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Clinical aspects and management of Hodgkin's disease and other tumours in HIV-infected individuals

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Abstract

As the AIDS epidemic advances, the spectrum of malignancies encountered is expanding. Several non-AIDS defining cancers, i.e. Hodgkin's disease (HD), anal and testicular cancer, are increasing in incidence in HIV-infected patients. The widespread use of highly active antiretroviral therapy (HAART) in industrialised countries has resulted in substantial improvement in the survival of HIV-infected patients. It is likely that in the future, cancers associated with long-term mild immune suppression will occur at an increased rate in long-term survivors of HIV infection. The natural history of the majority of non-AIDS defining tumours differs from that of the general population. Unusual aspects of tumour localisation, growth behaviour and therapeutical responses distinguish tumours in patients with HIV infection from those without. This paper reviews the most relevant data on the epidemiology, pathology, clinical features and treatment of the most frequently reported non-AIDS defining tumours, i.e. HD, lung, testicular and skin cancers.

Keywords: HIV; Non AIDS-defining tumours; Hodgkin's disease; Testicular germ cell cancer; Lung cancer; Skin cancer

1. Introduction

The full spectrum of HIV-induced malignancies has not been fully elucidated, but a large variety of cancers, other than AIDS-defining tumours, have been diagnosed in HIV-infected individuals [1–11]. Prospective epidemiological studies have demonstrated an increased risk of some non-AIDS-defining tumours, including Hodgkin's disease (HD), anal carcinoma, oropharyngeal malignancy, testicular carcinoma, multiple myeloma and melanoma [10–12]. HIV-related immunodeficiency increases the risk of HD approximately 8-fold compared with the general population, whereas the evidence for a relationship between HIV and the other non-AIDS defining tumours is still a matter of controversy [10].

The widespread use of highly active antiretroviral therapy (HAART) in industrialised countries has resulted in substantial improvement in the survival of HIV-infected patients [13–16]. It is likely that in the future, cancers associated with long-term mild immune suppression will occur at an increased rate in long-term survivors of HIV infection.

Regardless of epidemiology, however, the natural history of the majority of non-AIDS-defining tumours is altered in the setting of HIV infection. Moreover, the diagnosis of a non-AIDS defining tumour may be very difficult in HIV-infected patients, because symptoms and radiological abnormalities of cancer may coincide with those of more common opportunistic infections (OIs) or HIV infection itself.

This review will summarise the pathology, clinical features and treatment of the most frequently reported non-AIDS-defining tumours, i.e. HD, lung cancer, testicular and skin cancers.

2. Hodgkin's disease

HD represents the most common type of a non-AIDS-defining tumour that occurs in the HIV population [9–12]. More than 500 cases of HD in HIV-infected individuals have been reported, namely from the European countries (i.e. Italy, Spain and France) and to a lesser extent from the United States [9–12,17–22]. All

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series have documented unusually aggressive tumour behaviour, including higher frequency of unfavourable histological subtypes, advanced stages and poorer therapeutic outcome compared with the behaviour of HD outside of the HIV setting.

2.1. Clinical features

One of the most peculiar features of HIV-HD is the widespread extent of the disease at presentation and the frequency of systemic 'B' symptoms, including fever, night sweats and/or weight loss >10% of the normal body weight. At the time of diagnosis, 70–96% of the patients have 'B' symptoms and 74–92% have advanced (stage III–IV according to Ann Arbor staging classification) disease with frequent involvement of extranodal sites, the most common being bone marrow, liver and spleen.

In HIV-uninfected patients, HD typically involves contiguous lymph node groups and dissemination to extranodal sites is a late occurrence. In HIV-infected patients, noncontiguous spread of the tumour may be observed, e.g. liver involvement without spleen disease, lung involvement without mediastinal adenopathy, and extranodal disease has been described in approximately 60% of cases at presentation. Bone marrow involvement is common, occurring in 40–50% of patients, and it may be the first indication of the presence of HD, in approximately 20% of cases. Liver involvement develops in 15–40% of the patients, whereas the spleen is involved in approximately 20% [17–23]. Unlike HIV-non-Hodgkin's lymphoma (NHL), in HIV-HD unusual sites of disease are not common, but case reports with central nervous system (CNS), skin, rectum, tongue and lung involvement have been reported [17,20,23–25].

