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Management of AIDS and its Neoplastic Complications

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INTRODUCTION

THE acquired immunodeficiency syndrome (AIDS) was first reported in 1981 as a combined epidemic of *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma (KS) [1–3].

This syndrome has emerged as the most important epidemic diseases infection of our time. By the middle of 1990, nearly 270 000 cases of AIDS has occurred worldwide [4]. The number of AIDS cases officially reported to the WHO represents probably one third of the real total. Delay in reporting, underreporting and inadequate means of diagnosis almost certainly contribute to this gross underestimation. The identification of the aetiological agent, human immunodeficiency virus (HIV), a human T-lymphotropic retrovirus, represents one of the most significant steps in AIDS research [5–7]. HIV may infect many human cells, including those in the brain, but is able to recognise the T4 lymphocyte surface marker and has a strong affinity for this subset of lymphocytes. The selective cytopathic effect of HIV on T4 lymphocytes results in an imbalance in the usual ratio of T4 to T8 cells, with a decline in lymphocyte recognition and response to antigen. As the response to antigen by T-lymphocytes is a prime initiator of the immune response, the lack of cellular immune response results in increased susceptibility to opportunistic infections and neoplasms, which an intact immune system will ordinarily resist. Diagnosis of AIDS was based on detection of antibodies to HIV, or other serological evidences of exposure to the virus (such as viral p24 antigen, virus production or reverse transcriptase activity), in combination with defects of cellular immunity (such as the T-lymphocyte abnormalities noted above) and the presence of characteristic opportunistic infections or neoplasms, specifically defined by the United States Centers for Disease Control (CDC). In 1987, the CDC surveillance definition for AIDS was revised to emphasise HIV infection status through the inclusion of additional indicator diseases and acceptance of presumptive diagnosis of some indicator diseases [8].

The accumulated evidence strongly suggests the conclusion that transmissison of HIV occurs only through blood, sexual activity and perinatal events.

Antiretroviral therapy of AIDS

To date, only one agent, zidovudine (also known as azidothymidine, or AZT) has been definitely shown to alter the usually rapidly fatal course of AIDS.

Zidovudine (3′-azido-3′-deoxythymidine) is a thymidine analogue that inhibits the replication of the HIV *in vitro*. It is phosphorylated by cellular enzymes to a 5′-triphosphate form that interferes with the viral RNA dependent DNA polymerase (reverse transcriptase) and chain elongation of the viral DNA,

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thereby inhibiting viral replication. Anaemia and neutropenia are the most frequent adverse reactions associated with zidovudine therapy. The low-dose regimen (550 mg/day) is reportably more effective and better tolerated than the previously recommended higher dose (1000–1200 mg/day). Zidovudine in persons with AIDS as well as in those with advanced AIDS-related complex, prolongs survival, decreases the severity of opportunistic infections, improves neurological function, transiently improves T4-lymphocyte counts, and decreases the serum concentration of HIV antigen. In asymptomatic HIV-infected persons with CD_4 counts below 500/mm^3, zidovudine delays progression to advanced AIDS-related complex or AIDS [9, 10].

Management of opportunistic infections

The appearance of an opportunistic infection may be the first sign of underlying HIV infection. It is often present atypically in HIV infected patients frequently in the form of disseminated disease and characterised by a high density of organisms [11]. Conventional treatments are often inadequate since infections tend to persist in HIV patients and usually require long-term suppressive therapy. Typically, the infections may be either viral, bacterial, protozoan or fungal in origin.

Viral infections

Cytomegalovirus (CMV), a member of the human herpes family of viruses, infects directly through mucous membrane contact or via tissue or blood transfusion. Clinical features depend on the site of infection. CMV can cause retinitis, colitis, pneumonitis, esophagitis, encephalitis, hepatitis and adrenalitis [12, 13]. Recovery of CMV on culture only is not adequate to diagnose acute infection. Tissue biopsy or culture or bronchoalveolar lavage are necessary; retinitis can be diagnosed by ophthalmologic findings alone.

Ganciclovir has been shown to arrest the progression of disease and sometimes, due to CMV, it can cause regression of disease, especially chorioretinitis, but lesions progress with discontinuation of therapy, necessitating prolonged maintenance therapy [14–16]. Haematological toxicity frequently necessitates dose reduction or discontinuation of therapy [17]. Because AIDS patients often have low blood cell counts due to their underlying disease or treatment with zidovudine, this toxicity is often problematical. Primary prophylaxis for clinical illness due to CMV is not practical, given the high prevalence of subclinical CMV infection in HIV-infected individuals, the toxicities and difficulties in administration of available agents [18]. Recently Metroka *et al.* [19] reported results on efficacy and tolerance of high dose acyclovir as prophylaxis for CMV.

