PERGAMON

European Journal of Cancer 37 (2001) 1296–1305

European Journal of Cancer

www.ejconline.com

Clinical aspects and management of AIDS-related lymphoma

J.A. Sparano *

Albert Einstein Comprehensive Cancer Center, Montefiore Medical Center—Weiler Division, Department of Oncology, 2 South, Room 47–48, 1825 Eastchester Road, Bronx, NY, 10461 USA

Received 26 February 2001; accepted 13 March 2001

Abstract

The incidence of non-Hodgkin's lymphoma (NHL) is increased by approximately 100-fold in patients with advanced HIV infection. Clinical presentations may include systemic lymphoma, primary central nervous system (CNS) lymphoma, and primary effusion lymphoma. Systemic lymphoma is the most common presentation, is almost always of intermediate or high-grade histology and B-cell phenotype, and usually involves extranodal sites. The disease is potentially curable with combination chemotherapy used for immunocompetent patients with lymphoma, although cure is achieved in only approximately 10–35% of patients. Primary CNS lymphoma may be difficult to distinguish from cerebral infection. The prognosis is very poor, although approximately 10% of patients selected for therapy may survive beyond 1 year with brain irradiation. Attention to infection prophylaxis and antiretroviral therapy is important. Evidence suggests that highly active antiretroviral therapy (HAART) has resulted in a decreased incidence of lymphoma, and that patients with systemic lymphoma treated in the post-HAART era have a better prognosis.

Keywords: AIDS; HIV-associated lymphoma; Non-Hodgkin's lymphoma; Primary CNS lymphoma

1. Introduction

A relationship between congenital or acquired immune deficiency (AIDS) and lymphoma was first recognised more than 30 years ago [1–3]. An association between non-Hodgkin's lymphoma (NHL) and the acquired immune deficiency syndrome became evident in the early 1980s, first on the basis of several case reports [4,5], then several large series reported from urban areas where infection with the human immunodeficiency virus (HIV) was prevalent [6,7]. This led to the Centers for Disease Control (CDC) to expand its criteria for the diagnosis of AIDS in 1987 to include all HIV-seropositive persons with intermediate or high-grade lymphomas of B cell or indeterminate phenotype [8]. The incidence of NHL is increased by nearly 100-fold in HIV-infected individuals, and may be systemic or primarily involve the central nervous system [9]. It is the second most common neoplasm occurring among HIV-infected individuals. Estimates from the early 1990s indicated that as many as one in 9 patients with lymphoma diagnosed in the United States were HIV-infected [10]. Furthermore, the actuarial risk of lymphoma at 3 years was estimated to be a high as 30–40% [11]. Early evidence suggesting that antiretroviral agents were associated with an increased risk of lymphoma were not confirmed [12]. Since the introduction of highly active antiretroviral therapy (HAART), several reports have suggested a lower incidence of systemic and primary central nervous system lymphoma [13–17]. A recent report from an international collaborative group that included data regarding approximately 48,000 HIV-seropositive individuals from the United States, Europe, and Australia found a 42% decline in the incidence of non-Hodgkin's lymphoma in 1997–1999 compared with 1992–1996, including a 58% decline for cerebral lymphoma and a 43% decrease for systemic immunoblastic lymphoma [18].

2. Clinical presentation

Lymphoma occurring in the HIV-infected individual may be systemic, may primarily involve the central nervous system, or may be localised in the body cavities. Systemic lymphoma is the most common presentation, accounting for approximately 80% of all cases. The histology usually is diffuse large cell, immunoblastic, or small non-cleaved cell lymphoma, and is usually of

* Tel.: +1-718-904-2555; fax: +1-718-904-2892.
E-mail address: sparano@jimmy.harvard.edu (J.A. Sparano).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00111-3

B-cell phenotype; low-grade histology is rare. Small non-cleaved lymphoma tends to occur in patients with a relatively high CD4 cell count (median 150/ul) compared with diffuse large cell or immunoblastic types (median 50/ul). Extranodal involvement occurs in approximately 80% of patients, with the most commonly involved sites including the bone marrow, gastrointestinal tract, meninges and liver. Other very unusual sites have also been reported such as anorectum, gingiva, heart, common bile duct, muscles and the placenta and products of conception. In many instances, involvement of these extranodal sites is the result of extensive, widely disseminated disease. In other cases, however, the lymphoma may arise in the extranodal site due to site-specific chronic antigenic stimulation and trauma.

Primary CNS lymphoma accounts for approximately 20% of all cases. Most patients are profoundly immunosuppressed and typically have a CD4 lymphocyte count below 50/μl. Approximately two-thirds or more of them have AIDS-defining conditions prior to the development of primary CNS lymphoma [19,20]. The lesions are typically few in number (1–3), large (2–4 cm), and contrast enhance approximately 50% of the time [21]. Lesions are most common in the cerebrum, but also occur frequently in the cerebellum, basal ganglia and brain stem, and are nearly always found to be multifocal at autopsy [22,23]. The lymphoma cells tend to be distributed along vascular channels as perivascular cuffs, are of B cell origin, display large cell and immunoblastic histologies, and uniformly exhibit Epstein–Barr virus-associated DNA.

Body cavity-based lymphomas are uncommon, accounting for approximately 3% or less of HIV-associated lymphomas [24]. They exhibit a unique constellation of clinical, morphological, immunophenotypic and molecular characteristics, and thus represent a distinct clinicopathological entity [25,26]. They present in the pleural, pericardial or peritoneal cavities as lymphomatous effusions, usually in the absence of a tumour mass. Typical features include immunoblastic cytomorphology, indeterminate immunophenotype, B cell genotype, clonal EBV genome, and absence of *C-MYC* gene rearrangements; Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8 (KSHV/HHV-8) sequences are a consistent finding [27]. This has only been rarely described in the general population unassociated with HIV infection, although KSHV DNA sequences are also found in this setting [28,29]. The response to therapy has generally been poor.