HD tends to develop as an earlier manifestation of HIV infection with higher median CD4+ cell count, ranging from 275 to 306/μl, than seen in patients with HIV-diffuse large cell lymphoma [17–21]. At the time of diagnosis, the majority of patients with HD have persistent generalised lymphadenopathy (PGL) (65% of cases in the Italian series) and in approximately 50% of cases the HD may be concurrently present with PGL in the same lymph node group. HD may be clinically confused with PGL, therefore an increase in size of a preexistent adenopathy in patients with PGL should be evaluated with a biopsy [17,26]. The initial diagnostic work-up may also require, in particular cases, lymph node biopsies at multiple sites. On the other hand, clinicians should recognise the possibility that HIV-positive patients may be overstaged with computed tomography (CT) scan of the abdomen as well as lymphangiography, owing to the possible presence of PGL in enlarged retroperitoneal lymph nodes. Hilar and mediastinal lymphadenopathy are not usually part of HIV-related PGL [26].

Systemic symptoms are frequently associated with both advanced HIV infection and OIs. Thus these symptoms mandate a careful evaluation to exclude other causes, including the presence of tuberculosis, cryptococcosis or cytomegalovirus infection.

The Italian series is the largest published series collected so far [17]. In fact, from November 1986 to September 2000, within the Italian Cooperative Group on AIDS and Tumors (GICAT) we have collected data on 206 patients with HIV-associated HD. 180 patients (87%) were males and the median age was 31 years (range 19–63 years). With regard to the risk group, the majority (69%) of patients were intravenous (i.v.) drug users, in accordance with the epidemiology of HIV infection in Italy. At the time of diagnosis of HD, 44 out of 188 patients (23%) had a diagnosis of AIDS, 33 out of 188 (18%) had PGL, 37 out of 188 (20%) had an AIDS-related complex, and 74 out of 188 (39%) were asymptomatic for HIV infection. The median CD4 cell count at the diagnosis of HD was 231/μl (range 4–1100/μl).

9 out of 200 (5%) patients had stage I disease, according to Ann Arbor staging, 27 (14%) had stage II, 56 (28%) had stage III and 108 (54%) had stage IV. 150 out of 188 patients (80%) had B symptoms at the onset of HD. The overall extranodal involvement was 65% with bone marrow, spleen and liver involved in 39, 31 and 19, respectively. (Table 1) (data not shown).

Table 1
Clinical findings of 206 evaluable patients with HIV-related Hodgkin's disease (HD)

	n (%)
Histology	
LP	4 (2)
NS	48 (27)
MC	96 (53)
LD	32 (18)
Stage (Ann Arbor)	
I	9 (5)
II	27 (14)
III	56 (28)
IV	108 (54)
Extranodal involvement	130 (65)
Bone marrow	78 (39)
Spleen	62 (31)
Liver	37 (19)
Lung	11 (6)
Bone	7 (4)
Gastrointestinal tract	3 (2)
Skin	2 (1)
CNS	2 (1)
Waldyer ring	1 (0.5)
Testis	1 (0.5)
B symptoms ($n=188$)	150 (80)

LP, lymphocytes predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; CNS, central nervous system.

Another distinctive feature of HIV-HD is the lower frequency of mediastinal adenopathy compared with 'primary' HD. Overall, the absence of mediastinal disease ranges from 77 to 87% in HIV-infected patients versus only 29–42% of HIV-negative control cases [17–21]. It is noteworthy that in the Italian series this difference was significant also in patients with the nodular sclerosis subtype (27% in HIV-positive versus 80% in HIV-negative patients, $P < 0.001$) [17].

