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Clinical and Biological Characteristics of Malignant Lymphomas in HIV-infected Patients

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INTRODUCTION

THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) was described at the beginning of the last decade with the observation of opportunistic infections (especially Pneumocystis pneumonia) and Kaposi's sarcoma within homosexual men with marked acquired immunosuppression [1, 2]. Besides homosexual men, other groups (intravenous drug users, haemophiliacs) presented a similar syndrome in the USA and Europe. In Africa, AIDS spread rapidly in young adults of both sexes as well as in infants of infected mothers. In 1983–84, the pathogenic virus was first isolated in France and then in the USA [3, 4].

The main targets of the human immunodeficiency virus (HIV) are the T-helper lymphocytes, which are infected through the surface CD4 receptor that is recognised by the viral envelope glycoprotein gp120 [5–7]. Some monocytes and macrophages also express the CD4 receptor and may also be infected by HIV [8, 9]. The virus causes the destruction of CD4 lymphocytes by direct cytolysis, syncitia formation, as well as by other immune and auto-immune mechanisms [10–13]. The result is progressive and severe impairment of cellular immunity.

In addition to the T-cell deficit, HIV causes important disorders in humoral immunity. HIV proteins trigger B-cell proliferation either in a mitogenic or an antigen-specific manner [14, 15]. The mitogenic response may be directly caused by the virus (independently of accessory cells), and also by the release of cytokine, such as interleukin 6 [16, 17]. B-cell activation is characteristic of patients with mild as well as severe manifestations of HIV infection [18]. Infected subjects display increasing serum levels of immunoglobulins, circulating immunocomplexes and also an increased number of peripheral lymphocytes spontaneously secreting immunoglobulin [19, 20]. In addition, seropositive individuals develop a persistent generalised lymphadenopathy (PGL) in approximately 30% of the cases. This lymphadenopathic syndrome is characterised by an exuberant hyperplasia of the germinative centres, where B-cell maturation occurs, with polyclonal B-cell proliferation [21, 22]. Severe immunodeficiency together with chronic antigenic/mitogenic stimulation has been associated with lymphoid malignancies [23–27]. Thus, HIV infection may be considered as a prelymphomatous state.

The first cases of Burkitt's lymphomas (BL) in homosexual men were reported in 1982 [28, 29]. In 1983, with the observation of several cases of aggressive non-Hodgkin lymphomas (NHL) in risk groups for AIDS, a definitive relation between NHL and AIDS was established [30]. This association was further confirmed epidemiologically [31, 32]. In 1985, the incidence of high grade NHL was 6.5 times greater than in the 1970s. In single men in Los Angeles high grade NHL constituted 7.7% of all NHL before 1980, but exceeded 50% between 1983 and 1985. In the same period, the incidence of cerebral lymphoma (which is well known in other immunosuppressive conditions) doubled in the same population. Therefore, in 1985, disseminated high grade NHL and cerebral lymphomas were included in the Centers of Disease Control (CDC) definition of AIDS [33]. Intermediate grade NHL (diffuse large cell lymphomas) were included in the CDC definition in 1987 [34]. Although Hodgkin's disease (HD) has not so far been included in the CDC case definition of AIDS, an increasing number of HIV-associated HD (HIV–HD) has been reported, with a particular clinicopathological profile [35–37].

Other haematological malignancies, such as plasmocytoma [38], multiple myeloma [39], low grade NHL [30], chronic lymphocytic leukaemia [40, 41] and acute leukaemia [42, 43], have been described but, so far, they do not appear to be significantly associated with HIV disease.

This review will first focus on the clinical and biological characteristics of HIV-associated NHL. Then a specific chapter will be devoted to HD in HIV seropositive cases. Much of the information is based on data of the French Registry of HIV-associated tumours [44, 45].

NON-HODGKIN LYMPHOMAS

The present estimates indicate that NHL account for approximately 3% of newly diagnosed AIDS cases [46]. However, this is largely an underestimation, since a large number of NHL occur after a first AIDS diagnosis and are, therefore, not recorded by epidemiological studies [46, 47]. Moreover, the incidence of HIV–NHL may be increasing with the development of anti-retroviral therapy and the better control of opportunistic infections. In a prospective study at the NCI, including 55 patients treated with zidovudine or zidovudine-containing regimens, 14% of the patients presented a NHL after a median duration of 23.8 months of therapy [48]. The actuarial 3-year probability of developing NHL in this cohort was recently re-estimated to be as high as 29% (95% confidence interval 15–49%) [49]. In a series of 1030 patients treated with zidovudine, a rise in the risk of NHL with time was also detected, but it was lower than in the previous study (3.2% at 2 years) [50]. The risk was not correlated with the dose of drug, but appeared to be correlated with the prolonged survival of patients with severe immunodepression.

