Prevalence and mortality of cancer among people living with HIV and AIDS patients: a large cohort study in Turkey

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Abstract

Background: Cancer is responsible for elevated human immunodeficiency virus (HIV)-related mortality but there are insufficient data about cancer in HIV-positive patients in Turkey.

Aims: We aimed to investigate the prevalence and mortality of cancer among people living with HIV/AIDS patients in Istanbul, Turkey.

Methods: Between January 1998 and December 2016, people living with HIV and AIDS patients were enrolled in this study by the ACTHIV-IST Study Group, which consists of 5 centres to follow-up HIV-positive patients in Istanbul. The cancer diagnoses included AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs).

Results: Among 1872 patients, 37 (1.9%) were diagnosed with concurrent cancer. Eleven patients were diagnosed during follow-up; the prevalence of cancer among people living with HIV and AIDS patients was 2.6%. Among 48 cancer patients, 35 patients had ADCs, and 32 of them were diagnosed at their first hospital admission. There were 1007 late presenters and 39 of them had cancer (29 were ADCs). The most prevalent NADCs were gastrointestinal, genitourinary, and pulmonary cancers. NADCs were mostly diagnosed during follow-up of patients. The mortality of this group was significantly higher than that of patients with ADCs (53.9% vs. 22.9%).

Conclusions: These results indicate the importance of cancer screening at diagnosis and during follow-up of HIV infection. A detailed physical examination contributes to diagnosis of the most prevalent ADCs (Kaposi's sarcoma and non-Hodgkin's lymphoma), especially in late presenters. For NADCs, individual risk factors should be considered.

Keywords: human immunodeficiency virus, AIDS, cancer, prevalence, mortality

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Introduction

Patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are at increased risk of developing cancer (1). This link was observed first when Kaposi’s sarcoma (KS) was reported in young, homosexual men with severe immunosuppression, which was thereafter referred to as AIDS. The higher risk is mainly attributed to the impaired immune system. HIV-induced immunosuppression is responsible for the higher rates of KS and non-Hodgkin’s lymphoma (NHL) and the risk increases steadily as CD4+ cell count decreases. Antiretroviral therapy reduces the increased risk of these cancers (2,3). However, non-AIDS-defining cancers (NADCs) do increase and cancer remains a significant cause of mortality in HIV/AIDS patients. Although long lifespan provides time for cancer to develop, the increased cancer risk compared to that in the matched general population demonstrates the role of other factors (4). Coinfection with other viruses, alcohol consumption, tobacco smoking and advanced age in HIV/AIDS patients also increase the risk of cancer (5). People with HIV/AIDS have higher rates of tobacco smoking, hepatitis B and C coinfection, and human papillomavirus infection (6,7).

The increase in the number of NADCs is a challenge to the management of HIV/AIDS patients. The tumours are generally more aggressive and diagnosed at a younger age. HIV-infected patients with Hodgkin’s lymphoma are more likely to present with unfavourable histological type and with higher rate of bone marrow involvement (8). The antineoplastic agents have a high likelihood of interaction with antivirals since protease inhibitors, non-nucleoside reverse transcriptase inhibitors and many antineoplastic drugs are metabolized by the cytochrome P450 system. Coadministration of these antivirals and antineoplastic agents could result in greater adverse effects and decreased efficacy (9,10). Additionally, the risk of death in cancer patients with AIDS is significantly higher than in cancer patients without AIDS for almost all cancer types (10).
After nearly 2 decades of the availability of highly active antiretroviral therapy (HAART), the size of the HIV/AIDS population is growing. As well as late presenting cases, patients receiving HAART regimens have a prolonged, mild immunosuppressive state. Especially in the setting of known risk factors for cancer, the increased incidence of cancer in HIV/AIDS patients represents a significant cause of mortality. There are insufficient data in the current literature about cancer in Turkish HIV-infected patients. In the present study, we aimed to investigate the prevalence and mortality of cancer among HIV/AIDS patients in Istanbul, Turkey.

**Methods**

Between January 1998 and December 2016, 1872 HIV-infected patients were enrolled by the ACTHIV-IST (Action Against HIV in Istanbul) Study Group, which consists of 5 centres, to follow-up HIV-positive patients in Istanbul. All newly diagnosed HIV/AIDS patients had a confirmatory diagnosis using a western blotting verification test (HIV BLOT 2.2; MP Biomedicals Asia Pacific, Singapore). The CD4+ cell counts were obtained by standard flow cytometry (FACScalibur; Becton Dickinson, Franklin Lakes, NJ, USA), and HIV viral load was measured by polymerase chain reaction (COBAS Amplicore/COBAS TaqMan HIV-1 Test; Roche Molecular Systems, Pleasanton, CA, USA). Demographic data including age, sex, transmission routes, education level, marital status, history of imprisonment, CD4+ cell counts, and HIV RNA were collected from medical records and transferred to an HIV database system.