2.2. Therapy

Optimal therapy for HIV-HD has not been defined. Because most patients have advanced Hodgkin's disease, they have been treated with combination chemotherapy regimens, i.e. MOPP (mechlorethamine, vincristine, procarbazine and prednisone), and more recently with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), but the complete response (CR) rate remains lower than that of 'primary' Hodgkin's disease. Moreover, the therapy of HIV-HD presents many problems. The main one is represented by immunosuppression induced by antineoplastic treatment, that can further compromise the immunocellular deficit of HIV-infected patients, and can facilitate the onset of OIs and/or the evolution of the HIV infection itself. Furthermore, although CD4+ cell counts in these patients are usually normal or slightly decreased at diagnosis, they may become severely depressed during and after treatment, leading to a higher susceptibility to OIs. Finally, leucopenia, frequently present in patients with HIV-HD due to previous therapy with nucleoside analogues and/or to HIV-related myelodysplasia, sometimes makes conventional dosage of chemotherapy difficult to administer.

Retrospective evaluations of therapy reported in the literature have revealed that CR rate is far below that reported in patients with HD without HIV infection. Furthermore, tolerance to chemotherapy has been poor, and reduction of doses or delay of chemotherapy are often needed with the overall median survival time being approximately 1.5 years [17–21].

We retrospectively evaluated the CR rate and the incidence of OIs of 66 patients treated with MOPP, ABVD or MOPP alternating with or followed by ABVD. The complete remission rate was 45% in the MOPP-treated patients, 80% in the ABVD-treated patients and 77% in patients treated with MOPP/ABVD. Furthermore, a lower rate of OIs was observed in the ABVD-treated group (29%) in comparison to that observed in the MOPP group (71%) and in the MOPP/ABVD group (79%).

In a prospective trial, conducted within the GICAT between March 1989 and March 1992, 17 previously untreated patients with HIV-HD were enrolled in a study employing a regimen of epirubicin, vinblastine and bleomycin (EBV) [27]. EBV is a modification of the EBVP (epirubicin, vinblastine, bleomycin and prednisone) regimen, an ABVD-like regimen with low bone marrow toxicity developed by Zittoun and colleagues for patients with 'primary' HD [28]. The patients were stratified into those with Eastern Cooperative Oncology Group (ECOG) performance status of less than 3 and without history of OI (group A), and those with ECOG performance status of 3 or more, or previous OI (group B). The latter group received a 50% reduction in the doses of epirubicin and vinblastine, with full-dose bleomycin. Furthermore, zidovudine (the only anti-HIV drug available at that time) was also administered from the outset of chemotherapy to this group, whereas patients in group A received full-dose chemotherapy, with zidovudine beginning only after the third cycle. Courses were repeated every 21 days for six cycles. Overall, CR was achieved in 53% of the total group, lasting a median of 20 months. 67% of group A patients experienced complete remission, whereas only 1 of 5 patients in group B (20%) experienced a complete remission, which lasted for 5 months. The median survival for the group as a whole was 11 months and the 2-year disease free survival rate was 55% [27].

In an attempt to improve upon these results, from 1993 to 1997, a second prospective trial consisting of full dose EBV plus prednisone (EBVP regimen), concomitant antiretroviral therapy (zidovudine or didanosine), primary use of granulocyte-colony stimulating factor (G-CSF) and Pneumocystis carinii pneumonia prophylaxis was conducted. The results of this trial, in which 35 patients were enrolled, showed a complete remission rate of 74% and an OI rate during or after chemotherapy of 8% (median follow-up 22 months). Toxicity was moderate with grade 3–4 leucopenia and thrombocytopenia in 29 and 9% of patients, respectively. 38% of patients who achieved a CR relapsed. Overall, HD progression alone and in association with OIs was the cause of death in 48 and 9% of patients, respectively. The 3-year survival rate and the 3-year disease-free survival was 32 and 53%, respectively [29].

An overall evaluation of these two trials (EBV and EBVP) on 59 patients shows a CR rate of 66% and an incidence of OIs of 31%.

The AIDS Clinical Trials Group (ACTG) reported the preliminary results of a phase II study in 21 patients treated with ABVD chemotherapy for four to six cycles and primary use of G-CSF. Antiretroviral therapy was not used. The vast majority (90%) had systemic 'B' symptoms at diagnosis and 67% had stage IV disease. Despite the routine use of G-CSF, 48% experienced absolute neutrophil counts $< 500/10^6$ cells/l. The CR rate, on an intent-to-treat analysis was 43% with an overall objective response rate of 62%. Median survival for all patients was 18 months [30].

