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NEW AND OLD ASSUMPTIONS ON LUNG CANCER IN PEOPLE LIVING WITH HIV

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Abstract – *People living with HIV nowadays have an average life-length similar to the general population and new pathologies, such as lung cancer, emerged. The likelihood of developing lung cancer in HIV-infected people is related to the increase of the mean age, male sex, smoke, persistent lung inflammation, and new studies are being conducted to find new soluble markers which could lead to an early diagnosis of lung cancer. Moreover, treatment opportunities are being enriched with new biological medicine, even though further studies are needed to determine if their use is safe in people living with HIV. The aim of this review is to identify key data and factors about lung cancer in HIV-infected patients.*

KEYWORDS: *Lung cancer, HIV, Screening, Therapy, Markers.*

INTRODUCTION

The Acquired Immuno-Deficiency Syndrome (AIDS) outbreak started in 1981. HIV infected people, predominantly previously healthy young men, started to develop diseases considered to be limited to the immunocompromised patients. Acquiring the HIV infection lead to an extremely reduced life expectancy in those years. The introduction of Highly Active Anti-Retroviral Therapy (HAART) in 1996 completely changed this scenario. Nowadays, people living with HIV (PLWH) have an average life-length similar to the general population and new pathologies linked to adverse-effects of a life-long therapy, aging and HIV-related persistent inflammation emerged, leading to new issues to deal with and hopefully resolve[1-22].

Infectious, inflammatory and neoplastic lung diseases have been a major co-morbidity in HIV-infected patients since the beginning of the HIV epidemic, because of the high prevalence of smokers within the HIV-positive population and the role played by viral and host factors. Lung cancer, the most common cancer in the world, heavily affects PLWH, representing today the leading cause of death in this population, having a three-fold higher incidence than general population with the worst prognosis[1-3,21,23-26].

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Independent factors specifically associated with HIV infection, such as a direct oncogenic action, recurrent lung infections and immune depression, contribute to this increased risk; then, lung cancer is nowadays the most common non-AIDS defining cancer (NADC) in HIV patients[23,25,27].

In this report, we review the diagnostic and therapeutic management of lung cancer in HIV infected patients.

RISK FACTORS AND PATHOGENESIS

The likelihood of developing lung cancer is related to the increase of the mean age in PLWH[1,28-30]. After the introduction of HAART, life expectancy of PLWH has considerably increased, leading to a directly proportional rise in the prevalence of lung cancer[31-35]. Male sex is related with the highest risk, probably because of the higher prevalence of HIV-infection and smoke in men than women[36,37].

Smoking is the most important risk factor. HIV-infected smokers seem to develop lung cancer at a younger age than non-smokers. Bonnet et al[38] claim that 90% of the PLWH died from lung cancer during a period going from 2000 to 2005. Smoking history is crucial for the development of lung cancer, seen that a 20 to 35 pack-year smoking history has been associated with the development of lung cancer in PLWH[39]. A number ≥ 30 of pack years is one of the parameters used for determining the need of lung cancer screening in PLWH, as suggested in the 2017 Italian's HIV-guidelines[40].

Persistent lung inflammation due to recurrent infections can only partially explain the increased risk of developing lung cancer in PLWH, and Shebl et al[41] demonstrated that pneumonitis, but not tuberculosis or PCP, is associated with an increase in lung cancer incidence. However, this association was not confirmed when adjusted for smoking.

As reported by Sigel et al[42], Drummond et al[43] and Crothers et al[44], Chronic Obstructive Pulmonary Disorders (COPDs) are major risk factors for developing a lung cancer in PLWH who, in addition, have a higher risk of developing COPD because of an increased lung inflammation, in a vicious cycle that seems to have no escape.

HIV infection also brings with itself a series of risk factors related to immunosuppression, inflammation, viral oncogenesis, and HAART[42].

A low CD4+ T-cell count is reported to be associated to an increased incidence of lung cancer incidence in more than one longitudinal study, which highlighted that PLWH who do not recover a CD4+ count of at least 500/μL during their life are at increased risk of developing it[42,45]. Moreover, Borges et al[46] highlighted how, before the diagnosis of lung cancer, pro-inflammatory cytokines, such as IL-6, can be found to be elevated.

