Lung cancer in HIV-infected patients and the role of targeted therapy

Marco Ruiz, MD MPH, FACP, and Robert A Ramirez, DO, FACP

Section of Hematology Oncology, Louisiana State University Health Sciences Center, New Orleans

Lung cancer is one of the most common malignancies in HIV-infected patients. Prevalence and mortality outcomes are higher in HIV-infected populations than in noninfected patients. There are several oral agents available for patients who harbor specific mutations, but little is known about mutations and affected pathways in HIV-infected patients with lung cancer. Recent trials have facilitated the inclusion of HIV-infected patients in clinical trials, but the population is remains underrepresented in oncology trials. Here, we review the literature on lung cancer in HIV-infected patients, and discuss common mutations in lung cancer and HIV-infected patients, the role of mutational analysis, and the potential role of targeted therapy in the treatment of lung cancer in HIV-infected populations.

Lung cancer is the most commonly diagnosed cancer worldwide and accounted for about 1.57 million deaths in 2012.[1] The American Lung Association predicted there would be about 221,200 new cases and 158,040 lung cancer-related deaths in the United States in 2015.[2] Notably, lung cancer is expected to account for almost 27% of all cancer-related deaths in 2015.[2] Ninety-five percent of lung malignancies are either non-small-cell lung cancer (NSCLC) or small-cell carcinoma, with small-cell carcinoma accounting for 16% of cases.[3] The incidence and mortality of lung cancer is increased in populations that are positive for the human immunodeficiency virus (HIV).[4-6] Some factors, such as young age, smoking, persistent HIV RNA viremia, use of intravenous drugs, and other comorbidities including chronic obstructive pulmonary disease, recurrent pneumonia, and chronic inflammation have been identified as risk factors for lung cancer in these patients.[5] The clinical course of lung cancer in HIV-infected patients seems to be more aggressive, their survival is shorter, and their response to treatment (surgery, radiotherapy, and chemotherapy) is suboptimal compared with their non-HIV-infected counterparts.[6]

A recent study reported that HIV-infected NSCLC patients less frequently received cancer treatment than did uninfected patients.[7] Moreover, HIV infection was associated with higher lung cancer-specific mortality and the association with mortality is higher in untreated than in treated HIV-infected patients. Two other studies that examined the SEER-Medicare database, reviewed lung cancer mortality in aging HIV-infected patients (>65 years) and showed different results. In one of the studies, the population of aging HIV-infected patients seemed to have mortality rates similar to those of their non-HIV-infected counterparts across all stages of lung cancer, and in the second study, aging HIV-infected patients with lung cancer were more likely to die of causes other than lung cancer.[6,8,9]

Adenocarcinoma is the most common histological type of lung cancer found in HIV-infected patients.[4-6] Recent studies in general populations (non-HIV infected) have identified that epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) gene rearrangements, and Kirsten rat sarcoma viral oncogene (KRAS) mutations as common driver mutations in adenocarcinoma of the lung. These mutations may affect response to chemotherapy interventions and open new options in receptor-targeted therapy such as tyrosine kinase inhibition. Patients with EGFR mutations are more likely to respond to EGFR tyrosine kinase inhibitors (TKIs). In the case of ALK rearrangements, crizotinib – an oral ALK and c-Met inhibitor – is now used as first-line therapy in patients with metastatic lung cancer expressing this gene abnormality because its use improves response rates and survival.[10,11] KRAS is not currently a mutation that is actionable outside of a clinical trial. These mutations seem to be more frequent in Asian populations (30%-35%) but are not infrequently found in African-American populations (about 19%

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for EGFR mutations, 17% for KRAS mutations, and 2.3% for ALK gene rearrangements).[12-13]

Little is known about mutations and affected pathways in HIV-infected patients with lung cancer. This manuscript reviews the literature on lung cancer in HIV-infected patients, and discusses common mutations in lung cancer and HIV-infected patients, the role of mutational analysis, and the potential role of targeted therapy in the treatment of lung cancer in HIV-infected populations.

