

MANAGEMENT OF CANCER IN PATIENTS WITH HIV

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INTRODUCTION

As the incidence of HIV increases in Africa the coincidental infection of cancer patients will rise. Owing to the effects of HIV on haemopoiesis and immune function, HIV infection of patients with cancer poses management difficulties for both the physician managing the cancer and the physician managing the HIV infection. For most cancers, the dose intensity (total dose over total time) of the chemotherapy or radiotherapy is strongly associated with response rates. This is even more noticeable in haematological malignancies and cancers with curable potential. Maintaining dose intensity in the presence of HIV requires control of the HIV infection and frequently the use of external growth factor support, especially in intensive regimens. It is not usually appropriate to attempt anything except palliative treatment if these resources are not available

More conventionally we think of cancer in HIV as cancer as a result of the HIV infection. This is well described as either related to decreased immune surveillance, or secondary to other infections that are uncontrolled in a host with a compromised immune system. In addition to their unique problems these patients suffer the same disadvantages as discussed above in the cancer patient who is also co-incidentally infected with HIV.

This article will discuss the increased incidence of certain malignancies in patients with HIV, as well as the unusual features of these malignancies in HIV-infected individuals. In addition, some of the difficulties experienced in the management of these patients, their cancers and their HIV infection will be explored.

HIV AND CANCER INCIDENCE IN SUB-SAHARAN AFRICA

It is estimated that over 25 million HIV-infected individuals live in sub-Saharan Africa. Most countries in this region have no effective strategies in place to combat the growth in this epidemic, largely owing to a lack of political commitment together with a lack of resources. These factors are important because they extend beyond HIV-

related issues and affect the peoples of this region in many ways, not least of which is apathy among the medical profession and the sense of hopelessness that envelops both physicians and patients alike. These factors lead to under-reporting, inadequate record keeping and subsequent referral of HIV-infected patients with malignant disease. The extent of the problem is therefore vastly underestimated for many HIV-infected people, and ideal management of opportunistic infections – let alone management of their HIV with antiretrovirals and the management of more serious or complex problems – is unobtainable.

Because relatively little is known about cancer in African patients with HIV infection, reliance is placed on North American and European data, which have a bias to male homosexual patients and intravenous drug users. These patients have very different backgrounds, and therefore differing rates of smoking, cardiac disease, rectal carcinoma and exposure to other infections, population longevity and access to health care.^{1,2}

TYPES OF CANCER IN PATIENTS WITH HIV

AIDS-RELATED

The incidence of some cancers is so much higher in populations of patients with HIV infection that a causal relationship is difficult to exclude. These cancers are associated with declining immune function and are considered to be AIDS-defining.¹ They are:

- Non-Hodgkin's lymphoma (NHL) (300 x for diffuse large-cell and 14 x for low grade)
- Kaposi's sarcoma (KS) (86 x for males, 260 x for females)
- Cancer of the cervix (CaCx) (9 x).

NON-AIDS-RELATED

These cancers have a more modest increase in incidence but the risk is nonetheless increased, as shown in studies that link the diagnosis of these malignancies to the diagnosis of HIV by placing their diagnosis to within 60 months on either side of the diagnosis of AIDS.¹ They are:

- Hodgkin's disease (8 x)
- Trachea, bronchus and lung (3 - 7 x)
- Mouth (2 x)
- Brain and central nervous system (3 x)
- Skin, excluding KS (7 x)
- Multiple myeloma (3 - 7 x).

PATHOGENESIS OF HIV-RELATED MALIGNANCIES

Epstein-Barr virus (EBV) is a herpesvirus and has been shown to drive B-cell proliferation in many ways. This virus is ubiquitous in Africa, and immune suppression creates an environment that is permissive for its reactivation and hence B-cell stimulation. Reduced immunity also creates an environment that is rich in antigenic stimulation which further drives the proliferation of B cells with their associated immunoglobulin gene rearrangements, cell cycle and apoptotic pathway activation, creating a permissive milieu for genetic mutations. In addition, HIV itself has been shown to stimulate an inappropriate humoral immune response and this cytokine barrage further stimulates B-cell proliferation. Immune dysregulation contributes to the process and eventually decreased cytotoxic cell function leads to a decrease in immune surveillance, allowing malignant cells to escape detection and a failure of cell-mediated immune destruction. Human herpesvirus 8 (HHV8) has been shown to be causally linked to the development of body cavity-based lymphomas.³

Many of these factors, particularly the permissive environment, reactivation of dormant infections, and decreased cytotoxic immune surveillance, are thought to play a role in other cancers. In KS, HHV8 is causally related to the pathogenesis of this malignancy. Human papillomavirus (HPV) has been causally linked to carcinoma of the cervix and carcinoma of the anus. In particular, the AIDS-related malignancies have been shown to improve with control of the patient's HIV infection by antiretrovirals and subsequent immune reconstitution. Control of the patient's HIV infection should therefore be the first goal of therapy in any patient suffering from one of these malignancies.