3. Treatment of systemic lymphoma

Combination chemotherapy regimens that are commonly used for the treatment of intermediate or high-grade lymphoma have generally resulted in a poor outcome in patients with HIV-associated lymphoma. This has been attributed to a disease that is more refractory to therapy, diminished bone marrow reserve, treatment-associated toxicities, and opportunistic infection and other complications associated with advanced HIV infection. In one comprehensive review of nine reports published prior to 1992 that included 11 different chemotherapy regimens, the complete response (CR) rate ranged from 8 to 72% (median of 33%), median survival ranged from 2.6 months to 15 months (median of 6 months), and opportunistic infection (OI) occurred in 20–78% (median of 28%) [30]. In patients with intermediate-grade NHL not associated with HIV infection, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was equally effective and less toxic than other multidrug regimens (methotrexate, bleomycin, cyclophosphamide and etoposide (m-BACOD), MACOP-B, ProMACE-CytoBAM) [31]. It stands to reason, therefore, that the same principle should hold true in patients with HIV-associated lymphoma. Some experts have advocated that all patients receive prophylactic intrathecal chemotherapy to prevent meningeal relapse, although others have advocated prophylaxis only for those with bone marrow involvement or diffuse small non-cleaved cell histology, features known to be associated with a high risk of relapse in immunocompetent individuals [52].

3.1. Prognostic factors

Features that contribute to the poor prognosis include lymphoma-specific factors (i.e. aggressive histology, extranodal disease) and HIV-specific factors (i.e. poor bone marrow reserve, CD4 lymphopenia, opportunistic infection). Features that have been consistently associated with a poor outcome include low CD4 lymphocyte count, prior opportunistic infection, and poor performance status [32,33]. The AIDS Clinical Trials Group developed a prognostic model based upon four variables that were associated with a significantly worse survival in a multivariate analysis, including CD4 count <100/μl, age more than 35 years, intravenous (i.v.) drug use, and stage III/IV disease [34]. In their prognostic model, median survival was 46 weeks for patients with 0 or 1 adverse factors compared with 18 weeks for those with 3 or 4 factors. Several groups have reported that the International Prognostic Index (IPI) also is predictive for survival in patients with lymphoma and HIV infection [35,36]. Others have reported certain molecular characteristics to be predictive for poor survival, such as tumour-associated EBV DNA [37].

3.2. Reduced-intensity treatment approaches

In order to minimise treatment-associated toxicity, several groups have evaluated less intensive treatment

approaches. For example, the AIDS Clinical Trials Group (ACTG) evaluated a reduced-dose m-BACOD regimen in which the dose of cyclophosphamide and doxorubicin were reduced by approximately 50% of the standard dose [38]. In 42 patients with a median CD4 count of 150/μl, the complete response rate was 46%, but the median survival was only 5.6 months and opportunistic infection occurred in 21%. Remick and colleagues evaluated an oral regimen consisting of lomustine, etoposide, cyclophosphamide and procarbazine. In 18 patients who had a median CD4 count of 73/ul, complete response occurred in 39% and median survival was 7 months [39]. Tosi and colleagues evaluated oral zidovudine (2, 4, and 6 gm/m^2) and moderate-dose i.v. methotrexate (1 gm/m^2) plus leucovorin rescue weekly for three to six cycles in 29 patients who had a median CD4 count of 133/μl; 46% had a complete response; the median survival was 12 months [40].

3.3. Infusional therapy

Some preclinical [41] and clinical [42] evidence suggests a therapeutic advantage for administering cytotoxic therapy via a protracted infusion rather than a bolus schedule, which has prompted several groups to evaluate infusional therapy (Table 1). A series of studies that evaluated cyclophosphamide, doxorubicin and etoposide given as a 96-h continuous i.v. infusion (CDE) included a total of 62 patients treated with infusional CDE ($n=25$) [43,44], CDE plus didanosine ($n=25$) [45], or CDE plus saquinavir and stavudine ($n=12$) [46]. The CR rate was 53% and median survival was 18 months for the entire study population. The median CD4 count was 70/μl, 20 (32%) had a prior opportunistic infection, and 58% were considered high-intermediate or high risk by the age-adjusted IPI. In multivariate analysis, low CD4 count was associated with a significantly lower CR rate (odds ratio (OR) 0.16; $P=0.01$) and survival (hazard rate for death 2.38; $P=0.01$) [47]. These studies were performed prior to the introduction of HAART, and the CD4 count of the study population was relatively low. A multi-institutional trial using an identical regimen was subsequently performed in 48 patients with HIV-associated lymphoma who had a median CD4 count of 78/μl [48]. Complete response occurred in 46% and the median survival was only 8.2 months. However, findings suggestive that infusional therapy may be more effective included an improved median time to disease progression (17.4 versus 8.0 months) and survival at 1 year (48% versus 25%) and 2 years (31% versus 10%) compared with historical data from a multi-institutional trial (m-BACOD) [49]. Likewise, Little and colleagues evaluated a 96 h infusion of doxorubicin (10 mg/m^2/day), etoposide (50 mg/m^2/day), and vincristine (0.4 mg/day) plus i.v. bolus cyclophosphamide (187 or 375 mg/m^2), oral prednisone (60 mg/m^2 for 5 days) and granulocyte-colony stimulating factor (G-CSF) in 24 patients with HIV-associated lymphoma who had a median CD4 count of 255/μl. [50]. The complete response rate was 79%, and median survival had not been reached after two years. A unique feature of this trial was the deliberate discontinuation of all antiretroviral therapy, even in patients who had undetectable viral load and good immunological function, without any apparent untoward consequences. Randomised trials will be necessary in order to test whether this novel drug administration schedule results in a truly better outcome compared with CHOP.

Table 1
Infusional therapy for HIV-associated lymphoma

Author [Ref.]	Median CD4	Regimen	*n*	CR rate (%)	Median survival (months)
Sparano [43–46]	70/μl	CDE	62	53	18
Sparano [48]	78/μl	CDE	48	46	8.2
Little [50]	255/μl	EPOCH	24	79	24+

CDE, cyclophosphamide, doxorubicin, etoposide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; CR, complete response.

3.4. Phase III trials

Several phase III trials have been reported in HIV-associated lymphoma or are in progress (Table 2). It is noteworthy that the reported studies were performed before the widespread availability of HAART. These trials in general tested the importance

Table 2
Phase III trials of chemotherapy in HIV-associated lymphoma

Author [Ref.]	Median CD4	Comparison	*n*	CR rate (%)	Survival
Kaplan [49]	100/μl	Full-dose m-BACOD	94	45	Median 7.2 months
		Reduced-dose m-BACOD	98	40	Median 8.2 months
Tirelli [51]	200/μl	Intensive ACVB	80	65	51% at 2 years
		Standard-dose CHOP	79	56	43% at 2 years
Tirelli [51]	60/μl	Full-dose CHOP	50	63[a]	35% at 2 years
		Reduced-dose CHOP	51	39	28% at 2 years

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; ACVB, doxorubicin, cyclophosphamide, vindesine and bleomycin; m-BACOD, methotrexate, bleomycin, cyclophosphamide and etoposide; CR, complete response.

