Abstract

Background: Cancer is responsible for elevated human immunodeficiency virus (HIV)-related mortality but no sufficient data about Turkish HIV-infected patients exist in the literature.
Aims: We aimed to investigate the prevalence and mortality of cancer among HIV/AIDS patients in Istanbul, Turkey.

Methods: Between January 1998 and December 2016, HIV-infected patients were enrolled in this study by the ACTHIV-IST Study Group, which consists of five 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. Additively, 11 patients were diagnosed during follow-up; the prevalence of cancer among our HIV/AIDS patients was 2.6%. Among totally 48 cancer patients, 35 patients had ADCs, and 91% of them were diagnosed at their first hospital admission. Late presenters were 53% and 81.2% of all cancers (82.8% of ADCs) were detected in this group. The most prevalent NADCs were gastrointestinal, genitourinary, and pulmonary cancers. NADCs were mostly diagnosed during follow-up of the patients. The mortality of this group was significantly higher than ADCs (53.9% vs 22.9%).

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

Keywords: Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome, 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 has been observed first when Kaposi 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 lymphoma (NHL) and the risk increases steadily as CD4+ cell counts decrease. Antiretroviral therapy reduces the increased risk of these cancers (2,3). However, non-AIDS-defining cancers (NADCs) do increase and cancer remains to be a significant mortal problem in HIV/AIDS patients. Although longer life providing time for cancers to develop is one explanation, increased cancer risk compared to the matched general population demonstrate the role of other factors (4). Co-infection with other viruses, alcohol consumption, tobacco smoking and advanced age in HIV/AIDS patients also increase the risk (5). People with HIV/AIDS have higher rates of tobacco smoking, hepatitis B and C co-infections, and human papillomavirus infection (6,7).

The increase in the number of NADCs is challenging the management of HIV/AIDS patients. The tumours have a generally more aggressive behaviour and diagnosed at a younger age. HIV-infected patients with Hodgkin lymphoma are more likely to present with unfavourable histologic 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. Co-administration of these two groups could result in greater side 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 two decades of the availability of highly active antiretroviral therapy (HAART), the size of the HIV/AIDS population is growing. As well as late presented cases, patients under HAART regimens represent a prolonged, mild immunosuppressive state. Especially in the setting of known risk factors for cancer, the emergence of cancers in HIV/AIDS patients represents a significant cause of mortality. No sufficient data about Turkish HIV-infected patients exists in the current literature. 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 in this study by the ACTHIV-IST (Action Against HIV in Istanbul) Study Group, which consists of five centers to follow-up HIV-positive patients in Istanbul. All newly diagnosed HIV/AIDS patients had a confirmed diagnosis through the Western Blot verification test (HIV BLOT 2.2, MP Biomedicals Asia Pacific, Singapore). The CD4+ cell counts were obtained by standard flow cytometry (FACScalibur, Becton Dickinson, New Jersey, USA) and HIV viral load was measured by PCR (COBAS Amplicon/COBAS TaqMan HIV-1 Test, Roche Molecular Systems, USA). Demographic data including age, sex, transmission routes, education level, marital status, and history of imprisonment, CD4+ counts, and HIV RNA were collected from medical records and were transferred to a HIV database system.

All the patients in every site took standardized care and diagnosis services. The diagnosis of cancer was established by clinical (a detailed history taking and a thorough physical examination), radiology and pathology/histology. Each cancer was reviewed using a standardized protocol to confirm the diagnosis and collect detailed information regarding cancer type, histology, grade, staging, 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, anal, and lung) and/or histopathologic reports (i.e. lymphoma, leukaemia). Histology, grade, tumour nodes and metastasis and staging were obtained from information provided in pathology reports and imaging studies. The cancer diagnoses included ADCs (Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer) and NADCs.

Survival probability was calculated as the proportion of patients that survive beyond a specified time, and mean survival was used as the average length of time from the date of HIV/AIDS diagnosis of the patients that are still alive.