Epidemiology of lung cancer in HIV-infected patients

Lung cancer is one of the most common non-AIDS-defining malignancies and ranks third after anal carcinoma and Hodgkin lymphoma in HIV-infected patients.[4,6] Lung cancer risk is 3 to 4 times higher in HIV-infected patients than in uninfected persons after adjusting for other factors such as smoking intensity and duration.[6] Studies have calculated the incidence between 1.5 to 6.7 per 100,000 HIV-infected patients in the post-antiretroviral (ARV) era.[4,6,14,15] Table 1 lists some of the more common HIV-associated tumors.

As in the non-HIV infected population, the leading cause of cancer mortality in the HIV-infected population is lung cancer, accounting for nearly 30% of all cancer deaths and 10% of all non-HIV-related deaths. Of note, the average age of onset of lung cancer in the HIV-infected population is 25-30 years earlier than that in the general population and at lower exposure to cigarette smoke.[14] Table 2 shows the number of deaths and risk ratio of HIV-infected patients with non-AIDS-defining malignancies in the United States 1996-2006.

Many studies have identified risk factors in the HIV-infected population for lung cancer development. Young age, male sex, and extensive smoking history seem to be important. Most of the patients were diagnosed at advanced stages (IIIB and IV).[15-21] The results of some studies suggest that immunosuppression may not play a role in lung cancer development.[15,16] Other studies suggest that nadir in T-cell count and length of immunosuppression may be important to take into consideration in lung cancer development.[21-25] The role of persistent HIV-RNA viral load in the pathogenesis and development of lung cancer still undefined.

There seems to be conflicting findings on the impact of antiretroviral therapy on survival outcomes. One study suggested that survival of HIV-infected patients is similar to that in non-HIV-infected patients,[10] and another study showed worse outcomes for HIV-infected patients than for non-HIV-infected patients, with a median survival of 3.5-6.3 months in patients with HIV infection, compared with 9.4-10 months in those without HIV infection. In the latter study most of the HIV-infected patients were diagnosed at advanced stages of disease and were off highly active antiretroviral therapy (HAART) therapy when they were diagnosed with lung cancer.[21]

TABLE 1 Standardized incidence ratio of HIV-associated malignancies in the United States, 1996-2002[a]

Cancer type	SIR
Non-Hodgkin lymphoma	23
Hodgkin lymphoma	14
Lung	3
Head and neck	3

HIV, human immunodeficiency virus; SIR, standardized incidence ratio

[a]SIR is defined as the relative frequency of the cancer in HIV-infected patients compared with the general population.

TABLE 2 Number of deaths per 1,000 person-years according to calendar year of AIDS onset non-AIDS-defining cancers

Cancer type	No. of deaths, (risk ratio, 95% CI)
Lung[2]	40 (0.32, 0.21-0.46)
Hodgkin lymphoma[2]	7 (0.01, 0.00-0.06)
Anal[2]	2 (0, 0-0.04)
Other non-AIDS malignancies[2]	47 (0.45, 0.32-0.61)
All[2]	102 (0.84, 0.66-1.05)

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus

Diagnosis and treatment options

Most HIV-infected patients with lung cancer present in the late stage. There are no specific recommendations for the management of lung cancer in the HIV-infected population. Surgery is the mainstay of treatment for early-stage disease. In later stages, chemotherapy or combinations of chemotherapy and radiation are used. In general, patients with advanced NSCLC are usually treated with a platinum doublet.[26] Those who harbor EGFR mutations (exon 19 deletion or exon 21 substitution) or ALK rearrangements can be treated with EGFR or ALK inhibitors respectively.[26]

Caution must be exercised in combining agents, because some antiretroviral agents may interact with chemotherapy or targeted therapy and cause significantly increased side effects including myelosupression, neuropathy, nephrotoxicity, and liver failure. Effects on the cytochrome P450 (CYP450) family occur when common lung cancer

