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HIV and Lung Cancer

Yusuke Okuma, Naoki Yanagisawa, Yukio Hosomi,
Atsushi Ajisawa and Masahiko Shibuya
Tokyo Metropolitan Cancer and Infectious diseases Center, Komagome Hospital
Japan

1. Introduction

Lung cancer patients with HIV infection are expected to become an emerging issue with respect to morbidity and mortality, as the number of such patients is rapidly increasing. However, few reports or textbooks dealing with this issue have documented the details of these cases. Thus, in clinical settings, infectious disease physicians or medical oncologists occasionally hesitate to treat HIV-infected patients with lung cancer. Since 1996, the outcome of HIV-infected patients has improved, because CD4 cell counts and viral load are generally well controlled with the advent of highly active antiretroviral therapy (HAART), which strongly inhibits HIV viral proliferation and restores the patient's immunological status. Furthermore, the prognosis in the HIV population has improved significantly due to the prevention and treatment of opportunistic infections (OIs). As a result, HIV infection is chronically manageable. In the pre-HAART era, the median survival time in the HIV population was 10 years, while, at present, 85% of patients survive more than 10 years.(Sepkowitz, 2001)

In the pre-HAART era, most HIV-infected patients died of acquired immunodeficiency syndrome (AIDS). Recently, however, one-third of all such patients die of malignant tumor,(Bonnet *et al.*, 2009) and deaths due to AIDS-defining cancers (ADCs), such as Kaposi's sarcoma (KS), primary central nervous system lymphoma (PCNSL) and non-Hodgkin's lymphoma (NHL), and invasive cervical carcinoma, which were defined by the Centers for Disease Control and Prevention (CDC), are decreasing. On the other hand, the number of deaths due to non-AIDS-defining cancers (NADCs) is increasing.(Engels *et al.*, 2008, Silverberg *et al.*, 2009) At present, in the population with HIV infection, lung cancer accounts for 5% of all deaths and 15% of all deaths by malignant tumors.(Bonnet *et al.*, 2009) Of all of the NADCs, lung cancer is the most common,(Engels *et al.*, 2006, Lavole *et al.*, 2006, Patel *et al.*, 2008) followed by breast cancer, soft tissue sarcoma, Hodgkin's lymphoma (HL), penile cancer, lip cancer, and testicular seminoma.(Frisch *et al.*, 2001) In 1984, Irwin *et al.* reported the first case with simultaneous HIV infection and lung cancer,(Irwin *et al.*, 1984) and several dozen patients have since been reported in the United States and Europe. (Table. 1) The clinical demographics of lung cancer with HIV infection differ slightly from the general population and are characterized by younger age, advanced stage at diagnosis, and aggressive tumor extension. Thus, the prognosis of lung cancer in the HIV population is poorer than that of lung cancer in the general population.(Lavole *et al.*, 2006) Moreover, patient fragility to treatment needs to be considered.

In the general population, lung cancer is the most common cause of cancer death worldwide. Furthermore, in the last decade, there has been progress in lung cancer

treatment modalities. The development of novel antitumor agents and molecular targeted drugs has increased the lines of chemotherapy, and new treatment strategies, such as maintenance therapy and biomarker-based therapy (personalized therapy), provide diverse options. At present, in front-line chemotherapy for lung cancer patients, platinum-doublet chemotherapy with the third-generation antitumor agent has been shown to prolong survival and contribute to symptom palliation. Before the 1990s, the median survival time with the best supportive care was 4-5 months, and the 1-year survival rate was 10% in Stage IV non-small cell lung cancer (NSCLC). In 1995, the benefits of chemotherapy for Stage IV NSCLC were confirmed, and the median survival time was prolonged to 8 months.(Non-small Cell Lung Cancer Collaborative Group, 1995) At present, median survival time is 12 months, and the 1-year survival rate has improved to 50-60% from 30-35% in 2002.(Azzoli *et al.*, 2009) Thus, the reported data dealing with lung cancer in HIV patients are not comparable. In addition, drug interactions between antiviralagents and antitumor agents

Author	Nº of patients	Years	Median age (y)	Male (%)	Smoking (%)	Median pack-years	IVDU (%)	Homosexual (%)	NSCLC (%)	Adenocarcinoma	Squamous cell carcinoma	SCLC (%)	Median CD4 (cells/μL)	CD4 < 200 cells/μL	Latency (y)	PS > 2 (%)	Stage III/IV	Median Survival (mo)
Sridhar et al.	*19*	*86-91*	*47*	*100*	*94*	*60*	*21*	*32*	*95*	*42*	*31*	*5*	*121*	*53*	*-*	*37*	*79*	*3*
Trielli et al.	*36*	*86-98*	*38*	*89*	*94*	*40*	*69*	*17*	*86*	*36*	*33*	*14*	*150*	*44*	*-*	*43*	*84*	*5*
Brock et al.	*92*	*86-04*	*46*	*67*	*99*	*30*	*58*	*-*	*91*	*48*	*17*	*9*	*305*	*-*	*5.5*	*-*	*87*	*6.3*
Vyzula et al.	*16*	*88-95*	*45*	*94*	*100*	*30*	*63*	*38*	*88*	*50*	*19*	*12*	*184*	*54*	*-*	*69*	*81*	*5.4*
Alshafie et al.	*11*	*90-94*	*50*	*82*	*90*	*-*	*81*	*0*	*100*	*46*	*36*	*0*	*329*	*30*	*-*	*-*	*90*	*3*
Spano et al.	*22*	*93-02*	*45*	*86*	*95*	*40*	*23*	*45*	*95*	*36*	*50*	*5*	*364*	*30*	*-*	*-*	*90*	*3*
Pakkala et al.	*80*	*95-08*	*52*	*80*	*100*	*37*	*25*	*33*	*91*	*41*	*32*	*9*	*304*	*-*	*-*	*-*	*-*	*-*
Lavole et al.	*49*	*96-07*	*46*	*67*	*99*	*33*	*17*	*18*	*100*	*67*	*17*	*0*	*350*	*-*	*8.6*	*71*	*84*	*8.1*
D'Jaen et al.	*75*	*96-08*	*50*	*83*	*99*	*41*	*30*	*47*	*81*	*46*	*35*	*19*	*340*	*-*	*11*	*-*	*77*	*9*
Bertolaccini et al.	*26*	*03-07*	*39*	*85*	*85*	*30*	*58*	*23*	*81*	*-*	*-*	*19*	*143*	*-*	*-*	*-*	*76*	*23*

IVDU: intravenous drug user; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; PS: performance status

Table 1. Documented clinical demographics of lung cancer patients with HIV.

must be considered, as they may increase or decrease efficacy by inhibiting cytochrome P450 (CYP450) induction, and the actual efficacy of and tolerance to therapy in such patients are uncertain.