Categorical variables were compared by Chi-square (or Fisher’s exact) test and continuous variable (age) was compared by Mann-Whitney U test. P < 0.05 was accepted as significant.

Results

Among 1907 patients, 35 were lost to follow-up (Figure 1). Remaining patient records were analyzed with a total of 146 922 patient-months of follow-up. Out of 1872 patients, 37 (1.9%) were diagnosed with concurrent cancer. Additionally, 11 patients were also diagnosed during
follow-up; the prevalence of cancer among our HIV/AIDS patients was 2.6%. Among 48 cancer patients, 4 were female and mean age was 41.3 years. Thirty-five patients (73%) had ADCs, and 91% of them were diagnosed at their first hospital admission (Figure 2). Eight out of 35 ADC patients and 7 out of 13 NADC patients died during the study period. The mortality was 1.75% (32 out of 1824) in non-cancer patients (Figure 1). The most prevalent NADCs were gastrointestinal, genito-urinary, and pulmonary cancers (Table 1). The characteristics of the patients with or without cancer are given in Table 2. The patients with NADCs were significantly older than the patients with ADCs (53 years vs 45 years) and also infected with HBV (15.4% vs 5.7%). Mortality rate was higher among patients with NADCs than ADCs (53.8% vs 22.8%). The survival probability of HIV-infected cancer patients was significantly lower than that of HIV-infected cancer-free patients (31.3% vs 1.7%).

The survival rates between patients diagnosed with cancer on admission and those diagnosed on follow-up were comparable. Among patients diagnosed as cancer on admission, mean survival was 18.9 months and the survival was 12.2 months among cancer patients diagnosed on follow-up (P > 0.48). Low CD4 count was more frequent in cancer patients; cancer patients (both those diagnosed on admission and those developed on follow-up) were more likely late presenters. Considering all cancer patients (diagnosed at any time), CD4 count below 350/mm3 was 38/48 (79%). This figure was 968/1824, 53% among patients without cancer (P < 0.001) (Table 3). The cancer incidence was not associated with HIV treatment or change in the treatment. Mortality rate was not different between patients diagnosed on admission versus those diagnosed during the follow-up. The cancers were more frequently AIDS-defining cancers in patients diagnosed on admission compared to those diagnosed on follow-up (87% vs 27%, P = 0.0004) (Table 4).

Thirty-five patients did not come to follow-up visits. Admission from one HIV/AIDS center to another is frequent among patients in the country. However, this was not confirmed since the patients were not reached. Death due to causes other than cancer is given in Table 5.

**Discussion**

Before HAART, cancers were responsible for a minority (around 10%) of deaths in HIV-infected individuals (11). Despite the substantial decrease in ADCs with HAART, cancers are responsible for approximately one third of deaths in this population (10,12). This increased role
of cancers may be explained by longer expectancy of survival afforded by HAART (13), the probable oncogenic role of HIV (12), the effect of other viruses (mainly HBV, HCV, HHV, HPV), advancing age, and higher prevalence of risky behaviours (alcohol consumption, tobacco smoking (5). In the United States of America, the estimated number of AIDS-defining cancers decreased by more than threefold whereas non-AIDS-defining cancers increased by approximately threefold (anal cancers, liver cancers, prostate cancers, and lung cancers, and Hodgkin lymphoma) in the period from 1991 to 2005. The increases in non-AIDS-defining cancers were mainly attributed to growth and aging of the AIDS population (14). In the setting of AIDS, the risk of cancer death is higher than in cancer patients without AIDS for many cancer types (10).

