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Malignancies in human immunodeficiency virus infected patients in India: Initial experience in the HAART era

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***Background & objectives*: Limited data are available on malignancies in human immunodeficiency virus (HIV)-infected patients from India. We undertook this study to assess the frequency and spectrum of malignancies in HIV-infected adult patients during the first eight years of highly active antiretroviral therapy (HAART) rollout under the National ART Programme at a tertiary care centre in New Delhi, India.**

***Methods*: Retrospective analysis of records of patients registered at the ART clinic between May 2005 and December 2013 was done.**

***Results*: The study included 2598 HIV-infected adult patients with 8315 person-years of follow up. Malignancies were diagnosed in 26 patients with a rate of 3.1 (IQR 2.1-4.5) cases per 1000 person-years. The median age for those diagnosed with malignancy was 45 (IQR 36-54) yr, which was significantly (P<0.01) higher compared with those not developing malignancies 35 (IQR 30-40) yr. The median baseline CD4+ T-cell count in patients with malignancy was 135 (IQR 68-269) cells/µl compared to 164 (IQR 86-243) cells/µl in those without malignancies. AIDS-defining cancers (ADCs) were seen in 19 (73%) patients, while non-AIDS-defining cancers (NADCs) were observed in seven (27%) patients. Malignancies diagnosed included non-Hodgkin's lymphoma (16), carcinoma cervix (3), Hodgkin's lymphoma (2), carcinoma lung (2), hepatocellular carcinoma (1), and urinary bladder carcinoma (1). One patient had primary central nervous system lymphoma. There was no case of Kaposi's sarcoma.**

***Interpretation & conclusions*: Malignancies in HIV-infected adult patients were infrequent in patients attending the clinic. Majority of the patients presented with advanced immunosuppression and the ADCs, NHL in particular, were the commonest malignancies.**

Key words Acquired immunodeficiency syndrome - human immunodeficiency virus - India - malignancy

Kaposi's sarcoma (KS) was among the first clinical diagnoses that led to the recognition of acquired immunodeficiency syndrome (AIDS) in 1981[1]. Subsequently, three types of cancers were classified as AIDS-defining cancers (ADCs), including KS, non-Hodgkin's lymphoma (NHL), and invasive cervical carcinoma (ICC) based on their dramatically increased risk in patients with human immunodeficiency virus (HIV) infection[2,3]. The spectrum of malignancies has changed since the introduction of highly active

antiretroviral therapy (HAART) in 1996 with increased proportion of cases in the developed world now being caused by non-AIDS-defining cancers (NADCs)[4,5]. Malignancy is also contributing to increased proportion of deaths among AIDS patients in the developed world[6].

The accessibility of HAART in developing countries, including India, is still poor due to a number of factors including a low level of awareness, illiteracy, and poverty[7]. According to estimates, two million HIV-infected people are living in India, and 0.6 million of them are on first line therapy under the National ART Programme[8]. However, epidemiological data on AIDS-associated cancers from India are lacking. While there are many studies assessing the spectrum of malignancies in HIV-infected patients attending the oncology centres[9-12], there are scant data, with small number of patients, to assess the risk of malignancy among patients with HIV/AIDS in India[13]. We reported two cases of HIV-associated lymphoma in a series of 135 patients before the rollout of the National ART Programme[14]. This study was carried out to assess the frequency and types of malignancies among patients with HIV/AIDS attending an ART clinic under the National ART programme.

Material & Methods

We retrospectively reviewed the charts of HIV-infected adult patients attending the ART centre at the All India Institute of Medical Sciences hospital, a tertiary care centre in New Delhi, India. For the purpose of the present study, adult patients registered at the centre between May 2005 and December 2013 and having a complete baseline work-up available, were included. Ethical clearance was taken from the Institute Ethics Committee.