HIV could also have a direct oncogenic action in the development of lung cancer. Cribbs et al[47] demonstrated that a wide percentage of a small cohort of non-smoker PLWH with a suppressed serological viral load, had detectable pro-viral DNA in alveolar macrophages.

Further studies are needed to increase our knowledge about lung cancer pathogenesis in PLWH, in order to prevent its development, if possible.

DIAGNOSIS

Non-Invasive Screening and Diagnostic Techniques

Patients are mostly asymptomatic at early stages or they can have non-specific symptoms. Patients diagnosed at Stage I are commonly curable and have a 5-year survival rate of 50-80%[28,30,48,49].

Unfortunately, in PLWH the diagnosis is often delayed exactly because of the lack of specific symptoms. As a matter of fact, the most commonly reported symptoms in HIV patients with lung cancer are: cough, weight loss, dyspnea, night sweats, chest pain, and anorexia[50-53].

Screening of high-risk individuals is necessary to find the disease at an early stage and improve the patients' survival. Moreover, it is fundamental in offering a better opportunity for treatment. Italian Guidelines for the management of HIV infection suggest that PLWH who smoke more than 30 pack of cigarettes per year should undergo a low-dose Computed Tomography (CT) scan[40].

However, asymptomatic PLWH have a high prevalence of pulmonary nodules unrelated to lung cancer. Therefore, in 2004 the US Preventive Service Task Force concluded that a screening program of asymptomatic people for lung cancer was not cost-effective[54-56] and in 2017 the European AIDS Clinical Society (EACS) still chose to not include lung cancer in their guidelines for the management of patients with HIV infection[57].

In the suspect of lung cancer, the first examination performed is a chest x-ray. A wide spectrum of radiological signs can suggest the presence of a primary lung tumor, making a Computed Tomography (CT) necessary to confirm the diagnosis.

Recently, the emergence of combined PET/CT imaging has greatly aided the investigation of lung cancer; this technique has been shown to be an accurate tool for the work-up of solitary pulmonary nodules and improves the detection of metastatic disease[58-61].

An accurate assessment of the disease extent is important to discern the best management: surgery, chemotherapy, radiotherapy or any combination of them[62-69].

New molecular markers

Many authors investigated about noninvasive and molecular methods to detect and monitor tumors. Micro-RNAs, a group of endogenous and non-coding RNAs working as post-transcriptional regulators of gene expression by affecting the stability and translation of mRNAs, are currently under investigation for being involved in development, invasion and metastasis of tumors, playing a role as both tumor suppressors and oncogenes. Wang et al[70], starting from an observation of Zhao et al[71], showed that the serum miR-411 levels increase in patients with NSCLCs and are significantly associated with TNM stage, differentiation degree and survival. Therefore, it can be concluded that miR-411 works as a tumor promoter in lung cancer, and particularly in NSCLC. This result may have clinical potentials and this marker could be used as a non-invasive diagnostic/prognostic biomarker.

Long noncoding RNAs, poorly conserved and not translated into proteins transcripts, are also currently being studied in search for any association with the development of neoplasms.

Speaking of NSCLCs, several studies observed that LINC00152 was upregulated in both NSCLC tissues and plasma samples of patients affected by lung cancer. Moreover, levels of plasma/serum LINC0052 in patients affected by NSCLC are significantly higher than those expressed in patients affected by benign lung diseases or healthy controls[72-75].

Two other lncRNAs (DKFZP434 L187 and LOC285548) are correlated with lung adenocarcinoma and may have prognostic value for the survival[72].

Aldehyde dehydrogenase 1 family, member A1 (ALDH1A1) is highly expressed in non-small-cell lung cancer and studies demonstrated that ALDH1A1 correlated with carcinogenesis and progression of NSCLCs[76-80]. Further studies are required to establish the ability of these biomarkers to discriminate between inflammation during lung diseases and cancer. Moreover, studies including PLWH are needed to determine if these soluble biomarkers are equally related to lung cancer in this population.