Late presentation severely affects HIV management. It is documented in many cohorts that late presentation is associated with higher morbidity and mortality (15,16). The patients were admitted with AIDS-defining disorders including cancers. A late presentation means missed opportunities for prevention and for early diagnosis in most cases (17). A multicentre European study including 30 454 patients from 34 countries reported that 48.7% were late presenter in 2013 (18). This figure is even higher in Asian (19) and African (20) cohorts, reaching up to 72% and 85.6% respectively. In Turkey, 50–70% of patients admit to clinical care with a CD4 count of less than 350 cell/mm3 (21–26). In this series, late presenters were 53% and 81.2% of all cancers and (82.8% of ADCs) were detected in this group. The fact that the majority of patients with cancers were detected on admission with a low CD4 count emphasizes the importance of early detection of the disease, thus preventing the further decrease of CD4 and allowing screening of other co-morbidities including ADCs and NADCs.

In our series, the cancers among ADCs are KS and NHL. Among the NADCs are gastrointestinal, genito-urinary, and lung cancers followed by larynx and medulla spinalis tumours. The most prevalent cancers, in decreasing order, are lungs, prostate, colon, urinary bladder, stomach, NHL, kidney, larynx, thyroid, and central nervous system tumours in males in 2014, according to the registry of the Turkish Health Ministry. In females, breast, thyroid, colon, uterus, lungs, stomach, ovary, NHL, central nervous system, and cervix tumours are the most prevalent (27). When compared to general populations, genito-urinary cancers appear to have a higher prevalence among HIV-infected patients in the country.

Most of the HIV-infected patients with concurrent cancer had ADCs. NADCs were mostly diagnosed during follow-up of patients. The mortality of this group was significantly higher than ADCs. In our group, ADCs and NADCs were 32 and 5 on admission respectively; however, these figures were 3 and 8 on follow-up. These results highlight the importance of promoting cancer screening during initial diagnosis of HIV infection as well as during follow-up.
Compared to the general population, HIV-infected patients have a 3640-fold increased risk of KS. This figure is 77-fold for NHL and six-fold for cervical cancer (28). These cancers are associated with human herpes virus 8, Epstein-Barr, virus and oncogenic subtypes of human papillomavirus, respectively. The increased risk of a number of non-AIDS defining cancers can be explained by the co-infection theory: anal and oropharyngeal cancers with human papillomavirus, liver cancers with hepatitis B and C viruses, and Hodgkin lymphoma with Epstein Barr-virus (2,29,30). In our cohort, nearly 2/3 of ADCs were KS and the remaining ADCs were NHL. The availability of HAART has improved the immune function and decreased the risk of AIDS and ADCs (31,32). Although the incidence of KS decreased significantly after the use of HAART, it is one of the most frequently diagnosed cancers among HIV-infected individuals (10). In existing KS, HAART has been shown to provide regression in the size and number of the lesions (33). NHL is the most common ADC in the world and second most common in our cohort. Although its incidence is decreasing in post-HAART era, its risk is rather high in HIV-infected individuals (2).

**Limitations**

The study has some limitations. First, sample size is small and thus making clear conclusions is difficult. Second, the beginning of the HIV infection is not known in most of the cases and nearly half of the HIV-infected patients present to clinical care in a late stage. Therefore, the effect of HIV infection on cancer development cannot be easily assessed. Third, 35 patients did not come to follow-up visits, and they were not reached. This would potentially affect the outcomes since it is not known whether the non-attendance is due to any cancer-related mortality or morbidity.

**Conclusion**

Almost half of the patients with HIV infection admit to clinical care or are diagnosed late with AIDS-defining disorders including cancers. Late presentation is highly associated with ADCs. A detailed physical examination is contributory to the diagnosis of the most prevalent ADCs (Kaposi’s and non-Hodgkin lymphoma) especially in late presenters. Those diagnosed early still carry the higher risk cancer. As the HIV/AIDS population survives and gets older, non-AIDS defining cancers represent a new challenge in the care of these patients. For NADCs, individual risk factors should be considered. Additionally, the behaviour and relative frequency of NADCs may change in the setting of AIDS. Preventive strategies, screening and the management should be clearly determined.

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References

16. Ormaasen V, Sandvik L, Dudman SG, Bruun JN. HIV related and non-HIV related


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