As with CMV, the prevalence of herpes simplex virus (HSV) infection in AIDS risk groups is extremely high. Ulcerative disease in an HSV-positive individual is now considered an AIDS-defining diagnosis [8]. HSV types 1 and 2 and varicella-zoster virus (VZV) typically infect epithelial and nerve tissues. Herpes simplex occurs in repeated attacks as an acute disease marked by grouped vesicles on erythematous bases, often on the border of the lips, anus or genitals. Herpes zoster is an acute reactivation of virus residing in the nerve roots near the base of the spine. Symptoms are vesicular dermatitis associated with neuralgia. The diagnosis of HSV infections is usually a clinical one but HSV as grows easily and rapidly in cell culture, therefore, such culture should be performed to confirm the diagnosis. The diagnosis of VZV infections, which are almost always cutaneous, is usually an obvious one and rarely requires viral isolation or biopsy. Perianal ulcers, proctitis and other HSV related syndromes can be treated with acyclovir and recurrence prevented by daily acyclovir maintenance [12]. Severe mucocutaneous disease, due to acyclovir-resistant, HSV infections can be treated with for scarnet [20]. Treatment of severe VZV infection may require hospitalisation and intravenous acyclovir.

Epstein–Barr virus (EBV) has been reported to be associated with HIV infected patients or as cause of oral hairy leucoplakia, lymphadenopathy, B-cell lymphoma and interstitial pneumonitis [21, 22]. There is currently no effective therapy for EBV infection.

Bacterial infections

Mycobacterium tuberculosis infection is increasingly being reported in AIDS patients, particularly among those from areas where tuberculosis (TB) is prevalent. TB occurs in an estimated 4% of AIDS cases [23]. Patients often present with extrapulmonary, particularly lymphatic involvement and atypical disseminated disease. The clinical presentation of TB depends on the degree of immunosuppression [24]. The tuberculosis skin test is not reactive in most cases of TB with AIDS. Culture of sputum, blood or tissue biopsy is necessary for confirmation of TB. Patients with AIDS and TB usually respond to standard anti-TB therapies such as isoniazid and rifampicin for at least 6 months augmented with pyrazinamide, ethambutol or streptomycin during the first two months. The drugs used should be determined by sensitivities of the isolates. The CDC has recommended that HIV seropositive patients with latent *M. tuberculosis* infection receive isoniazid preventive therapy [23].

Mycobacterium avium intracellulare (MAI) infections are the commonest disseminated bacterial infections in AIDS [25]. Symptoms of MAI infection are non-specific. Fever, malaise and weight loss are the commonest. Diarrhoea, malabsorption and abdominal pain are symptomatic of gastrointestinal involvement. Lymphatic involvement may be seen as lymphonode enlargement and splenomegaly. Anaemia, leukopenia and thrombocytopenia may result from bone marrow infection. Blood culture techniques are most sensitive for diagnosis of MAI; however, culture time may be 1–7 weeks. MAI is typically treated with a combination of bactericidal and bacteriostatic drugs, since no single drug is effective against all strains. Ansamycin, amikacin, ciprofloxacin, clofazamine, ethambutol and rifampicin are commonly used agents in combination therapy. Therefore, it is not possible to recommend a regime for treatment or suppression other than to suggest a combination of agents to which the particular isolate demonstrates susceptibility *in vitro* [18]. Future investigations will be necessary to guide clinicians in its appropriate management.

Other bacteria are a common source of serious infection in patients with HIV infection. 2–10% of AIDS-related pneumonias are caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* or other Streptococci [26]. Salmonellae, shigellae and campylobacteria are common causes of enteritis [28]. Standard antimicrobial therapies are generally effective for bacterial infections in AIDS. Further studies will be necessary to clarify if persons with these conditions will benefit from special approaches.

Protozoal infections

Pneumocystis carinii pneumoniae (PCP) is the commonest opportunistic infection and has been estimated to occur in 80–85% of patients with AIDS at some point in their illness

[28]. Clinical presentation may be sudden with rapid onset of hypoxia and respiratory failure or more gradual, with breathlessness, non-productive cough and fever. PCP can also occur in extrapulmonary sites such as the liver and skin. The diagnosis of PCP is made by microscopic examination of induced sputum, bronchoaveolar lavage, or transbronchial biopsy [29, 30]. An indirect immunfluorescent assay using monoclonal anti-pneumocystis antibodies is under development [31, 32]. Co-trim oxazole is the first-line treatment for acute PCP; intravenous pentamidine is frequently used as the second line treatment. The major disadvantage of co-trimoxazole is the high rate of adverse reaction in patients with HIV infection [33, 34] and pancreatitis may be a cumulative dose-dependent toxicity of pentamidine. Approximately 80% of patients with PCP recover fully from their first episode of pneumonia. In patients in whom these agents failed, a salvage regimen of trimetrexate and leucovorin has shown promise [35]. Zidovudine decreases the frequency of subsequent episodes of PCP [36]. Recurrent infection and relapse are common in AIDS-related PCP. Aerosolised pentamidine is approved for prophylaxis of PCP and the US Public Health Service has recently issued guidelines for PCP prophylaxis in people with HIV infection [32].