All the patients at all 5 sites received standardized care and diagnosis services. Diagnosis of cancer was established by clinical (detailed history taking and thorough physical examination), radiological and pathological/histological characteristics. Each cancer was reviewed using a standardized protocol to confirm the diagnosis and collect detailed information regarding cancer type, histology, grade, stage, and treatment from the medical records. Each site in the study used the same protocol for cancer evaluation and data collection. Cancer types were classified according to location (i.e., mucocutaneous, oral, breast, cervix, anus and lung) and/or histopathological reports (i.e., lymphoma and leukaemia). Details of histology, grade, and tumour node metastasis (TNM) staging were obtained from pathology reports and imaging studies. The cancer diagnoses included ADCs (Kaposi’s sarcoma, non-Hodgkin’s lymphoma, thyroid cancer, and cervical cancer) and NADCs.

Survival probability was calculated as the proportion of patients that survived beyond a specified time, and mean survival was the average length of time passed from the date of HIV/AIDS diagnosis. Categorical variables were compared by χ² (or Fisher’s exact) test and continuous variables (age) were compared by Mann–Whitney U test. P < 0.05 was accepted as significant. This study was accepted by the Ethical Committee of Cerrahpasa Medical Faculty (83045809-604.01.02), Istanbul, Turkey.

**Results**

Among 1907 patients with HIV infection, 35 (1.8%) were lost to follow-up (The remaining 1872 (98.2%) patients were followed up for a total of 146,922 patient-months. Thirty-seven (2.0%) patients were diagnosed with cancer. Additionally, 11 (0.6%) patients were diagnosed during follow-up. The prevalence of cancer among our HIV/AIDS patients was 2.6%. Among the 48 cancer patients, 4 were female and mean age was 41.3 years. Thirty-five (72.9%) patients had ADCs, and 32 (91.4%) were diagnosed at their first hospital admission. Eight (22.8%) of 35 ADC patients and 7 (53.8%) of 13 NADC patients died during the study period. The mortality was 1.75% (32 of 1824) in non-cancer patients.

The 35 ADCs comprised 23 Kaposi’s sarcomas and 12 NHLs. Among the 13 patients with NADCs, 5 had gastrointestinal cancer (3 colon, 1 esophageal and 1 liver), 3 urogenital cancer (1 kidney, 1 prostate and 1 testicular), 3 lung cancer, and 1 each laryngeal and spinal cord cancer.

The patients with NADCs were older than those with ADCs (mean age 53 vs 45 years) (Table 1). The patients with NADCs had a higher rate of HBV infection (15.4% vs 5.7%). Most importantly, the mortality rate was higher among patients with NADCs than ADCs, 53.8% vs 22.8% respectively. Moreover, while 91.4% of ADCs were diagnosed with HIV concurrently, this ratio among NADCs was 38.4%.

The survival probability of HIV-infected cancer patients was significantly lower than that of HIV-infected cancer-free patients (31.3% vs 1.7%) (Table 2). Low CD4 count was more frequent in cancer patients; cancer patients (both those diagnosed on admission and those who developed cancer during follow-up) were more likely late presenters, whose CD4 count was below 350 cells/mm³ at the moment of presentation at a healthcare facility or presenting with an AIDS-defining condition. Considering all cancer patients (diagnosed at any time), CD4 count < 350/mm³ was 38/48 (79%) compared with 968/1824 (53%) among patients without cancer (P < 0.001) (Table 2).

The survival rate between patients diagnosed with cancer on admission and those diagnosed during follow-up were comparable: 18.9 and 12.2 months, respectively (P > 0.48) (Table 3). Similarly, mortality did not differ significantly between the 2 groups. The cancers were more frequently ADCs in patients diagnosed on admission compared to those diagnosed during follow-up (87% vs 27%, P = 0.0004).

Thirty-five patients did not come to follow-up visits. Admission from one HIV/AIDS centre to another is frequent among patients in Turkey. However, this was not confirmed since the patients were not reached.

