Lung Cancer in HIV-Seropositive Patients.

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Citation: Corti M. (2016). Lung Cancer in HIV-Seropositive Patients. M J HIV. 1(2): 007.

ABSTRACT

Introduction: AIDS related mortality has been accompanied by an increase in the proportion of deaths attributable to non-AIDS defining solid tumors, especially lung cancer.

Aim: The aim of this manuscript is to review the epidemiology, clinical aspects, diagnostic methods, prognosis and treatment of lung cancer in HIV/AIDS patients.

Materials and Methods: An exhaustive bibliographic research was performed in main biomedical databases, including PubMed, Scopus, Index Copernicus, DOAJ, EBSCO, Iranmedex, Scielo and Google Scholar. The databases were searched to identify review articles, original manuscripts, observational studies and remarkable case reports, about lung cancer in HIV patients that were included in the revision. Terms used in the search were: lung cancer, AIDS, HIV, carcinoma, adenocarcinoma, treatment. A narrative review of the included articles was performed.

Results: The risk of developing lung cancer seems to be higher in HIV infected subjects than in the general population of the same age, partly because the more frequently history to be smokers, especially, in intravenous drug users. Interestingly, there is no clear relationship between the degree of immunosuppression and the risk of lung cancer, so the reason for the increased risk is unknown. Adenocarcinoma is the most frequent histopathological subtype. The prognosis is worse in HIV infected patients than in the general population. Efficacy and toxicity data for chemotherapy and radiation therapy are few and imprecise in HIV subjects. Surgery remains the treatment of choice for localized disease in patients with adequate pulmonary function and general good health, regardless of immune status.

Conclusion: Prospective clinical trials are needed to define the optimal diagnosis methods for early detection and treatment strategies for lung cancer in HIV infected patients.

KEYWORDS

Lung Cancer; HIV; AIDS; Chemotherapy; HAART; Review.

INTRODUCTION

Highly active antiretroviral therapy (HAART) introduced in 1996 decreased the incidence of certain AIDS-defining cancers, especially Kaposi's sarcoma and primary central nervous system lymphoma [1]. Several epidemiological studies have shown that patients infected with human immunodeficiency virus (HIV) infection have a high risk of cancer; apart from the malignancies included as AIDS-defining neoplasms, subjects with diagnosis of HIV/AIDS also have an increased risk of oth-

ers cancer [2,3]. Lung cancer is the most common non-aids defining cancer in people with HIV infection and is associated with a high mortality in this population [2].

These malignancies named as non-AIDS-defining tumors include Hodgkin lymphoma, anal squamous carcinoma, liver cancer and lung carcinoma. Approximately 50% of the estimated non-AIDS-defining cancers are cases of lung, liver and anal cancers and Hodgkin disease [3].

Epidemiology

The risk of developing lung cancer, especially non-small cell lung carcinoma (NSCLC), seems to be higher in HIV infected patients in comparison with the general population of the same age. Bronchogenic lung cancer in HIV/AIDS patients presents different characteristics in comparison with the general population. HIV-infected patients with lung cancer are predominantly young males with significant smoking history, intravenous drug users (IVDU) and a shorter median survival in comparison with non-HIV-infected patients with lung cancer [4]. The mean age of HIV infected patients at the time of lung cancer diagnosis is 45 years and the majority of them are symptomatic and with locally advanced or metastatic (stage III-IV) disease. Men have significantly more risk than women, with a male:female ratio of 9-10:1 [5,6]. This male predominance may be less in the future. A recent epidemiological study demonstrated that lung cancer was higher in HIV positive women than in men [7]. The proportion of smokers is high between the HIV population with lung cancer (> 85%) and also the number patients with history of IVDU is > of 96% [6, 8, 9, 10]. Cigarette smoking seems to be an important risk factor to develop lung cancer in HIV-infected patients. However, it is uncertain if the increased risk of lung cancer observed in the HIV-population is only due to the higher prevalence of smoking. Also, several studies failed to demonstrate a relationship between lung cancer and smoking in HIV individuals. The ALIVE study (AIDS Link to the Intravenous Experience) included approximately 2100 IVDU since 1988 [11]. Twenty five percent of them were HIV-seropositive at baseline and another 334 subjects seroconverted during the follow up. The mean of age was 35 years, 75% were males and 84% reported smoking. The authors detected a total of 27 lung cancers; 14 of them in HIV-positive individuals. All deaths due to lung cancer occurred at least 4 years after HIV seroconversion. HIV-positive subjects with lung cancer were younger (51 vs. 55 years) in comparison with HIV-negative, but the difference was not significant. IVDU did not increase the risk of lung cancer but history of lung chronic previous disease seems to increase the risk of death due to lung cancer. In this study, lung cancer mortality was unrelated with the level of CD4 T cell counts (median 260 cells/uL) and with the viral load. Finally, the authors explain that HIV infection contributes to lung cancer independent of smoking, but smoking remained as the primary predictor of lung cancer and the risk increasing 70% each additional 20 cigarettes smoked [11].