Toxoplasmosis associated with AIDS has become one of the commonest cause of encephalitis [38, 39]. Symptoms include neurological abnormalities such as headache, motor changes, seizures, sensory loss, tremor, blindness, personality changes, confusion, disorientation and coma. Computed tomography (CT) reveals the diagnostic solitary or multiple focal lesions in most cases, but magnetic resonance imaging (MRI) is more sensitive. Antibody detection does not give definitive diagnosis because most cases of toxoplasma encephalitis are a reactivation of latent infection. Brain biopsy can give a definitive diagnosis, but therapy is usually begun after a presumptive diagnosis based on CT or MRI [40]. Should a single lesion be observed by MRI scanning, other diagnoses such as lymphoma and, less commonly, tuberculoma, cryptococcoma or Kaposi's sarcoma should be pursued [29]. Pyrimethamine in combination with sulphadiazine is the first line of treatment for toxoplasma encephalitis. If treatment is begun with a presumptive diagnosis, clinical and CT scan response are usually seen within 10 days. Without lifelong maintenance therapy, recurrence rates reach 80%. Pyrimethamine and sulfadiazine therapy is associated with a high incidence of toxicity including bone marrow suppression and sulphadiazine allergy. Clyndamycin in combination with pyrimethamine is being investigated for efficacy in toxoplasma encephalitis [41]. Further studies to determine the optimum regimens for secondary prophylaxis are necessary. For patients seropositive for toxoplasmosis, further studies will be necessary to determine whether primary prophylaxis regimens exist where the potential protective benefits outweigh the risks of adverse effect [18].

Isosporiasis is an enteric coccidioisis caused by *Isospora belli* and in patients with AIDS usually causes a chronic watery diarrhea, which may be intermittent and may be difficult to be distinguish clinically from other diarrheal illness. It is diagnosed by finding the organism on microscopic examination of the stool [42]. Isosporiasis usually responds within one week to treatment with oral co-trimoxazole [43].

Lower dose co-trimoxazole or sulphadoxine/pyrimethanine suppressive treatment has been recommended to prevent recurrence.

Cryptosporidium species is a protozoan parasite which is a common cause of enteritis in patients with AIDS. Symptoms of cryptosporidiosis include watery diarrhea, abdominal cramping pain and weight loss. Diagnosis is by identification of oocystis on fecal smear [44]. There is currently no treatment available for cryptosporidial enteritis.

Microsporidia are parasites that have only recently been determined to be pathogenic in humans and may be responsible for some cases of colitis in AIDS. Microsporidia are difficult to detect because they do not stain well and require electron microscopy for identification [45]. There is no known treatment for microsporidiosis.

Fungal infections

Candidiasis is the most frequent mycotic opportunistic infection in HIV patients. The most clinically important species is *Candida albicans* although other species may cause the same syndromes. Oral candidiasis occurs in nearly all AIDS patients at some point in their illness and is characterised by frequent recurrences after treatment [46]. *Candida albicans* infection can also affect the oesophagus, vaginal mucosa, gastrointestinal tract and skin. Particularly, oesophagitis is the second commonest manifestation of Candida infection in AIDS, characteristically causing retrosternal pain. The diagnosis is based on clinical appearance or on the recovery of pathogenic fungi from direct cultures of specimens.

There are many agents effective against candidiasis, including nystatin, clotrimazole, ketoconazole and fluconazole [42, 48].

Cryptococcosis occurs in 6–13% of AIDS patients, with more than two thirds of cases presenting meningoencephalitis [49, 50]. Symptoms of cryptococcal meningitis include fatigue, fever, headache, personality changes and seizures.

Pulmonary infection may be asymptomatic or appear with lobar or interstitial pneumonitis and pleural effusion; disseminated disease may involve virtually any organ system. Analysis of cerebrospinal fluid (CSF) often shows a heavy burden of organisms with a markedly positive India-ink slide and very high CSF cryptococcal antigen titres. In addition to CSF evaluation, patients with extraneural sites of infection should have specimens obtained for histology and culture when appropriate (skin, bone, lung, blood and urine).

Initial choice of therapy remains amphotericin B with or without oral flucytosine. Suppressive therapy is necessary. Fluconazole was recently approved for treatment and maintenance of cryptococcal meningitis [51]. Preliminary results suggest that itraconazole may also be useful in preventing relapse [52].

Histoplasma capsulatum is a fungus that has been recognised with increasing frequency in patients with HIV infection. In AIDS patients, disseminated disease is the primary clinical presentation [53–54]. Presenting symptoms are non-specific and include fever, chills, sweats, weight loss, vomiting and diarrhoea. Pneumonitis with diffuse or patchy reticulonodular infiltrate are also common. Diagnosis of histoplasmosis depends on documenting the organisms in clinical specimens by culture or histopathology. Amphotericin B followed by maintenance therapy with either amphotericin B or ketoconazole are the standard therapies for histoplasmosis. Relapses are common.