[a] Statistically significant difference.

of cytotoxic dose intensity by comparing standard dose therapy with either more intensive or less intensive regimens.

The AIDS Clinical Trials Group compared a reduced-dose m-BACOD versus standard m-BACOD plus granulocyte macrophage colony stimulating factor (GM-CSF) in 198 patients with systemic HIV-associated NHL [49]. They reported no significant difference in the complete remission rate (50% versus 46%), relapse after complete remission (19% versus 23%), median time to progression (22 versus 28 weeks), median survival (31 versus 34 weeks), death from AIDS (20 vs. 12 patients), and death from lymphoma (23 vs. 36 patients). Severe and life-threatening toxicity occurred more often in the standard dose arm.

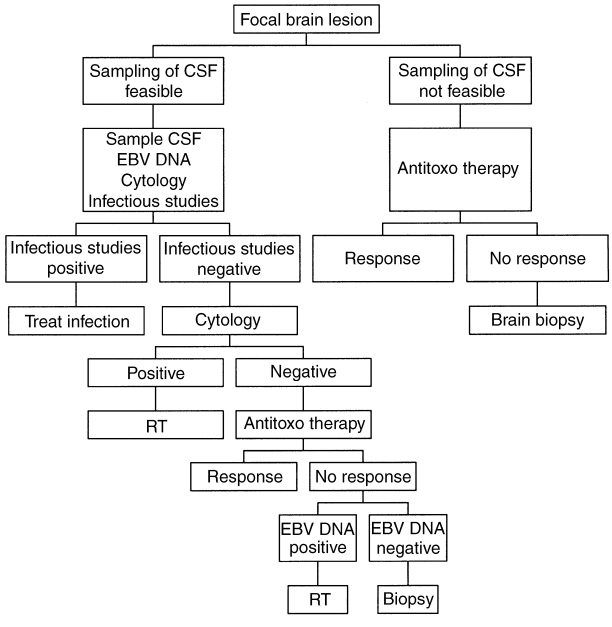
The French–Italian Cooperative Group compared two different treatment strategies in patients who had low risk and intermediate-high risk features [51]. High-risk features were defined as a prior history of AIDS, CD4 count $<100/\mu l$, or an Eastern Cooperative Oncology Group (ECOG) performance status of 2, 3 or 4. In 159 patients with no poor prognostic factors (median CD4 count 200/μl), an intensive ACVB regimen was compared with CHOP, and G-CSF was used in both arms. Compared with CHOP, the ACVB regimen consisted of a higher dose of doxorubicin (75 versus 50 mg/m^2) and cyclophosphamide (1200 versus 750 mg gm/m^2), was given every 2 weeks (rather than every 3 weeks), and included vindesine 2 mg/m^2 days 1 and 5 (instead of vincristine on day 1), bleomycin (10 mg days 1 and 5), and prednislone (60 mg days 1–5). There was no significant difference in the complete response rate, event-free survival (EFS), or survival. Similar to this group's previous experience, approximately 25% of patients in complete remission died of AIDS-related complications. In patients in the intermediate risk group (one adverse prognostic factor), standard dose CHOP was compared with reduced-dose CHOP (50% reduction in cyclophosphamide and doxorubicin) in 110 patients (median CD4 count of 60/μl). The complete response rate favoured full dose CHOP (63% versus 39%; $P=0.001$), although there was no difference in EFS or overall survival. Currently, the United States AIDS Malignancy Consortium is comparing CHOP plus the anti-CD20 monoclonal antibody rituximab with CHOP alone in patients with HIV-associated B-cell lymphoma.

4. Diagnosis and treatment of primary CNS lymphoma

The clinical and radiographical presentation of patients with primary central nervous system lymphoma (PCNSL) occurring in immunocompromised and non-immunocompromised individuals has been reviewed [21]. The analysis included data derived from 40 published series reported between 1980 and 1992 that included 792 patients. The most common presenting symptoms and signs included neurological deficits (51%), mental status changes (53%), seizures (27%), and evidence of increased intracranial pressure (14%).

4.1. Diagnosis

In patients with HIV infection, the differential diagnosis of a patient with focal brain lesions includes PCNSL, cerebral toxoplasmosis, and other infections. Focal brain lesions have also been described in conjunction with relapsed systemic lymphoma [52]. A proposed algorithm for the diagnostic approach to a patient with HIV infection and focal brain lesions is shown in Fig. 1. Antitoxoplasmosis therapy usually produces clinical and radiographical improvement within 1–3 weeks in the majority of patients with cerebral toxoplasmosis [53]. For this reason, many experts recommend biopsy only in patients who have not responded to a trial of toxoplasmosis therapy [54]. In a recent retrospective case and literature review, stereotactic biopsy established definitive histopathological diagnoses in 88% of cases [55]. Morbidity and mortality attributed to the biopsy was 8.4 and 2.9%, respectively. Among cases biopsied after failure of anti-toxoplasmosis therapy, the diagnosis of PCNSL was established in 65%. Features associated with biopsy-related morbidity were poor functional status, thrombocytopenia and greater number of lesions at presenta-



CSF, cerebrospinal fluid
Antitoxo, antitoxoplasmosis
RT, radiotherapy

Fig. 1. Algorithm for management of HIV-infected individuals with focal brain lesions.

tion. Examination of the cerebrospinal fluid (CSF) may also be useful. Cytological examination may reveal malignant cells in 10–20% of patients, and should generally be performed prior to brain biopsy in those who can safely undergo lumbar puncture. Viral DNA is detectable by polymerase chain reaction (PCR) in the CSF. Cingolani and colleagues [73] evaluated EBV DNA by PCR in the CSF of 122 patients with HIV infection, including 42 patients with PCNSL and 80 with a variety of non-malignant conditions [56]. CSF EBV DNA had a sensitivity of 80% (95% confidence intervals (CI) 61%, 92%) and a specificity of 100% (95% CI 93%, 100%). Sampling of the lumbar CSF would have led to a correct diagnosis in 63% of patients with HIV-associated PCNSL, and would have excluded this diagnosis in 76%. Single-photon emission computed tomography (SPECT) with thallium-201 and positron emission tomography (PET) with [^{18}F]-fluoro-2-deoxyglucose (FDG) are other techniques that may be useful in differentiating between lymphomatous and infectious lesions, although they may lack specificity [57].