Considering that HD is an earlier manifestation of HIV infection than NHL (i.e. higher CD4+ cell count, significant lower percentage of previous AIDS), the treatment approach for the two entities may be different. We have recently started a prospective phase II study using the Stanford V regimen, consisting of short-term chemotherapy (12 weeks) with adjuvant radiotherapy (RT). When employed in unfavourable HD in the HIV-negative population, excellent complete remission rates and disease-free survival (DFS) rates have been shown [31].

From May 1997 to June 1999, 20 patients (19 males and 1 female) were treated in seven centres participating in the European Intergroup Study HD-HIV. The median age was 36 years (range 28–56 years). Only 3 patients (15%) had been diagnosed with AIDS before starting chemotherapy (2 patients for oesophageal candida and 1 patient for PCP). The median CD4 cell count was 230/μl (range 45–468) and 10/20 (50%) patients had a detectable HIV viral load (median 30.785 copies/μl, range 60–455.000). The median performance status (PS) according to ECOG was 1 (range 0–3). As for the HD histological subtype, the distribution was as follows: mixed cellularity in 9/20 (45%) cases, nodular sclerosis in 6/20 (30%) and lymphocyte depletion in 1/20 (5%). In 4 cases, the histological subtype was not determined. Stage II was detected in 5/20 (25%) patients, stage III in 5/20 (25%) and stage IV in 10/20 (50%) cases. 14 out of 20 patients (70%) had B symptoms. Half the patients had extranodal involvement, in particular, bone marrow in all patients and liver in 2 patients. Overall, Stanford V was well tolerated and 11/20 (55%) patients completed treatment with no dose reduction and no delay in chemotherapy administration. In 8 patients (40%), the dosage of all the drugs, with the exception of prednisone had to be reduced to 75% of the planned dose because of constipation in 3 cases (grade 3), parasthesias in 3 (2 G2 and 1 G3), bone marrow toxicity in 1 patient and worsening PS in another. Only in 1 patient who had developed life-threatening sepsis was chemotherapy definitely discontinued after the second cycle. No toxic deaths were observed. All patients, but 2, experienced G3–G4 bone marrow toxicity and 7 (38%) developed febrile neutropenia treated with i.v. antibiotics. Sepsis occurred in only 2 cases. As far as extra-haematological toxicity is concerned, 9 patients had mucositis (G2 in 6 cases and G3 in 3 cases) and 8 had sensorial neurotoxicity (G1 in 1 case, G2 in 6 cases and G3 in 1 case). One patient had G2 hepatic toxicity.

Out of the 10 patients with stage II–III disease, only 2 showed bulky disease and were then eligible for RT. However, one refused treatment, while the other one was lost to follow-up at the time of RT because of the concomitant use of illicit drugs.

16 patients (80%) achieved a CR, 3 (15%) a partial remission and 1 patient (5%) progressed. 4 patients (25%) out of the 16 who had achieved CR have already relapsed. 3 patients have died from HD progression, mycobacterium avium infection and myocardial infarction, respectively. The latter cause of death is not apparently treatment-related in that the patient died 2 months after the end of chemotherapy and was affected by primary pulmonary hypertension. The actuarial overall survival (OS) and DFS at 18 months are 76 and 61%, respectively.

The CD4 cell count after 3 months from the end of chemotherapy was 231/μl (range 21–594) and only 2/10 patients with undetectable HIV viral load before chemotherapy had become positive, probably as a result of HIV progression. On the contrary, 6/10 patients with a detectable viral load when chemotherapy was started had become negative. Table 2 shows the response to therapy in Italian series.

Our preliminary results [23] demonstrate that Stanford V is feasible and active in the setting of HIV-related HD. Furthermore, the concomitant use of HAART does not seem to increase chemotherapy toxicity [32].