Coccidioidomycosis is endemic to the South Western US and Central America. Reports suggest that patients with HIV infection are at increased risk for disseminated coccidioidomycosis [55]. Symptoms are non-specific. Pulmonary involvement is common and disseminated infection may involve kidneys, spleen, lymph nodes, brain and thyroid. Diagnosis is based on detection of the organism by examination or culture of broncoscopically obtained specimens. The infection may

respond to treatment with amphotericin B, but relapse may occur rapidly upon discontinuation of therapy.

Management of neoplastic complications of AIDS

HIV-related cancers are being seen in increasing numbers. The most frequent neoplasias are Kaposi's sarcoma (KS) and non-Hodgkin lymphomas (NHL), while other types of tumours occur at lesser frequencies. Overall, the natural history of cancers in HIV infected patients is quite different from those of the general population. The aggressive course of tumours, leukopenia, opportunistic infections and pre-existing AIDS-related problems make treatment extremely difficult.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is the commonest neoplasm in AIDS patients. This tumour, epidemic KS (EKS), develops predominantly in homosexual men and to a lesser extent in other risk groups. In USA the proportion of AIDS cases presenting as KS has decreased from nearly half in 1981 to less than 20% in 1987 [56]. In the european countries where the AIDS epidemic has a 2 year delay in comparison with the USA, the incidence of EKS ranges from 22% (1987) to 13% (1988–1989) [52, 58]. Recent analyses of combined prospective studies in homosexual men indicate, however, that the decreasing risk of KS may be attributable to an increasing risk of other opportunistic infections with progression into more extreme immunodeficiency [55].

KS is a tumour of vascular origin; however, little is known of the nature of the malignant cells, which are presumably spindle-shaped endothelial cells. KS is a multifocal neoplasm capable of arising simultaneously in multiple sites, as a possible consequence of local production of unique growth factors. The cause of KS in patients with HIV infection is not yet known, but it is highly conceivable that a prevalently sexually transmitted infectious agent could be associated with KS in presence of immunodeficiency [59, 60].

EKS is usually characterised by multifocal, widespread lesions at the onset of illness. These lesions may involve the skin, oral mucosa, lymph nodes and visceral organs such as the gastrointestinal tract, lung, liver and spleen. At two years, survival is more than 80% in patients without opportunistic infections and less than 20% in patients with opportunistic infections. The majority of patients present with skin lesions that occur as flat or raised plaques ranging from a few millimetres to 2–3 centimetres and from blue–purple to red–brown. The Kaposi lesions in patients may be quite subtle at onset. Clinicians caring for persons at risk for AIDS should consider any new skin lesion with suspicion. Lymph node involvement occurs frequently. However, the precise incidence of nodal involvement specifically due to KS is unknown because of the multiplicity of other processes involving the nodes in these patients. Visceral involvement, particularly in the gastrointestinal tract, affects nearly half of the reported cases. Stomach, duodenum, colon and rectum may be involved simultaneously, or only one site may be involved at one time. However, gastrointestinal involvement may be asymptomatic, and only in advanced disease it may result in blood loss, diarrhoea, weight loss, abdominal cramps or even rectal pain. Although, pulmonary involvement is less frequent than disease in the gastrointestinal tract, it may also exhibit a broad spectrum of disease in EKS. KS lesions may be noted incidentally during bronchoscopy to evaluate a pneumonic process. Alternatively, lung involvement may result in radiographic abnormalities (bilateral, mixed interstitial and alveolar infiltrates or bilateral nodular infiltrates, pleural effusions) with symptoms of cough, dyspnea and fever. Lesions from KS have been observed at autopsy in all organs including brain, pancreas, heart and major vessels. These lesions remain generally asymptomatic, although in some cases patients present with headache or bowel obstruction [61, 62]. Despite the overall progressive course of EKS, there may be a wide range of disease progressions in different patients. A rapid course with short survival is seen in patients with opportunistic infections, systemic symptoms (fever, night sweats or weight loss) and in those with significant depletion of T4 lymphocytes. Alternatively, prolonged survival with minimal disease has been noted in other patients with EKS whose immune systems are relatively intact. The overall prognosis for survival in patients with EKS appears to depend on the severity of immune suppression and HIV infection, rather than on the neoplastic proliferation and tumour load [63].