Engels et al [12] in a retrospective study analyzed 33 clinically and histopathological lung cancer diagnostics in a cohort of 5238 HIV-infected patients. Twenty-eight patients (85%) were current smokers. Sixty seven percent were male and the mean of age at lung cancer diagnosis and the incidence of lung cancer increased significantly with age. The incidence was unrelated to HIV related immunosuppression but remain high after adjustment of smoking, suggesting involvement of other additional factors in the pathogenesis. There is no clear relationship between the grade of immunosuppression and the risk of lung cancer. In this aspect, Tenholder et al. [13] and Shidar et al. [9] demonstrated no predictive correlation between CD4 T cell counts and the development of lung cancer. The degree of immune deficiency is generally moderate at the time of lung cancer diagnosis; the proportion of patients with CD4 T-cell counts less than 200 cell/μL varies from 9% to 54% in different series [14, 15]. These findings emphasize the importance to consider lung cancer in early stage of HIV infection [16].

Clinical Presentation

Most patients are symptomatic at diagnosis, reflecting extensive disease. Indeed, lung cancer is diagnosed when locally advanced or metastatic (stage IIIB–IV) in 75–90% of HIV positive patients, similar to lung cancer control groups [15, 16]. Clinical presentation is variable and unspecific [17]. A few patients are asymptomatic, diagnosed incidentally because of nodules and cists on radiographs. The majority of patients presents with symptoms that varies from non-productive cough, dyspnea, pleuritic chest pain, fatigue, fever and spontaneous pneumothorax [18].

Radiological Findings

A few small studies have examined the radiological features in HIV positive patients with lung cancer [19, 20]. Most primaries were T2 but, in HIV positive patients with one or more nodules on the CT scans, only 4% had lung cancer [15, 21]. The most common finding is a mass (80-100%) measuring a median of 4.5 cm (range 2.0-8.0), more often peripheral than central, and located in the upper lobes as we could see in our experience [22]. Karp et al. [18] showed a higher frequency of mediastinal adenopathies (6/7 *vs* 7/14) and pleural effusion (4/7 *vs* 4/14) in HIV seropositive patients with adenocarcinoma type lung cancer than in HIV seronegative patients with adenocarcinoma, but these differences were not statistically significant. Other studies found that extensive pleural disease in the absence of a primary was not uncommon [23].

Histopathological Subtypes

The distribution of histopathological subtypes of lung cancer in HIV infected patients differs to the usual distribution in the general population. Adenocarcinoma appears to be the most frequent histopathological subtype. NSCLC represents 86% to

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94% of histopathological diagnosis of lung cancer in HIV positive patients. Small cell carcinoma accounts only 5% to 13% [24]. Adenocarcinoma include 31% to 50% of all NSCLC; squamous cell carcinoma 19% to 52% and large cell carcinoma 9% to 19% [24, 25].