4.2. Treatment

Radiation therapy has generally been the mainstay of treatment for PCNSL, whether associated or not associated with HIV infection. Irradiation is generally administered to the whole brain to a total dose of 50–60 Gy in 1.8–2.0 Gy daily fractions. Patients with HIV infection generally have a median survival of approximately 3 months, and fewer than 10% survive 1 year, a result that is clearly inferior to PCNSL occurring in immunocompetent individuals [58]. Features associated with a favourable outcome included good performance status and no prior opportunistic infections. The US Intergroup conducted a phase II trial of a single cycle of cyclophosphamide, doxorubicin, vincristine and dexamethasone followed by whole brain irradiation (40 Gy in 16 fractions) in 35 patients with HIV-associated PCNSL [59]. The median survival was 2.4 months, and only 11% of patients survived beyond 1 year, thus failing to demonstrate an advantage for combined modality therapy, The impact of HAART for patients with HIV-associated PCNSL is unclear. Klein and colleagues reported a retrospective analysis of patients treated in the post-HAART era demonstrating a 1-year survival of approximately 20% [60]. However, spontaneous regression of PCNSL has been reported after HAART therapy without other systemic or local therapy for the lymphoma [61,62]. Raez and coworkers have reported long-term remission in several patients with PCNSL treated with parenteral zidovudine, ganciclovir and low-dose interleukin-2 (IL-2) [63]. Further investigation will be necessary to confirm this encouraging report.

5. Effects of chemotherapy on host immunity and HIV infection

5.1. Haematopoiesis

Myelosuppression and opportunistic infection are frequent complications of chemotherapy in patients with HIV infection, particularly in lymphoma patients treated with combination chemotherapy. Low baseline CD4 count is associated with significantly greater neutropenia and thrombocytopenia, greater duration of neutropenia, and greater incidence of febrile neutropenia in patients with lymphoma treated with infusional cyclophosphamide, doxorubicin and etoposide (CDE) [45].

5.2. Opportunistic infection

Opportunistic infection occurs in 20–80% of patients with systemic lymphoma treated with a variety of chemotherapy regimens. The risk of infection is a function of the intensity of the chemotherapy regimen and the degree of immunosuppression. For example, Gill and colleagues reported opportunistic infection in 7 of 9 patients (78%) treated with an intensive regimen compared with 1 of 13 patients (8%) treated with a standard regimen [64]. Tirelli and coworkers reported a 44% risk of opportunistic infection in 'poor risk' patients (median CD4 count of 37/ul) treated with a low-dose CHOP regimen [65], compared with a 10% risk of opportunistic infection for full-dose CHOP in a group of patients with a mean CD4 count of 230/ul reported by Levine and colleagues [66].

Although opportunistic infections frequently occur, it is unclear to what degree chemotherapy contributes to the risk of infection. In order to address this issue, Sparano and coworkers performed a case control study in which the incidence of AIDS-defining events in patients with systemic lymphoma treated with the CDE regimen (cases) was compared with a cohort of HIV-infected patients without malignancy matched for CD4 count and prior infection (controls) [67]. The relative risk of developing an AIDS-defining event was approximately 2-fold greater in the cases, and was principally due to an increased risk of cytomegalovirus (CMV) infection (e.g. colitis, retinitis) and severe mucocutaneous herpes simplex (HSV) infection. The increased risk persisted beyond the period of chemotherapy administration, and was evident in patients with both severe immunodeficiency (CD4 <100/ul) and less profound immunodeficiency (CD4 $\geqslant 100$/ul). In addition, the CD4 count was also significantly lower in the lymphoma patients after one year compared with the controls.

5.3. Immunological function and HIV load

The increased risk of infection is most likely a consequence of the effects of chemotherapy on immunological

function. The T lymphocytes, including CD4 and CD8 cells, decrease significantly during chemotherapy, even in immunocompetent individuals. Furthermore, the decrease in CD4 cells may persist for up to 1 year. Studies evaluating the effect of cytotoxic therapy on HIV viral load have demonstrated no substantial increase in viral load during chemotherapy, whether or not antiretroviral agents were used concurrently [50,68].

6. Haematopoietic growth factors

GM-CSF was shown in a prospective, randomised trial to reduce the severity and duration of neutropenia as well as the incidence of febrile neutropenia, in patients with HIV-related lymphoma treated with CHOP [69]. Others have reported that G-CSF produces similar beneficial effects [70]. If the expected incidence of febrile neutropenia exceeds 40% for the chemotherapy regimen selected, there seems to be sufficient justification for using myeloid growth factors as primary prophylaxis [71].

Some evidence suggests that certain haematopoietic growth factors may influence viral load and CD4 count, although the data is inconsistent. For example, Kaplan and colleagues reported that GM-CSF produced a significant increase in p24 antigen levels in patients with lymphoma treated with CHOP [69]. One study found that the addition of GM-CSF to antiretroviral therapy had no effect on viral load (p24 antigenemia or plasma/peripheral blood mononuclear cell HIV culture) [72], whereas several other trials found an association between administration of GM-CSF and increased CD4 cells and in some cases reduced viral burden [73,74].

7. Integrating chemotherapy and antiretroviral therapy

Although there have been anecdotal reports of regression of systemic or primary effusion lymphoma associated with antiretroviral therapy [75–77], the use of HAART has not yet been demonstrated to improve the responsiveness or curability of the lymphoma. For patients with lymphoma, therefore, important issues include overlapping toxicities of antiretrovirals and cytotoxics and the potential for drug–drug interactions. Furthermore, chemotherapy-induced nausea and vomiting may lead to non-compliance with antiretrovirals, which may in turn lead to acquired HIV resistance. Antiretrovirals may also influence the toxicity and efficacy of cytotoxic agents by altering their absorption, distribution, metabolism or excretion; the converse may also be true. The protease inhibitors and non-nucleoside reverse transcriptase inhibitors (RTIs) have variable effects on cytochrome P450, especially CYP3A, which may alter the metabolism of various cytotoxic agents. Furthermore, the initiation of protease inhibitor therapy may induce acute enzyme changes that may further enhance the potential for interaction [78].