No universally accepted classification exists for this disease. The most widely used staging classifications are those of Krigel (Table 1) and Mitsuyasu (Table 2) [61, 64]. Krown *et al.* have also recently published criteria for evaluation of EKS. This new staging system offers uniform and precise criteria for disease evaluation, response to treatment and clinical staging. It incorporates measures of extent of disease, severity of immunodefficiency and presence of systemic symptoms (Table 3) [65]. The staging procedures to determine disease extent in KS are reported in Table 4. According to the general opinion, full staging of KS is not required in all circumstances but only when indicated by symptoms, findings on physical examination, or laboratory studies. It is clear, however, that the determination

Table 1. Epidemic Kaposi's sarcoma: Krigel staging system

Stage I	Cutaneous, locally indolent
Stage II	Cutaneous, locally aggressive or without regional lymph nodes
Stage III	Generalised cutaneous and/or lymph node involvement*
Stage IV	Visceral
Subtypes	
A	No systemic symptoms
B	Systemic symptoms: weight loss (10%) or fever (> 37.8°C, unrelated to an identificable source of infection lasting > 2 weeks)

*Generalised includes minimal GI disease.

Table 2. Epidemic Kaposi's sarcoma: Mytsuyasu staging system

Stage I	Limited cutaneous (<10 lesions or one anatomical area)
Stage II	Disseminated cutaneous (>10 lesions or more than one anatomical area)
Stage III	Visceral only (GI, LN)
Stage IV	Cutaneous and visceral, or pulmonary KS
Subtypes	
A	No systemic symptoms
B	Fever >37.8°C, unrelated to identificable infection for 2 weeks or weight loss (10%)

GI = gastrointestinal tract, LN = lymph nodes.

Table 3. Epidemic Kaposi's sarcoma: recommended staging classification (Krown et al.) [65]

	Good risk (0) (all of the following)	Poor risk (1) (any of the following)
Tumour (T)	Confined to skin and/or lymph nodes and/or minimal oral disease*	Tumour-associated oedema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
Immune system	CD4 cells >200/μl	CD4 cells >200/μl
Systemic illness	No history of OI or thrush No "B" symptoms Performance status >70 (Karnofsky)	History of OI and/or thrush "B" symptoms present Performance status <70 Other HIV-related illness (e.g. neurological disease, lymphoma)

*Minimal oral disease in non-nodular KS confined to the palate.
"B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhoea persisting more than 2 weeks.

Table 4. Staging of epidemic Kaposi's sarcoma

Complete physical examination (including rectal and oral examination)
Biopsy of skin lesions and/or lymph nodes
Chest X-ray
Gastroscopy and colonendoscopy (bronchoscopy*)
CT scan of abdomen
Laboratory studies: complete blood count, common serum chemistries, HIV serology, T4–T8 lymphocytes count

*In patients with abnormal chest X-ray.

and accurate documentation (e.g. photographs) of the disease extent is essential for the evaluation of new possible active drugs.

Therapy. Because the natural course of EKS disease progression is highly variable, evaluating the long term efficacy of systemic treatment has been difficult. Instead, neither local or systemic treatment of KS has been shown to alter the ultimate course of the disease. Both treatments may, however, result either in a disappearance or reduction in size of specific skin lesions and thereby alleviate the discomfort associated with the disease. However, no data show that treatment improves survival.

Local modalities include surgical excision, electrodessication and radiation therapy. However, surgery is usually used in order to make a diagnosis. KS is generally very responsive to radiation therapy; good palliation can be obtained with doses in the range of 20 Gy [66]. Most of the experience of radiation therapy has been collected in cutaneous lesions of EKS. Oral and pharyngeal lesions are equally radiosensitive but successful control of this lesion is less frequent.

Table 5 shows the results of single and multiple chemotherapy agents in EKS. Overall single chemotherapy agents may control the disease in approximately 30% of patients, while combination chemotherapy produces responses in about 70% of patients [67–76]. The wide variation in response rates reflects patient selection rather than a significant difference in chemosensitivities. Combination chemotherapy has not been shown to be consistently superior to single-agent treatment. What one gains in overall efficacy tends to be lost in toxicity and *vice versa*. Although cytotoxic chemotherapy is effective in KS, it may further compromise immune response in AIDS patients.

Table 5. Single and multiple agents chemotherapy of epidemic Kaposi's sarcoma

Ref.	Drug	Overall response rate (%)
Volberding 1985 [68]	Vinblastine (VCR)	26
Mintzer 1985 [69]	Vinblastine (VLB)	61
Wernz 1986 [70]	Bleomycin (BLM)	77
Laubenstein 1984 [71]	VP16	76
Bakker 1988 [72]	VP16	0
Gill 1988 [73]	Doxorubicin (ADM)	53
Kaplan 1986 [74]	VLB/VCR	43
Wernz 1986 [70]	VLB/BLM	62
Laubenstein L. 1984 [71]	ADM-BLM-VLB	86
Gill 1986 [75]	ADM-BLM-VCR	67
Minor 1988 [76]	VLB-VCR-Methotrexate	81

Many studies have confirmed the efficacy of high doses of alpha-2 recombinant interferon (IFN-α_2) followed by a maintenance regimen three times a week. Percentage of response to IFN-α_2 in patients without opportunistic infections ranging from 30% to 50%. On the contrary, if patients have a history of opportunistic infections and or B symptoms, the percentage of response is lowered to 20% [72, 78]. In general treatment with IFN-α_2 is well tolerated, but no decrease in the incidence of opportunistic infections has been observed. Combination of IFN-α_2 with chemotherapy has shown no benefit in comparison with either agent alone. Encouraging results have been obtained with the combination of IFN-α_2 and zidovudine IFN-α_2 [74].

