable tumour remissions. Nonetheless, these encouraging findings have led to a more aggressive approach to the management of AIDS-associated NHL.

Search strategy

We reviewed articles published in English found using the PubMed and Medline search engines, with the search terms ‘HIV’, ‘AIDS’, ‘non-Hodgkin’s lymphoma’, ‘antiretrovirals’ and ‘highly active antiretroviral therapy’. Papers reviewed were limited to those published since the introduction of highly active antiretroviral therapy, which was taken as the mid-1990s. Citations from papers were also reviewed, and where possible primary sources have been quoted.

References