PRINCIPLES OF MANAGEMENT

EFFECTS OF CHEMOTHERAPY AND RADIOTHERAPY ON HAEMOPOIESIS AND IMMUNE FUNCTION

Therapy for malignancies is by nature cytotoxic and also leads to varying degrees of immunosuppression. In particular, the chemotherapy used in the management of haematological malignancies is by the nature of its target profoundly myelosuppressive and immunosuppressive. Although some latitude may be used when treating with

palliative intent, if the goal is cure, for optimal results these regimens should be adhered to. In this scenario growth factor support is frequently required to achieve optimal scheduling.

In addition, intensive chemotherapy and radiotherapy frequently lead to sub-optimal nutrition due to mucositis, nausea, diarrhoea, oral thrush and reactivation of herpes. Infections, including bacterial community-acquired pneumonia and urinary tract infections, are increased as a result of chemotherapy and radiotherapy. In the context of HIV this increase in antigenic load and immune stimulation will serve to aggravate the immune dysfunction. Repeated admission to hospital also increases the risk of nosocomial infections.

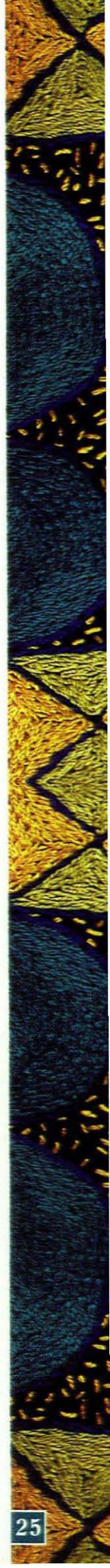
Direct tissue damage secondary to the cytotoxic effects of chemo- and radiotherapy may in turn lead to multiple organ dysfunction such as hepatitis, renal failure and respiratory impairment. These conditions further compromise the patient's ability to withstand infections or tolerate other medications, including antibiotics and antiretrovirals.

However, newer agents such as monoclonal antibodies, biological response modifiers, antisense RNA and anti-angiogenic drugs hold promise of enhanced efficacy with reduced toxicity and would be useful in this setting.⁴

EFFECT OF HIV ON HAEMOPOIESIS AND IMMUNE FUNCTION

As patients progress to more advanced stages of HIV infection and their viral load rises progressively, they become more immune-compromised. Infection of bone marrow stromal cells, microvascular endothelial cells and macrophages leads to impaired haemopoiesis with progressive cytopenias. Even before this becomes apparent the marrow has a decreased capability to withstand suppression, and patients generally have a poor tolerance of cytotoxic therapies. This is immediately improved if the rate of viral proliferation is controlled, even if the CD4+ lymphocyte count is not increased in the face of chemotherapy.

In addition, the obvious susceptibility to infection is synergistic with the immune suppression of cytotoxic therapy. The HIV-positive patient undergoing treatment for cancer is therefore at serious risk of fatal acute infection. This must be carefully explained to the patient and the risk weighed up against the potential benefit. There must be resources available to manage iatrogenic complications, and these must be in place before initiating therapy and thus committing the patient and the health care system to a course of action that cannot be sustained or completed.



ANTIRETROVIRAL THERAPIES HAVE MULTIPLE TOXICITIES AND DRUG INTERACTIONS

The nucleoside analogues, in particular zidovudine (AZT), are myelosuppressive and should be avoided or closely monitored in patients receiving myelosuppressive chemotherapy. In addition peripheral neuropathies are relatively common with stavudine (D4T), didanosine (DDI) and zalcitabine (DDC)⁵ and these should be avoided or used with caution in patients receiving the vinca-alkaloids (vincristine, vinblastine) and the platinum-based drugs.

Protease inhibitors, in particular ritonavir, have an effect on drugs metabolised via the cytochrome P450 pathway and may enhance toxicities of some chemotherapeutic agents such as cyclophosphamide and anthracyclines at higher doses.