In conclusion, no significant impact of available treatments

Table 6. Treatment of Kaposi's sarcoma by Krigel

Extent of disease	Preferred treatment*
Localised	Surgical excision or radiation therapy
Indolent disseminated Cutaneous and/or lymphadenopathic	Immunotherapy and/or single agent chemotherapy
Aggressive, disseminated or with systemic B symptoms	Combination chemotherapy

*Protocol therapies whenever possible.

on survival among patients with EKS has been demonstrated. Since optimal therapy of all stages is still in an early phase of development, patients should be treated according to study protocols whenever possible. This is especially advisable for patients also receiving AZT, due to the possible overlapping myelotoxicity of this agent with antiproliferative agents. Even if a patient is not entered in a well established treatment protocol, the general recommendations reported in Table 6 should be followed. Ultimately, the ideal treatment for the EKS will be a combination of antiretroviral therapy to reverse the immunological defects, chemotherapy to control tumour development and haematopoietic growth factors to ameliorate treatment toxicities.

Non-Hodgkin lymphoma (NHL)

There is an increase of non-Hodgkin lymphomas, parallel to the time course of the AIDS epidemic. In all registry studies, the proportional morbidity has increased significantly above the levels observed in the pre-AIDS period, although, less strikingly than KS. These tumours appear most frequently at the end of stages of AIDS, at a time when the immune system is markedly impaired. Because with ancillary care of opportunistic infections, patients with AIDS can be expected to survive longer, while HIV-related destruction of their T-cell immunity will continue. As a consequence of longer survival as well as better diagnosis, the incidence of lymphomas in AIDS patients will probably increase in the near future unless therapies are devised that halt or reverse the progressive immunodestruction of HIV [57].

The majority of cases of HIV related NHL consists of high-grade NHL, with B-phenotype; the most represented histologies are Burkitt's lymphomas, immunoblastic lymphoma and the otherwise not specified "undifferentiated" lymphoma. Taking into account these as well as other epidemiological data, the Center of Disease Control (CDC) of Atlanta have produced a third definition of AIDS. According to this last definition, primary CNS-NHL is considered diagnostic of AIDS, as is high grade NHL with B-phenotype or with both non-B and non-T-phenotype developing in HIV positive persons even in absence of opportunistic infections and/or KS [8].

Pathogenesis of these lymphomas has been linked to Epstein–Barr (EBV) latent infection of B lymphocytes and abnormal immune regulation of these infected cells. Oncogene activation in an EBV infected cell may lead to malignant transformation [80].

The clinical findings in patients with HIV-related lymphomas have been remarkably uniform in all reported series, and are summarised in Tables 7 and 8 [80, 92]. The prevalence of high grade istotypes ranges from 60% to 98% of cases in the principal

Table 7. Principal case series of HIV-related in NHL in USA

Ref.	No. of patients	Risk group	Clinico-pathological characteristics
Ziegler [8]	90	Homosexual	High grade 62%, intermediate 29% Stages III–IV 58% Extranodal sites 98% (CNS, bone marrow, GI, mucocutaneous sites) Median survival 6 months
Di Carlo [89]	29	Homosexual (28) Polytransfused (1)	High grade 28%, intermediate 45% Extranodal sites 90% Phenotypes B Median survival 6 months for intermediate and 3 months for high grade
Ioachim [90]	31	Homosexual (30) IVDU (1)	High grade 97% Extranodal sites 48% (CNS, GI, heart, testis, bladder, kidney) Low response rate to therapy
Levine [83]	68	Homosexual (59) IVDU (6) Unknown [3]	High grade 87% Stages IV 63% Extranodal sites: CNS 32%, GI tract 26%, bone marrow 25% Median survival <1 year Opportunistic infections after intensive CT
Markowitz [83]	8	Homosexual (5) IVDU (3)	Stage IV 100% Severe cytopenia after conventional doses of CT Short survival
Knowles [84]	89	Homosexual (71) IVDU (17)	High grade 69% Stages III–IV 53% Extranodal sites 87% (GI, CNS, liver) Phenotypes B, polyclonality Median survival 5 months
Kaplan [85]	84	Homosexual (78) IVDU (4) Heterosexual (2)	High grade 77% Stages III–IV 82% Extranodal sites (bone marrow 31%, liver 26%, CNS 12%) Median survival <4.3 months
Egert [91]	31	Homosexual (31)	High grade 98% Stage I 68% (CNS 43%) Phenotypes B
Lowenthal [86]	43	Homosexual (41) IVDU (2) Homosexual-IVDU (1)	Intermediate high grade 93% Stage IV 49% Extranodal sites 65% (bone marrow 46%, CNS 40%, lung 25%) Median survival 6 months

IVDU = intravenous drug user. GI = gastrointestinal tract.

