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Review Article

Epidemiological trends of cancers in AIDS patients

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ABSTRACT

Since the advent of highly active antiretroviral therapy (HAART), patients with human immunodeficiency virus (HIV) infection have seen a significant improvement in their morbidity, mortality and life expectancy. The incidence of AIDS-defining illnesses, including AIDS-defining malignancies, has been on the decline. However, deaths due to non-AIDS-defining illnesses have been on the rise. These so-called non-AIDS-defining cancers (NADCs) include cancers of the lung, liver, anus, and Hodgkin's lymphoma. The development of NADCs appears to be multifactorial. Risk factors include immunosuppressive effects of the HIV, higher rates of oncogenic viral coinfections and traditional cancer risk factors. New strategies for screening, prevention and treatment of NADCs need to be developed to reverse these epidemiologic trends and improve the survival of HIV-infected patients.

1. Introduction

Since the beginning of the HIV epidemic, cancer has figured prominently in the spectrum of immunodeficiency-related manifestations. Kaposi sarcoma (KS) and aggressive non-Hodgkin lymphoma (NHL), because of their dramatically elevated risk (100,000 and 282, respectively, in the U.S.) with HIV and cervical cancer (CC) with less dramatic increase (10 times), were categorized as AIDS defining cancers (ADCs) to facilitate AIDS surveillance [1]. Only a few other cancers were noted to be modestly elevated with HIV, including Hodgkin lymphoma (10 times), anal cancer (15–30 times) and lung cancer (4 times) and were categorized as non-AIDS-defining cancers (NADCs) [2]. Since 1996 when highly active antiretroviral therapy (HAART), became widely available in the West, dramatic decreases in HIV mortality have been observed and substantial decrease in the incidence of ADCs. Coincidentally, the burden of NADCs has increased as people with HIV age with chronic HIV infection. While ADCs contributed the majority of cancer early in the AIDS epidemic, NADCs have assumed greater importance as survival has lengthened and patients are aging with HIV [3]. Apart from a bona fide increased prevalence of NADCs, the spectrum of NADC has expanded as the size of the HIV-positive population has increased [4]. NADCs are responsible for significant morbidity and mortality in the highly active antiretroviral therapy (HAART) era [5]. In general, patients with NADC have been reported to have an overall poor outcome manifesting with advanced cancer at presentation, rapid progression, frequent metastases, a high rate of relapse, and poor therapeutic response. In this paper, we review current literature of NADCs incidence, spectrum, risk factors and outcome.

2. Incidence

As shown in Fig. 1 the incidence of NADC has increased in the HAART era. A nationwide epidemiological study was conducted in Japan to evaluate the incidence of non-AIDS-defining hematological malignancies (NADHMs), excluding non-Hodgkin's lymphomas, in HIV-infected patients. Comparison of patients over the two periods (1991–2000 and 2001–2009) revealed a 4.5-fold increase in the incidence of hematological malignancies [6]. Another recent study retrospectively analyzed all incident NADCs occurring in a cohort of HIV-positive patients in Italy followed up between 1985 and 2011. 5924 patients (4382 males and 1542 females) contributed 50,990 person-years (py) to the follow-up. Among them 144 had new NADC diagnosis. The overall incidence increased from 1.0 case/1000 py in the pre-HAART period (1985–1996) to 4.5 cases/1000 py in the HAART period (1997–2011) ($p < 0.01$) [7].

Investigators from the National Cancer Institute in the United States linked HIV/AIDS and cancer registries in three states where 57,350 HIV-infected persons were registered during 1991–2002. Risk was shown to be elevated for Hodgkin lymphoma, lung cancer

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; ADCs, AIDS defining cancers; NADCs, non-AIDS-defining cancers; NADC-IR, non-AIDS-defining cancers-infection related; NADC-IUR, non-AIDS-defining cancers infection unrelated; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; CC, cervical cancer; HPV, human papilloma virus; MSM, men who have sex with men; AIN, anal intraepithelial neoplasia; NADHMs, non-AIDS-defining hematological malignancies; py, person-years; SIR, standardized incidence ratio; HBV, hepatitis B virus; HCV, hepatitis C virus.

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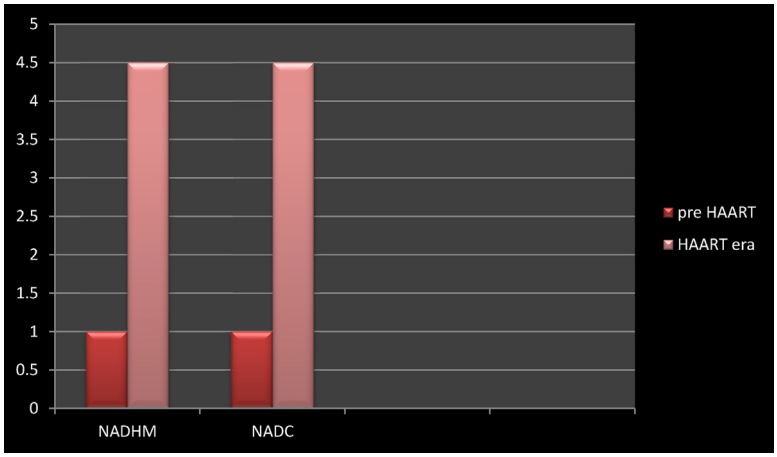

Fig. 1. Increase in incidence of NADC.