The clinical and biological characteristics of HIV-associated NHL are remarkably constant in all reported series [30, 41, 45, 51–57] (Table 1). First, in contrast with Kaposi's sarcoma, which is more frequent in homosexual men [58], NHL affects all AIDS risk groups and clinicopathological features are similar in sexually or intravenously infected patients [59, 60]. Secondly, most HIV–NHL are disseminated or extranodal tumours. Thirdly, histologically, most cases are high or intermediate grade NHL. In our series (131 patients), diffuse small non-

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Table 1. Clinical characteristics of HIV-associated NHL

	France [45]	Italy [56]	USA [41,55,57]	Australia [89]
Patients (*n*)	142	95	225	41
Median age (range)	39(19–73)	27(19–64)	38(21–75)	39(22–64)
Male patients (%)	94	79	96	100
Risk group (%)				
Homosexual	56	18	85	95
Intravenous drug abusers	13	68	13	0
Both	4	5	0	5
Neither	27	9	2	0
Prior AIDS (%)	31	93	47	34
Clinical stage (%)				
I+II	12	7	15	27
III+IV	63	65	70	73
Ie	25	28	15	†
Histological subtype (%)				
Burkitt-type	33	20	36	31
Diffuse large cell	37	9	31	6
Immunoblastic	23	33	31	50
Other*	7	38	2	13
Complete response rate (%)	37	35	44	NS‡
Median survival (months)	5	4	4.3–6	4

* High grade NHL without subtype specification.
† Included within clinical stage III+IV.
‡ NS = not significant.

cleaved cell, Burkitt-like lymphomas represent 36% of the cases, diffuse large cell lymphomas 40% and immunoblastic lymphomas 24%. Finally, phenotypic and genotypic studies show that almost all tumours originated in B cells, although sporadic cases of T-cell NHL have been reported [61, 62].

Based on clinicopathological correlations and immunological features, we have divided HIV-related NHL into two main groups: large cell lymphomas (including immunoblastic lymphomas) and BL (Table 2).

Diffuse large cell and immunoblastic lymphomas

These tumours generally appear at the terminal phase of HIV disease. Most often, the patients had already presented other manifestations of AIDS associated with severe immunosuppression. In our series of 84 patients with diffuse large cell/immunoblastic lymphomas (DLC/IL), 60% had presented a previous AIDS-related event (opportunistic infection or Kaposi's sarcoma) and the median CD4 cell count at NHL diagnosis was 112/μl (range 0–1125). The count was 125/μl for DLC (0–1125) and 80/μl for IL (13–890) [45].

HIV-DLC/IL present frequently as isolated extranodal lymphomas (37% of our cases), notably as primary cerebral lymphoma. Other sites of isolated extranodal presentation (clinical stage Ie) were digestive tract, liver, oral cavity, ano-rectal area and uterine-cervix. Localised nodal disease (stages I and II) accounted for only 10% of the cases. Among patients with disseminated (stage IV) disease, frequently involved sites were bone marrow (37%), leptomeninges (35%), liver (20%) and gastro-intestinal tract (15%). Other sites of visceral involvement were skin, pleura, pericardium, bone, testis, ovary, kidney, lung, pancreas, adrenals and oral cavity [45].

Immunophenotyping and immunoglobulin gene rearrangement studies have confirmed the B-cell origin of these NHL [41, 63, 64]. In the study by Knowles *et al.* [41], 8/8 were Ia+ (HLA-DR) and 7/8 B1+ (pan-B), while 4/8 were surface immunoglobulin positive (2 IgM lambda, 1 IgM kappa, and 1 IgG kappa), 4/7 expressed B2 antigen (the B cell C3d complement receptor and also the Epstein–Barr virus [EBV] receptor) and 2/7 were cALLa+. In the same study, 6/6 cases displayed clonal IgH gene rearrangements, including the case with a negative B1 marker. In many cases, Southern blotting indicated the presence of multiple B-cell clonal expansions [65, 66].

