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AIDS associated malignancies

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ABSTRACT

There is a markedly increased risk of Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer during the course of infection with the human immunodeficiency virus (HIV). Therapy for these acquired immunodeficiency syndrome (AIDS) defining illnesses first involves anti-retroviral therapy to suppress HIV viremia and maintain CD4 counts. Subsequent chemotherapy is complicated by the underlying immunoparesis and options in the management of all three diseases are discussed herein. Improved understanding of their aetiopathogenesis will hopefully delineate new therapeutic options and strategies to control viral replication and virally induced diseases including malignancy.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) following infection with human immunodeficiency virus (HIV), was brought to the world's attention in 1981 with the first case reports of *Pneumocystis carinii* pneumonia in homosexual men in Los Angeles [1]. These reports were quickly followed by descriptions of Kaposi's sarcoma in similar patient groups [2,3]. There followed a cornucopia of opportunistic infections and isolated reports of high grade B-cell non-Hodgkin's lymphomas (NHL), both primary cerebral lymphomas and systemic NHL. By 1985 high grade B-cell NHL was included along with Kaposi's sarcoma as an AIDS defining illness by the Centre for Disease Control (CDC) following the publication of series of 90 homosexual men with NHL [4–8]. A final AIDS defining malignancy, invasive cervical cancer was added as an AIDS defining illness in 1993, although the incidence of this malignancy is not increased as dramatically in HIV seropositive women [9].

A number of other cancers occur at an increased frequency in people with HIV infection including Hodgkin's disease, anal cancer, lung cancer and testicular seminoma [10]. However, these malignancies have not been included in the definition of AIDS and they fall outside the scope of this chapter.

Dramatic improvements in the anti-viral therapy of HIV infection occurred in the second half of the 1990s that have altered the natural history of HIV infection in those economies where these medicines are widely available. The introduction of highly active anti-retroviral therapy (HAART) has led to a fall in the incidence of both opportunistic infection and AIDS associated malignancies.

2. Highly active anti-retroviral therapy

Studies by the World Health Organisation have estimated that by July 2004, 21.8 million people had died of AIDS and the number of people newly infected with HIV is approximately 6 million per year [11]. The development of effective anti-retroviral therapies commenced with the introduction of nucleoside reverse transcriptase inhibitors starting with zidovudine in 1987. In the last 8 years, three new classes of anti-retroviral agents have been introduced: protease inhibitors (PI) (saquinavir, indinavir, ritonavir, nelfinavir, lopinavir, atazanavir), non-nucleoside reverse transcriptase inhibitors (NNRTI) (nevirapine, delaviridine, efavirenz) and fusion inhibitors (enfurvirtide). The introduction of the first

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two classes in the late 1990s led to the use of combination highly active anti-retroviral treatment. HAART has had an enormous impact on the treatment of HIV in terms of overall survival, incidence of opportunistic infections and quality of life. In randomised studies HAART leads to a dramatic decline in the mortality and morbidity of HIV [12]. However, only 1 million of the estimated 42 million people infected with HIV worldwide are receiving HAART as the majority of affected people live in developing countries [13]. In addition, even in the established market economies with access to medical treatment many individuals remain undiagnosed and consequently do not receive HAART. For the commonest AIDS defining malignancy, Kaposi's sarcoma, HAART remains an effective therapy [14] though its effect on lymphoma has been more controversial [15,16].

2.1. *AIDS-related systemic lymphoma*

2.1.1. *Epidemiology of AIDS-related lymphoma (ARL) in era of HAART*

Non-Hodgkin's lymphomas are associated with both congenital and iatrogenic immunosuppression and so it was perhaps not surprising that an increased incidence was demonstrated early in the AIDS epidemic. Registry linkage studies in the pre-HAART era found that the incidence of NHL in HIV-positive individuals was 60–200 times higher than in the matched HIV negative population [17,18] and the relative risk was even greater for primary cerebral lymphomas [19]. Following the introduction of HAART the incidence of both Kaposi's sarcoma and primary cerebral lymphoma has fallen significantly in both registry linkage and cohort studies [20–22], this is thought to be secondary to the immune reconstitution that occurs with HAART [23,24].