In conclusion, the outcome of patients with HIV-HD should be improved with better combined antineoplastic and antiretroviral approaches. The availability of the new and effective antiretroviral drugs (i.e. protease inhibitors), used in conjunction with nucleoside analogues might improve the control of underlying HIV infection when used during treatment of HD with chemotherapy. In fact, the possibility of reducing viral load to undetectable levels and the increase of CD4+ cell count reduce the risk of OIs during antineoplastic treatment. The inclusion of haematopoietic growth factors in the treatment of patients with HIV-HD might allow the administration of a higher dose intensity chemotherapy and the prolonged use of antiretroviral drugs, with the aim of improving the survival times of these patients. Finally, more effective antineoplastic regimens, as the aggressiveness of HIV-HD would require, should be used in order to improve the response rate and disease-free survival of patients with HIV-HD.

3. Lung cancer

In the general population, lung cancer is the second most common cancer in men and women and it is the most common cause of cancer mortality for both sexes. An approximately 2-fold increased risk of lung cancer has been noted among people with AIDS, but the equal risk pre- and post-AIDS ($P \geqslant 0.13$) suggests that the risk is likely attributable to higher levels of cigarettes smoking or other confounders rather than to HIV-related immunodeficiency [11].

Many features of lung cancer in HIV-infected patients differ from the disease in the general population [33–46].

The median age at diagnosis ranges from 38 and 48 years compared with 55–70 years in the general population (Table 3).

Adenocarcinoma is the predominate histopathological type, ranging from 29 to 100% of cases, whereas small cell histology is rare (approximately 5–14% of cases). This feature differs from the usual distribution of tumour type in most lung cancer series of the general population, where adenocarcinoma, squamous cell and small cell carcinoma each account for approximately one-third of cases. However, a larger percentage of adenocarcinoma has been reported in studies of lung cancer occurring in the subset of younger HIV-uninfected patients [43]. These findings stress the need for case–control studies to compare the prevalence of adenocarcinoma in young age groups, with and without HIV infection.

Lung fibrosis is one of the most common cofactor risks for the development of adenocarcinoma in the general population. In one of the two largest published series of HIV-infected patients with lung cancer, a high (54%) association between tuberculosis infection (a fibrosing disease) and adenocarcinoma has been found. Severe immunodeficiency may not be a significant cofactor in the pathogenesis of lung cancer in these patients, median CD4 cell count ranging from 103 to 150/μl [44]. Overall, tobacco smoking appears to be the major carcinogen in HIV-infected patients, being present in more than 80% of cases, similar to figures in the general population [35,37,40,41,44,45].

More than 70% of HIV-infected patients present with advanced (stages III–IV according to TNM classification) or inoperable disease, including two-thirds with metastases at the time of diagnosis. Two studies, however, did not identify a difference in clinical stage between HIV-seropositive and HIV-indeterminated control subjects [37,44].

The typical symptoms of lung cancer (cough, chest pain, haemoptysis, dyspnoea) do not distinguish HIV-infected from non-infected patients. However, diagnosis of lung cancer may be delayed in HIV-infected patients, because the signs and symptoms of the disease may be similar to that of common thoracic OI.

Lung cancer must be considered in the diagnosis of an abnormal chest X-ray film, especially when one or more

Table 2
Response to therapy in patients with HD and HIV infection

	MOPP		ABVD		MOPP/ABVD		EBVP		Stanford V	
Regimen	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
No. of assessable patients	20/24	(83)	15/16	(94)	22/26	(85)	59/60	(98)	20/20	(100)
No. of cycles										
Median (range)	5 (1–7)		4 (1–10)		6 (1–11)		6 (1–8)		3 (1–3)	
Complete remission	9/20	(45)	12/15	(80)	17/22	(77)	39/59	(66)	16/20	(80)
Initial CD4+ count/μl										
Median (range)	345 (78–829)		270 (67–850)		254 (110–842)		175 (4–1100)		230 (45–468)	
Opportunistic infections follow-up	12/17	(71)	4/14	(29)	15/19	(79)	17/54	(31)	1/20	(5)
Median follow-up (months)	22		19		33		16		10	

MOPP, mechlorethamine, vincristine, procarbazine and prednisone); ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; EBVP, epirubicin, vinblastine, bleomycin and prednisone).

