Modern management of non-Hodgkin lymphoma in HIV-infected patients

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Summary

Patients infected with human immunodeficiency virus (HIV) are at greater risk of developing non-Hodgkin lymphoma than the general population and aggressive B-cell lymphoma has become one of the most common of the initial acquired immunodeficiency syndrome (AIDS)-defining illnesses. This review considers the prognostic factors and new approaches to the treatment of patients with AIDS-related lymphoma (ARL). As highly active antiretroviral therapy (HAART) became available, the survival of many ARL patients has become comparable to that of HIV-negative patients. This is partly due to the decrease in the incidence of opportunistic infections and improved prognosis. Both developments can also be attributed to new treatment strategies for ARL, such as the use of effective infusional regimens, Rituximab combinations and high-dose therapy with autologous stem-cell transplantation for relapsed disease. However, unresolved issues persist, such as the optimal therapy for patients with Burkitt ARL or central nervous system involvement.

Keywords: AIDS-related lymphoma, highly active antiretroviral therapy, rituximab, peripheral blood stem-cell transplantation, prognosis.

Non-Hodgkin lymphoma (NHL) has been recognised as being associated with human immunodeficiency virus (HIV) infection since the beginning of the acquired immune deficiency syndrome (AIDS) epidemic. The incidence of NHL in HIV-infected individuals is over 100 times the incidence among the general population (Goedert et al, 1998). Worldwide, NHL is the second most common HIV-associated cancer, and accounts for AIDS-defining illness in about 3% of patients in the USA, and 3-6% in Europe (Franceschi et al, 1999). Since 1996, the use of combination antiretroviral therapy, consisting of protease inhibitors and nucleoside analogues to achieve maximal viral load (VL) reduction, a treatment known as highly active antiretroviral therapy (HAART), has been followed by a substantial reduction in morbidity and mortality secondary to HIV infection. In addition, it appears that the use of HAART has reduced the incidence of AIDS-related lymphoma (ARL).

Different chemotherapy regimens have been tested in ARL patients (Gisselbrecht et al, 1993; Kaplan et al, 1997; Little et al, 2003; Costello et al, 2004; Sparano et al, 2004) but there is still disagreement regarding the optimal treatment, even in the post-HAART era. Overall improvement was observed by some investigators (Besson et al, 2001; Gerard et al, 2002) but not others (Matthews et al, 2000; Noy, 2004). The four-drug CHOP regimen (cyclophosphamide, Adriamycin, vincristine and prednisone) seems to confer some benefit with regard to the duration of remission, and to improve the results of the standard treatments for HIV-negative patients with high-grade NHL (Fisher et al, 1993). However, the aggressive presentation of ARL suggests the need for more intensive treatment regimens, which have resulted in high complete response (CR), and survival rates for patients with HIV-negative NHL (Tilly et al, 2003; Pfleudschnau et al, 2004; Reyes et al, 2005). On the contrary, the poor tolerability associated with chemotherapy has prompted investigators to test reduced-dose regimens (Tirelli et al, 1992; Kaplan et al, 1997; Mounier et al, 2006a). Recently, the impressive results of anti-CD20 monoclonal antibody therapy in HIV-negative NHL patients, and the fact that most cases of ARL are CD20-positive, prompted several teams to conduct multicentre phase 2 and phase 3 trials to evaluate the safety and efficacy of adding rituximab to the chemotherapy regimen (Spina et al, 2005a; Kaplan et al, 2005; Boue et al, 2006). The aim of the present review was to assess the results of these trials, which focused on modern treatments for ARL.

Pathology and epidemiology

AIDS-related lymphoma is generally a late event in the course of HIV infection. Risk factors for the development of NHL include a low CD4-cell count, a high HIV VL and advanced age. ARL pathogenesis and pathology have been the subjects of two recent reviews (Carbone & Gloghini, 2005; Navarro &
According to the World Health Organisation, ARL is divided into three categories: first, lymphomas also occurring in immunocompetent patients, such as Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) including centroblastic, immunoblastic and anaplastic variants; secondly, lymphomas occurring more specifically in HIV-infected patients, such as primary effusion lymphoma (PEL) and plasmablastic lymphoma; and thirdly, lymphomas also occurring in other immunodeficiency states, such as the polymorphic or post-transplant lymphoproliferative disorders associated with HIV infection, such as B-cell lymphoma (Harris et al., 1999).

AIDS-related lymphoma is more common in men than in women, which is consistent with the sex ratio for de novo lymphoma in HIV-negative patients. The usual age of ARL patients seems to vary according to a bimodal distribution. Thus, the first peak of disease appears in adolescents and young adults, and the second peak, in middle age (below 60 years). Younger patients are more likely to present with BL, and immunoblastic lymphoma has been seen in older patients.

Diffuse large B-cell lymphoma and BL are the most common forms of ARL (about 90% of cases; Besson et al., 2001; Stebbing et al., 2004a). Burkitt lymphoma exhibits the special feature of occurring at relatively higher CD4-cell counts (>0.2 × 10⁹/l) than immunoblastic lymphomas (<0.05 × 10⁹/l; Gabarre et al., 1999; Powles et al., 2000). Patients are usually diagnosed as having advanced disease, B symptoms, extranodal disease, including bone marrow involvement (Levine et al., 2000; Aboulafia et al., 2004) and leptomeningeal disease (Sparano, 2001). Unusual sites may be involved in ARL, including the lung, oral cavity, adrenal glands, kidney, gall bladder, heart, or even the earlobe. In HIV infection, primary central nervous system lymphoma (PCNSL) constitutes a distinctly extranodal presentation of DLBCL, usually of the immunoblastic type associated with severe immunosuppression (CD4-cells <0.05 × 10⁹/l), Epstein–Barr virus (EBV)-positivity and a poor prognosis. Note that imagery alone cannot distinguish between PCNSL and cerebral toxoplasmosis, which is the most common cause of focal cerebral lesions. Leptomeningeal involvement in lymphoma occurs in about 20% of patients with newly diagnosed ARL. It is associated with higher CD4-cell counts than those seen in patients with primary central nervous system (CNS) lymphoma and is confined to the craniospinal axis; there is no systemic involvement. Patients may be entirely asymptomatic as regards the CNS (Stebbing et al., 2004a). When symptoms occur, the most common include altered mental status, cranial nerve palsy and headache.