In this chapter, we discuss the epidemiology, frequency, risk factors, clinical management, and treatment of HIV-infected lung cancer patients.

2. Incidence

Between 2001 and 2006, 71% of deaths were due to malignant tumors, as compared to only 20% in the pre-HAART era.(Crum-Cianflone *et al.*, 2009) It is evident that the HIV-infected population has a higher risk for lung cancer. In many studies comparing the incidence of lung cancer in patients with HIV to that in the general population, the standardized incidence ratio (SIR), adjusted for age and sex, has been calculated. SIR is an estimate of the ratio of the incidence of cancer in a given patient subset compared with the projected cancer incidence in the population at large. For instance, an SIR > 1 would indicate that lung cancer occurs more frequently in HIV-infected patients than in the general population; in fact, the SIR was 1.4-4.5. In the period before the advent of HAART, the SIR was 6.5 (95% confidential interval (CI) 4.5-8.9),(Frisch & Hjalgrim, 1999, Parker *et al.*, 1998) from 1978-1996, the SIR was 4.5 with 808 patients,(Frisch *et al.*, 2001) and in most European studies, the SIR did not exceed 1.13.(Bower *et al.*, 2003, Herida *et al.*, 2003, Powles *et al.*, 2009) In the HAART era, the SIR was 2.27-3.3.(Powles *et al.*, 2009, Patel *et al.*, 2008) In a meta-analysis with seven observational studies of NADCs (n=1016), the SIR was 2.72 (95% CI 1.91-3.87).(Grulich *et al.*, 2007) In many studies, the number of lung cancer patients with HIV infection has been shown to increase from the HAART era to the post-HAART era. The incidence, however, has not changed. On the other hand, there are few data from Asian countries. The TAHOD study, a retrospective study of 617 patients between 2000 and 2008 in 10 Asian countries, reported that the number of patients with simultaneous HIV infection and NADCs is increasing, even in developing countries. Infection-unrelated NADCs (NADC-IURs), including lung cancer, account for 22%, with lung cancer being the most common (1.9%, 12 patients). In this study, the authors concluded that the Asian patient demographic differs from the Western demographic.(Petoumenos *et al.*, 2010)

3. Pathogenesis & risk factors

The risk factors for lung cancer in the HIV population are strongly associated with immunity and cigarette smoking. The higher risk for carcinogenesis in immune-compromised patients and the increased risk for lung cancer occurrence are particularly well known; kidney transplant patients have a significantly higher incidence of lung cancer than hemodialysis patients.(Vajdic *et al.*, 2006) Carcinogenesis in lung cancer is not directly associated with viral load and CD4 cell counts, and the mechanism of the increased risk for lung cancer is not fully understood. The reasons for the increased incidence of lung cancer in HIV-infected patients therefore remain uncertain.

3.1 Smoking exposure & other traditional risk factors

Cigarette smoking in the HIV population is a major contributing factor for carcinogenesis, as in the general population. The American Lung Association has reported that 87% of all lung

cancer is caused by smoking, and smoking cessation decreases the annual risk.(Samet *et al.*, 1988) The rate of smoking in the HIV population is 57%, higher than in the general population (33%),(Saves *et al.*, 2003) and a smoking history of 30-40 pack-years is seen in the HIV population.(Benard *et al.*, 2007, Friis-Moller *et al.*, 2003) In particular, in the Women's Interagency HIV Study (WIHS) cohort study in the HIV population in the United States, female lung cancer patients with HIV infection were significantly more common than in the general population, showing the increased risk for lung cancer.(Levine *et al.*, 2010) Thus, smoking cessation programs need to be directed to the HIV population when infection is diagnosed. On the other hand, smoking is reported to be an independent risk factor for carcinogenesis in lung cancer.(Kirk *et al.*, 2007)

Recently, the National Cancer Institute reported that an annual low-dose computed tomography (CT) scan in the general population decreased lung cancer death by 80% by detecting the early stages of lung cancer.(Aberle *et al.*, 2010) In a study at Johns Hopkins University and associated hospitals, most of the 92 lung cancer patients with HIV infection died of lung cancer. Overall, 60% of the 32 patients who underwent chest radiography were not diagnosed as having lung cancer within a year. With regard to CT, 1 out of 28 patients was not diagnosed.(James, 2006) Smoking cessation and low-dose CT scans to detect the early stages of lung cancer would therefore be beneficial for HIV population.

Among other behavioral risk factors, intravenous drug users had been considered as a higher risk for developing lung cancer. However, the higher rate of smoking among intravenous drug users may be a confounding factor in some studies.

3.2 Immunosuppression as a risk factor

Immunodeficiency is a significant risk factor for carcinogenesis in some types of cancer. However, there is no evidence that decreased CD4 cell counts are associated with carcinogenesis in NADCs.(Clifford & Franceschi, 2007) In many case-control studies, the incidence of NADCs was not associated with the CDC classification (Table 2).

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	**B** Symptomatic Conditions, not A or C	**C** AIDS-Indicator Conditions
>500/μL	A1	B1	C1
200-500/μL	A2	B2	C2
< 200/μL	A3	B3	C3

CDC = U.S. Centers for Disease Control and Prevention; PGL = persistent generalized lymphadenopathy.