Adapted and modified from Refs. [6,7].

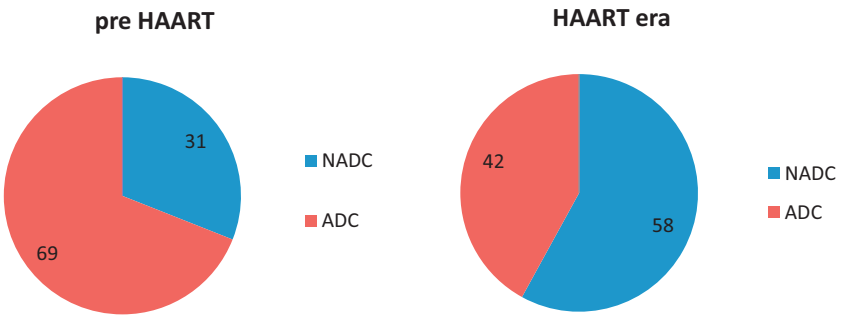

Fig. 2. Increase in prevalence of NADC in HAART era.

Adapted and modified from Ref. [8].

and hepatocellular carcinoma. In this study, NADC comprised 31% of cancers in 1991–1995 (pre-HAART) versus 58% in 1996–2002 (HAART era) [8] as is represented in Fig. 2. In another retrospective cohort study for the period from 1999 to 2009 of HIV-infected patients residing in northern Italy a total of 5090 HIV-infected patients were included in the study, with 32,390 person-years of follow-up. 416 tumors were recorded in 390 HIV-infected patients. Two hundred of these (48.1%) were ADCs, 138 (33.2%) were non-virus-related NADCs and 78 (18.7%) were virus-related NADCs [9]. Similar results 53% ADC and 47% NADCs seen in a sectional study conducted among HIV infected adults attending an AIDS outpatient clinic in Vitória, State of Espírito Santo, Brazil [10].

3. Spectrum

Categorization of cancers in AIDS patient is done in Table 1. In HIV-infected patients cancers are grouped as AIDS-defining cancers (ADCs), and non-ADCs. Non-ADCs are further categorized as being infection related (NADC-IR) and unrelated (NADC-IUR). The incidence and spectrum of NADC has increased in different regions of the world. TREAT Asia HIV Observational Database (TAHOD) sites retrospectively reviewed clinic medical records to determine cancer diagnoses since 2000. A total of 617 patients were included in this study. The most common NADCs were lung (6%), breast (5%) and hepatocellular carcinoma and Hodgkin's lymphoma (2% each). There were also three (1.4%) cases of leiomyosarcoma, a smooth-muscle tumor, usually seen in children and young adults with AIDS, yet overall quite rare, reported in this study [11]. In a study exploring the spectrum of HIV related cancers at the largest tertiary referral cancer center in India amongst the non-AIDS defining cancers anal cancer, testicular cancer, Hodgkin's disease, colon cancer and certain head and neck cancer sites in men and vaginal cancers among women were found to occur more frequently [12].

A retrospective cohort study using the Taiwan Longitudinal Health Insurance Database between January 1, 2002, and December 31, 2007 found the risk of overall malignancies in the HIV-infected cohort was 1.88 times higher than the risk of a first malignancy in the age-matched non-HIV infected cohort. However, the difference in the risk of developing nasopharyngeal carcinoma (NPC), a highly prevalent malignancy in Taiwan, between the two cohorts was not significant [13]. Similarly, the few studies conducted in sub-Saharan Africa, where two thirds of the HIV epidemic is concentrated, the risks for many cancers with established viral associations, including liver and nasopharynx, which are found in Africa; do not appear to be increased [14]. However, a recent case-referent study conducted in referral hospitals among patients hospitalized for diagnosis or treatment of cancer in West Africa

Table 1
Categorization of cancers in HIV infection.

AIDS defining cancers	Kaposi sarcoma Non Hodgkin lymphoma Invasive cervical cancer
Non-AIDS defining cancer-infection related	Anal cancer Hodgkin lymphoma Hepatocellular cancer
Non-AIDS defining cancer-infection unrelated	Lung cancer Cancer of the vulva Tonsil cancer

Adapted and modified from Ref. [7].