Classification of lung cancer

In 2015, the World Health Organization (WHO) published a new textbook of lung cancer classification with a number of important changes, compared to previous editions[81].

Unrepressed cell growth, tissue invasion and the development of metastasis due to anomalous expression of oncogenes are distinguishing signs of a cancer cell. In PLWH the risk to develop a neoplasm is increased because of the role played by HIV protein Tat in regulating cell proliferation[22,82,83]. However, as previously discussed, studies failed in finding a link between HIV viral load and lung cancer[84-86].

There are two major types of lung cancer classified as non-small cell lung cancer (NSCLC) and small cell lung cancer. The new WHO classification includes types and subtypes of epithelial tumors, such as: adenocarcinoma (subtypes acinar, papillary, micropapillary); squamous cell carcinoma (types: keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma, basaloid); neuroendocrine tumors (small cell carcinoma and large cell carcinoma). The non-epithelial tumors are included in specific tables[87-89]. The extension of a tumor is definite by the TNM classification[90-93]. The most frequently encountered cancers in HIV-patients are NSCLCH. The most common histologic type of lung cancer is adenocarcinoma (67%), followed by squamous cell carcinoma, large cell carcinoma and bronco-alveolar carcinoma; small cell lung cancer comprises a small group with unidentified subtypes[3,23,94-97].

THERAPIES

The first step to obtain a better outcome is a proper diagnosis with an accurate staging of the cancer and the application of the principles of personalized medicine. Surgery remains the treatment of choice and has an important role in definitive management of lung cancer[98,99]. Early stages (I-II) are usually treated with surgery and evaluation of the lymph nodes. Darling et al[100] showed that, for patients treated with a resection of the tumor in an early stage, the disease-free rate at 5 years was 68%[93]. Lobectomy is the current technique for lung cancer resection; in the case of small tumors, a sub-lobar resection removing a small portion of pulmonary tissue may be used[101].

Advanced stages (III) of lung cancer need to be treated with combination therapies[102]. The use of chemotherapy or radiation before surgery (neoadjuvant therapy) may help the surgeon to remove the mass reducing its diameter. Evidence suggests that chemotherapy after surgery may help to prevent a relapse (adjuvant therapy)[103]. Targeted treatments are a new option for the management of NSCLCs. Several monoclonal antibodies are currently used, like Erlotinib and Afatinib, inhibitors of the epithelial growth factor receptor of the tyrosine-kinase family[104-106], or Crizotinib, an inhibitor of the anaplastic lymphoma kinase and the c-ros oncogene 1[107].

Immunotherapy is generally well-tolerated and has recently emerged as a new treatment possibility with significantly improved outcomes in patients affected by lung cancers.

Two different immune checkpoint inhibitors that target Programmed Cell Death 1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) have been discovered during the past years. These inhibitors seem to be effective even against metastatic NSCLCs and play an inhibitory function on T-cells activation in peripheric tissues[108].

Several studies[109,110] have been performed to define the interactions between HIV disease and immune checkpoint molecules. However, there is poor evidence that the immunotherapies can be used in patients with immune-compromised systems like HIV-positive people are. Marra et al[111], published a paper describing the use of immunotherapy in PLWH affected by melanoma. Furthermore, the American Cancer Association (ACA) suggests that patients with HIV should no longer be excluded from new therapies for cancer. Furthermore, a study by ACA highlighted how the PD-1 inhibitor pembrolizumab does not show significant risks for patients with HIV and cancer[112].

CONCLUSIONS

Lung cancer has a high incidence and mortality, independently from HIV serological status. Because of that, it is a major worldwide public health problem. Early diagnosis is crucial. Detection of the cancer in an early stage means that a patient's disease-free at 5 years survival is over 60%. Furthermore, when a lung cancer is detected at an early stage, a curative treatment such as surgery is possible. Whenever it is possible, advanced tumors must be treated with combined treatments of surgery, chemo and radiotherapy. A pharmacological approach in advanced stage cancers is possible with the new experimental drugs, but guidelines for the use of monoclonal antibodies in HIV-patients with lung cancer are needed.

Conflict of interests

The Authors declare that they have no conflict of interests.

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