Table 2. CDC Classification System for HIV-Infected Adults and Adolescents

However, the incidence in HL, anal cancer, or hepatocellular carcinoma is affected by decreased CD4 cell counts. CD4 cell counts less than 200 cells/μL were associated with the incidence of NADCs (hazard ratio (HR), 1.67).(Powles *et al.*, 2009) CD4 cell counts increased by 100 cells/μL with the introduction of HAART, and the risk for NADCs decreased by 19%.(Bruyand *et al.*, 2009) However, carcinogenesis in lung cancer is not considered to be associated with immunological status (CD4 cell counts and viral load).(Kirk *et al.*, 2007, Spano *et al.*, 2004)

3.3 HIV as a risk factor

Many cases of carcinogenesis in HIV-related carcinomas are related to viruses such as Epstein Barr virus or Human Herpes virus-8. The International Agency for Research on Cancer (IARC), an agency of the World Health Organization (WHO), is examining the relationship between viruses and carcinogenesis**,** including: Epstein Barr virus for HL, NHL, nasopharyngeal carcinoma, and Burkitt's lymphoma; human herpes virus-8 for KS and primary effusion lymphoma; human papilloma virus for cervical, vulvar, and vaginal carcinoma, penile carcinoma, anal carcinoma, oral cavity carcinoma, and oropharyngeal and tonsillar carcinoma; hepatitis C virus for hepatocellular carcinoma and NHL; hepatitis B virus for hepatocellular carcinoma; and HIV for cervical and conjunctival squamous cell carcinoma, NHL, PCNSL, KS, and HL (particularly mixed cellularity and lymphocyte depleted subtypes). Of these, HIV is not organ-specific and is unique in that carcinogenesis occurs indirectly through immune suppression. Considering immunological status and infection, carcinomas accompanying HIV infection are classified into three categories: first, KS, NHL, and head and neck cancer, including AIDS-defining disease; second, NADC-IRs (infection-related), related to infection, hepatocellular carcinoma, HL, leiomyosarcoma, anal cancer, bladder cancer, laryngeal cancer, oral cavity cancer, penile cancer, gastric cancer, tongue cancer, and tonsillar cancer; and lastly, NADC-IURs (infection-unrelated), not related to infection, such as lung cancer and breast cancer.

Currently, carcinogenesis in lung cancer is considered not to be associated with HIV infection itself. On the other hand, microsatellite alternation resulting in genetic instability is seen in lung cancer patients with HIV infection.(Wistuba *et al.*, 1998) In another study, HIV-infected patients easily developed pulmonary disease because of decreased glutathione and antioxidant levels, as well as increased lysosome and chemokine ligand 5 (CCL5) levels in broncho-alveolar lavage fluid.(Agostini *et al.*, 1995, Allard *et al.*, 1998, Buhl *et al.*, 1989, Gordon *et al.*, 2005) Chronic inflammation is associated with carcinogenesis in lung cancer.(Buhl *et al.*, 1989) (Fig. 1) Furthermore, downregulation of HIV Tat-interacting protein

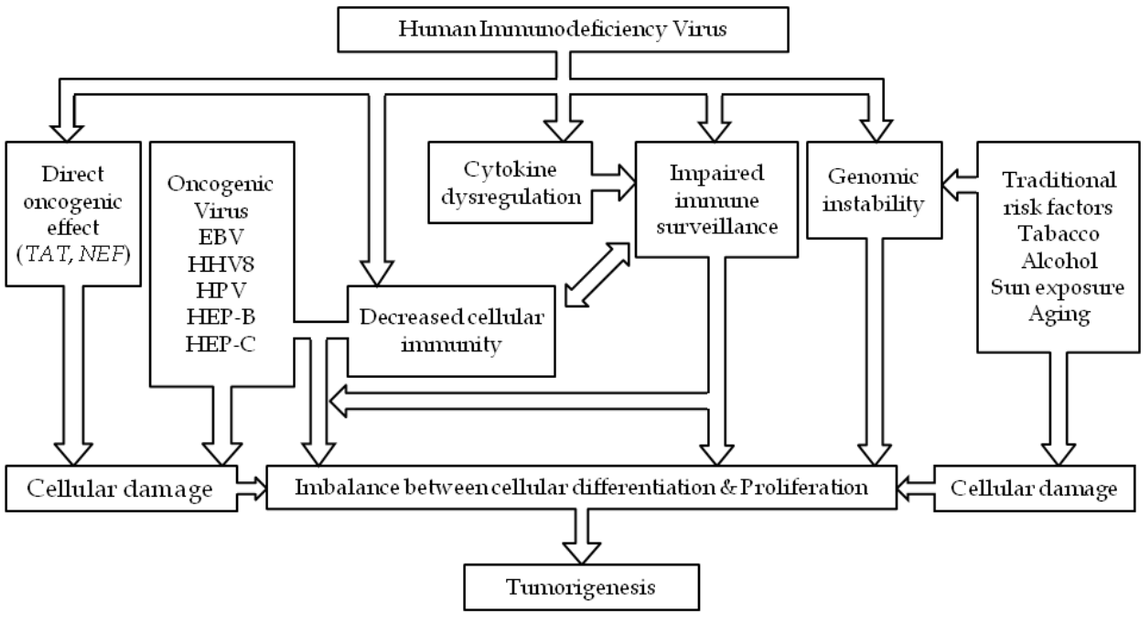

Fig. 1. Potential mechanisms for carcinogenesis in non-AIDS-defining cancer(Nguyen *et al.*)

30 (TIP30) has been verified to promote metastasis of lung cancer *in vitro* and in nude mice.(Baker *et al.*, 2000, Tong *et al.*, 2009) Thus, lung cancer in the HIV population tends to be aggressive with poor prognosis. Inhibiting HIV appears to inhibit carcinogenesis in lung cancer; however, there is no clear evidence of decreased incidence of lung cancer with the use of HAART. HAART reconstitutes immunity and decreases the risk of OIs.