Primary effusion lymphoma accounts for <5% of ARL cases and is associated with infection by Human-Herpes virus 8 (HHV-8) and frequent co-infection by EBV. Two types of PEL have been described: classic PEL or ‘body cavity-based lymphoma,’ which exhibits a unique tropism for serous body cavities, and extracavitary or solid PEL, an extraserous lymphoma reported in HIV-positive patients, with or without associated effusions. In classic lymphomatous PEL, effusions may involve the pleural, pericardial or peritoneal body cavity. In solid PEL, the tumour primarily involves extraserous sites, such as the large bowel, skin, lung and lymph nodes. Despite the B-cell origin of lymphomas, they rarely express CD20. Prognosis is poor, as PEL occurs in advanced AIDS and seems resistant to chemotherapy (Boulanger et al., 2005). Ongoing gene expression profile analysis of PEL may help to explain its pathogenesis, and also facilitate the identification of potential therapeutic targets (Fan et al., 2005).

Plasmablastic lymphoma (PBL) is another unique large B-cell lymphoma subtype, characterised by plasmacytoid differentiation that typically involves the jaw and oral cavity of HIV-infected individuals. In this condition, the tumour is closely associated with EBV infection. Pathological findings include large plasmablasts that retain the blastoid morphology of immunoblasts but otherwise have acquired the immunophenotypic features of plasma cells. Immunophenotypically, PBL can be distinguished by the absence of CD20-cells and the presence CD138/syndecan-1, VS38c and CD79a cells (Delecluse et al., 1997). HHV-8 may play a role in HIV-associated PBL, though it is still unclear whether that role is causative or whether HHV-8 infection of PBL tumour cells is secondary (Cioc et al., 2004). PBL has been documented in sites other than the oral cavity, including the anorectum, nasal and paranasal regions, skin, testes, bones and lymph nodes (Schichman et al., 2004). Its prognosis is poor despite the use of HAART and chemotherapy.

Since 1996, the use of HAART to achieve maximal VL reduction has led to differences between the estimates of ARL epidemiology (Ho, 1995; Carpenter et al., 1997; Besson et al., 2001). The EuroSIDA cohort reported that the proportion of AIDS-defining illnesses attributed to NHL increased from 4% in 1994 to 16% in 1998 (Mocroft et al., 2000) mainly due to a decrease in Kaposi sarcoma. In contrast, a large meta-analysis of 23 cohort studies (International Collaboration on HIV and Cancer, 2000) found a decline in ARL, from 0.62% per year between 1992 and 1996, to 0.36% per year between 1997 and 1999. The decline was marked for PCNSL and immunoblastic NHL, but was not found for BL.

This variable decline in only certain NHL subsets underlines the possibility that immune function involvement in ARL is differential (Kirk et al., 2001). As the CD4-cell count is predictive of the development of ARL, immune reconstitution with HAART may lead to the decrease of the incidence of ARL (Stebbing et al., 2004b). Nevertheless, ARL remains one of the leading causes of death among HIV patients (Mocroft et al., 2000; Dore et al., 2002).

**Prognostic factors**

During the pre-HAART era, some of the features indicating a poor prognosis included lymphoma-specific factors (e.g. aggressive histology or extranodal disease) and HIV-specific factors (e.g. poor bone marrow reserve, a CD4-cell count <0.1 × 10⁹/l or opportunistic infection). Straus et al. (1998)
proposed an index that included the CD4 cell count, stage III or IV disease, age over 35 years, a history of drug injection, and elevated lactate dehydrogenase (LDH). The European groups GELA (Groupe d’Etude des Lymphomes de l’Adulte) and GICAT (Gruppo Italiano Cooperativo AIDS e Tumori) used an index comprising a combination of three independent risk factors: Eastern Cooperative Oncology Group (ECOG) performance status of 2–4, prior AIDS, and a CD4-cell count below 0.1 × 10^9/l. (Gisselbrecht et al, 1993) The pathological type of lymphoma did not influence survival, and patients with DLBCL or BL fared similarly, with median survival times of 6 months.

Today, in the post-HAART era, patients with DLBCL exhibit markedly longer median survival, from 6 months to 4 years (Lim et al, 2005a), which is similar to the survival of patients with HIV-negative aggressive lymphoma. Prognostic factors have also changed. In the post-HAART era, only lymphoma-related factors, such as the attainment of complete remission or a high International Prognostic Index (IPI) score remained independent risk factors for survival (see Table I; Lim et al, 2005b; Mounier et al, 2006a). The impact of a low CD4 cell count is still a matter for discussion (Bower et al, 2005). It may provide further independent prognostic information, in particular regarding the infectious toxicity of intensified chemotherapy. In addition, after HAART combined with standard chemotherapy, patients with AIDS-related BL still have a median survival time of only 6 months, i.e. unchanged from the pre-HAART era. Consequently, ARL treatment strategy should focus not only on the efficacy of chemotherapy but also on the interactions between optimal HAART and pre-existing risk factors.

**Low versus standard doses**

Various chemotherapy regimens have been tested (Kaplan et al, 1989; Tirelli et al, 1992; Gisselbrecht et al, 1993; Little, 1999). Table I. Prognostic factor analysis in 335 ARL patients treated by CHOP in the LNH-HIV 93 trial.

<table>
<thead>
<tr>
<th>Pathological sub-type</th>
<th>Pre-HAART (n = 199)</th>
<th>Post-HAART (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-year OS (%)</td>
<td>P-value</td>
</tr>
<tr>
<td>aa-IPI score (0–1)</td>
<td>27</td>
<td>0.0001</td>
</tr>
<tr>
<td>2–3</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>HIV score 0</td>
<td>39</td>
<td>0.0001</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>2–3</td>
<td>2</td>
<td>34</td>
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<tr>
<td>Strauss score 0–1</td>
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<td>0.0006</td>
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<tr>
<td>2</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>3–4</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Pathological sub-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>29</td>
<td>0.21</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Burkitt</td>
<td>24</td>
<td>32</td>
</tr>
</tbody>
</table>

AaIPI, age-adjusted International Prognostic Index.