Prognosis

The prognosis of lung cancer in the HIV population seems to be worse than in the general population, probably because the disease is in a more advanced stage at the time of diagnosis. When compared by tumor, nodes, metastasis (TNM) classification of malignant tumors, no significant differences are observed between the HIV population and the general population [26, 27]. Makinson et al. [28] evaluated the factors associated with an increase in survival of the patients with HIV infection and non-small-cell lung cancer in a French cohort (the Dat'Aids cohort). The study included 52 patients. These authors found that a performance status of less than 2, a CD4 T-cell count > 200 cells/µl at the time of the cancer diagnosis and the use of HAART after the cancer diagnosis were independent factors associated with increased survival in the multivariate analysis. Neither the use of cytotoxic chemotherapy nor the stage of the neoplasm was significant factors that influencing the prognosis. Hessol et al. [29] also observed an increase in the survival of non-AIDS-associated cancer with the use of HAART for at least 6 months. In a recent study, Sigel et al. [30] observed a median of survival of 6 months among HIV infected patients with NSCLC in comparison with 20 months in subjects without retroviral infection.

Treatment

Patients with HIV infection and lung cancer should be treated following the standard protocols for the general population based on surgery, chemotherapy and radiotherapy according to the stage of the neoplasm, regardless of the CD4 T-cell count [20]. However, one must take into account the possible pharmacological interactions between the chemotherapy agents and the antiretroviral agents due to the risk for severe hematological toxicity. Makinson et al. [28] found that the use of antiretroviral treatment guidelines that included a protease inhibitor (PI) with chemotherapy increased the risk for several hematological toxicity. PIs, whether ritonavir enhanced or not, may alter the metabolism of antineoplastic agents by inhibiting CYP450 3A4. The anti-neoplastic agents indicated for the treatment of non-small-cell lung cancer that are metabolized by this pathway are taxanes, vinca alkaloids, etoposide and the anilinoquinazolines erlotinib and gefitinib. In addition, AZT can promote the risk for myelosuppression secondary to antineoplastics, and its use should therefore be avoided.

As in the general population, surgery should be considered for localized or locally advanced disease in HIV patients with adequate pulmonary function and good general status, independent of the immune status [31].

Chemotherapy can be used to treat metastatic disease or previously to surgery to reduce the tumor size [24, 32]. However, progression of neoplastic disease rates of 50% to 70% have been reported after the use of first line chemotherapy for lung cancer [33, 34].

The risk of opportunistic infections (OI) should be considered in HIV patients with lung cancer treated with chemotherapy. CD4 T-cell counts should be regularly evaluated (every one month) during chemotherapy. The indications for primary or secondary prophylaxis should be based on the absolute CD4 T-cell counts and the history of previous OI.

Thoracic radiotherapy can be used in patients with locally advanced or inoperable lung cancer disease [24, 33].

CONCLUSION

In conclusion, lung cancer is one of the most prevalent non-AIDS-defining malignancy in the HAART era and the cancer risk is 2 to 4 times greater in HIV-infected persons than in the general population. Lung cancer is typically diagnosed a decade or more earlier among HIV-infected persons compared to those without HIV infection. The risk of lung cancer seems to be greater in the HIV positive population, but differences in smoking habits are probably not the only explanation. Immunosuppression can also be included as other related risk factor for this malignancy. Histological types and stages are similar to those in the general population; adenocarcinoma is the commonest histopathological subtype, and the majority of patients are diagnosed with locally advanced or metastatic carcinoma [35]. The prognosis is poorer due, in part, to a lower PS at diagnosis. Treatment also appears to be more toxic and less effective, with a one year survival of only 10%. Surgery appears to be an effective treatment as in the general population, while prospective studies of the efficacy and toxicity of chemotherapy are necessary.

CONFLICT OF INTEREST

The author mentioned above have no declared conflict of interest.

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