Table 8. Literature review of HIV-related NHL in Europe

Ref.	No. of patients	Risk group	Clinico-pathological characteristics
Raphael [82]	16	?	Immunoblastic lymphoma 69% Burkitt's lymphoma 19% Extranodal sites 69% (CNS, bone marrow, mucosa) Median survival 9 months
Skinhoj [93]	3	Homosexual (2) Haemophilic (1)	High grade 3/3 Stages III–IV 3/3
Jara [94]	5	Homosexual ? IVDU	High grade 5/5 Stages III–IV 5/5 Reduced response rate to therapy
Huhn [95]	16	Homosexual ? IVDU ?	Intermediate-high grade 75% Stages II–IV 100% Extranodal sites 81% (CNS 38%, liver 31%, bone marrow 31%) Phenotypes B
Andrieu [82]	92	Homosexual (65) IVDU (8) Heterosexual (8) Polytransfused (6) Homosexual-IVDU (4) Unknown (8)	High grade 96% Stages III–IV 52% Complete response after chemotherapy plus radiotherapy 37% High mortality 54%
Schmid [96]	17	?	?
Oksendler [92]	53	Homosexual ? IVDU ?	High grade 100% Stages III–IV 58%
Italian cooperative group on AIDS-related tumours [88]	150	IVDU (96) Homosexual (31) Others (23)	High grade 73% Stages III–IV 66%)

American case series and in 75–100% of cases in the European case series. Widely disseminated disease is diagnosed at the time of initial presentation, with extranodal sites of disease described in 65% to 98% of patients. Also, common to all series is the description of unusual sites of lymphomatous disease. Lymphoma has been described in the myocardium, adrenals, earlobes, maxillae, gall bladder, orbit, rectum and other such sites. Aside from these unusual sites of disease, most series have been consistent in the description of bone marrow involvement, occurring in approximately 20–46% of cases, GI tract involvement occurring in 7–45%; and involvement of the CNS, presenting either as primary CNS lymphoma, or leptomeningeal lymphoma in patients with systemic disease. Primary CNS-HIV related lymphoma present on incidence ranging from 3% to 36% in the various series previously reported. The disease appears as a single or multiple lesion which is located preferably in the white paraventricular matter, in the basal ganglia in the thalamus, in the corpus callosus and in the cerebral veins [98]. To distinguish between CNS-involvement lymphoma and opportunistic infections within the CNS is extremely difficult on purely clinical criteria, in absence of biopsy. The clinical and radiological characteristics are quite often similar. On the other hand, invasive diagnostic procedures such as sterotactic biopsy or open-sky biopsy after craniotomy may present practical problems in patients with poor performance status and in bad general condition. This consideration explains why an elevated number of cases of CNS involvement from NHL is diagnosed only at autopsy.

In one-third of cases the onset of lymphomas is preceeded by the persistent generalised lymphadenopathy (PGL). Enlargement of pre-existent lymphnodes always requires a biopsy to exclude the suspicion of evolution toward the malignant lymphoma. Staging procedures in HIV-related lymphomas ideally should be superimposable on those used for the general population of non-Hodgkin lymphomas. Although poor performance status and bad general conditions may be an obstacle to a thorough staging assessment, bone marrow biopsy, chest X-ray, CT scan of thorax and abdomen, gastrointestinal tract X-ray, ENT examination and lumbar puncture are recommended in all instances.

Therapy. The treatment of AIDS-associated NHL presents several problems. First, the majority of patients have advanced stage IV disease at initial presentation. Second, the high grade lymphomas frequently involve the bone marrow and the CNS. Third, the immunodeficiency and the history of previous opportunistic infections complicate the immunosuppressive chemotherapy. Fourth, the leukopenia commonly seen in patients infected with HIV makes the use of conventional multiagent chemotherapy regimen very difficult.