In contrast, the effects of HAART on systemic NHL are less clear [25,26] although some cohort studies suggest a modest non-significant decline in the incidence [27] including in the haemophilia population [28]. An international meta-analysis of 20 cohort studies compared the incidence of systemic NHL between 1992–1996 and 1997–1999. This meta-analysis confirmed an overall reduction in the incidence of both primary cerebral lymphoma (rate ratio = 0.42) and systemic immunoblastic lymphoma (rate ratio = 0.57) but not Burkitt's lymphoma (rate ratio = 1.18) [25].

2.1.2. *Predictors of AIDS-related lymphoma*

Genetic, infectious and immunological factors influence the development of AIDS-related lymphoma. For example, germ line chemokine and chemokine receptor gene variants have been found to influence the chance of developing these tumours. Acyclovir has mild activity against Epstein Barr in vivo and one case-control study has shown that administration of high-dose acyclovir (≥800 mg/day) for ≥1 year was associated with a significant reduction in the incidence of NHL [29]. However, data concerning the association between serum Epstein Barr viral DNA loads and lymphoma development are controversial [30,31].

In 2000, an analysis of our cohort of 7840 HIV-positive patients, identified three factors in multivariate analysis that are significantly associated with the development of systemic NHL: age, nadir CD4 cell count and no prior HAART. As the CD4 count falls, the development of lymphoma becomes more likely [15]. This may explain the declining incidence of NHL since the introduction of HAART as it is thought that the immune restoration that accompanies HAART protects against the development of AIDS-related lymphoma.

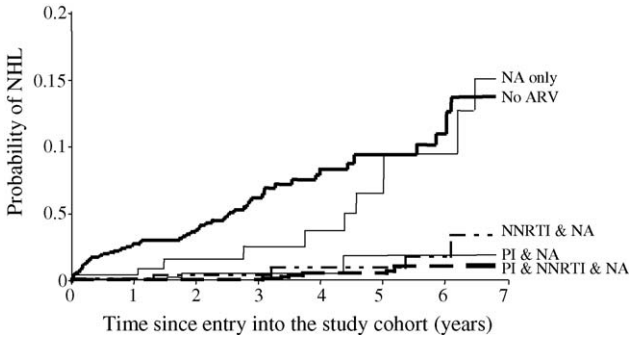

Fig. 1 – The probability of NHL and baseline exposure to different anti-retroviral drugs over 7 years, since HAART was commenced at our institution. ARV, anti-retroviral therapy; NA, nucleoside analogue; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

These data were updated in 2004 using 9621 HIV-1 infected patients in our cohort. Here, it was again found that the use of HAART protected against NHL development. Moreover, non-nucleoside reverse transcriptase inhibitor-based HAART (adjusted rate ratio, 0.4; 95% CI, 0.3–0.5) was as protective as protease inhibitor-based HAART, and these were significantly more protective than nucleoside analogues alone (rate ratio, 0.5; 95% CI, 0.4–0.7) or no anti-retrovirals (Fig. 1; $P < 0.001$) [27].

2.1.3. *Clinical presentation of AIDS-related lymphoma*

The majority of patients with systemic AIDS-related lymphomas present with advanced stage disease and B symptoms. Extranodal disease, bone marrow involvement and leptomeningeal disease are all common features. Hepatic involvement occurs in up to 25% patients whilst one in five patients has bone marrow involvement by NHL [8]. In addition, HIV infection itself is associated with tri-lineage abnormalities of haematopoiesis and the poor haematological reserves add to the myelotoxicity of cytotoxic chemotherapy [32,33]. Central nervous system involvement by systemic AIDS associated NHL is frequent; leptomeningeal disease is present at diagnosis in 3–10% and is significantly associated with Burkitt's lymphoma and both bone marrow and paraspinal or paranasal involvement [34–36], all of which necessitate intrathecal treatment.

In the published series from our institution that compared the clinical characteristics of 99 AIDS-related lymphomas presenting prior to 1996 and 55 that presented between 1996 and 1999, there were no differences in the stage at presentation, presence of B symptoms, bone marrow infiltration or performance status between the two groups. However, the patients who developed lymphoma in the HAART era were less likely to have had a prior AIDS diagnosis, were older and had higher CD4 cell counts at the time of lymphoma diagnosis [15]. Thus, although there has been a change in the immunological parameters of lymphoma patients, this would seem to reflect changes in the population at risk rather than any alteration of