Table 3
Clinical features and survival of 84 patients with lung cancer and HIV infection

	Krap *n* (%)	Shridhar *n* (%)	Gruden *n* (%)	Bazot *n* (%)	Tirelli *n* (%)
No. of patients	7	19	7	15	36
Age years, median (range)	38 (?)	47 (36–66)	42 (?)	48 (29–71)	38 (28–58)
CD4 count/μl median (range)	?	121 (13–628)	103 (7–468)	136 (10–579)	150 (3–835)
Histology					
Small cell carcinoma	–	1 (5)	1 (14)	2 (13)	5 (14)
Squamous cell carcinoma	–	6 (32)	2 (29)	5 (33)	12 (39)
Adenocarcinoma	7 (100)	8 (42)	2 (29)	7 (47)	13 (36)
Other	–	4 (21)	2 (29)	1 (7)	6 (17)
Stage					
III–IV	7 (100)	15 (79)	4 (57)	10 (67)	26 (72)
Survival (months)	1	3	?	14	5

of the following features are present: presence of a mass lesion in the lung, unilateral hilar adenopathy, rib destruction, Pancoast's syndrome, hard and/or fixed scalene lympadenopathy, phrenic and/or left recurrent nerve paralysis and paraneoplastic syndromes commonly associated with lung cancer. However, the syndrome of inappropriate secretion of antidiuretic hormone may occur in patients with infections and/or cancer of the lung. The neoplasia may also appear unexpectedly during broncoscopy and broncoalveolar lavage in the workup of an OI.

The diagnosis of lung cancer should be made by sputum/bronchoalveolar lavage cytology and/or histologically examination of the tissue obtained by invasive procedures, i.e. bronchoscopy (brush or transbronchial biopsies) or percutaneous needle biopsy (PTNB). Other diagnostic procedures may include thoracentesis, pleural biopsy and mediastinoscopy. If indicated liver, brain and bone scans should be also performed.

While bronchoalveolar lavage has a high diagnostic yield for opportunistic organisms, cytological examination of the lavage fluid has been disappointing in confirming malignancy. However, viral infections can produce cellular changes difficult to distinguish from malignancy, especially adenocarcinoma.

In patients with peripheral masses, PTNB under computer tomography (CT) guidance is the diagnostic procedure of choice, lacking significant morbidity in the majority of series [45].

Lung cancer may be missed in some patients with HIV infection. Underdiagnosis may occur due to the difficulty in performing invasive diagnostic procedures because of the poor general and respiratory status and/or to patients' non-compliance.

The available survival data suggest a very poor prognosis for HIV-seropositive patients with lung cancer, with few survivors beyond 1 year from diagnosis. In the majority published series (Table 3) the median survival was only 1–14 months, and most patients died of cancer progression [33–46].

There are few data to support specific treatment recommendations for HIV-infected patients with lung cancer. However, it is important that characteristics of the underlying HIV disease are not ignored. Therapy should be individualised, based not only on tumour histology and stage, but on the degree of HIV-related immunodeficiency, as well as the feasibility of effective HAART.

HIV infection is not a contraindication to surgery in patients with potentially resectable disease and absence of severe immune deficiency. Unfortunately, the large majority of patients present with advanced inoperable disease and are candidates for palliative RT or chemotherapy. Careful attention must be paid to the patients' quality of life.

4. Testicular germ cell cancer

Testicular germ cell cancer is relatively rare and among the most curable malignancies. However, testicular germ cell cancer is a relatively common disease in young men between 15 and 35 years of age, an age group in whom HIV infection is commonly seen. Therefore, this malignancy should not be expected to be a rare event in young men with HIV infection. To date, more than 110 cases of testicular tumours in HIV-infected patients have been published in the literature [1,6,47–56]. Moreover, recent cohort data form the Pittsburgh area Multicenter AIDS Cohort Study indicate that HIV-seropositive homosexual men have a significant increase in the incidence of testicular cancer (standardised incidence rate = 3.9) compared with that of the general male population [12].

Current reports suggest that the natural history of these diseases in the HIV setting is remarkably similar to that in the general population.

The ratio of seminoma to non-seminoma germ cell tumours has varied in the reported series. In the GICAT's series (the largest published so far), 54% of patients had seminoma and 46% non-seminoma, a proportion similar to that reported in HIV-uninfected individuals with testicular cancer. The median CD4 cell count of 260/μl reported in this series of 26 patients, 60% of whom had asymptomatic HIV disease, suggests that the risk of testicular cancer is not directly related to the level of immune function [56].