The clinical, histological and phenotypic characteristics of these HIV–DLC/IL closely resemble those of NHL occurring in post-transplantation patients undergoing therapeutic immunosuppression. These post-transplantation tumours also represent monoclonal or multiclonal proliferations with extranodal localisations, primary cerebral lymphomas being particularly frequent [67–69]. The increased frequency of NHL in severely immunodepressed patients irrespective of the origin of immunosuppression is a strong argument to implicate immunodeficiency itself in the pathogenesis of these tumours and to underline the role of the immune system in controlling certain types of malignant proliferations.

EBV has also been implicated in the pathogenesis of both post-transplantation and HIV-related large cell lymphomas [69–72]. EBV genoma has been found in 3/6 and 11/19 cases of HIV-DLC/IL by Southern blot and *in situ* DNA hybridisation, respectively [64, 73]. In a more recent study, MacMahon *et al.* [74] found evidence of EBV infection of the malignant cells in all 21 cases of primary brain HIV–DLC/IL. These workers have refined a very sensitive RNA *in situ* hybridisation capable of detecting non-protein coding EBV-transcripts (small non-polyadenylated viral RNA), which are highly expressed in latent infected cells [75]. The implication of EBV in tumour pathogenesis is further indicated by the fact that EBV found within tumour cells have a monoclonal pattern, as assessed by Southern blotting of the structure of the viral genomic termini [76]. This finding indicates that EBV infection precedes clonal expansion, and excludes the alternative possibility of secondary infection of the malignant clone (in this case, the EBV would be expected to present heterogeneity in the length of its variable terminal region).

The balance between EBV and the immune system is strongly modified in HIV disease. HLA-specific anti-EBV cellular immunity, as well as natural killer (non HLA-restricted) cytotoxicity are impaired, allowing the proliferation of B cells immortalised by EBV [77–79]. This EBV-driven B-cell proliferation is originally polyclonal, but may progress to an oligoclonal and eventually to a monoclonal disease, through still unknown mechanisms. On the other hand, HIV genoma has never been found in these tumours [66, 71, 73], indicating that this virus does not have a direct role in the lymphomagenesis.

Burkitt's lymphoma

In contrast to DLC/IL, BL is not usually associated with therapeutic or congenital immunosuppression and its high incidence in HIV infected patients is quite surprising.

These HIV-associated BL (HIV–BL) have clinical, histological and phenotypic characteristics similar to primary (non HIV-related) BL. They are frequently disseminated tumours (80% of the cases in our series) [45]. Among patients with stage IV disease, the most frequently involved sites were bone marrow (65%), leptomeninges (35%), liver (27%) and gastro-intestinal tract (23%). Isolated extranodal presentation, which is frequent in HIV–DLC/IL, is rare in HIV–BL (2 of 46 in our series, both involving the gastro-intestinal tract).

Table 2. Comparison of different types of HIV-associated lymphomas

	DLC/IL	BL	HD
Incidence	Increased	Increased	Increased (?)
Preferential risk group	No	No	IVDA (?)
Prior AIDS diagnosis	Frequent	Rare	Rare
CD4 cell count decrease	Marked	Mild	Mild
Clinical particularities	Similar to post-transplant NHL; high % of primary brain NHL	Similar to primary sporadic BL; high % of clinical stage IV (bone marrow, meninges)	Increased % of mixed cellularity type; high % clinical stage IV; very rare mediastinal involvement
B-cell origin	Yes; frequently multiclonal	Yes	?
Presence of EBV genoma	> 60%	< 30%	> 70%
Presence of HIV genoma	No	No	No(?)
C-*myc* activation	Rare	Always (typical BL chromosomal translocations)	No(?)
Response to therapy	Poor	Poor	Rather good
Clinical outcome	Poor survival, death by tumour progression	Poor survival; death by tumour progression	Poor survival, death by opportunistic infections

DLC/IL = diffuse large cell/immunoblastic lymphomas, BL = Burkitt's lymphoma, HD = Hodgkin's disease.