TABLE 3 Interactions between chemotherapy agents and antiretroviral therapy

Chemotherapy or targeted therapy	Route of metabolism	Interaction	Effect on HIV therapy	Outcome
TKI	CYP3A4 inhibitor	Increased TKI toxicity[24,36]	■ Dose reduction of ritonavir needed[65-68] ■ Possible less efficacy of HIV therapy[65-68] ■ Decreased dose of TKIs may be needed[65-68]	Possible toxicities associated with higher doses of TKIs[65-68]
TKI	CYP3A4 inhibitor	Reduced efficacy of TKIs when using with efavirenz (NNRTIs) [65-68]	■ Potential less efficacy of HIV therapy[69] ■ Possible increased dose of TKIs may be needed[67-69]	Unknown
Taxanes[a]	CYP2C8, CYP3A4	■ May increase taxane concentration and increase myelosuppression and peripheral neuropathy[65-67] ■ Case reports of severe toxicity with co-administration of lopinavir and ritonavir[65-67] ■ Clinical trial supports low-dose paclitaxel with PI co-administration[65-68] ■ Co-administer with close monitoring[65]	Unknown	Unknown
Antimetabolites[b] cisplatin, mito-mycin, and rituximab	Independent of CYP3A4 oxidation	■ Drug-drug interactions with PIs and NNRTIs unlikely[61,69] ■ Use standard doses[61,69]	Unknown	Unknown
VEGF inhibitors	CYP3A, CYP2B6	■ Potential interaction with abacavir, lamivudine, nevirapine[61,69]	Unknown	Unknown

HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TKI, tyrosine kinase inhibitor; VEGF, vascular epithelial growth factor

[a]paclitaxel and docetaxel. [b]methotrexate, floxuridine, capecitabine, cytarabine.

chemotherapy agents including paclitaxel, docetaxel, and targeted therapy including erlotinib are used in combination with CYP3A4 inhibitors (ritonavir, atazanavir, lopinavir, nelfinavir, saquinavir), and CYP3A4 inducers such as nevirapine and evarirenz.[26] Therefore, treatment agents and antiretrovirals should be carefully selected before the start of therapy, and if complications develop it is advised that the antiretroviral or chemotherapy or targeted agent is substituted with a different agent. The use of the antibody bevacizumab seems to be safe when used in combination with antiretrovirals.[27,28] Table 3 shows interactions between chemotherapy agents and antiretroviral therapy. To our knowledge, there are no recommendations regarding specific antiretrovirals in patients with lung cancer. Of note is that in a recent phase 1 trial, nelfinavir, a proteosome inhibitor that was used as a radiosensitizer showed promise when it was used in conjunction with chemoradiotherapy for non-HIV infected patients with advanced NSCLC. Further studies are being conducted to evaluate the role of nelfinavir in treatment of NSCLC cancer.[29]

Equally important is the impact of chemotherapy interventions on CD4 cell counts and HIV viral loads in all lung cancer patients. Studies have demonstrated a reduction in CD4 counts and the need to monitor levels to determine initiation of immune-deficiency prophylactic therapy (eg, for treatment of pneumocystis jirovecci pneumonia, PJP).[26] Those studies also showed minimally affected viral loads and lack of accelerated development of resistant HIV strains in HIV-infected patients. It is interesting to note that no studies have shown the need to adopt PJP prophylaxis in HIV-infected patients with lung cancer. Other strategies aimed to improve survival in patients with advanced NSCLC include the addition of targeted drugs, such as vascular endothelial growth factor (VEGF) monoclonal antibodies[30] or EGFR antibodies and pursuing maintenance therapy after first-line chemotherapy. However, although there were no spe-

cific exclusion criteria for patients with HIV in these trials, it is not known how many, if any, patients with HIV were included.[30-34] The safety of VEGF antibodies has not been explored in HIV-infected patients.

Mutations in lung cancer in HIV-infected patients

Few studies have analyzed mutations in lung cancer in HIV-infected patients. In a small Japanese study that examined NSCLC patients with HIV, about 29% of samples harbored EGFR mutations in lung adenocarcinoma, which is similar to what has been previously described in the Asian population (30%-35%).[35] In this latter study in 6 patients who were treated with chemotherapy for unresectable disease, 5 (83.3%) achieved a partial response. These patients did not receive targeted therapy interventions. Median overall survival was 17 months for all stages and 14 months for advanced stages. One possible explanation for that could be fact that Asians in general may have a better prognosis compared with Caucasians because they harbor EGFR mutations.[35] Many studies have shown that patients with advanced NSCLC who have the EGFR mutation respond better to treatment than do those who are EGFR wild type.[35-43]