4. Clinical manifestations

When compared to lung cancer in the general population, lung cancer in HIV-infected patients affects younger patients and is more aggressive. The median age of HIV-infected lung cancer patients is 45-50 years, while it is 62 years in the general population.(Spano *et al.*, 2004) With regard to the clinical stage of the lung cancer, 75-90% of all HIV-infected patients are advanced, 18-29% are in a locally advanced stage, and 50-68% are in the metastatic stage.(Lavole *et al.*, 2006) Adenocarcinoma is the most common (31-52%), followed by squamous cell carcinoma (17-39%), large cell carcinoma (3-16%), small cell carcinoma (SCLC) (1-14%), and bronchial alveolar carcinoma (less than 2%).(Tirelli *et al.*, 2000, Vyzula & Remick, 1996, Sridhar *et al.*, 1992, Alshafie *et al.*, 1997, D'Jaen *et al.*, 2010) This is similar to the distribution seen in the general population, as NSCLC accounts for 85% of all lung cancer patients in the general population. Comparing the pre-HAART era and the HAART era, the rate of adenocarcinoma was unchanged (48%), but the rate of squamous cell carcinoma was 21% in the pre-HAART era, as compared to 10% in the HAART era.(Brock *et al.*, 2006) Epidermal growth factor receptor (EGFR) mutation is a predictive factor for EGFR-tyrosine kinase inhibitors (EGFR-TKIs), and the incidence of harboring EGFR mutation among Asians is 30-35%, while it is ~10% among Caucasians.(Maemondo *et al.*, 2010, Mitsudomi *et al.*, 2009, Rosell *et al.*, 2009) A lung cancer patient harboring EGFR mutations with HIV infection has been reported.(Erickson *et al.*, 2008) CD4 cell counts at diagnosis range between 120 and 360 cells/μL,(Spano *et al.*, 2004, Tirelli *et al.*, 2000, Vyzula & Remick, 1996, Sridhar *et al.*, 1992, Brock *et al.*, 2006, Bedimo *et al.*, 2009, Tenholder & Jackson, 1993) while median CD4 cell counts in the HAART era are more than 300 cells/μL.

Overall, 25-50% of lung cancer patients with HIV infection had AIDS,(Alshafie *et al.*, 1997, Lavole *et al.*, 2006, Spano *et al.*, 2004, Sridhar *et al.*, 1992, Tirelli *et al.*, 2000, Vyzula & Remick, 1996) and 55% underwent HAART. The latency from diagnosis of HIV infection to the diagnosis of lung cancer differs by sex, being 4.1 years in women and 7.7 years in men ($p=0.02$). However, the gender-based difference has not been discussed.(Pakkala *et al.*, 2010) The frequency of metastatic organ involvement is uncertain. Release of interleukin-1 by intracerebral gp-120 components with HIV promotes brain metastasis *in vivo*.(Hodgson *et al.*, 1998) In the clinical setting, a patient with two intracerebral hemorrhages has been reported (the incidence of intratumoral hemorrhage in NSCLC is 0.52%).(Okuma *et al.*, 2010) Of note, HIV-infected patients have a higher risk of intracranial events(d'Arminio Monforte *et al.*, 2004); thus, careful follow-up is required for HIV-infected patients in clinical settings.

5. Multidisciplinary treatments & management

The fundamental modalities of treatment for lung cancer are surgery, radiotherapy, and chemotherapy.

SCLC is sensitive to both chemotherapy and radiotherapy; thus, radical concurrent chemoradiotherapy is indicated for limited-disease SCLC. When compared to NSCLC,

SCLC is characterized by higher grade, rapid progression with proliferation, and ease of metastasis to lymph nodes/distant organs in the early stage. Untreated, the median survival time is between 2 and 4 months. The response rate and median survival time in limited-disease SCLC are 70% and between 14 and 20 months, respectively. In extended-disease SCLC, chemotherapy is basic, and palliative radiotherapy is added according to the symptoms. The response rate in extended disease is 45-95%, and the median survival time is 7-10 months.(El Maalouf *et al.*, 2007)

In NSCLC, radiotherapy or chemotherapy is less sensitive than SCLC. Radical surgery is limited in Stage I-III NSCLC, and palliative chemotherapy is indicated in Stage IV NSCLC, while surgery alone is for Stage IA, and surgery-based multidisciplinary treatment is required in Stage IB-III. A decision on the treatment strategy should take into account histology, age, performance status (PS), and co-morbidities. In Stage IV patients with poor PS (≥ 3) best supportive care is recommended. The 5-year survival is 50% in Stage IA, 43% in Stage IB, 36% in Stage IIA, 25% in Stage IIB, 19% in Stage IIIA, 7% in Stage IIIB, and 2% in Stage IV. The median survival time is 14 months in Stage III and 10 months in Stage IV.(Goldstraw *et al.*, 2007)

In the period before the advent of HAART, HIV-infected patients were considered to have decreased immune competence of lymphocytes or CD4 cell counts because of accompanying complications or fragility to treatment. Toxicity and tolerance data in the treatment of other cancers are available. No fewer than 25% of advanced cancer patients with HIV infection were not treated,(Achenbach *et al.*) and among NSCLC patients with HIV infection, initial treatment consisted of chemotherapy in 31%, radiotherapy in 23%, and both in 15%.(D'Jaen *et al.*, 2010)

5.1 Surgery

Surgery is a promising modality of treatment for Stage I and II NSCLC, and is the first-line choice of treatment for all operable patients. In previous reports, patients with CD4 cell counts of more than 500 cells/μL were considered operable, while in those with lower CD4 cell counts, the indication for surgery needed careful consideration. The treatment of HIV-infected lung cancer patients at present, however, should follow the standard of care for safety and efficacy, as their prognosis depends on their lung cancer, not their HIV status. Moreover, complications, such as cardiovascular diseases and interstitial pneumonia associated with cigarette smoking, need to be taken into account, because more of these patients have a history of smoking.(Aberg, 2009)