Immunophenotypic and genotypic profiles confirmed the B-cell origin of these tumours. In the study by Knowles *et al.* [41], all 18 cases were Ia and B1 positive, 16/18 presented surface immunoglobulin (mostly IgM kappa), 10/13 were cALLa+, but only 1/7 was B2+ (C3d). All 12 cases had clonal rearranged IgH gene and all presented TCR beta (T-cell receptor) in its germinal configuration.

HIV–BL present the typical chromosomic translocations of primary BL, namely t(8,14) and, less frequently, t(2,8) and t(8, 22) translocations [80–83]. Molecular analysis of translocation breakpoints in tumour cells has yielded mixed results [73, 84], but most cases resemble the sporadic European/American form of BL (as opposed to endemic, EBV-related, African BL). In sporadic BL, the typical chromosomal breakpoint occurs within the first exon of *myc*, and the translocation puts the coding exons of the proto-oncogene in close contact with enhancer elements of the switch region of the immunoglobulin heavy-chain gene on chromosome 14, leading to c-*myc* deregulation [85, 86]. Activation of c-*myc* has been consistently correlated with malignant B-cell transformation [87, 88].

Similarly to sporadic BL, EBV genoma is present within tumoural cells in less than 30% of cases [64, 73]. Thus, EBV does not have a role in the pathogenesis of the majority of HIV–BL cases.

An important difference between these HIV–BL and HIV–DLC/IL is the timing of occurrence of the tumours during the course of HIV disease. In BL, the median CD4 cell count (266/μl, range 28–1198) is significantly higher than in DLC/IL (112/μl, 0–1125), at the time of NHL diagnosis [45]. Most BL (87%) occur in patients without previous manifestations of AIDS. Similar findings have also been identified in smaller series [52, 89].

The development of BL does not seem to be primarily associated with a profound immune deficiency, as is the case for DLC/IL, and other still unidentified factor(s) related to HIV infection are probably involved in the pathogenesis of HIV–BL. As already pointed out, there is extensive B-cell proliferation since the first stages of HIV infection, triggered by HIV itself. In the African form of BL, it has been suggested that B-cell proliferation caused by early and repetitive malaria attacks may be an important cofactor in the origin of the tumour [90]. Hence, we may hypothesise that the corresponding HIV-related B cell proliferation, combined with mild immunosuppression, participates in BL genesis.

Another possibility would be a direct participation of HIV in tumorigenesis. HIV is not considered to be a transforming retrovirus, but it may have transforming properties *in vitro*: malignant transformation was documented in B-cell lines derived from EBV-seropositive subjects and infected *in vitro* by HIV [91]. The malignant clones had marked enhancement of EBV-LMP (latent membrane protein) and c-*myc* transcripts, which could mediate transformation. After subcutaneous injection into severe combined immunodeficiency (SCID) mice, these transformed cells formed invasive tumours of the BL phenotype. However, the fact that HIV genoma has not been identified within tumour cells is an important limitation to this *in vitro* model, and more data are required to define the relevance of these findings.

Finally, retroviruses other than HIV may also be viral cofactors in lymphomagenesis. A type D retrovirus, closely related to Mason–Pfizer monkey virus (MPMV) [92] has now been isolated from cell lines derived from two HIV–BL of the same patient [93]. The study provided evidence that the isolated virus was not a laboratory contaminant, including identification of specific viral DNA sequences in patient's diagnostic bone marrow specimen by polymerase chain reaction, and detection of strong reactivity to MPMV antigens in patient's serum by both immunoblot and immunoprecipitation analysis. Further screening of patients with HIV–BL will be required to ascertain whether this was an isolated case or the harbinger of other coinfections of this type.

Clinical outcome of HIV-associated NHL

The overall outcome of our group of patients was extremely bad [45]. Of the 100 treated patients, only 37 achieved complete remission (CR). The CR rate was 69% for patients with localised nodal disease (stages I and II), 31% for patients with disseminated disease (stages III and IV) and 33% for those with stage Ie disease. These patients were treated in different centres affiliated with the French Registry of HIV-associated tumours, with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-based regimens, sometimes combined with focal radiotherapy. There was a trend to a lower CR rate in DLC/IL (30%) than in BL (46%), but it was not statistically different. The overall 2-year actuarial survival rate was 17% and median survival was only 5 months. The standard treatment was clearly unsatisfactory and most patients died from tumour progression. Furthermore, AIDS-related opportunistic infections frequently developed (especially in patients with previous infectious episodes), and were responsible for 30% of deaths. The HIV disease clinical status at the moment of NHL diagnosis seems to be a useful prognostic factor. Patients with previous AIDS-related opportunistic infections had a lower CR rate (16% vs. 53%) and a poorer survival (median 3 months vs. 8 months) than patients without previous AIDS diagnosis.