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efficacy and toxicity, with more deaths due to infection among patients on full-dose CHOP than Ld-CHOP (31% vs. 18%). However, this hypothesis needs to be confirmed by competing risk analysis of the causes of death; in order to ascertain whether, among patients on CHOP, death due to infection occurred early in the trial, i.e. while subjects were on therapy and their neutrophil count was depressed. In that case, the cause of death cannot have been lymphoma. With the addition of HAART to chemotherapy, standard-dose therapy has become feasible and advantageous. Recent trials of CHOP-like regimens in ARL patients resulted in CR rates of 45–65% (Sparano, 2003; Noy, 2004). In the GELAG-GICAT randomised study referred to above, CHOP and Ld-CHOP, each combined with HAART (the latter typically consisting of stavudine, lamivudine and indinavir), were compared. We confirmed the difference of 15% in CR rates with HAART for CHOP versus Ld-CHOP but again found no increase in OS or event-free survival (EFS). The use of HAART together with dose-reduced and standard-dose CHOP was evaluated by the AIDS Malignancy Consortium (AMC) sponsored by the USA National Cancer Institutes (NCI), in a group of 65 patients with newly diagnosed ARL (Ratner et al, 2001) HAART consisted of indinavir, stavudine and lamivudine; indinavir is a protease inhibitor, and stavudine and malivudine are nucleoside reverse transcriptase inhibitors. Grade 3–4 neutropenia was more common among patients receiving full-dose CHOP (25% vs. 12%), but the numbers of patients with other forms of toxicity were similar. The doxorubicin clearance and indinavir concentration curves were also similar in the patients in this study compared to the curves for historical controls. Cyclophosphamide clearance decreased 1.5-fold in patients compared to controls, although the decrease had no apparent clinical consequences.

All these results suggest that HAART could be administered safely with concomitant low-dose or standard-dose CHOP chemotherapy. Under these conditions, the CD4 cell count declines by about 50% and then recovers within 1 month of the completion of chemotherapy, without any significant change in the VL (Powles et al, 2002). It is generally recommended that azathioprine (AZT) be avoided during chemotherapy because of its myelosuppressive effects (Gabarre et al, 1995). HAART containing protease inhibitors such as indinavir and saquinavir or the nucleoside analogue didanosine is well tolerated when administered with standard CHOP-like regimens, and their concurrent use is recommended.

**Standard versus intensified dose**

Several studies recently confirmed that HIV-negative patients with DLBCL could benefit from more intensive treatment than standard CHOP (Tilly et al, 2003; Milpied et al, 2004; Mounier et al, 2004; Pfriemuschuh et al, 2004; Reyes et al, 2005). However, dose-intensive chemotherapy for ARL remains a matter of debate.

Our first cooperative trial of the ACVBP regimen in ARL patients demonstrated that this regimen was not excessively toxic for patients with no adverse prognostic factors for HIV, which led us to evaluate these patients’ HIV scores (Gisselbrecht et al, 1993). Consequently, the NHL–HIV–93 trial was designed to evaluate different dose-intensive treatments, according to the patient’s HIV score. In low-risk patients on the ACVBP regimen (n = 109), the theoretical dose intensities of doxorubicin and cyclophosphamide were 37.5 and 600 mg/m²/week, respectively, and the median doses actually administered were 91% and 91% of the designated doses respectively. For the CHOP regimen (n = 109), the theoretical dose intensities of doxorubicin and cyclophosphamide were 17 and 250 mg/m²/week, respectively, and the median doses actually administered were 98% and 98% of the designated doses respectively. Nine of the 218 patients died during chemotherapy. Other deaths were due to lymphoma in 77 patients (67%), infection in 28 (24%) and toxicity or other factors in 11 (9%). There was no difference regarding the cause of death between the ACVBP and CHOP treatment groups. Most cases of haematological toxicity and mucositis occurred in the ACVBP treatment group. Leucopenia and thrombocytopenia were more frequent with ACVBP than CHOP (75% vs. 36% and 46% vs. 12% respectively). CR was higher for ACVBP (61% vs. 51%), but not significantly. Five-year OS was estimated at 51% for ACVBP vs. 47% for CHOP (P = 0.85). Because of our past experience of tolerance in 1993, we chose to give only 3 cycles of ACVBP (Gisselbrecht et al, 1993). However, we wondered whether the treatment outcome would have been better if chemotherapy had been prolonged (i.e. had comprised 2 additional cycles after CR).

This issue seems to have been approached differently in the pre- and post-HAART eras. In the latter, a minimum of six cycles of CHOP and up to eight seems to be the standard protocol. In our randomised LNH–HIV–93 trial of ACVBP versus CHOP, which included 86 patients during the post-HAART era, intensive ACVBP treatment was not shown to be at all beneficial for low-risk patients (3-year OS: 60% vs. 57%). The time-dependent Cox model demonstrated that the only significant factors for OS were HAART [relative risk (RR): 1.6, P = 0.0002], HIV score (RR: 1.7, P = 0.0001) and the International Prognostic Index (IPI) score (RR: 1.5, P = 0.0012), but not the intensity of the CHOP-based chemotherapy. These results for ACVBP are similar to those of Costello et al (2004), who showed that at a median follow up of 40 months, a modified high-dose CHOP regimen including high-dose cyclophosphamide (2000 mg/m²), gave OS and EFS estimates of 43% and 39% respectively. Encouraging results were reported for the EPOCH infusional regimen (etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin) in which the doses were individualised on the basis of nadir counts. CR was achieved in 74% of the patients, and at a median follow up of 53 months, the OS was 60% (Little, 2003). Note that the CR rate and OS in this study were the best reported to date. Outside the framework of a clinical
trial, infusional dose-intensified regimens (see Table II) might be a reasonable strategy for the treatment of ARL patients.