Causes of death other than cancer were: infection (tuberculosis, toxoplasmosis, cryptococcosis, Pneumocystis jirovecii pneumonia and sepsis; n = 12), wasting (n = 7), myocardial infarction (n = 2), suicide, cerebrovascular accident, progressive multifocal leukoencephalopathy, gastrointestinal bleeding, illicit drug use/intoxication,
renal failure, HIV encephalopathy, alcohol intoxication, traffic accident, liver failure and undetermined (all n = 1).

**Discussion**

In this study, there were 32 ADCs and 5 NADCs on admission; however, on follow-up, 3 ADCs and 8 NADCs developed additionally. In other words, most of the HIV-infected patients with concurrent cancer had ADCs. NADCs were mostly diagnosed during follow-up of patients. The mortality of patients with NADCs was significantly higher than that in patients with ADCs. These findings highlight the importance of promoting cancer screening during initial diagnosis of HIV infection as well as during follow-up.

Before HAART, cancer was responsible for a minority (around 10%) of deaths in HIV-infected individuals (11). Despite the substantial decrease in ADCs in patients with HAART, cancer is responsible for approximately one third of deaths in this population (10,12). This increased role of cancer may be explained by the longer survival expectancy afforded by HAART (13), probable oncogenic role of HIV (12), effect of other viruses (mainly hepatitis B, hepatitis C, human herpesvirus and human papillomavirus), advancing age, and higher prevalence of risky behaviours (e.g., alcohol consumption and tobacco smoking) (5). In the United States of America, from 1991 to 2005, the estimated number of ADCs decreased by >3-fold whereas NADCs increased by ~3-fold (anal, liver, prostate and lung cancers, and Hodgkin’s lymphoma). The increase in NADC was mainly attributed to growth and ageing of the AIDS population (14). The risk of cancer mortality is higher in patients with than without AIDS for many cancer types (10).

Late presentation with AIDS-defining disorders, including cancer, severely affects HIV management and is associated with high morbidity and mortality (15,16). Late presentation means missed opportunities for prevention and early diagnosis in most cases (17). A multicentre European study in 2013 including 30 454 patients from 34 countries reported that 48.7% were late presenters (18). This figure is even higher in Asian (19) and African (20) cohorts, reaching up to 72% and 85.6%,

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**Table 1** Characteristics of HIV-infected patients with cancer

| Characteristic                  | Patients with cancer |
|---------------------------------|----------------------|
|                                 | ADCs n = 35 (%)      | NADCs n = 13 (%)  |
| **Sex**                         |                      |                    |
| Female                          | 3 (8.6)              | 1 (7.7)            |
| Male                            | 32 (91.4)            | 12 (92.3)          |
| Mean age (years)                | 45 ± 11              | 53 ± 13            |
| **Age groups, n (%)**           |                      |                    |
| 20–30 years                     | 7 (20)               | 0 (0)              |
| 31–40 years                     | 16 (45.7)            | 3 (23.1)           |
| 41–50 years                     | 5 (14.3)             | 3 (23.1)           |
| 51–60 years                     | 5 (14.3)             | 4 (30.7)           |
| > 61 years                      | 2 (5.7)              | 3 (23.1)           |
| **CD4 count on diagnosis, n (%)** |            |                    |
| 0–200/mm³                       | 27 (77.1)            | 4 (30.7)           |
| 201–350/mm³                     | 2 (5.7)              | 5 (38.5)           |
| 351–500/mm³                     | 4 (11.4)             | 1 (7.7)            |
| > 500/mm³                       | 2 (5.7)              | 3 (23.1)           |
| **Transmission route n (%)**    |                      |                    |
| Heterosexual                    | 15 (42.9)            | 11 (84.6)          |
| MSM                             | 20 (57.1)            | 2 (15.4)           |
| IVDU                            | 0                    | 0                  |
| Blood transfusion               | 0                    | 0                  |
| HBV coinfection, n (%)          | 2 (5.7)              | 2 (15.4)           |
| HCV coinfection, n (%)          | 0                    | 0                  |
| Patients died, n (%)            | 8 (22.9)             | 7 (53.8)           |
| Cancer on HIV diagnosis, n (%)  | 32 (91.4)            | 5 (38.4)           |
| Cancer during follow-up, n (%)  | 3 (8.6)              | 8 (61.5)           |

ADC = AIDS-defining cancer; IVDU = intravenous drug use; MSM = men who have sex with men; NADC = non-AIDS-defining cancer.