HIV infection was documented by a licensed third generation enzyme-linked immunosorbent assay (ELISA) kit (Microlisa-HIV; India and SDHIV1/2 3.0, AIDSAN HIV-1/2 TRISPOT TEST kit; COMBAIDS HIV 1+2 immunodot test kit; India). All patients attending the clinic gave a complete history and underwent a detailed clinical examination at the first visit. Patient came every month to the clinic for follow up, and collection of antiretroviral drugs. The timing of HAART initiation was decided as per National AIDS Control Organisation (NACO) guidelines, and the regimen comprised two nucleoside reverse transcriptase inhibitors (zidovudine or stavudine plus lamivudine) and one non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine)[15]. CD4+ cell counts were performed by flow cytometry at baseline and every six months thereafter in accordance with the NACO guidelines. There was no active screening for cancer detection. Relevant investigations were done for diagnosis of malignancy guided by the clinical features.

Statistical analysis: Continuous data are presented as median, interquartile range (IQR). Categorical data are presented as numbers with proportions. The analysis was done using SPSS (version 20) (Stata Corporation, College, Station, Tx, USA).

Results

The study included 2598 HIV-infected adult patients, with 1783 (68.6%) patients being males who were registered at the clinic and followed up for 8315 person-years. The median age of patients with malignancy (n=26) was 45 yr (IQR, 36, 54) while those without malignancy (n=2572) was 35 yr (IQR, 30, 40) (P<0.01). The median duration of follow up was 29 (IQR 11-63) months. Median baseline CD4+ T-cell count was 164 (IQR 86-243) cells/µl; with 1633 (63%) patients having advanced immunosuppression with CD4 count less than 200 cells/µl at the time of diagnosis. The baseline characteristics of HIV-infected patients with and without malignancy are given in Table I.

Malignancies were diagnosed in 26 patients with a rate of 3.1 (IQR 2.1-4.5) cases per 1000 person-years. The median age at the time of diagnosis was 45 (IQR 36-54) yr which was significantly (P<0.01) higher than those not having malignancy. The median CD4+ T-cell count was 135 (IQR 68-269) cells/µl, with 16 patients (62%) having a CD4 count less than 200 cells/µl. Majority of the malignancies were ADCs including

Table I. Baseline characteristics of HIV-infected adult patients with and without malignancy

	With malignancy (n=26)	Without malignancy (n=2572)
Age (median, IQR) yr	45 (36,54)**	35 (30,40)
Male: Female n (%)	20 (77): 6 (23)	1763 (69): 809 (31)
CD4 (median, IQR) cells/µl	135 (68,269)	164 (86,243)

**P<0.01 compared with without malignancies

16 cases with NHL and three carcinoma cervix (Table II). The incidence of NHL was 1.9 (IQR 1.1-3.1) cases per 1000 person-years. One patient had primary central nervous system lymphoma at the time of diagnosis of HIV infection. Hodgkin's lymphoma was diagnosed in three patients; lung carcinoma in two, hepatocellular carcinoma and urinary bladder carcinoma in one each. There was no case of Kaposi's sarcoma. Majority of patients (22) with malignancy were diagnosed at the baseline work up, while only four patients developed malignancy in the setting of HAART. All the patients with malignancy received HAART.

The patients visited different centres for management of the malignancy based on their affordability and convenience. The details were not captured in the records.

Discussion

In the present study, the malignancies in HIV-infected patients were diagnosed with a rate of 3.1 cases per 1000 person-years. Compared to the background malignancy rates, the frequency of the overall malignancies was higher in the study group. The age adjusted incidence rates for all types of malignancies were 102.9 and 113.9 for males and females, respectively per 1,00,000 populations in Delhi[16]. The average age adjusted incidence rate for non-Hodgkin's lymphoma for Delhi Registry was 4.4 and 2.9 for males and females, respectively per 1,00,000 populations[17]. We reported two cases of lymphoma in a series of 135 HIV-infected patients before the rollout of the National ART Programme[14]. HIV-associated cancers were reported in 10 per cent of HIV-infected individuals in a large cohort from the United States with a rate of 9.8 cases per 1000 person-years in the post-HAART era[5]. However, the population was followed for a long period of time, and the time to cancer diagnosis was an average of six years, which was longer than our follow up. With longer follow up, it is likely that more patients in our series may develop cancer. The plausible explanation for the low rates may be the overall low background rate of malignancies in the Indian population compared to the Western population[18], and lack of screening programme for malignancy in these patients. Further, Kaposi's sarcoma which is a common ADC in the Western population and constitutes a significant proportion of the malignancies, is rarely seen in India[19,20]. The rarity is believed to be due to a very low incidence of human herpesvirus-8 (HHV-8) infection, likely due to the heterosexual route of HIV transmission; however, this view has been recently challenged[21].