The place of HAART within the dose-intensity framework

With the availability of HAART, the administration of intensified dose chemotherapy became feasible as infectious complications were reduced. However, there is concern about potential drug interactions between chemotherapy and concurrent HAART. It should be noted that, in this connection, the use of azidothymidine with intensified chemotherapy is contraindicated, because it is associated with potential marrow failure and may worsen chemotherapy-induced haematological toxicities (Gabarre et al, 1995). Another cause for concern is the possible increase in organ toxicity due to the reduction, by protease inhibitors, of the activity of specific cytochrome P-450 enzymes, which are important for chemotherapy metabolism. This reduction leads to increased intracellular drug levels. Thus, in a case report of solid organ transplantation in a patient with HIV, the patient developed seizures, probably due to impairment of his metabolism by supratherapeutic levels of the immunosuppressive agents which were part of his HIV antiretroviral regimen (Sparano et al, 1998). The increased neurotoxicity and hepatotoxicity seen with concomitant HAART and chemotherapy may be additional causes of concern within the dose-intensity framework.

To avoid possible pharmacokinetic interactions between HAART and chemotherapy, Little et al (2003), at the NCI, investigated the feasibility of omitting HAART during the administration of intensified-dose chemotherapy. In their study, six cycles of dose-adjusted EPOCH were administered to 39 patients with newly diagnosed ARL. The dose of cyclophosphamide in cycle 1 was based on the patient’s CD4-cell count at study entry (<0·1 × 10⁹/l vs. >0·1 × 10⁹/l) and was thereafter adjusted by increments or decrements of 187 mg/m² (maximum dose, 750 mg/m²) according to the absolute neutrophil nadir. Antiretroviral agents were not used during chemotherapy but were restarted immediately after its completion. Three-quarters of the patients received all six planned chemotherapy cycles, and the administered dose intensity was 100% for doxorubicin, 99% for etoposide, 99% for vincristine and 65% for cyclophosphamide. This intensity was achieved with acceptable toxicity. The CR rate was 74%, and among patients with CD4-cell counts >0·1 × 10⁹/l, 87%. Five-year OS was 87%, but it was only 16% for patients with CD4-cell counts <0·1 × 10⁹/l. Although by the end of chemotherapy the median CD4-cell count had decreased to 0·19 × 10⁹/l and the VL had increased by 0·5–1·0 log10 copies/ml, the CD4-cell count returned to baseline 6–12 months after the resumption of HAART. No opportunistic infections occurred during chemotherapy, but three patients developed such infection during the 3 months after its completion.

This suggests that withholding HAART until the completion of chemotherapy does not result in the progression of AIDS but does allow the full delivery of chemotherapy. When considering whether HAART should be omitted during chemotherapy, the degree of immunosuppression required in the individual patient (which would in turn affect the risk of death from bacterial and opportunistic infections), and the benefit of viral suppression for survival and tumour response, should be weighed against the possible overlapping of HAART and chemotherapy toxicities. In this connection, the study by Little et al (2003) showed, in particular, that the outcome for patients with CD4-cell counts <0·1 × 10⁹/l remained unsatisfactory. In this series, it might also have been possible to avoid certain cases of opportunistic infection if HAART had not been discontinued during chemotherapy. In addition, the drug toxicities of chemotherapy with HAART were reported not to differ from those of chemotherapy alone (Levine et al, 2004).

Sparano et al, (2004) aimed to determine the effectiveness of infusional chemotherapy with CDE (cyclophosphamide, doxorubicin and etoposide) plus filgrastim before and after the administration of HAART in routine clinical practice. Ninety-eight patients were studied; and for the first 43 patients enrolled in the pre-HAART group, concurrent antiretroviral treatment consisted of the nucleoside analogue didanosine. CR occurred in 45% of the entire series and 2-year EFS and OS were 36% and 43% respectively. At the time of the analysis, 30% of the pre-HAART group were alive compared with 47% in the HAART group. After adjustment for the various of follow up times, the OS of patients in the HAART group improved more than that of pre-HAART patients (P = 0·039). HAART group patients also experienced less grade 4 non-haematological toxicity (22% vs. 42%, P = 0·04), thrombocytopenia (31% vs. 52%, P = 0·03) and less anaemia (9% vs. 27%, P = 0·02) and had fewer treatment-associated deaths (0% vs. 10%; P = 0·01).

Overall, infusional intensified chemotherapy together with HAART has proved an effective and potentially curative

**Table II.** Infusional chemotherapy regimens.

<table>
<thead>
<tr>
<th>CDE</th>
<th>Cyclophosphamide, 187·5–200 mg/m²/d for 4 d</th>
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<tbody>
<tr>
<td></td>
<td>Doxorubicin, 12·5 mg/m²/d for 4 d</td>
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<tr>
<td></td>
<td>Etoposide, 60 mg/m²/d for 4 d, continuous intravenous infusion over 96 h</td>
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<tr>
<td></td>
<td>Granulocyte colony-stimulating factor filgrastim (G-CSF), 5/kg/d, subcutaneous injection from day 6 until neutrophil recovery</td>
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<tr>
<td></td>
<td>Every 28 d, repeat for a maximum of six cycles</td>
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<table>
<thead>
<tr>
<th>EPOCH</th>
<th>Etoposide, 50 mg/m²/d for 4 d</th>
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<tbody>
<tr>
<td></td>
<td>Vincristine, 0·4 mg/m²/d for 4 d</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin, 10 mg/m²/d for 4 d</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide, 187 mg/m²² IV on day 5 when CD4-cell count &lt;0·1 × 10⁹/l</td>
</tr>
<tr>
<td></td>
<td>or 375 mg/m²² IV on day 5 when CD4-cell count &gt;0·1 × 10⁹/l</td>
</tr>
<tr>
<td></td>
<td>Prednisone, 60 mg/m²² orally, from days 1 to 5</td>
</tr>
<tr>
<td></td>
<td>Granulocyte colony-stimulating factor: start on day 6</td>
</tr>
<tr>
<td></td>
<td>Every 21 d, repeat for a maximum six cycles</td>
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</tbody>
</table>
treatment for ARL patients. However, as prevention of infection seems crucial within the dose-intensity framework; we recommend continuing Trimethoprim–Sulfamethoxazole (TMP–SMX) and oral acyclovir for zoster prophylaxis for 3 months after chemotherapy (see Table III). In addition, azithromycin could be used for *Mycobacterium avium* prophylaxis until CD4-cell counts increase.