With surgery, a reported case series did not demonstrate an increased risk of postoperative complications because of CD4 cell counts or immunological status.(Massera *et al.*, 2000) Thus, the indication for surgery in HIV-infected lung cancer patients should be determined based on pulmonary function, PS, and staging, as in the general population. Furthermore, the prognosis of such patients is good.(Spano *et al.*, 2004) In addition, the clinician should consider the medical staff's perioperative risk for blood-borne infection and ensure that standard precautions are taken. The reported blood-borne infection rate associated with surgery ranges from 0.2-0.5%.(Bell, 1997)

In determining the clinical stage, ^{18}F-fluorodeoxyglucose-positoron emission tomography-computed tomography (PET-CT) scan is a highly sensitive and specific examination. However, prudent assessment with regard to lymph nodal diagnosis is needed in the HIV population because of potential false positive to lymph nodes and upstaging in anal cancer.(Cotter *et al.*, 2006)

With respect to adjuvant chemotherapy (postoperative chemotherapy) for patients with NSCLC, a 13% decrease in the risk of death was demonstrated with chemotherapy (HR 0.87, 95%CI 0.74-1.02, p=0.08) in 1995.(Non-small Cell Lung Cancer Collaborative Group, 1995) This rate is equivalent to a 5% improvement in the 5-year survival rate. In later studies, a 5-15% improvement in the 5-year survival rate was demonstrated (HR 0.89, 95%CI 0.82-0.96, p=0.005) in NSCLC patients with Stage II-IIIA with cisplatin-based chemotherapy.(Pignon *et al.*, 2008) However, as described later, toxicity, efficacy and prognostic factors for HIV-infected lung cancer patients are uncertain.

5.2 Radiotherapy

The role of radiotherapy in HIV-infected lung cancer patients is uncertain. In general, radiation therapy for ether ADCs or NADCs leads to severe mucosal toxicity in acute phase and late-phase disturbances, even when low-dose radiation is used. In KS patients who undergo thoracic irradiation, esophagitis occurs frequently and is often severe.(Chak *et al.*, 1988, Cooper *et al.*, 1984) The mechanism of the more severe mucositis is considered to be related to decreased mucosal restoration due to a shortage of glutathione antioxidant(Buhl *et al.*, 1989, Vallis, 1991) or to be related to OIs (Fungi, Candida species, herpes, cytomegalovirus, and Cryptococcus infections).(Boal *et al.*, 1979, Rodriguez *et al.*, 1989)

In the patient with good PS or without weight loss, unresectable locoregionally advanced NSCLC or limited-disease SCLC, the standard of care is concurrent chemoradiotherapy. The 3-year survival rate in unresectable locoregionally advanced NSCLC is around 10% with radiotherapy alone, and at present, the 3-year survival rate improves by more than 25% with concurrent platinum-based chemoradiotherapy.(Blackstock & Govindan, 2007) Concurrent chemoradiotherapy is more effective but more toxic than sequential chemoradiotherapy. At present, it is recommended that HIV-infected lung cancer patients be treated with the same standard care as the general population. However, aggressive treatment requires consideration of the risk of interactions between antiretroviral agents and antitumor agents, and fragility to treatment and safety of chemoradiotherapy are uncertain. A reported case having locally advanced squamous cell lung cancer, concurrently treated with nelfinavir and 5 species of HAART and intensity modulated radiotherapy, died of massive hemoptysis because of bronchial perforation, whereas pathological complete response (CR) was achieved with intensity modulated radiotherapy at a dose of 20 Gy.(Chapman *et al.*, 2009) In a phase I study involving pancreatic cancer patients with HIV infection, a radiosensitizing effect with nelfinavir was reported.(Brunner *et al.*, 2008)

Conformal radiotherapy is appropriate, as in the general population, because of narrowing of the irradiation fields. Palliative radiotherapy is indicated according to symptoms in Stage IV.

5.3 Chemotherapy

With regard to chemotherapy, adjuvant chemotherapy is used for Stage IB-IIIA NSCLC, concomitant chemoradiotherapy is given in locoregionally advanced NSCLC, and palliative chemotherapy is given in Stage IV.(Azzoli *et al.*, 2009) In the meta-analysis of Stage IV NSCLC, which accounts for 40% of all lung cancer, platinum doublet chemotherapy prolonged the median survival to 1.5-2.8 months and improved the 1-year survival rate to 10%.(Non-small Cell Lung Cancer Collaborative Group, 2008, Grilli *et al.*, 1993, Marino *et al.*, 1994, Souquet *et al.*, 1993) Chemotherapy significantly improved survival, with a HR of 0.73 ($p<0.0001$) in 1995.(Kivisto *et al.*, 1995) In 2008, the same group reported the results of a meta-analysis of 16

randomized studies, and chemotherapy showed a survival benefit with an HR of 0.73 (95% CI 0.71-0.83, $p < 0.0001$) again. On the other hand, the survival benefit is no different between 1995 and later studies ($p = 0.77$) (Non-small Cell Lung Cancer Collaborative Group, 2008). However, the survival time has gradually improved because of trials with novel antitumor drugs that were excluded from this meta-analysis and diversification of treatment strategies. As the population with HIV infection is excluded from clinical trials, information regarding the efficacy and safety of chemotherapy in these patients is limited to retrospective reports.