However, the use of antiretrovirals controls HIV replication, leading to improvement not only in immune function, but also in the haemopoietic reserve and the patient's ability to tolerate cytotoxic therapy. Immune reconstitution may lead to regression of the tumour and an improved clinical outcome.

A recent trial⁶ showed a marked reduction in the incidence of NHL in patients on highly active antiretroviral therapy (HAART) compared with patients in the pre-HAART era. This reduction was shown to result from fewer patients with severe immune compromise. This shows that not only is immune impairment necessary for the development of the AIDS-related NHL, but controlling the HIV infection leads to an improvement in the health of this patient population.

GOALS OF MANAGEMENT

CURATIVE V. PALLIATIVE INTENT

For most patients with cancer and HIV, palliation is the best option. Palliation does not mean automatically giving up on the cancer; the patient may still benefit from its appropriate local or systemic management. However, there is a group of patients who have potentially curable malignancies and should be evaluated for aggressive therapy.

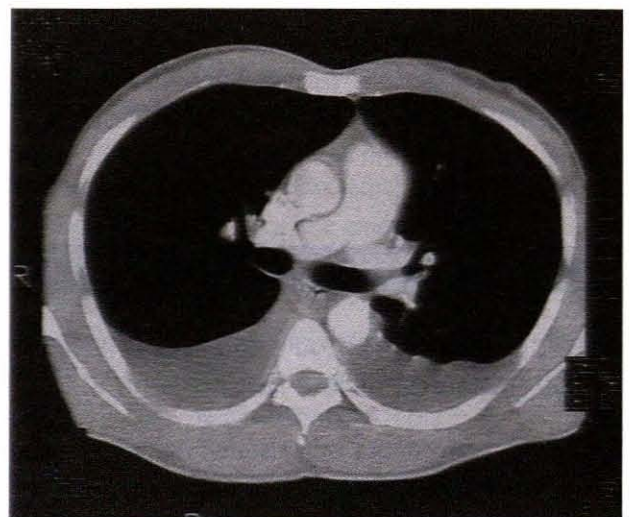
Patients who have a better outcome are:

- those with localised cancers
- those with earlier-stage cancers
- the younger age group
- those with good performance status
- those with earlier stage of HIV disease
- those on antiretrovirals.

It is advisable that any patient who is to undergo aggressive cancer therapy should be on HAART.

Although NHL may be curable in these patients, they should be carefully selected as the majority have very aggressive disease. These patients therefore require aggressive multi-agent chemotherapy with its attendant risks. Frequently they need external growth factor support to either maintain dose intensity or give support during sepsis. Their disease presentation is often atypical, with extranodal or central nervous system disease which may require a multidisciplinary approach between the surgeon, radiotherapist and oncologist. High-grade histological subtypes predominate, and as mentioned earlier an association with EBV and HHV8 infection is common. Sadly only the best risk patients will tolerate these intensive regimens, and the risk remains high. However, good durable remissions are achieved in a significant number ($\pm 30\%$) of patients.

KS is often a fairly indolent malignancy, and response can be achieved with control of the patient's HIV infection alone. This angiosarcoma has a propensity for the skin and lymph nodes, causing unsightly and embarrassingly characteristic lesions or lymphoedema. Local radiotherapy can give excellent results in the majority of patients. The addition of anthracycline chemotherapy can further enhance these results to complete local responses in over 80% of patients. However, the disease is usually progressive and will ultimately involve the lungs, gastrointestinal tract and other organs, causing death. This AIDS-defining illness usually presents in earlier stages of immune compromise (median CD4 lymphocyte count 300/ml), and as such these patients tolerate chemotherapy reasonably well. The sarcoma responds well to anthracycline-containing regimens, with good responses in about 40% of patients. Liposomal daunorubicin combinations have the same results as single agents (or better ones) and are very well tolerated, with little haemopoietic or other toxicities.



Kaposi's sarcoma with chylous pleural effusion secondary to lymph node obstruction.

Most patients with HIV and cancer can benefit from the management of their HIV. In addition, local therapies (surgery and radiotherapy) can lead to a cure, and frequently significant improvement in quality of life results. If selection of patients is careful, results can be excellent. A multidisciplinary approach and co-operation between the oncologist and the infectious diseases physician are essential to optimise the outcome in these patients.

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