In the case series of Ziegler *et al.* which reported results obtained with various combination of chemotherapy regimens (cyclophosphamide/doxorubicin/vincristine/prednisone [CHOP]; prednisone/methotrexate/doxorubicin/cyclophosphamide/etoposide [ProMAC]; mechlorethamine/vincristine/procarbazine/prednisone [MOPP] and methotrexate/bleomycin/doxorubicin/cyclophosphamide/vincristine/dexamethasone [M-BACOD] with or without radiation therapy), complete remission (CR) was not superior to 53%, relapses were 54% and median survival was only 6 months [81]. Comparable results in term of response of survival have been reported by Lowenthal and coworkers with the same combination chemotherapy regimens [86]. In these series, patients achieved a 50% CR rate, but with, 41% relapses after a median of 4 months (range 3–7). CR rate with the regimen M-BACOD in the series of Gill *et al.* was 54% (7 of 13 patients) the median survival being, however, not longer than 11 months [94]. With the new combination chemotherapy regimen, COMET-A (cyclophosphamide, vincristine, methotrexate, etoposide and intrathecal methotrexate) Kaplan *et al.* obtained CR in 58% of cases with 31% relapse rate [85]. These data are superimposable on these obtained with the aforementioned conventional chemotherapy. In this case series unfavourable prognostic factors for survival were low value of T4 lymphocytes in the presence of opportunistic infections, low performance status according to Karnofsky and the administration of high doses of cyclophosphamide (more than 1 g/m^2). At the current time, it may be concluded that while the majority of patients with AIDS-lymphoma will not experience long term disease-free survival after combination chemotherapy, a small percentage of these patients will be expected to live a median of 1 or 2 years in complete remission. Those patients more likely to tolerate intensive therapy and to do relatively well are those without prior history of AIDS, with higher performance status, and perhaps, with lower stage disease.

New regimens using short courses of chemotherapy,

granulocyte–colony stimulating factor (G-CSF) or granulocyte–macrophage-colony stimulating factor (GM-CSF) and antiviral therapy have raised hopes that those measures will lead to improved response to therapy and survival in patients with HIV related NHL.

Hodgkin's disease

Hodgkin's disease (HD) is one of the most frequent neoplasia reported in patients with HIV infection after EKS and NHL. Since HD occurs typically in young patients it is not clear whether cases described in the literature are the expression of an increase of the incidence of the disease or more probably the expression of a coincidence. However, the clinical syndrome of HD in HIV infected patients is changed. There is a higher incidence (80–86%) of stages III and IV disease. Additionally, an atypical pattern of spread of the disease with dissemination without mediastinal and hilar involvement has been noted. Histopathology is notable for the majority of the cases being of mixed cellularity (56%), followed by nodular sclerosis (34%) and lymphocyte depletion (6%). Treatment with standard chemotherapy (MOPP, MOPP+ABVD, ABVD) has resulted in long-term remissions, but chemotherapy is tolerated poorly and opportunistic infections are increased. Survival is shortened by refractory disease and AIDS-related complications [84–86, 100–101].

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Adjuvant Therapy of Breast Cancer

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Adjuvant systemic therapy has been shown to reduce relapses in treated women and to prolong their survival. This is true for all studied subpopulations. Multidrug chemotherapy for the duration of 6 months for the premenopausal patients, and tamoxifen or short-term chemotherapy with long-term tamoxifen for the postmenopausal patients represent the treatments of choice to reduce the risk of relapse. Some of the high priority questions relate to i) the definition of a population for which the risk of relapse is low enough to avoid the use of systemic adjuvant therapy, and ii) the definition of an optimal way of using available adjuvant therapies. These might find answers from ongoing research. The modest but real improvement of the prognosis in operable breast cancer was exclusively obtained only by means of clinical trials, and it is mandatory that participation in programs of clinical research becomes medically and socially the treatment of choice.
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INTRODUCTION

MOST BREAST cancer patients who remain disease-free after local and regional treatment eventually relapse and die of or with overt metastasis. This is true regardless of whether they received an appropriate local therapy. The current hypothesis ascribes the failure to obtain freedom from disease to occult micrometastatic disease already present at the time of diagnosis and first surgery [1]. This hypothesis has acquired indirect support from the results of clinical trials which show no additional advantage in terms of disease-free or overall survival for a more radical local therapy [2, 3].

There is evidence that occult metastases can still be eliminated by current therapeutic means, but that the overt metastatic phase of the disease is incurable. These observations lead in turn to substantially different attitudes towards the treatment of patients in these two distinct clinical situations.

Long before the present hypothesis of disease spread (presence of micrometastases at diagnosis), adjuvant systemic therapy was applied in a form of hormonal ablative treatment consisting of ovarian radiation [4]. At that time, observations made of tumour regression after oophorectomy justified investigation of ablative therapy in patients with operable disease after completion of the local treatment.

Systemic adjuvant chemotherapy was based upon observations of substantial rates of response to cytotoxic agents of measurable metastatic disease. In addition, the first hypothesis concerning their value as adjuvant treatment was related to the attempt to kill cells which detach during operation. The detached cells were at that time considered to be responsible for the subsequent development of overt metastases. This hypothesis of perioperative migration of cells with metastatic potential has been abandoned in favour of one which argues for the presence of micrometastatic disease at the time of primary diagnosis [5].

Experimental observations which have helped to guide the use of adjuvant systemic therapy after surgical removal of the primary tumour have been made on the basis of animal models [6–10]. There is an inverse relationship between the number of viable tumour cells in the animal and response to treatment with cytotoxic agents, i.e. the smaller the number of tumour cells the greater the chemotherapeutic effect. Another principle related

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