### High-dose therapy and autologous stem-cell transplantation (ASCT)

ASCT is the treatment of choice for HIV-negative patients with relapsed aggressive NHL who still respond to salvage chemotherapy (Philip *et al.*, 1995), but whether ASCT has a role as front-line therapy is still a matter of debate. So far, several randomised phase III studies have shown controversial results. Some of the authors concerned claimed that ASCT was beneficial because it at least ensured freedom from progression in patients who achieved CR after induction (Gianni *et al.*, 1997; Santini *et al.*, 1998; Haioun *et al.*, 2000a; Milpied *et al.*, 2004; Mounier *et al.*, 2004). However, because of concern over the potential toxicities associated with ASCT, it has not been routinely proposed to patients with ARL. The literature describing the use of ASCT in ARL is limited. Most of the reports published originate from French and Italian groups and the American City of Hope Medical Center (COHMC; Gabarre *et al.*, 2000, 2004, , Krishnan *et al.*, 2001; Re *et al.*, 2003).

French investigators reported results for 14 patients with relapsed or resistant ARL (eight with NHL and six with Hodgkin disease) who were treated with ASCT while on HAART (Gabarre *et al.*, 2004). For eight of them, the conditioning regimen was radiotherapy-based, and for six, chemotherapy-based. The HIV-1 VL was quantified in 11 cases. Haematological reconstitution was good and no deaths occurred from toxicity. Despite the large number of cells containing VL re-infused with the graft (105–109), HAART controlled HIV replication and led to CD4-cell reconstitution in seven of the eight patients who were still alive six months after ASCT. Only two patients had opportunistic infections after ASCT. There were transient increases in the VL of two of the nine patients whose VL was previously undetectable. Although the difference in the VL or CD4-cell count for the 14 patients before and after ASCT was marked, it was not significant; neither were there any significant changes in the VL or CD4-cell count. One month after ASCT, 10 patients were in CR. Seven died of lymphoma between 1 and 10 months after ASCT, and another two died in CR (one of AIDS at 16 months and the other of a neoplastic tumour at 28 months). Five patients were alive: four are in CR, respectively 14, 19, 32 and 49 months after ASCT (median CD4-cell count: 0·45 × 10⁹/l; undetectable VL in three patients) and one was being treated for relapsed lymphoma 36 months after ASCT. Although Gabarre *et al.* (2004) also demonstrated that ASCT is feasible; eight of the patients in their cohort have died, mostly of relapsed lymphoma. The patients in their study had more advanced disease at the time of transplant, suggesting that ASCT should be proposed earlier in the course of poor-risk ARL.

Similarly, the Italian group reported the results of a multi-institutional programme of ASCT as salvage therapy in 16 patients with resistant or relapsed ARL after first-line chemotherapy (Re *et al.*, 2003). Effective HAART was maintained during the entire programme. Adequate collection was obtained in 80% of patients. Three patients experienced early progression. Ten (62%) received a chemotherapy-based conditioning regimen and ASCT, with prompt engraftment in all cases (neutrophil and platelet engraftment after medians of 10 and 13 d respectively). No patient died of opportunistic or other infections or treatment-related complications. Eight of the nine assessable patients achieved CR and one patient achieved PR. Two patients experienced relapse and died 10 and 14 months after treatment. Six patients are alive and disease-free at a median of 8 months after transplantation.

The COHMC studies attempted to apply the same criteria to ARL patients as those used for HIV-negative lymphoma patients evaluated for transplant (i.e. chemosensitive relapse or first remission disease with poor-risk features by IPI criteria; Krishnan *et al.*, 2001). Most of the patients concerned had relapsed chemosensitive disease, although three in first remission and two with refractory disease were also treated. Sixteen ARL patients were given a chemotherapy-based conditioning regimen and three, a radiotherapy-based regimen. All 19 patients were maintained on HAART throughout the transplant, although 10 could not tolerate it because of gastrointestinal toxicity manifested by nausea, vomiting or mucositis. Three patients developed grade 3–4 liver toxicity, which was a result of the conditioning regimen in two cases. The remaining patient developed late liver toxicity 10 months after ASCT, which was ultimately ascribed to his antiretroviral regimen. The median time to neutrophil engraftment was 11 d (range: 9–23). Three of the

Table III. Practical points.

| Diagnosis |
| Lumbar puncture with cytology |
| Bone marrow biopsy |
| Assessment of viral load |
| History of recent opportunistic infection |

| Standard Chemotherapy Treatment |
| Continue HAART but watch for drug interactions |
| Non-zidovudine HAART regimen |
| Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole |
| Herpes zoster prophylaxis (acyclovir) |
| Granulocyte colony-stimulating factor: start on day 6 |
| Antifungal prophylaxis using fluconazole |
| Monitor for hepatotoxicity |

| Intensified regimen |
| *Mycobacterium avium* infection prophylaxis (azithromycin) |
| Monitoring for CMV till day +100 |
AZITHROMYCIN IS USED FOR CONTINUED FOR ZOSTER PROPHYLAXIS FOR 1 YEAR. IN ADDITION, ASCT, TMP–SMX AND HIGH-DOSE ORAL A adjunction to the standard chemotherapy regimen.

Efficacy of rituximab adjunction to the standard chemotherapy regimen.

Spina et al (2005a) reported the pooled results of three phase II trials using rituximab plus infusional chemotherapy in patients with ARL. The trials were conducted by the Italian GICAT, the Division of Haematology at Vienna University and the Albert Einstein Cancer Center in New York. Patients were treated with intravenous R-CDE including 375 mg/m² of rituximab on day 1 of each cycle, followed by a 96-h continuous daily intravenous infusion consisting of cyclophosphamide, doxorubicin and etoposide every 4 weeks, for up to six cycles. Patients were also given preventive filgrastim and HAART was recommended in all cases, thus avoiding zidovudine and ritonavir. Seventy-four patients were treated. Their median CD4-cell count was 0.16 × 10⁹/l; 72% had DLBCL and 70%, stage III-IV disease. Grade 3–4 toxicity included neutropenia in 78%, anaemia in 32% and thrombocytopenia in 24% of patients; in addition, 31% developed an infection during the treatment or within 3 months of the end of chemotherapy. Ten patients (14%) developed opportunistic infections, including CMV retinitis (n = 3), cryptosporidiosis (n = 3), pulmonary tuberculosis (n = 2), Pneumocystis carinii pneumonia (n = 1) and salmonellosis (n = 1). Overall, there were six deaths due to infection, including bacterial sepsis attributed to R-CDE (n = 2) and four cases of opportunistic infection that occurred after the completion of the treatment. The opportunistic infections included cryptosporidiosis (n = 2), pulmonary tuberculosis and pulmonary aspergillosis and they developed 5, 8, 2 and 8 months, respectively, after completion of R-CDE. Fifty-two patients (70%) achieved CR and 4 (5%), PR, so that the overall response rate was 75%. Twenty-seven patients (36%) have since had progressive or relapsed disease, including seven of the 52 who achieved complete remission (14%). Two-year OS and EFS were 64% and 52% respectively.