Overall, approximately 60–80% of patients have clinical stage I and II (i.e. disease confined to the testis and retroperitoneal lymph nodes), and only 20–30% have clinical stage III (i.e. disseminated disease above the diaphragm or visceral disease), again a proportion similar to that observed in the general population [6,49,54–56].

A testicular mass in a young man with or without HIV infection should be initially considered malignant. In the majority of cases, testicular tumours are painless, but approximately 30% of patients have moderate testicular pain. Cough (pulmonary metastases), abdominal pain (lymph node or retroperitoneal soft tissue metastases, hydronephrosis) or weight loss may all occur with testicular neoplasms.

The diagnosis of testicular germs cancer should be made by radical inguinal orchiectomy. Staging evaluations should include tumour marker studies (i.e. chorionic gonadotropin, alpha fetoprotein and lactic acid dehydrogenase), chest radiographs and abdominal CT scan. As in HD, the presence of PGL should be considered, alerting clinicians to the danger of overstaging carcinoma by abdominal CT scan. In patients with normal serum markers and limited abdominal lymphadenopathy, the PGL should be suspected and careful surveillance alone may be reasonable after orchiectomy.

Germ cell neoplasms are among the most sensitive to chemotherapy and RT, resulting in long-term DFS for patients in the general population of approximately 90% [55]. The majority of HIV-infected patients with germ cell tumours reported in the literature tolerates standard therapy and achieves cure rate similar to that of HIV-uninfected patients [50–56].

Survival of HIV-infected patients with testicular tumours closely parallels the natural history of HIV disease. One-year survival in the study by Bernardi and colleagues was not different from that reported for HIV-infected patients without testicular tumours with similar CD4 cell counts (85 versus 87%) [56]. In the report by Timmerman and colleagues, shorter survival was associated with advanced HIV disease, but not with advanced tumour stage. The median survival times for patients without AIDS and CD4 cell count $\geqslant 200/\mu l$ versus those with AIDS or CD4 cell count $<200/\mu l$ were 40 and 26 months, respectively. The median survival times for patients with limited versus advanced-stage tumours were 42 and 22 months, respectively [55].

For early-stage seminoma, standard treatment is RT, while for advanced disease, it is combined treatment that includes chemotherapy (cisplatin, etoposide and bleomycin (PEB) or cisplatin, vinblastine and bleomycin (PVB)) and RT [57]. In the Italian series, all patients affected by seminoma received standard treatment at the time of diagnosis, according to the stage of disease and irrespective of HIV-seropositivity. As far as patients affected by non-seminoma, all received post surgical chemotherapy (PEB or PVB), also irrespective of HIV status. A 95% of CR rate was observed in the 20 evaluable patients, approximately half of whom received chemotherapy and the other half irradiation (Table 4). Less than 50% of these patients experienced severe grade 3 and 4 haematological toxicity [56]. As was the case in the Italian study, all patients in the Timmerman's series also received standard therapy based on histology and stage, and among 7 evaluable patients who received chemotherapy, 5 achieved CR. It is remarkable that in both these series investigators reported no OI occurring during the treatment [55].

In conclusion, patients with HIV infection affected by testicular cancer should be offered the standard therapeutic approach, since the majority can be cured of their tumour and have a good quality of life. Attention should be paid to effective therapeutic options for the underlying HIV infection and for OI prophylaxis.

5. Skin cancer

5.1. Non-melanomatous skin cancers

The occurrence of non melanomatous skin cancers in patients with primary or iatrogenic immunodeficiency is well known [8]. It is not surprising therefore that HIV-infected patients may be at a high risk of developing cutaneous neoplasms [8,9]. Other risk factors other than immunodeficiency appeared applicable to HIV-infected individuals as well and they include fair skin, a family history and excessive exposure to sunlight [58]. Concurrent human papilloma virus infection in HIV-infected individuals is also an important cofactor [59].