Most of the information regarding combination of chemotherapy and antiretroviral agents concerns the use of nucleoside RTIs. Anaemia and leucopenia are prominent toxicities of zidovudine, which has rendered it problematic in combining with other myelosuppressive drugs [65], although some reports suggested that these cytopenias may be abrogated by G-CSF and erythropoietin [79,80]. In contrast to zidovudine, didanosine produces a significant increase in the leucocyte, neutrophil, red cell, and platelet count in patients with advanced HIV infection [81]. Didanosine has been safely combined with infusional chemotherapy for lymphoma, and resulted in significantly less neutropenia and thrombocytopenia and fewer red cell and platelet transfusions, although it did not ameliorate chemotherapy-induced CD4 lymphopenia [45]. Another report also suggested a higher response rate and less toxicity when didanosine was added to chemotherapy for lymphoma [82]. Zalcitabine has also been safely combined with low-dose m-BACOD [83].

There is less information regarding the use of protease inhibitors or non-nucleoside RTIs in combination with chemotherapy. All of these agents that are currently available have some effects on the cytochrome P450 enzymes, including some that inhibit the enzymes (all protease inhibitors and delavirdine), induce the enzymes (nevirapine), or have mixed effects (efavirenz). All of the protease inhibitors effect the P450 cytochrome 3A4, with ritonavir having the most potent effect. This effect has resulted in a host of potential drug interactions with other agents that are commonly used in the management of patients with advanced HIV. There is therefore potential for interaction with any cytotoxic agent that is metabolised by the cytochrome P450 system, including etoposide, the vinca alkaloids, the taxanes and ifosfamide. Few studies have formally evaluated this question. The combination of saquinavir with a 96-hour infusion of cyclophosphamide, doxorubicin and etoposide for lymphoma was reported to result in a significantly greater incidence of severe mucositis [46]. In contrast, indinavir was found to have no appreciable effect on toxicity in patients treated with i.v. bolus injection of cyclophosphamide, doxorubicin and vincristine with oral prednisone (CHOP) for lymphoma; when compared with historical pharmacokinetic data, indinavir had no effect on the pharmacokinetics of doxorubicin, although cyclophosphamide clearance was approximately 40% lower [84]. Recent evidence suggests that patients treated in the post-HAART era have a better prognosis and exhibit less toxicity, although the responsiveness of the lymphoma to systemic therapy is not effected [85].

8. Infection prophylaxis

Although primary PCP prophylaxis is indicated only for patients with fewer than 200 CD4 cells/μl, combination chemotherapy typically produces a substantial and precipitous reduction in CD4 cells. It is therefore reasonable to institute prophylaxis irrespective of the CD4 count in those selected to receive chemotherapy. Since oral and oesophageal candidiasis is a frequent complication of combination chemotherapy for lymphoma, primary prophylaxis with fluconazole may also be reasonable. HSV-associated stomatitis, balanitis, and/or perianal infection are also common complications of intensive chemotherapy. HSV-associated stomatitis may be confused with chemotherapy-induced stomatitis, and should be suspected if there is severe oral pain that is out of proportion to the degree of stomatitis, or stomatitis that develops or worsens after neutrophil recovery. Prompt recognition and implementation of therapy is important, and the infection will usually relapse unless secondary prophylaxis with acyclovir is maintained throughout the course of cytotoxic therapy. Evidence-based guidelines for infection prophylaxis (as developed by the United States Public Health Service and the Infectious Disease Society of America) and antiretroviral therapy (as developed by the United States Department of Health and Human Services) are regularly updated and are available at http://www.hivatis.org

9. Conclusions

Systemic lymphoma in patients with HIV infection is a potentially curable disease, although the potential for cure is less than in immunocompetent individuals. Appropriate use of supportive care is an important component of therapy (Table 3). Whenever feasible, patients should receive standard combination chemotherapy. CNS prophylaxis is indicated for those with features suggestive of a high risk of isolated CNS relapse. Patients should receive appropriate infection prophylaxis, and treatment with a colony-stimulating factor is prudent given the high risk of neutropenia and infectious complications. The decision regarding antiretroviral therapy must be individualised, although recent evidence suggests that temporary discontinuation of antiretrovirals during cytotoxic therapy is safe. Long-term

Table 3
Suggested supportive care for the patient with HIV infection and lymphoma or other malignancies

Indication	Drug(s)
Primary infection prophylaxis	
Pneumocystis carinii, Toxoplasma	TMP-SMZ 1 DS QD
Oral and/or oesophageal candidiasis	Fluconazole 100 mg QD
MAI Complex (CD4 <50/ul)	Azithromycin 1200 mg weekly
Secondary infection prophylaxis	
Herpes simplex infections	Acyclovir 400 mg BID or 200 mg TID
Cytomegalovirus infection	Ganciclovir 1 g TID
Mycobacterium–avium complex	Clarithromycin 500 mg BID plus ethambutol 15 mg/kg QD, with or without rifabutin 300 mg QD
Toxoplasma gondii	Sulphadiazine 1–1.5 gm q6h, pyrimethamine 25–75 mg QD, Leucovorin 10–25 mg QD — QID
Cryptococcus neoformans	Fluconazole 200 mg QD
Salmonella bacteraemia	Ciprofloxacin 500 mg BID
Haematopoietic growth factors	
For selected patients in whom the risk of febrile neutropenia $\geqslant 40\%$	G-CSF 5 mcg/kg or GM-CSF 250 mcg/M^2 s.c. daily beginning after completion of chemotherapy and continue until neutrophil recovery
Antiretroviral agents	
Selecting patients for therapy	Follow NIH guidelines (http://www.hivatis.org)
Role of therapy in controlling malignancy	
Kaposi's sarcoma	Essential
Lymphoma	Unknown
Other tumours	Unknown
Factors influencing selection of agents	
May be used with myelosuppressive drugs	Didanosine, zalcitabine
Avoid with myelosuppressive drugs/regimens	Zidovudine
Avoid with neurotoxic drugs/regimens	Didanosine, zalcitabine, stavudine
May alter the metabolism of cytotoxic drugs metabolised by cytochrome p450 enzymes	All protease inhibitors and non-nucleoside RTIs

QD, daily; TID, three times daily; BID, two times daily; QID, four times daily; s.c., subcutaneous; G-CSF, granulocyte colony stimulating factor; GM, CSF, granulocyte-macrophage colony stimulating factor; NIH, National Institute of Health; RTIs, reverse transcriptase inhibitors.

remission is patients with primary CNS lymphoma is uncommon, but selected patients with good performance status and adequate immunological reserve may benefit from brain irradiation or novel treatment approaches.