Our results are similar to other reported series, in which median survival ranged from 4 to 7 months [30, 41, 55, 57, 94, 95]. In one trial, intensive chemotherapy (MACOP-B) appeared to benefit a small group of 11 selected patients: complete remission rate was 64% and median survival 20 months [96]. Interestingly, most of these patients had a good initial clinical condition, with localised disease and no previous AIDS-related events. Mucositis and myelosuppression were severe in patients with previous opportunistic infections. Kalter *et al.* [52] had previously reported that therapy could be better tolerated and survival improved in the subset of patients without severe previous or concomitant opportunistic infections. Similarly, patients with CD4 cell counts higher than 200/μl had a better prognosis [95]. In this study, besides a lower CD4 cell count, a history of prior AIDS, bone marrow involvement and stage IV disease were independently associated with decreased survival.

Myelosuppression has been the major dose-limiting chemotherapy toxicity in HIV-infected patients, even with low-dose regimens [95]. Therefore, inclusion of haematopoietic growth factors is a logical alternative in clinical trials on HIV–NHL patients. In a phase I trial, Walsh *et al.* [97] reported that use of recombinant human granulocyte–macrophage colony stimulating factor (GM–CSF) allowed safe dose escalation of a modified m-BACOD regimen. In a randomised trial on 26 patients, Kaplan *et al.* [98] showed that GM–CSF given on days 4 through 13 after each cycle of CHOP was useful in reducing haematological and infectious complications. Dose reductions and treatment delays were less frequent in comparison with patients who had not received GM–CSF. The study did not demonstrate significant advantages in clinical response or survival, probably due to the small number of patients enrolled. One troubling observation was that GM–CSF seems to have stimulated viral replication, as indicated by an important rise (median 320%) in the HIV p24 antigen level in the third week following administration of a first cycle of chemotherapy. p24 levels returned to baseline 4 weeks after the last cycle of chemotherapy, and the clinical significance of this finding remains to be clarified. Recent studies have shown that GM–CSF directly enhances HIV replication either in cultured monocyte–macrophages [99, 100], or in HIV-infected patients who received subcutaneous GM–CSF [101]. Clinical trials of cytokines should incorporate appropriate laboratory assessments of the viral load progression [102].

Table 3. Randomised clinical trial for HIV-associated NHL

	Dose (mg/m² per day)	
Arm 1*		
Vincristine	1.2	Days 1 and 5
Cyclophosphamide	1500	Day 2
Bleomycin	10	Days 2 and 5
Mitoxantrone	12	Days 1 and 2
Methylprednisolone	80	Days 1–5
Arm 2*		
Vincristine	1.2	Days 1 and 5
Cyclophosphamide	1 500	Day 2
Bleomycin	10	Days 2 and 5
Mitoxantrone	12	Days 1 and 2
Etoposide	120	Days 3 and 4
Cisplatin	30	Days 2 and 4
Methylprednisolone	80	Days 1–5

Three cycles are done each 21 days. Patients in complete remission after 3rd cycle receive three additional cycles. Central nervous system prophylaxis is done by intrathecal methotrexate, 15 mg, in each chemotherapy cycle.

* Patients with CD4 cell counts lower than 200/μl or prior opportunistic infections receive half-doses.

We are now conducting a multicentre trial of a multidrug regimen, with chemotherapy intensity modulated by the patient's immunological state (Table 3). In this protocol, patients with no previous AIDS-related episode and with CD4 cell count higher than 200/μl are treated with full intensive doses, while the others are treated with a lower dose. Central nervous system prophylaxis with intrathecal chemotherapy is systematically performed. Pneumocystis pneumonia prophylaxis is also done for all patients. Zidovudine is given when possible, since its combination with chemotherapy is often limited by cumulated haematological toxicity.