Recently, Boue et al (2006) reported a phase 2 trial involving 61 patients with CD20-positive ARL. They were given rituximab at the standard dose of 375 mg/m² on day 1 of each cycle, plus CHOP. This combination was repeated every 3 weeks for up to six cycles. All patients received preventive filgrastim and HAART was recommended in all cases, again thus avoiding the need for zidovudine and ritonavir. The median baseline CD4-cell count was 0.17 × 10⁹/l; 69% of the patients had DLBCL and 70% had stage III or IV ARL. Half the patients had an age-adjusted IPI of 0 or 1. The most common forms of toxicity in stages III and IV included anaemia (32%) and febrile neutropenia (25%). Only two patients (4%) experienced an AIDS-defining event (one developed CMV disease and the other, HIV encephalitis). Of the 18 patients who died (35%), the cause of death was lymphoma in 14, infection in one and heart failure in one. Forty patients (67%) achieved CR and 10% obtained a PR. Estimated 2-year OS and 2-year EFS were 75% and 65% respectively. When this trial was designed in 1998, the safety of R-CHOP was uncertain in patients with very advanced HIV disease and the investigators therefore decided

Chemo therapy combined with rituximab

Recent studies indicate that the prognosis of ARL has improved in the HAART era, possibly owing to higher CD4-cell counts at lymphoma onset, effective antiretroviral therapy and certain features of the lymphomas. On the basis of the impressive results of anti-CD20 monoclonal antibody therapy in HIV-negative patients (Coiffier et al, 2002) and the fact that most cases of ARL are CD20-positive, multicentre phase 2 and phase 3 trials have been conducted to evaluate the safety and

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to enrol only patients with no more than one of the following adverse prognostic factors: CD4-cell count \(<0.1\times10^9/l\), prior opportunistic infections and poor general status. Nevertheless, the baseline characteristics of the patients are similar to those of patients enrolled in other trials and observational studies. Thus, patients with an IPI score of 0 or 1 and a CD4-cell count above \(0.1\times10^9/l\) appear to form a subgroup for which the results of R-CHOP are very satisfactory.

Taken together, these two trials showed that R-CHOP and R-CDE were feasible and highly effective for ARL and that these treatments exhibited an acceptable toxicity level which was comparable to that observed in a HIV-negative population (Coiffier et al., 2002).

The only randomised (2:1) phase 3 trial held to date was conducted by the AMC. In this trial, the results of the standard CHOP regimen were compared with those of R-CHOP in 150 patients with newly diagnosed ARL (Kaplan et al., 2005). Patients were randomly assigned to receive a minimum of six cycles of either standard CHOP \((n = 50)\) or R-CHOP \((n = 99)\). After the achievement of CR, the R-CHOP patients also received maintenance rituximab. All patients received HAART and filgrastim. Their median baseline CD4-cell count was \(0.13\times10^9/l\), 69% had DLBCL and 79%, stages III–IV disease. The incidence of febrile neutropenia was similar in the two groups (30% for R-CHOP vs. 21% for CHOP, \(P = 0.86\)). Treatment-related infectious deaths occurred in 15 of the patients receiving R-CHOP, i.e.14%, compared with 2% in the CHOP group \((P = 0.035)\). Nine of these 15 deaths occurred in patients who had a baseline CD4-cell count of \(<0.05\times10^9/l\) and six occurred during the maintenance phase of rituximab treatment \((n = 35)\), a strategy not routinely used in aggressive NHL. The CR rate was 57% for R-CHOP to 47% for CHOP \((P = 0.147)\). With a median follow-up of 137 weeks, the median times to progression, EFS and OS were 125, 45 and 139 weeks, respectively, for R-CHOP and 85, 38 and 110 weeks, respectively, for CHOP \(P\) not significant for any comparisons; 2-year OS = 55%). EFS was significantly affected by the CD4-cell count and IPI score.

This randomised phase III trial raised several issues. Although the authors noted that most treatment-related deaths from infection occurred in patients with CD4-cell counts below \(0.05\times10^9/l\), survival curves were only shown for counts below, equal to and \(>0.1\times10^9/l\), which did not enable the effects of rituximab to be estimated in patients at the lowest risk of death from infection. The time course of disease in the patients whose death was jointly attributed to R-CHOP and infection varied, suggesting different causes of death. Sixty-two per cent of the deaths occurred during cycle 1 or 2 and were attributed to chemotherapy-related neutropenia, whereas 38% occurred during or within 6 months of maintenance rituximab. The combination of rituximab with chemotherapy is known to increase the risk of grade 4 neutropenia and of infection during treatment and the risk of late-onset neutropenia after treatment (Dunleavy et al., 2005). Nevertheless, the benefit of rituximab for tumour control should not be underestimated. It is well established that rituximab is an important treatment adjunct in HIV-negative DLBCL, especially for bcl-2 positive tumours (Mounier et al., 2003, 2006b; Bonavida & Vega, 2005). In the study by Kaplan et al. (2005), both the progression of disease and the number of deaths due to lymphoma diminished significantly in patients treated with R-CHOP.

The USA NCI lymphoma group, headed by W. Wilson, is at present investigating EPOCH treatment with high-dose rituximab (375 mg/m² on days 1 and 5) in untreated ARL patients. The results for 21 patients suggest that rituximab is beneficial for patients with CD4-cell counts below \(0.1\times10^9/l\), because OS in this group was 57% compared with only 16% for treatment with EPOCH alone, whereas among patients with CD4-cell counts above \(0.1\times10^9/l\), the proportions of survivors in each treatment group (90% and 87%) were similar (Dunleavy et al., 2004). In particular, it is noteworthy that the results for R-EPOCH were achieved with half the number of cycles used for treatment with EPOCH alone. More cases of neutropenia were observed with R-EPOCH, but these were managed without the occurrence of any deaths.