5.3.1 Chemotherapy for metastatic stage in patients with HIV infection

5.3.1.1 Front-line setting

Chemotherapy is more frequently used for advanced lung cancer in HIV-infected patients because 75-90% of lung cancer patients with HIV infection have advanced disease.(Lavole *et al.*, 2006, Lavole *et al.*, 2009, Cadranel *et al.*, 2006) However, the benefit of chemotherapy is questionable, as the prospective clinical benefits and toxicities have not been realistically evaluated. In a phase II prospective study with carboplatin and gemcitabine combination chemotherapy followed by paclitaxel maintenance therapy involving 47 patients consisting mainly of lung cancer patients with poor PS (2 or 3) and immunologically fragile patients, including HIV infection and post-bone marrow transplantation, tolerance and efficacy were demonstrated to be adequate.(Bridges *et al.*, 2008) Previous reports have concluded that the benefit of chemotherapy was controversial, but the prognosis of NSCLC patients with HIV infection treated with chemotherapy was reported to be the same as the prognosis of the general population with NSCLC. D'Jean *et al.* reported that, among HIV-infected lung cancer patients, 81% (taxanes 45%, gemcitabine 26%, vinca alkaloid 10%) were treated with platinum-doublet chemotherapy in the front-line setting. Patients treated with singlet chemotherapy or oral antitumor agents outside of standard regimens were 3% each.(Previous study, 2010) Elderly lung cancer patients and lung cancer patients with poor PS in the general population have a poorer prognosis with chemotherapy and singlet chemotherapy, not platinum-doublet chemotherapy, is generally recommended.(D'Addario *et al.*, 2009) Among lung cancer patients with HIV infection, PS is poor (before 1996, 37~57% of patients had PS of more than 2; after 1996, this decreased to less than 30% of patients)(Spano *et al.*, 2004) Thus, for treatment of fragile patients, chemotherapy would be applied to lung cancer patients with HIV infection.

Current standard chemotherapy for advanced NSCLC is based on platinum doublet (cisplatin or carboplatin) plus third-generation antitumor drugs (irinotecan, docetaxel, gemcitabine, vinorelbine, paclitaxel,(Schiller *et al.*, 2002, Kelly *et al.*, 2001, Ohe *et al.*, 2007) and pemetrexed(Scagliotti *et al.*, 2008)) or EGFR-TKIs; gefitinib(Maemondo *et al.*, 2010, Mitsudomi *et al.*, 2009) and erlotinib(Rosell *et al.*, 2009), and an antiangiogenic inhibitor (bevacizumab).(Sandler *et al.*, 2006) Maintenance therapy with pemetrexed(Ciuleanu *et al.*, 2009) and erlotinib(Cappuzzo *et al.*, 2010) is known to prolong survival. In SCLC, platinum and etoposide or irinotecan combination therapy is used.(Murray & Turrisi, 2006) For relapsed SCLC, amrubicin or topotecan is given. In locally advanced NSCLC and limited disease (LD) SCLC, thoracic irradiation is added. D'Jean *et al.* reported that, among HIV-infected lung cancer patients, the agents combined with platinum agents were topoisomerase in 67%, vinca alkaloid in 22%, and taxanes in 11%. The response rate to front-line chemotherapy was 39% in 41 patients. Of the treated patients, 63% had adverse events,

and 34% were Grade 3/4. Treatment-related deaths were seen in 2 patients (0.05%); 1 with pneumonitis, and 1 from an unknown cause.(Previous study, 2010)

5.3.1.2 Second-line setting

Overall, 60% of lung cancer patients treated with front-line chemotherapy proceed to second-line chemotherapy. In NSCLC patients with good PS, the standard of care is docetaxel (Shepherd *et al.*, 2001, Fossella *et al.*, 2000), pemetrexed(Hanna *et al.*, 2004) and erlotinib.(Shepherd *et al.*, 2005) Docetaxel is indicated for all histological types of NSCLC. Pemetrexed is expected to be active for non-squamous cell histology.(Scagliotti *et al.*, 2009) Erlotinib is effective for both patients harboring EGFR mutation and EGFR wild-type,(Ciuleanu *et al.*, 2010) although the response rate and survival time differ between them. Platinum doublet chemotherapy or non-platinum doublet chemotherapy is not anticipated to have efficacy in the second-line setting.(Azzoli *et al.*, 2009) For SCLC, intravenous or oral topotecan,(Eckardt *et al.*, 2007, von Pawel *et al.*, 1999) amrubicin,(Inoue *et al.*, 2008, Onoda *et al.*, 2006) and carboplatin and paclitaxel, re-treatment for sensitive-relapse cases are considered.(Giaccone *et al.*, 1987, Postmus *et al.*, 1987, Groen *et al.*, 1999) In the HIV population, details concerning second-line chemotherapy in Stage IV are uncertain. The rates of HIV-infected lung cancer patients treated with second-line chemotherapy in HIV population were 32% (17/53) in NSCLC and 10% (1/9) in SCLC. The response rate in this study was 11%, as in the general population.(D'Jaen *et al.*, 2010)

5.3.1.3 Molecular targeted agents

The understanding of cancer at the molecular level is profound, and proteins playing significant roles in tumor proliferation, invasion, and metastasis have been identified. As a result, molecular targeted inhibitors or antibodies for these proteins have recently been developed. Of these, drugs targeting EGFR, vascular endothelial growth factor (VEGF), and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase translocation (EML4-ALK)(Kwak *et al.*, 2010) have been shown to be efficacious. EGFR-targeted drugs have particularly strong evidence supporting their use. In NSCLC harboring EGFR mutation in the general population, use of EGFR-TKIs doubles survival.(Mitsudomi *et al.*, 2009, Maemondo *et al.*, 2010, Rosell *et al.*, 2009) Thus, despite the potential for drug interactions, use of EGFR-TKIs is indicated in HIV-infected patients. Though no drug interactions are expected, prudence is required from the perspective of cost and safety.

5.3.2 Pharmacodynamic interactions between HAART & cytotoxic antitumor agents

HAART reconstructs immunity and decreases risk of OIs to inhibit HIV viral load and increase CD4 cell counts for patients infected with HIV. The goal for HAART is to continuously suppress the viral load to undetectable and maintain CD4 cell counts above 500 cells/μL.(Silverberg *et al.*, 2007) However, decreases in antiretroviral agent concentrations can exacerbate clinical status, and increased/decreased concentrations of antitumor agents lead to severe toxicity or reduced antitumor effects. Both increases and decreases in serum concentrations can occur for either/both antiretroviral agents and/or cytotoxic antitumor agents.(Kivisto *et al.*, 1995) Therefore, decreased effectiveness and increased toxicity of chemotherapy must be considered. In addition, failure of virological treatment may occur. Interactions between antiretroviral agents and chemotherapeutic agents must always be considered and are a cause for concern for oncologists in clinical settings.