HODGKIN'S DISEASE

Clinical characteristics

Since 1984, an increasing frequency of HD in patients at risk of AIDS has been reported [35–37, 41, 55, 103–110]. Between January 1987 and March 1990, we recorded 45 cases of HIV–HD (i.e. a mean of 15 patients per year) [111]. This number is far from representing all HIV–HD cases observed in France during this period. Many other large specialised haematological centres not affiliated with the registry deal with these patients. At best, we may have tracked down 25% of French HIV–HD cases. Considering that the number of HIV-infected subjects in France is between 80 000 and 200 000 [112], and even assuming that 50% of the cases were included in the registry, the annual incidence of HD would be at least 15 to 37.5 per 100 000 seropositive subjects. This largely underestimated incidence is at least 3–7 times greater than the incidence of HD in western countries [113].

However, epidemiological studies have not detected an increase in the incidence of HD in single men (surrogate of homosexual population) in the past decade in the USA [32, 114]. In our registry, the ratio of HD to NHL is significantly higher in patients who abused intravenous drugs (0.7) than in homosex-

uals (0.16). Similar data were reported by others [56, 108] and it is possible that HD may occur preferentially in this particular risk group [115].

HIV–HD has a particular clinical and histological profile, which is constant in all reported series. In our series, mixed cellularity subtype represents 49% of the cases (22/45). In a study where histology was carefully reviewed, Ree *et al.* [116] suggest that typical nodular sclerosis, which is the most frequent subtype in primary HD, virtually never occurs in the HIV setting. Instead, some tumours are characterised by fibrohistiocytoid stromal cells, that may mislead to a diagnosis of HD of a nodular sclerosis type. In contrast to primary HD, immunological tissue marker studies in HIV–HD demonstrated severe depletion of helper T-lymphocytes, with a predominance of suppressor/cytotoxic cells [41, 105].

HIV–HD frequently presents as disseminated disease: in our series 19/45 patients had clinical stage III and 15/45 had stage IV. Bone marrow was involved in 12 cases (27%), and liver in 7 (16%). 80% of the cases presented with constitutional symptoms (high temperature, sweats and weight loss). Unusual sites of HD involvement have been described, such as rectum, skin, Waldeyer ring, meninges, colon, base of tongue and paraspinal tissue [37, 103, 109, 117, 118].

One striking feature of HIV–HD is the lack of mediastinal involvement, even in cases with extensive nodal and visceral disease. In our series, 88% of patients had no mediastinal involvement. Similar findings have been reported [37, 41, 108, 116]. This contrasts with primary HD, in which approximately 70% of the patients have mediastinal disease [119]. Interestingly, when we analysed only mediastinal tumour-free patients, mixed cellularity type predominated similarly in both HIV–HD (38%) and primary HD (37%) [111]. This result confirms reports that histological type and clinical profile are correlated in HD [120]. Nodular sclerosis tends to predominate in mediastinal tumours, whereas mixed cellularity is more frequent in the other forms of HD. Interestingly, the "peripheral" (mediastinal tumour free) presentation is more frequently seen in men [119].

Thus, overall, the increased incidence of HD in HIV-infected subjects does seem to be the result of a specific clinicopathological entity, occurring preferentially in intravenous drug abusers. This hypothesis should be confirmed by large epidemiological studies.

As described for HIV–BL, HD appears in patients without profound immunodepression. 65% of the patients were asymptomatic (CDC II/III) in the 3 months preceding diagnosis of HD, and only 11% had a previous episode of AIDS. Median CD4 cell count was 306/μl (72–800) [111]. This is not surprising, considering that HD is not usually associated with other types of severe immunosuppression. If HD is actually associated with HIV, other factors specifically related to HIV disease should be involved. In this regard, it is interesting to note that the frequency of EBV genoma found in HIV–HD seems to be higher than in primary HD [121]. EBV has been associated with primary HD [122–124], and particularly with the mixed cellularity subtype [125].