Basal cell carcinoma (BCC) accounts for the majority of epithelial skin neoplasms seen in HIV-infected patients. In a prospective 3-year follow-up study of 724 HIV-infected military personnel, BCC was the second most common cutaneous tumour (prevalence 2%) after Kaposi's sarcoma (6%). In a large retrospective case–control study of 48 HIV-infected patients with non-melanoma skin cancer, 87% of the 116 tumours were BCC. Linkage of AIDS and cancer registries in Italy showed significantly increased standardised incidence ratios (SIR) for HD (SIR 9.3; 95% confidence interval (CI): 4.6–16.6), invasive cervical carcinoma (ICC) (SIR

Table 4
Therapy and response to treatment in 26 patients with germ cell cancers and HIV infection [56]

Therapy	Response	
	n	%
Surgery only	4/26 (1 S, 3 NS)	15
Chemotherapy only (PEB)	1[a]/26 (1 NS)	4
Surgery + chemotherapy (8 PEB, 1 PVB)	9/26 (1 S, 8 NS)	35
Surgery + radiotherapy	10/26 (10 S)	38
Surgery + chemotherapy (PEB) + Radiotherapy	1/26 (1 S)	4
Unknown	1/26 (1 S)	4
No. of patients assessable for response	20/26 (11 S, 9 NS)	
CR	19/20 (11 S, 8 NS)	95
PR	1/20 (1 S)	5
PD	0	
Relapses	6/19 (4 S, 2 NS)	32

S, Seminoma; NS, non-seminoma; PEB, cisplatin, etoposide and bleomycin; PVB, cisplatin, vinblastine and bleomycin.
[a] Extranodal.

17.2; 95% CI: 4.5–44.4) and non-melanomatous skin cancer (SIR 3.1, 95% CI: 1.3–6.1). In this series, the majority (67%) of skin cancers were BCC.

BCC is usually present as small, purely bordered papule or nodule with telangiectasias and a tendency to slow enlargement and central ulceration. Unlike in the normal population, where the head and neck region is involved in 85% of cases, HIV-BCC most commonly involves the trunk, with the head–neck area involved in only 29% of cases. In addition, HIV-infected patients tend to develop BCC at a younger age with 54% of cases occurring in patients under 40 years of age, compared with a 5% incidence rate in this age group in the general population [58,60–63].

The course of squamous cell carcinoma (SCC) in HIV-infected patients resembles that seen in transplant patients. An increased prevalence occurs in the younger population along with markedly increased aggressiveness. The head–neck region is the most common site of HIV-SCC, accounting for 47% of cases [63]. These tumours generally present a non-healing ulcers, with raised borders and marked induration, showing an increased tendency for multicentricity and early metastases. HIV-SCC lesions tend to recur, up to 20%, following curettage and electrodessication, unlike BCC for which acceptable cure rates are obtained with this approach. Wider excision of SCC may thus be warranted because of the higher reported recurrence rates in HIV setting [60]. Close inspection and surveillance of the skin is warranted in HIV-infected patients, with prompt biopsy of any suspicious lesion.

5.2. Malignant melanoma

Immunosuppressed patients have a 3- to 6-fold increased risk for the development of malignant melanoma (MM) [8,64]. However, MM remains rare in HIV-infected patients. MM in the presence of HIV infection displays increased aggressiveness, showing deeper invasion at the time of presentation, with the majority of patients presenting as Clark's level 5 involvement. In addition, multicentricity and metastases are common in these patients making the overall prognosis poor [6,64,65].

The ideal treatment for HIV-MM remains unknown. However, wide excision with removal of involved lymphatics is the best modality in patients who can tolerate surgery.

6. Conclusion

As the AIDS pandemic advances, the spectrum of malignancies encountered is expanding. The widespread use of HAART has significantly improved the survival of HIV-infected patients. In the future, as people with HIV disease will survive with long-term mild to moderate immunodeficiency, non-AIDS defining tumours might become an increasingly common problem. However, only long-term monitoring of HIV-infected people will answer the question of which cancers will emerge as long-term complications of HIV infection or its treatment.

It is apparent from this review that chemotherapy can be used safely in combination with HAART in HIV-HD. In the HAART era, the exploration of more dose-intensive therapy, such as high-dose chemotherapy with autologous stem cell transplantation, must be considered in poor prognosis HIV-HD patients.

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