	Expected chemotherapeutic concentration modifications based on antiretroviral drugs used						Expected interactions between HAART and chemotherapy
	NRTI	NNRTI	PI	INSTI	FI	MVC	
Platinum	→	→	→	→	→	→	Hematological toxicity with ZDV, Neuropathy, Nephropathy with TDF
Taxanes	→	↓	↑	→	→	→	Hematological toxicity with ZDV Neuropathy with d4T and DDI
Etoposide	→	↓	↑	→	→	→	Hematological toxicity with ZDV
Gemcitabine	→	→	→	→	→	→	Hematological toxicity with ZDV Nephropathy with TDF
Pemetrexed	→	→	→	→	→	→	Hematological toxicity with ZDV
Topotecan	→	→	→	→	→	→	Hematological toxicity with ZDV
Irinotecan	→	↓	↑	→	→	→	Hematological toxicity with ZDV
Gefitinib Erlotinib	→	↓	↑	→	→	→	None
Bevacizumab	→	→	→	→	→	→	None

INSTI: integrase strand transfar inhibitor; FI: fusion inhibitor; MVC: maraviroc; ZDV: zidovudine; TDF: tenofovir; ddI: didanosine

Table 3. Expected drug interactions between antiretroviral agents and antitumor agents commonly used in NSCLC and SCLC.(Makinson *et al.*, 2010)

However, the available pharmacokinetic data for antiretroviral drugs and antitumor agents are not predictive: 1. available pharmacokinetic data are limited to case reports, and limited individual data cannot be generalized; 2. antitumor agents of a similar class can have variable pharmacokinetics; and 3. unexpected drug interactions can occur because metabolism by CYP450 is associated with single nucleotide polymorphisms (SNPs).

Antiretroviral agents are classified into six categories: nucleoside reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); integrase inhibitors; fusion inhibitor enfuvirtide; and C-C chemokine receptor type 5 (CCR5) coreceptor antagonists. Interactions among these during treatment for ADCs, such as PCNSL or KS, enhance adverse toxicities. For instance, KS patients with CD4 cell counts greater than 200 cells/μL are reported to have a good response to paclitaxel treatment, with the same prognosis as patients with a normal immunological status.

Drug interaction between antiretroviral agents and antitumor agents is assumed when the drug is metabolized by CYP450 pathway. Many PIs and NNRTIs are metabolized by this pathway, and competitive metabolism between antitumor drugs must be considered. (Table 3) Increases in toxicity between antiretroviral agents and antitumor agents have been reported. Among NNRTIs, efavirenz increases toxicity with concomitant use of vinka alkaloids and taxanes.(Makinson *et al.*, 2010) All NRTIs and most PIs have increased drug sensitivities *in vitro*, and this leads to increased toxicity. The NRTIs efavirenz, delavirdine, and nevirapine are primarily metabolized by CYP450.(Gulick, 1998, Flexner, 1998) In a study of patients with NHL undergoing treatment with concomitant antiretroviral agents and cyclophosphamide, doxorubicin, and etoposide, significantly lower nadir neutrophil counts were seen. As compared to the group with/without PIs, the group with PIs had greater toxicity (48% vs. 27%; p=0.0025). Drug interactions have also been confirmed *in vitro*; cultured cells that expressed P-glycoprotein (P-gp) accumulated increased concentrations of paclitaxel or vinblastine concomitant with PIs.(Washington *et al.*, 1998) PIs such as ritonavir and indinavir have a strong affinity for CYP450 and also strongly inhibit CYP3A4. These enzymes are used in metabolic pathways with ifosfamide, docetaxel, paclitaxel, irinotecan, vinca alkaloids, and

etoposide.(Rowinsky & Donehower, 1997, Stebbing & Bower, 2006) Severe myelosuppression with atazanavir(Richman *et al.*, 1987, Tan & Ratner, 1997) and peripheral neuropathy with didanosine, stavudine, and zalcitabine occur.(Rowinsky & Donehower, 1997) Thus, their combined use with platinum or paclitaxel leads to increased toxicities. Combination treatment with irinotecan and atazanavir is also contraindicated. Cisplatin, the key drug in lung cancer chemotherapy,(Azzoli *et al.*, 2009, Barlesi & Pujol, 2005) is not metabolized by the CYP450 enzyme pathway. Thus, drug interactions with HAART do not occur, but accumulating toxicity, such as nephrotoxicity and neurotoxicity, must be considered. In addition, patients on antiretroviral agents having nephrotoxicity such as tenofovir disoproxil require careful follow-up.

Of the molecular targeted agents, EGFR-TKIs have been poorly evaluated, but they are known to be metabolized by CYP3A4, and ritonavir should be avoided. Raltegravir is metabolized by UGT1A1 (uridine diphosphate glucuronosyl transferase isoform 1) and does not induce or inhibit hepatic enzymes; thus, drug interactions appear to be absent. Maraviroc, a CCR5 antagonist, also does not interact with CYP3A4. As for PIs, indinavir and sequinavir inhibit cell proliferation or invasion by acting through matrix metalloprotease.(Toschi *et al.*, 2011) Due to the increased toxicity of such drug interactions, the drugs that are better to apply in HAART regimens with antiretroviral drug are those not associated with CYP450, such as NRTI, raltegravir, or enfuvirtide.

In the future, dose adjustments will be used to investigate Pharmacokinetic data via a prospective study; however, the prognosis of lung cancer patients with HIV infection is anticipated to be similar to that in the general population. Thus, conventional doses and regimens are adequate.