References

1. Miller DG. The association of immune disease and malignant lymphoma. *Ann Intern Med* 1967, **66**, 507–521.
2. Penn I, Hammond A, Brett Scheider L, Starzl TE. Malignant lymphomas in transplantation patients. *Transplant Proc* 1969, **1**, 106.
3. Gatti RA, Good RA. Occurrence of malignancy in immunodeficiency disease: a literature review. *Cancer* 1971, **28**, 89–98.
4. Doll DC, List AF. Burkitt's lymphoma in a homosexual. *Lancet* 1982, **i**, 1026–1027.
5. Ziegler JL, Miner RC, Rosenbaum E, *et al*. Outbreak of Burkitt's like-lymphoma in homosexual men. *Lancet* 337;1982, **ii**, 631–633.
6. Ziegler JL, Beckstead JA, Volberding PA, *et al*. Non-Hodgkin's lymphoma in 90 homosexual men: relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome (AIDS). *N Engl J Med* 1984, **311**, 565–570.
7. Levine AM, Meyer PR, Begandy MK, *et al*. Development of B-cell lymphoma in homosexual men. *Ann Intern Med* 1984, **100**, 7–13.
8. Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR* 1987, **36**(Suppl.), 1S–15S.
9. Lyter DW, Bryant J, Thackeray R, Rinaldo CR, Kingsley LA. Incidence of human immunodeficiency virus-related and non-related malignancies in a large cohort of homosexual men. *J Clin Oncol* 1995, **3**, 2540–2546.
10. Gail MH, Pluda JM, Rabkin CS, *et al*. Projections of the incidence of non-Hodgkin's lymphoma related to acquired immunodeficiency syndrome. *J Natl Cancer Inst* 1991, **83**, 695–701.
11. Pluda JM, Venzon DJ, Tosato G, *et al*. Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. *J Clin Oncol* 1993, **11**, 1099–1107.
12. Levine AM, Bernstein L, Sullivan-Halley J, Shibata D, Mahterian SB, Nathwani BN. Role of zidovudine antiretroviral therapy in the pathogenesis of acquired immunodeficiency syndrome-related lymphoma. *Blood* 1995, **86**, 4612–4616.
13. Sparano JA, Anand K, Desai J, Mitnick R, Hannua L. Effect of highly active antiretroviral therapy on the incidence of HIV-associated malignancies at an urban medical center. *J AIDS Hum Retrovirol* 1999, **21**, S21–22.
14. Wiggins CL, Aboulafia DM, Ryland LM, Buskin SE, Hopkins SG, Thomas DB. Decline in HIV-associated Kaposi's Sarcoma and non-Hodgkin's lymphoma following the introduction of highly active antiretroviral therapy. *J AIDS Hum Retrovirol* 1999, **21**, A15 (abstr 24).
15. Dal Maso L, Serraino D, Hamers F, Franceschi. Non-Hodgkin's lymphoma and primary brain lymphoma as AIDS-defining illness in Western Europe:1988–97. *J AIDS Human Retrovirol* 1999, **21**, A34 (abstr 97).
16. Ammassari A, Cingolani A, Pezzotti P, *et al*. AIDS-related primary central nervous system lymphoma:changes of epidemiological trend and of diagnostic attitudes in the era of HAART. *J AIDS Human Retrovirol* 1999, **21**, A34 (abstr 99).
17. Besson C, Katlama C, Charlotte F, *et al*. Frequency, localisations and histological distribution of lymphomas in AIDS-patients before and after the use of multitherapies. *J AIDS Human Retrovirol* 1999, **21**, A34 (abstr 100).
18. International Collaboration on HIV Infection and Cancer. Highly active antiretroviral therapy and incidence of cancer in HIV-infected individuals. *J Natl Cancer Inst* 2000, **92**, 1823–1830.
19. Gill PS, Levine AM, Meyer PR, *et al*. Primary central nervous system lymphoma in homosexual men: clinical, immunologic, and pathologic features. *Am J Med* 1985, **78**, 742–748.
20. Goldstein JD, Dickson DW, Moser FG, *et al*. Primary central nervous system lymphoma in acquired immunodeficiency syndrome: a clinical and pathologic study with results of treatment with radiation. *Cancer* 1991, **67**, 2756–2765.
21. Fine HA, Mayer RJ. Primary central nervous system lymphoma. *Ann Intern Med* 1993, **119**, 1093–1104.
22. Loureiro C, Gill PS, Meyer PR, Rhodes R, Rarick MU, Levine AM. Autopsy findings in AIDS-related lymphoma. *Cancer* 1988, **62**, 735–739.
23. MacMahon EME, Glass JD, Hayward SD, *et al*. Epstein Barr virus in AIDS-related primary central nervous system lymphoma. *Lancet* 1991, **338**, 969–973.
24. Carbone A, Tirelli U, Gloghini A, *et al*. Herpesvirus-like DNA sequences selectively cluster with body cavity-based lymphomas throughout the spectrum of AIDS-related lymphomatous effusions. *Eur J Cancer* 1996, **32A**, 555–556.
25. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences are present in AIDS-related body cavity based lymphomas. *N Engl J Med* 1995, **332**, 1186–1191.
26. Nador RG, Cesarman E, Chadburn A, *et al*. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpesvirus. *Blood* 1996, **88**, 645–656.
27. Chang Y, Cesarman E, Pessin MS, *et al*. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994, **266**, 1865–1869.
28. Nador RG, Cesarman E, Knowles DM, Said JW. Herpes-like DNA sequences in a body-cavity-based lymphoma in an HIV-negative patient. *N Engl J Med* 1995, **333**, 943.
29. Said JW, Tasaka T, Takeuchi S, *et al*. Primary effusion lymphoma in women: report of two cases of Kaposi's sarcoma herpes virus-associated effusion-based lymphoma in human immunodeficiency virus-negative women. *Blood* 1996, **88**, 3124–3128.
30. Levine AM. Acquired immunodeficiency syndrome-related lymphoma. *Blood* 1992, **80**, 8–20.
31. Fisher RI, Gaynor ER, Dahlberg S, *et al*. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993, **328**, 1002–1006.
32. Kaplan LD, Abrams DI, Feigal E. AIDS-associated non-Hodgkin's lymphoma in San Francisco. *JAMA* 1989, **261**, 719–724.
33. Levine AM, Sullivan-Halley J, Pike M, *et al*. Human immunodeficiency virus-related lymphoma. Prognostic factors predictive of survival. *Cancer* 1991, **68**, 2466–2472.
34. Straus DJ, Huang J, Testa MA, *et al*. Prognostic factors in the treatment of human immunodeficiency virus- associated non-Hodgkin's lymphoma: analysis of AIDS Clinical Trials Group protocol 142 — low-dose versus standard-dose m-BACOD plus granulocyte-macrophage colony-stimulating factor. National Institute of Allergy and Infectious Diseases. *J Clin Oncol* 1998, **16**, 3601–3606.
35. Navarro JT, Ribera JM, Oriol A, *et al*. International prognostic index is the best prognostic factor for survival in patients with AIDS-related non-Hodgkin's lymphoma treated with CHOP. A multivariate study of 46 patients. *Haematologica* 1998, **83**, 508–513.
36. Rossi G, Donisi A, Casari S, *et al*. The International Prognostic Index can be used as a guide to treatment decisions regarding patients with human immunodeficiency virus-related systemic non-Hodgkin's lymphoma. *Cancer* 1999, **86**, 2391–2397.