Hence, routinely increased medical surveillance during rituximab-based chemotherapy seems necessary for patients with low CD4-cell counts and all patients should be informed of the risk of neutropenia and fever after this treatment. Nevertheless, we believe it is unwise to omit rituximab from the treatment of ARL and we hasten to add that treatment-related deaths from infection can be reduced by careful medical attention. The AMC is committed to exploiting the beneficial effects of rituximab while minimising its potential risks in this patient population. One way to accomplish this is through the use of antibiotic prophylaxis for enteric organisms. Recently published data suggest that this approach is beneficial for non-immunocompromised patients with solid tumours and lymphomas (Bucaneve et al., 2005; Cullen et al., 2005). The current AMC trial is evaluating the use of sequential versus concurrent rituximab with the same dose-escalated EPOCH regimen as that used by the USA NCI. Unlike the previous AMC trial, the patients in the current study are being given enteric prophylaxis.

We look forward to the final results of both the AMC and NCI EPOCH-rituximab trials, in the hope that these will better define the most beneficial use of rituximab (see Table IV). In

<table>
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<th>Table IV. Research agenda with Rituximab combinations.</th>
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<tr>
<td>ARL therapy with Rituximab is recent and many aspects of this treatment remain to be explored.</td>
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<tr>
<td>What is the best timing for HAART (during or after chemotherapy) to prolong the remission of lymphoma?</td>
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<td>Should patients with relapsed/refractory ARL be offered transplantation as second-line therapy?</td>
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<td>Should PET assessment after induction chemotherapy help to select patients for a more intensive approach, such as transplantation or radio immunotherapy?</td>
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the meantime, patients with an IPI score of 0 or 1 and a CD4-cell count above $0.1 \times 10^9/l$ appear to form a subgroup in which the results for R-CHOP are very satisfactory.

**Special considerations**

**Burkitt lymphoma (BL)**

Before the availability of HAART, the pathological type of lymphoma did not affect survival and patients with BL or DLBCL fared similarly, with median survival times in the range of 6 months. However, in the post-HAART era, these prognostic factors have changed and the pathological type of lymphoma seems to affect the results of treatment. Thus, many authors reported that with CHOP-like regimens, patients with AIDS-related BL lymphoma were shown to have median survival times of only 6 months, unlike those with DLBCL, whose median survival progressed markedly, to about the same extent as that of patients with HIV-negative NHL.

Lim *et al.* (2005a) compared the outcomes of HIV patients with BL and DLBCL after treatment with CHOP or M-BACOD in the pre-HAART versus the post-HAART era, and retrospectively reviewed 363 patients diagnosed between 1982 and 2003, 262 of them in the pre-HAART era (BL, 117; DLBCL, 145) and 101 in the post-HAART era (BL, 18; DLBCL, 83). Compared with BL, DLBCL was associated with significantly lower CD4-cell counts before the introduction of HAART but not afterwards. Although overall median survival was similar for both groups without HAART (BL, 6.4 months vs. DLBCL, 8.3 months; $P = 0.43$), survival with HAART was significantly worse for patients with BL (BL, 5-7 months vs. DLBCL, 43-2 months; $P = 0.0003$). Failure to attain CR and a CD4-cell count below $0.1 \times 10^9/l$ were independent predictors of poor survival in the pre-HAART era, and the histology of BL and failure to attain complete remission, in the HAART era.

In their report of a phase II prospective study using R-CDE, i.e., rituximab plus infusional cyclophosphamide, doxorubicin and etoposide for 74 patients with ARL, Spina *et al.* (2005a) included both DLBCL and BL. In their multivariate analysis, a diagnosis of BL was significantly associated with a worse outcome than that of patients with a diagnosis of DLBCL. Patients with BL had a significantly lower CR rate than patients with DLBCL (52% vs. 77%; $P = 0.05$) and their median OS was significantly worse (14 months versus not reached; $P = 0.01$). The same authors also retrospectively reviewed 253 ARL patients diagnosed and treated at the Italian NCI from 1984 to 2003, including 125 cases during the pre-HAART era (77 of DLBCL and 48 of BL) and 128 during the post-HAART era (93 of HIV-DLBCL and 35 of BL; Spina *et al.*, 2005b). All the patients with DLBCL and BL were treated with the same chemotherapy regimens. In the pre-HAART era, median OS was similar in patients with BL and those with DLBCL (7 vs. 10 months) whereas in the post-HAART era, the median OS of BL patients was significantly shorter than that of DLBCL patients (8 months vs. 22).

Consequently, the data reported by both Spina *et al.* (2005a,b and Lim *et al.* (2005a)) suggest that as HAART is now available, BL and DLBCL should not be treated using the same approach. In addition, despite impressive results and the use of HAART, the outcomes of patients with BL treated with infusional R-CDE were significantly worse than those of similarly treated patients with DLBCL, suggesting that BL is indeed a more aggressive histological entity. Taking into consideration the possibility that in the HAART era, ARL patients are likely to tolerate intensive chemotherapy regimens, a more intensive approach, similar to that used for HIV-negative patients, should be prospectively investigated in HIV-positive BL patients.