Table II. Malignancies diagnosed among adult patients with HIV/AIDS (n=26)

Malignancies	n (%)
AIDS defining cancers	19 (73)
Non-Hodgkin's lymphoma	16
Carcinoma cervix	3
Non-AIDS defining cancers	**7** (27)
Hodgkin's lymphoma	3
Carcinoma lung	2
Hepatocellular carcinoma	1
Urinary bladder carcinoma	1

ADCs comprised 73 per cent of the cancers in the present study, NHL being overall the commonest malignancy observed. The high proportion of NHL observed in the study was similar to earlier reports from India and Asia[10,22,23]. In a report from south India, 43 per cent of HIV-infected patients who developed malignancy over a 10-year period had an AIDS-defining cancer, with 38 per cent developing NHL[22]. The spectrum of HIV-associated cancers in Western India was described in 251 patients from an oncology referral centre[10]. NHL was the most common cancer among HIV-infected cancer patients in men and second most common among women. The proportional incidence ratio (PIR) for NHL was significantly increased in the study group. Invasive cervical carcinoma was reported as the leading cancer site among the HIV-infected women diagnosed with cancer. The NADCs reported in higher proportion were anal cancer, Hodgkin's disease, testicular cancer, colon cancer and certain head and neck cancers in men and vaginal cancers in females[10]. Hodgkin's disease comprised 43 per cent of patients developing NADCs in the present study. In a study involving 13 sites in Asia, the majority of malignancies (66%) reported were ADCs[23]. Data from the Western countries show higher rates of ADC in the pre-HAART era which has declined in the HAART era; whereas, rates of NADCs have risen over the time period[5,24-28]. In the Western countries, the incidence of KS and NHL has declined markedly in recent years, reflecting HAART-related improvement in immunity, while incidences of some non-AIDS-defining cancers have increased[5]. Further,

the development of NADCs is shown to be associated with increasing age among HIV patients[5,28]. These have led to a shift in the spectrum of cancer among HIV-infected persons in the HAART era. The patients in the present study had advanced immunosuppression and majority were HAART naïve at the time of diagnosis of malignancy, both of which have been shown to be the predictors for ADCs[5].

The study had inherent limitations being a retrospective analysis of case records which was not designed to capture various details required for a comprehensive analysis of various types and associated factors for development of malignancies. The majority of patients at diagnosis of cancer had advanced immunosuppression and were diagnosed during the initial work up of presenting symptoms. Since screening for HIV infection in malignancy is not done routinely, not all HIV-infected patients with malignancy might have reported or been referred to the clinic. A survival bias cannot be ruled out. The data on the treatment and outcome of the cancers were not available. The patients were treated at different centres based on their affordability and convenience. An other limitation could be the bias due to this being a single centre study from a tertiary care centre from where the majority of patients are referred to their local centres after initial few months of therapy. There is also no proactive screening programme like Pap smear testing, which is required for comprehensive care of these patients in India.

In conclusion, malignancies in HIV-infected adult patients were infrequent in patients attending the ART clinic at a tertiary care centre in northern India. ADCs comprised majority of the cases, and NHL was the commonest malignancy in these patients. Information, education and communication (IEC) activities and integration of the regional cancer centres with the ART centres are imperative for comprehensive management of these patients.

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Conflicts of Interest: None.

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