37. Kaplan LD, Shiramizu B, Herndier B, *et al.* Influence of molecular characteristics on clinical outcome in human immunodeficiency virus-associated non-Hodgkin's lymphoma: identification of a subgroup with favorable clinical outcome. *Blood* 1995, **85**, 1727–1735.
38. Levine AM, Wernz JC, Kaplan L Jr. Low-dose chemotherapy with central nervous system prophylaxis and zidovudine maintenance in AIDS-related lymphoma. *JAMA* 1991, **266**, 84–88.
39. Remick SC, McSharry JJ, Wolf BC. Novel oral combination chemotherapy in the treatment of intermediate-grade and high-grade AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol* 1993, **11**, 1691–1702.
40. Tosi P, Gherlinzoni F, Mazza P, *et al.* 3′-Azido 3′-deoxythymidine + methotrexate as a novel antineoplastic combination in the treatment of human immunodeficiency virus-related non-Hodgkin's lymphoma. *Blood* 1997, **89**, 419–425.
41. Lai G, Chen Y, Mickley LA, *et al.* P-glycoprotein expression and schedule dependence of Adriamycin cytotoxicity in human colon carcinoma cell lines. *Int J Cancer* 1991, **49**, 696–703.
42. Sparano JA, Wiernik PH, Leaf A, Dutcher JP. Infusional cyclophosphamide, doxorubicin, and etoposide in relapsed and resistant non-Hodgkin's lymphoma: evidence for a schedule dependent effect favoring infusional administration of chemotherapy. *J Clin Oncol* 1993, **11**, 1071–1079.
43. Sparano JA, Wiernik PH, Strack M, *et al.* Infusional cyclophosphamide, doxorubicin, and etoposide in HIV- and HTLV-I-related non-Hodgkin's lymphoma: a highly active regimen. *Blood* 1993, **81**, 2810–2815.
44. Sparano JA, Wiernik PH, Strack M , *et al.* Infusional cyclophosphamide, doxorubicin, and etoposide in HIV-related non-Hodgkin's lymphoma: a followup report. *Leuk Lymph* 1994, **14**, 263–271.
45. Sparano JA, Wiernik PH, Hu X, *et al.* A pilot trial of infusional cyclophosphamide, doxorubicin and etoposide plus didanosine and filgrastim in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol* 1996, **14**, 3026–3035.
46. Sparano JA, Wiernik PH, Hu X, Sarta C, Henry DH, Ratech H. Saquinavir enhances the mucosal toxicity of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma. *Med Oncol* 1998, **15**, 50–57.
47. Sparano JA, Wiernik PH, Hu X, *et al.* Infusional cyclophosphamide, doxorubicin, and etoposide (CDE) for HIV-associated non-Hodgkin's lymphoma:long-term followup and analysis of prognostic factors. *J AIDS Hum Retrovirol* 1997, **14**, A38 (abstr 88).
48. Sparano JA, Lee S, Chen M, *et al.* Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in HIV-associated non-Hodgkin's lymphoma:an Eastern Cooperative Oncology Group Trial. *Proc Am Soc Clin Oncol* 1999, **18**, 12a (abstr 41).
49. Kaplan LD, Straus DJ, Testa MA, *et al.* Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. *N Engl J Med* 1997, **336**, 1641–1648.
50. Little R, Pearson D, Gutierrez M, Steinberg S, Rarchoan R, Wilson WH. Dose-adjusted EPOCH chemotherapy with suspension of antiretroviral therapy for HIV-associated non-Hodgkin's lymphoma. *J AIDS* 2000, **23**, A11 (abstr S16).
51. Tirelli U, Spina M, Gabarre J, *et al.* Treatment of HIV-related non-Hodgkin's lymphoma adapted to prognostic factors. *J AIDS* 1999, **21**, A32 (abstr 91).
52. Desai J, Mitnick RJ, Henry DH, Llena J, Sparano JA. Patterns of central nervous system recurrence in patients with systemic human immunodeficiency virus-associated non-Hodgkin's lymphoma. *Cancer* 1999, **86**, 1840–1847.
53. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med* 1992, **327**, 1643–1648.
54. Mathews C, Barba D, Fullerton SC. Early biopsy versus empiric treatment with delayed biopsy of non- responders in suspected HIV-associated cerebral toxoplasmosis — a decision analysis. *AIDS* 1995, **9**, 1243–1250.
55. Skolasky RL, Dal Pan GJ, Olivi A, Lenz FA, Abrams RA, McArthur JC. HIV-associated primary CNS morbidity and utility of brain biopsy. *J Neurol Sci* 1999, **163**, 32–38.
56. Cingolani A, De Luca A, Larocca LM, *et al.* Minimally invasive diagnosis of acquired immunodeficiency syndrome-related primary central nervous system lymphoma. *J Natl Cancer Inst* 2000, **90**, 364–369.
57. D'Amico A, Messa C, Castagna A, *et al.* Diagnostic accuracy and predictive value of 201T1 SPET for the differential diagnosis of cerebral lesions in AIDS patients. *Nucl Med Commun* 1997, **18**, 741–750.
58. Remick SC, Diamond C, Migliozzi JA, *et al.* Primary central nervous system lymphoma in patients with and without the acquired immune deficiency syndrome. A retrospective analysis and review of the literature. *Medicine (Baltimore)* 1990, **69**, 345–360.
59. Ambinder RF, Lee S, Wurran WJ, *et al.* Phase II trial of sequential chemotherapy and radiotherapy for AIDS-related primary central nervous system lymphoma:an Eastern Cooperative Oncology Group study (E1493). *J AIDS* 2000, **23**, A30 (abstr 63).
60. Klein C, Micciken S, Dolan G, Desai J, Henry DH, Sparano JA. Impact of highly active antiretroviral therapy on HIV-associated primary central nervous system lymphoma. *J AIDS* 2000, **23**, A26 (abstr 48).
61. McGowan JP, Shah S. Long term remission of AIDS-related primary CNS lymphoma associated with highly active antiretroviral therapy. *AIDS* 1998, **12**, 952–958.
62. Terriff BA, Harrison P, Holden JK. Apparent spontaneous regression of primary CNS lymphoma mimicking resolving toxoplasmosis. *J AIDS* 1992, **5**, 953–954.
63. Raez L, Cabral L, Cai JP, *et al.* Treatment of AIDS-related primary central nervous system lymphoma with zidovudine, ganciclovir, and interleukin 2. *J AIDS Hum Retroviruses* 1999, **15**, 713–719.
64. Gill PS, Levine AM, Krailo M, *et al.* AIDS-related malignant lymphoma: results of prospective treatment trials. *J Clin Oncol* 1987, **5**, 1322–1328.
65. Tirelli U, Errante U, Oksenhendler E, *et al.* Prospective study with combined low-dose chemotherapy and zidovudine in 37 patients with poor-prognosis AIDS-related non-Hodgkin's lymphoma. French–Italian Cooperative Study Group. *Ann Oncol* 1992, **10**, 843–847.
66. Levine AM, Wernz JC, Kaplan L, *et al.* Low-dose chemotherapy with central nervous system prophylaxis and zidovudine maintenance in AIDS-related lymphoma. *JAMA* 1991, **266**, 84–88.
67. Sparano JA, Hu X, Wiernik PH, *et al.* Opportunistic infection and immunologic function in patients with human immunodeficiency virus-related non-Hodgkin's lymphoma treated with chemotherapy: a case control study. *J Natl Cancer Inst* 1997, **89**, 301–307.
68. Kersten MJ, Verduyn TJ, Reiss P, Evers LM, de Wolf F, van Oers MH. Treatment of AIDS-related non-Hodgkin's lymphoma with chemotherapy (CNOP) and r-hu-GCSF: clinical outcome and effect on HIV-1 viral load. *Ann Oncol* 1998, **9**, 1135–1138.
69. Kaplan LD, Kahn JO, Crowe S, *et al.* Clinical and virologic effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. *J Clin Oncol* 1997, **9**, 929–940.
70. Rossi G, Donisi A, Casari S, *et al.* Effects of recombinant granulocyte colony-stimulating factor (G-CSF) in patients treated with ProMACE-CytaBOM for HIV-related non-Hodgkin's lymphoma. *Haematologica* 1998, **83**, 317–322.

71. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994, **12**, 2471–2508.
72. Scadden DT, Pickus O, Hammer SM, *et al*. Lack of in vivo effect of granulocyte-macrophage colony-stimulating factor on human immunodeficiency virus type 1. *J AIDS Res Hum Retroviruses* 1996, **12**, 1151–1159.
73. Perrella O, Finelli E, Perrella A, Tartaglia G, Scognamiglio P, Scalera G. Combined therapy with zidovudine, recombinant granulocyte colony stimulating factor, and erythropoietin inn asymptomatic HIV patients. *J Chemother* 1996, **8**, 63–66.
74. Skowron G, Stein D, Drusano G, *et al*. Safety and anti-HIV effect of GM-CSF in patients on highly active antiretroviral therapy. *5th Conference on Retroviruses and Opportunistic Infections*, 1998 (abstr 615).
75. Baselga J, Krown SE, Telzak EE, Filippa DA, Straus DJ. Acquired immune deficiency sydrome-related pulmonary non-Hodgkin's lymphoma regressing after zidovudine therapy. *Cancer* 1993, **71**, 2332–2334.
76. Harrington WJ Jr, Cab ral, L., Cai, J.P., Chan, A-Sue S, Wood C. Azothymidine and interferon-alpha are active in AIDS-associated small non-cleaved cell lymphoma but not large-cell lymphoma. *Lancet* 1996, **348**, 833.
77. Oksenhendler E, Clauvel JP, Jouveshomme S, Davi F, Mansour G. Complete remission of a primary effusion lymphoma with antiretroviral therapy. *Am J Hematol* 1998, **57**, 266.
78. Kumar GN, Rodrigues AD, Buko AM, Denissen JF. Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. *J Pharmacol Exp Ther* 1996, **277**, 423–431.
79. Errante D, Tirelli U, Gastaldi R, *et al*. Combined antineoplastic and antiretroviral therapy for patients with Hodgkin's disease and human immunodeficiency virus infection: a prospective study of 17 patients. *Cancer* 1994, **73**, 437–444.
80. Feigal E, Petroni GR, Freter C, Johnson JL, Barcos M, Peterson BA. Pilot trial of cyclophosphamide, doxorubicin, vincristine, prednisone etoposide + antiretrovirals + erythropoietin in AIDS-associated non-Hodgkin's lymphoma:CALGB 9155. *Proc Am Soc Clin Oncol* 1997, **16**, 56a (abstr 195).
81. Schacter LP, Rozencweig M, Beltangady M, *et al*. Effects of therapy with didanosine on hematologic parameters in patients with advanced human immunodeficiency virus disease. *Blood* 1992, **80**, 2969–2976.
82. Ucar A, Harrington WJ, Cabral L, Hurley J, Cohen J, Lai S, Byrnes J. Phase III trial of chemotherapy concomitantly with didanosine versus chemotherapy alone in patients with AIDS-non Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1994, **13**, 374 (abstr 1265).
83. Levine AM, Tulpule A, Espina B, *et al*. Low dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone with zalcitabine in patients with acquired immunodeficiency syndrome-related lymphoma. Effect on human immunodeficiency virus and interleukin-6 levels over time. Cancer 1996, 78, 517-526.
84. Ratner L, Redden D, Hamzeh F, *et al*. Chemotherapy for HIV-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy is not associated with excessive toxicity. *J AIDS* 1999, **21**, 132 (abstr 92).
85. Sparano JA, Lee S, Henry DH, Ambinder RF, VonRoenn J, Tirelli U. Infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin's lymphoma:a review of the Einstein, Aviano, and ECOG experience. *J AIDS* 2000, **23**, A11 (abstr S15).