To evaluate the feasibility of intensive chemotherapy in BL, Wang *et al.* (2003) studied 14 HIV-positive adults treated between 1988 and 2000 (Wang *et al.*, 2003). Eight patients were treated between 1996 and 2000 with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide and high-dose cytarabine (CODOX-M/IVAC), one of the currently preferred intensive-dose chemotherapy regimens for BL. The other six received other chemotherapy regimens. Outcomes were compared with those of 24 HIV-negative BL patients with similar characteristics who were treated concomitantly (13 with CODOX-M/IVAC and 11 with other regimens). Of the 14 HIV-positive patients, 63% achieved CR in response to CODOX-M/IVAC treatment, compared with 67% of patients receiving other chemotherapy combinations. Two-year EFS was 60% after both CODOX-M/IVAC and other regimens. Outcomes were similar, despite the fact that 88% of the CODOX-M/IVAC-treated HIV-positive patients had Stage IV disease, compared with 33% of HIV-positive patients treated with other chemotherapy regimens. HIV status did not adversely affect long-term EFS. HIV-positive patients treated with CODOX-M/IVAC tolerated chemotherapy well, but their rates of myelosuppression and infectious complications were close to those for HIV-negative patients. Similarly, in the Programa para el Estudio de la Terapéutica en Hemopatı́a Maligna acute lymphoblastic leukaemia trial (PETHEMA-LAL3/97), in which patients with BL were treated with an intensive regimen regardless of their HIV status, Oriol *et al.* (2005) failed to find differences between HIV-positive and HIV-negative individuals (2-year OS: 51%). These two groups of patients achieved CR in 71% and 77% of cases respectively. HIV patients who received HAART seemed to have slightly better disease-free survival. The only adverse prognostic factor was age above 60 years.

As intensive chemotherapy regimens used for BL outside an HIV setting seem to meet with similar success within such a setting, probably due to tolerance of treatment thanks to the relatively well-preserved immune function seen in ARL BL patients, intensive chemotherapy may, in the post-HAART era, prove to be appropriate for all adult patients with BL.
Central nervous system involvement

Meningeal involvement is common in ARL patients and indicates a poor prognosis. Thus, despite the use of intrathecal methotrexate treatment, CNS involvement remained a poor prognostic factor in the GELA-GICAT trial (5-year OS: 19% vs. 30% without, \( P = 0.07 \)).

In addition to systemic chemotherapy, patients received methotrexate, administered intrathecally to avoid the pharmacological sanctuary resulting from the breakdown of the blood-brain barrier. In the absence of cerebrospinal fluid (CSF) involvement, CNS prophylaxis consisted of intrathecal injection of 12 mg methotrexate before each chemotherapy course (maximum: four injections). In the presence of CSF involvement, intrathecal chemotherapy was administered at least twice weekly until the disappearance of NHL cells (maximum: nine injections). Similarly, for patients with leptomeningeal disease, chemotherapy maintenance should be considered after 9–12 intrathecal methotrexate injections, to reduce the risk of relapse.

The risk of meningeal relapse has been investigated in HIV-negative lymphoma patients in many studies. In a cohort of DLBCL patients, its incidence was 5% in the absence of prophylaxis, and rose to 20% in the presence of certain adverse prognostic factors, including increased LDH, disseminated stage and bone marrow involvement (Haïoun et al, 2000b). The improvement of lymphoma cell detection by immunophenotyping is under study (Schinistine et al, 2006). CNS prophylaxis is warranted in patients with adverse prognostic factors. However, despite the use of intrathecal methotrexate prophylaxis, 33 of the 485 patients in the GELA-GICAT trial experienced CNS relapses.

Treatment of meningeal involvement at presentation was reported by Mazhar et al (2006) in 22 ARL patients during the post-HAART era. They compared the results of a standard treatment comprising the alternative use of intrathecal methotrexate and cytarabine with those of a sustained-release formulation of intrathecal cytarabine (DepoCyt). This formulation maintains drug concentrations in the CSF by means of intraventricular diffusion, thus avoiding the use of an Ommaya reservoir in many cases. Compared to conventional intrathecal chemotherapy, the DepoCyt regimen also resulted in a higher rate of tumour clearance from the CSF and prolonged the time to neurological progression (Cole et al, 2003). Ten of the 22 ARL patients (45%) achieved a remission of CSF involvement: they comprised seven of the 17 patients on intrathecal methotrexate and cytarabine (41%) and three of the five on fivfDepoCyt (60%). However, six of these 10 patients in remission relapsed and again developed CSF disease, and all six died (2-year OS: 34%). Nevertheless, these results show that for compliant patients with well-documented outcomes, DepoCyt offers an effective alternative to the limited number of intrathecal agents.

Primary CNS ARL (PCNSL) has a very poor prognosis, with a median OS of about 3 months when treated with radiotherapy (RT) and chemotherapy. Improved survival with HIV-PCNSL has been associated with the use of HAART after diagnosis. Recently, Newell et al (2004) evaluated factors influencing survival in 111 patients treated between 1987 and 1998. The median survival period was 50 d, with improved survival for patients diagnosed after 1993. Patients treated with two or more antiretroviral agents had improved survival (\( P = 0.01 \)), as did patients treated by RT (\( P < 0.0001 \)). For the latter, completion of the prescribed course of at least 30 Gy was an independent predictor of a more favorable outcome. The combined use of RT and HAART had a cumulative positive effect on survival. These results suggest that RT+ chemotherapy indeed improve survival for PCNSL patients.

However, late complications of RT, such as leukencephalopathy and radiation necrosis are an emerging concern. To limit RT in front line patients, one possible alternative is to use high-dose methotrexate (3 mg/m² every 14 d) as this was shown to induce CR in seven out of 15 patients, whose median OS was 290 d (Skiest & Crosby, 2003). In HIV-negative PCNSL patients, an induction regimen based on high-dose methotrexate was successfully followed by consolidation RT. This combination of therapies may provide the basis for further trials combining functional and quality-of-life assessment in HIV-positive patients.

Future prospects

The poor prognosis of ARL and the palliative approach to treatment are no longer the rule since the introduction of HAART. Most ARL patients can now, like HIV-negative lymphoma patients, be treated with intensive-dose chemotherapy combined with HAART. Long-term CR can be observed with a possible cure of lymphoma. Obviously, ARL remains a serious disease and, despite HAART, the presence of a severe immunodeficiency syndrome may prevent the use of adequate chemotherapy. The different prognostic factors should be carefully evaluated, using a multidisciplinary approach, by the departments of haematology and infectious diseases. Prophylaxis of infection is mandatory during treatment. Patients will benefit from the introduction of rituximab combined with chemotherapy and eventually from the development of new agents directed against lymphoma. Within this framework, special attention should be paid to the question of whether a classification of responses based on the addition of fluorine-18-fluorodeoxyglucose positron emission tomography to the International Workshop Criteria would allow more accurate assessment of ARL patient responses than the present criteria alone, as already shown for HIV-negative patients (Cheson et al, 1999; Juweid et al, 2005).

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