Other mutations that include ALK rearrangements – KRAS, ROS-1 and others – have not been explored in HIV-infected patients. This represents a potential area of research for research studies.[44]

Treatment of lung cancer with targeted therapies

Targeted therapy presents a new horizon in the personalized treatment strategy approach. Most novel drugs seem to be of particular benefit in lung adenocarcinoma; however, newer genomic mapping of squamous cell carcinoma may expand treatment options for these patients.[45] To benefit from genomic mapping, there should be a very specific pathologic diagnosis, mutation analysis, and identification of predictive biomarkers of response and resistance.[46] The following are targeted therapies that have been studied in non-HIV infected patients and that may have applicability to HIV-infected patients.

EGFR TKIs: erlotinib and gefitinib

Erlotinib has been used for second- and third-line therapy to prolong survival in refractory NSCLC stage IIIb and IV patients, irrespective of EGFR status.[33] It was initially approved by the US Food and Drug Administration (FDA) for that patient population, but it became clear that there was a subset of patients that derived substantial benefit from these agents. The genetic mutation of the EGFR in exons 19 or 21 of chromosome 7 demonstrated an association with response to erlotinib in patients with mutations of the EGFR receptor, and the mutation is predictive of response to treatment with an EGFR TKI, which results in an increased response rate and progression-free survival compared with conventional chemotherapy.[46-68] Only 1 study has examined the use of EGFR receptor inhibitors in HIV-positive patients. In that study, 2 patients, both men (ages 67 and 59 years) with known HIV infection and immunologically stable disease with antiretroviral therapy had recurrent lung cancer. Case 1 was treated with erlotinib for recurrent adenocarcinoma metastasizing to the liver and brain harboring EGFR mutation in exon 21 L858R. The duration of treatment efficacy was 9.7 months. Case 2 had an EGFR mutation exon 19 in-frame deletion with bone metastasis and was treated with gefitinib for 22.1 months in combination with antiretroviral therapy.[67]

The use of EGFR inhibitors in the first-line setting in EGFR-mutated lung cancer and HIV-infected patients has not been studied.[66-71] Several second-generation TKIs that target EGFR as well as other strategies, including combination of targeted therapies, are in various stages of development for patients who progress on first-line treatment.[57] So far, no studies have been conducted in HIV-infected populations.

ALK inhibitors: crizotinib and ceritinib

The EML4-ALK fusion gene is a relatively recently discovered rearrangement in patients with lung cancer. EML4-ALK fusion occurs because of paracentric inversion in the short arm of chromosome 2 and is detected in 3%-5% of patients with NSCLC.[56,57] These patients should be treated with an ALK-targeted agent. The 2 FDA-approved ALK inhibitors are crizotinib and ceritinib. Crizotinib, an oral ALK and c-Met inhibitor used in patients who are positive for ALK gene rearrangements, has yielded remarkable treatment responses (57%) and increased progression-free survival with minimal toxicity.[56,58] However, as with all therapy, resistance eventually develops. Ceritinib is another oral oral ALK-targeted therapy that is highly active in patients with advanced, ALK-rearranged NSCLC, including those who had had disease progression during crizotinib treatment, regardless of the presence of resistance mutations in ALK.[59] No studies have evaluated in HIV-infected patients.

Other targets for treatment

EGFR and ALK are the only known molecular targets that have FDA-approved therapy, but many other mutations exist. Inhibitors of KRAS, BRAF, ROS1, HER-2, PIK3CA, FGFR, and MEK are some of the targets of current clinical trials, however, a large proportion of possible molecular drivers is still unknown.[57] As with EGFR and ALK, the frequency of these mutations in patients with HIV is unknown and deserve investigation.

Conclusion

Lung cancer is one of the most common malignancies in HIV-infected patients. Prevalence and mortality outcomes are higher in HIV-infected populations than in non-infected patients. There are several oral agents available for patients who harbor specific mutations, but there is a paucity of data in relation to the expression or overexpression of mutations in HIV-infected patients. Recent trials have facilitated the inclusion of HIV-infected patients in clinical trials, but the population is still underrepresented in oncology trials. The role of mutational analysis and targeted therapies deserves further investigation in clinical trials in HIV-infected patients.

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