5.3.3 Prevention of opportunistic infections & potential complications

An increased risk of OIs is considered to be a complication of chemotherapy because of the associated decrease in CD4 cell counts. In lung cancer patients, changes in CD4 cell counts with chemotherapy are unclear. However, previous reports on treatment for ADCs provide information about changes in CD4 cell counts. CD4 cell counts in NHL on chemotherapy decreased to 50% of baseline at the nadir and recovered within a month. CD4 cell counts and viral load do not change with chemotherapeutic treatment.(Powles *et al.*, 2002) In addition, in ADCs, CD4 cell counts in patients receiving concomitant HAART or HIV viral load-negative patients are considered to recover sooner.(Powles *et al.*, 2002, Hakim *et al.*, 1997) OIs on chemotherapy occurred in 8 of 25 patients (32%), and their CD4 cell counts were less than 150 cells/μL. These patients also had poor PS, and half of the patients developed Grade 3 or 4 hematological toxicity.(Tirelli *et al.*, 2000) Recent few reports have discussed the occurrence of OIs during chemotherapy. Primary prevention of OIs is adequate; no specific preventive therapies are necessary in patients with a well-controlled viral load. Generally, in patients with less than 200 cells/μL, trimethoprim-sulfamethoxazole or pentamidine inhalation is used for pneumocystis pneumonia prevention, and in patients with less than 50 cells/μL, a macrolide is used for Mycobacteriaum avium complex (MAC) prevention. Thus, a monthly CD4 cell count check is preferred during chemotherapy and one month after treatment.

5.4 Supportive care

In supportive care, drug interactions between antiretroviral agents and other agents must be considered (Table 4). However, in clinical settings, physicians must administer palliative

therapy. Interactions between morphine and some HAART drugs have been shown, but the benefit of morphine for palliation remains. In Stage IV NSCLC, early induction of palliative therapy after diagnosis significantly improves quality of life and mood, and prolongs survival by 2 months.(Temel *et al.*, 2010) As in patients from the general population, early palliative therapy is indicated for HIV-infected patients, as well as psychological support at the end-stage.
As for the lung cancer patients with bone metastasis, zoledronic acid, a new bisphosphonate, is an appropriate palliative treatment for skeletal-related events (SREs) and symptoms associated with bone metastases.(Rosen *et al.*, 2003a, Rosen *et al.*, 2003b) The efficacy and safety of zoledronic acid given concomitantly with HAART for the osteoporosis that is associated with long-term HAART administration have been evaluated in a clinical trial and found to be advantageous.(Bolland *et al.*, 2008, Bolland *et al.*, 2007, Huang *et al.*, 2009) When SREs occur, they are associated with decreased activities of daily living and shorter survival.(Tsuya *et al.*, 2007) Thus, zoledronic acid should be given to patients with bone metastases of lung cancer, even asymptomatic.

	Expected concentration modifications in drugs used supportive care based on antiretroviral drugs used					
	NRTI	NNRTI	PI	INSTI	FI	MVC
Dexamethasone	→	↓	↓	→	→	→
Lorazepam	→	↓	↑	→	→	→
Tricyclic antidepressants	→	→	↑	→	→	→
Fentanyl	→	→	↑	→	→	→
Carbamazepine	→	↓	↓	→	→	→

Table 4. Expected drug interactions between antiretroviral agents and frequently used supportive agents for chemotherapy.

6. Prognosis

Lung cancer patients with HIV infections are considered to have a poorer prognosis than the general population because of their younger age, immunodeficiency, aggressive extension, and more advanced stage at diagnosis. In a meta-analysis, the median survival time was 5-9 months.(Powles *et al.*, 2003, Karp *et al.*, 1993, Sridhar *et al.*, 1992, Tirelli *et al.*, 2000, Spano *et al.*, 2004, Alshafie *et al.*, 1997) The 1-year survival of HIV-infected lung cancer patients was 10% (0-15%), as compared to 40% (20-50%) in the general population.(Cadranel *et al.*, 2006, Cinti *et al.*, 2008, Grubb *et al.*, 2006, Vyzula & Remick, 1996) Over the last 20 years, survival by histology was about 7 months in SCLC and 5 months in NSCLC.(Hakimian *et al.*, 2007) Favorable prognostic factors are reported to be good PS and early stage at diagnosis. The concomitant use of HAART is controversial as a prognostic factor. The reason for these patients' poor prognosis is considered to be their more advanced stage at diagnosis.(Lavole *et al.*, 2009)
CD4 cell count is sometimes considered to be a prognostic factor for chemotherapy. The prognosis for patients with a CD4 cell count greater than 200 cells/μL is 11.5 months, while that for patients with a CD4 cell count less than 200 cells/μL is 3.4 months.(Hakimian *et al.*, 2007) At present, patients with CD4 cell counts greater than 200 cells/μL can be given chemotherapy, and they have been demonstrated to have the comparable survival to non-HIV patients. (Hakimian *et al.*, 2007)

7. Future directions

Lung cancer has become common in HIV-infected patients and appears to be increasing in clinical settings, and NADCs have become the main cause of death. Thus, lung cancer has significant clinical meaning in the management of HIV-infected patients. Knowledge about its epidemiology, screening, risk factors, and intervention will reduce the incidence of lung cancer. In particular, aggressively promoting smoking cessation programs and screening for lung cancer for earlier detection will play important roles as strategies in preventing lung cancer.

HIV-infected patients should receive standard care for lung cancer, and it is anticipated that they will have the same prognosis as the general population. However, for these patients, we need to consider previously reported toxicities and fragility to treatment. In addition, increased intensity of treatment due to drug interactions and increased radiosensitization with HAART must be considered. As the clinical details of such patients have not been well reported, infectious disease physicians and oncologists must collaborate when treating HIV-infected lung cancer patients.

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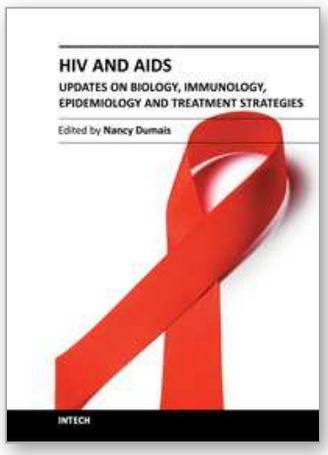

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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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