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**Table 2** Characteristics of HIV-infected patients with or without cancer

| Characteristic                  | No cancer n = 1824 | All cancers n = 48 | P   |
|---------------------------------|-------------------|-------------------|-----|
| **Sex**                         |                   |                   |     |
| Female                          | 248               | 4                 | > 0.05 |
| Male                            | 1576              | 44                |     |
| Mean age (years)                | 37 ± 9            | 42 ± 13           | 0.02 |
| **Age groups, n (%)**           |                   |                   |     |
| 20–30 years                     | 639 (35)          | 7 (4.5)           | 0.03 |
| 31–40 years                     | 581 (31.9)        | 19 (39.6)         | > 0.05 |
| 41–50 years                     | 371 (20.3)        | 8 (16.7)          | > 0.05 |
| 51–60 years                     | 167 (9.2)         | 9 (18.8)          | 0.049 |
| > 61 years                      | 66 (3.6)          | 5 (10.4)          | 0.03 |
| **CD4 count on diagnosis, n (%)** |                   |                   |     |
| 0–200/mm³                       | 445 (24.4)        | 31 (64.6)         | < 0.001 |
| 201–350/mm³                     | 523 (28.7)        | 8 (16.7)          | > 0.05 |
| 351–500/mm³                     | 386 (21.1)        | 4 (8.3)           | 0.03 |
| > 500/mm³                       | 470 (25.8)        | 5 (10.4)          | 0.017 |
| **Transmission route, n (%)**   |                   |                   |     |
| Heterosexual                    | 987 (54.1)        | 26 (54.2)         | > 0.05 |
| MSM                             | 821 (45.8)        | 22 (45.8)         | > 0.05 |
| IVDU                            | 3 (0.2)           | 0                 | > 0.05 |
| Blood transfusion               | 13 (0.7)          | 0                 | > 0.05 |
| HBV coinfection, n (%)          | 104 (5.7)         | 4 (8.3)           | > 0.05 |
| HCV coinfection, n (%)          | 16 (0.9)          | 0 (0)             | > 0.05 |
| Patients died, n (%)            | 32 (1.7)          | 15 (31.3)         | < 0.001 |
| Cancer on HIV diagnosis, n (%)  | 37 (77)           | –                 |     |
| Cancer during follow-up, n (%)  | 11 (2.2)          | –                 |     |

ADC = AIDS-defining cancer; IVDU = intravenous drug use; MSM = men who have sex with men; NADC = non-AIDS-defining cancer.
Méthodes

Objectifs

Contexte

Prévalence et mortalité du cancer chez les personnes vivant avec le VIH et les patients atteints de sida : étude de cohorte à grande échelle en Turquie

Résumé

Contexte : Le cancer est responsable d’une mortalité élevée liée au virus de l’immunodéficience humaine (VIH), mais les données relatives au cancer chez les personnes séropositives en Turquie sont insuffisantes.

Objectifs : Étudier la prévalence et la mortalité du cancer chez les personnes vivant avec le VIH et les patients atteints de sida à Istanbul (Turquie).

Méthodes : Entre janvier 1998 et décembre 2016, des personnes séropositives ont été recrutées comme sujets pour la présente étude par le groupe d’étude ACTHIV-IST, qui se compose de cinq centres de suivi des personnes séropositives pour le VIH à Istanbul. Les diagnostics de cancer incluaient les cancers classant sida et les cancers non classant sida.
Résultats : Sur 1 872 malades, 37 (1,9 %) ont reçu un diagnostic de cancer concomitant. La prévalence du cancer chez les personnes vivant avec le VIH et les patients atteints de sida était de 2,6 %. Sur 48 patients cancéreux, 35 avaient un cancer classant sida, parmi lesquels 32 avaient été diagnostiqués lors de leur première hospitalisation ; 1 007 personnes se présentaient à un stade avancé de l’infection, et 39 d’entre elles avaient un cancer (29 avaient un cancer classant sida). Les cancers non classant sida et les plus prévalents étaient les cancers gastro-intestinal, uro-génital et pulmonaire. Ces cancers avaient principalement été diagnostiqués chez les patients en phase de suivi post-thérapeutique. Dans ce groupe, la mortalité était considérablement plus élevée que celle des patients de cancers classant sida (53,9 % contre 22,9 %).

Conclusions : Ces résultats soulignent l’importance du dépistage du cancer lors du diagnostic et du suivi post-thérapeutique des infections à VIH. Un examen clinique détaillé contribue au diagnostic des cancers classant sida les plus prévalents (sarcome de Kaposi et lymphome non hodgkinien), en particulier chez les patients se présentant à un stade avancé. Concernant les cancers non classant sida, les facteurs de risque individuels devraient être pris en compte.

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