Treatment and outcome

HIV–HD seems to be exquisitely sensitive to chemotherapy, considering its aggressive clinical presentation. The complete remission rate in our series was 81%. In other studies, the rate was lower, ranging from 47 to 54% [41, 55, 108, 109]. Our patients were treated by conventional HD chemotherapy, generally including MOPP (mechloretamine, vincristine, procarbazine, prednisone) and/or ABVD (doxorubicin, bleomycine, vinblastine, dacarbazine) sometimes associated with focal radiotherapy. Most of the patients did not tolerate full doses of chemotherapy, due to severe haematological toxicity. Despite a reasonable treatment response, median survival was short in all the reported series, ranging from 8 to 18 months [37, 41, 108, 109]. Median overall survival was 20 months in our series. The principal cause of death was AIDS-related opportunistic infections, mainly *Pneumocystis carinii* pneumonia. Indeed, the progression-to-AIDS rate was very high after beginning of treatment. The 3-year AIDS progression rate was 71% for HIV–HD compared with 24% for seropositive subjects followed in our institution from 1984 to 1988 [126]. HD-related immunodeficiency seems to contribute to the manifestation of HIV-associated opportunistic infections.

At present, no prospective clinical trial of HIV–HD have been reported. The major problem is the heightened toxicity of standard therapy in HIV–HD patients. A preliminary report on 5 patients [127] suggests that a so-called non-myelotoxic regimen (bleomycin, vincristine, streptozocin and etoposide), may be well tolerated. Further evaluation of this kind of approach is required. In our series, a CD4 cell count below 300/μl was associated with worse prognosis. Prospective clinical trials should take the degree of immunosuppression of each patient into account. *Pneumocystis carinii* prophylaxis is mandatory, since interstitial pneumonia is the most frequent cause of death. Chemotherapy combined with haematological growth factors would also be an attractive strategy. Also, the feasibility of concomitant zidovudine should be evaluated.

CONCLUSIONS AND TREATMENT RECOMMENDATIONS

Malignant lymphomas are a frequent complication of HIV infection and their incidence seems to be increasing with the extended survival of seropositive individuals. HIV–NHL may be divided in two groups according to clinical, histological and immunological features. On the one hand, there are DLC/IL associated with profound immunosuppression, and frequently presenting as isolated extranodal tumours. These tumours are possibly associated with an EBV-related B-cell proliferation in the absence of cellular cytotoxic control. On the other hand, there is BL that almost always presents as a disseminated nodal and visceral disease, involving bone marrow and meninges. Most HIV–BL resemble sporadic BL of Western countries, both in terms of chromosomal translocation pattern and lack of EBV genoma. These HIV–BL occur at any stage of HIV disease, frequently at early stages, and seem to be associated with other factors, rather than with the immunodeficiency itself. Prognosis of HIV–NHL is very poor and new treatment approaches are urgently needed.

HD also appears to be increased in HIV-infected patients, and more specifically in intravenous drug abusers (at least in Europe). HIV–HD present with a particular clinicopathological profile: most patients have disseminated disease of the mixed cellularity type, sparing the mediastinum. HIV–HD is highly sensitive to conventional therapy but toxicity is severe and survival is poor because of AIDS-related infections.

Bearing in mind that these malignant lymphomas are actually secondary to HIV infection, the most effective ways of dealing with these tumours are effective primary HIV prevention and the development of drugs capable of stopping HIV disease progression early in its course. Further, even if these lymphomas were cured by new treatment approaches, patients would con-

tinue to die of AIDS. Nevertheless, available data indicate that at least some patients can be fully treated, achieve complete remission and have a prolonged survival.

Recommendations for the treatment of HIV-associated lymphomas include the following: first, regular staging should be followed. HIV clinical status prior to lymphoma diagnosis should be carefully assessed. CD4 cell count should be measured, as well as serum p24 antigen. Serum, plasma and peripheral blood mononuclear cell samples should be cryo-conserved for viral load measurements. Secondly, patients with a CD4 cell count over 200/μl and no previous AIDS episode should receive updated chemotherapy regimens (including autologous bone marrow transplantation). Central nervous system (CNS) prophylaxis should be performed for patients without initial CNS involvement. Treatment would be improved if all these patients were enrolled in prospective clinical trials. Thirdly, patients with CD4 below 200/μl and/or previous AIDS episode should be treated with less intensive regimens, taking into account the fact that long-term survival of these patients is not expected with available cancer and retroviral therapy. Fourthly, *Pneumocystis carinii* pneumonia prophylaxis is mandatory for all patients during treatment and thereafter. Fifthly, antiretroviral therapy, such as zidovudine 500 mg per day, should also be tried for all patients, with close monitoring of haematological toxicity. And finally, GCSF may be used with careful monitoring of viral load.

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