Lung cancer in HIV positive patients: the GICAT experience

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Abstract. – PURPOSE: AIDS incidence and mortality have decreased since the introduction of highly active antiretroviral therapy (HAART) into clinical practice. HIV-related malignancies, namely Kaposi’s sarcoma and Non-Hodgkin’s lymphoma, have decreased, whereas non-AIDS defining tumors have been increasing. Our aim was to study the impact of HAART on natural history of lung cancer in HIV-positive patients, comparing patients with HIV-lung cancer treated in the pre-HAART era versus the HAART era.

PATIENTS AND METHODS: We collected 68 patients with HIV-lung cancer diagnosed from 1986 to 2003. Pre-HAART era included 34 patients who did not receive HAART, whereas the HAART era included 34 patients diagnosed after January 1997 who received HAART.

RESULTS: At diagnosis Performance Status (PS) was significantly different, patients with PS = 2 were 44% in the pre-HAART era, versus 29% in the post-HAART era, p = 0.02. The 79.4% of patients in the post-HAART era received chemotherapy alone or with radiotherapy versus 47% in the pre-HAART era, p = 0.04. Cancer was the leading cause of death for both groups, with 29 (85.3%) and 21 (61.8%) patients in the pre- and post-HAART settings, respectively. The median overall survival (OS) was 3.8 months for the pre-HAART population vs. 7 months for the post-HAART patients, p = 0.01.

CONCLUSIONS: HIV-lung cancer patients have a longer overall survival in the post-HAART era versus the pre-HAART era due to a not detrimental effect of chemotherapy and positive effect of HAART. Lung cancer is the leading cause of death, showing that treatment of the cancer is the most important target now to improve their outcome.

Key Words: HIV, Lung cancer, HAART, Chemotherapy.

Introduction

It is well known that the incidence of malignant tumors among HIV-positive individuals is increasing. Kaposi’s sarcoma and non-Hodgkin’s lymphoma are the two most common HIV-related tumors and fall under the category of AIDS-defining conditions1-6. AIDS incidence and mortality have decreased significantly in Western countries since 1997 when highly active antiretroviral therapy (HAART) was introduced into clinical practice, and HIV-related malignancies have declined as well7-12. As for non-AIDS defining tumors the most frequently reported are Hodgkin’s disease, anal cancer, skin cancer and lung carcinoma13-25. The incidence of non-AIDS-defining malignancies has been increasing lately; actually several cohort studies on HIV-positive patients have demonstrated that lung cancer is more frequent in era following the introduction of HAART into clinical practice26-30.

It has been speculated that the increased incidence of lung cancer may be related to following factors: the prolonged life expectancy of HIV-positive patients during the HAART era, the longer period of immune suppression of these patients and in particular the excess number of cigarettes they smoke16,30,31. Furthermore, no data suggests that the introduction of HAART into clinical practice may account for the increased incidence of lung cancer by itself32, and probably the failure to identify a risk for lung cancer in pre-HAART cohorts is related to short overall survival.

Up to now, the impact of the new combination antiretroviral therapy on epidemiology and natural history of non-AIDS defining tumors is still
unknown. In order to evaluate the clinical outcome of HIV-infected patients with lung cancer in the era when HAART is available, we have compared clinical and demographical data, treatment and outcome in pre-HAART and post-HAART patients.

**Patients and Methods**

The Italian Cooperative Group on AIDS and Tumors (GICAT) has studied malignancies in HIV-positive patients since 1986. For the aim of this study a questionnaire was sent out on behalf of GICAT and through its completion by the participating centers the following data were collected: demographic features, HIV risk factors, cigarette smoking habits, exposure to environmental carcinogens, HIV immunological and clinical features at the time of diagnosis, histologic type and clinical stage of the tumor, type of treatment, response, survival and cause of death.

All consecutive cases of lung cancer diagnosed in HIV-infected patients referred to 20 GICAT centers were enrolled. Cut-off date to distinguish between pre- and post-HAART era was 1997, the year when HAART was introduced into clinical practice in Italy. All patients had HIV infection as detected by the ELISA test and confirmed by the Western blot, and also a cytologically or histologically proven thoracic neoplasia (lung or pleural cancer).

Staging investigations included physical examination, complete hematological and biochemical blood tests, chest X-ray and abdominal and chest CT scans. Bone scan, bone marrow biopsy and computed tomography of the brain were executed if clinically indicated. Bronchoscopy or CT-guided percutaneous fine needle aspiration were performed for diagnostic purposes.

The disease was staged according to the TNM System 6th Edition in 1996. The CDC criteria for diagnosis of HIV infection were applied.

Treatment of lung cancer included surgery alone, radiotherapy alone, chemotherapy alone or combined modalities. Chemotherapy was administered according to the ongoing treatment protocols used by each participating center and can be summarized as follows: single-agent therapy included Gemcitabine 1250 mg/sqm IV on days 1 and 8, every 3 weeks; Vinorelbine 30 mg/sqm on days 1 and 8, every 3 weeks; Etoposide 120 mg/sqm on days 1 and 5, every 3 weeks; Cisplatin 100 mg/sqm on Day 1 every 4 weeks; Epirubicin 80 mg/sqm on day 1, every 3 weeks; two-drug combination regimens consisted of Carboplatin AUC 5 on day 1 and Etoposide 120 mg/sqm on days 1 and 3, every 4 weeks; Cisplatin 100 mg/sqm on day 1 and Etoposide 120 mg/sqm on days 1 and 3 every 4 weeks; Cisplatin 100 mg/sqm on day 1 and Gemcitabine 1200 mg/sqm on days 1 and 8, every 3 weeks; Cisplatin 100 mg/sqm on day 1 and Vinorelbine 25 mg/sqm on days 1 and 8, every 3 weeks; Vinorelbine 25 mg/sqm on days 1 and 8 and Gemcitabine 800 mg/sqm on days 1 and 8, every 3 weeks; three-drug combination regimens included CAV (Doxorubicin, Cytosine Arabinoside and Vincristine), ACE (Doxorubicin, Cytosine Arabinoside and Etoposide) and CAP (Cyclophosphamide, Doxorubicin and Cisplatin).

HIV infection was treated according to the ongoing treatment guidelines of each center. During the pre-HAART era the following regimens had been used: Zidovudine alone; Zidovudine and Didanosine; Zidovudine and Lamivudine. HAART included at least three agents belonging to two or more of the therapeutic classes available at that time (protease inhibitor, nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor), with the following regimens: Zidovudine, Lamivudine and Indinavir; Stavudine, Lamivudine and Saquinavir; more recently, a boosted or non-boosted protease inhibitor associated with Stavudine and Lamivudine and two Nucleoside Reverse Transcriptor Inhibitors (NRTI) in combination with one Non-Nucleoside Reverse Transcriptor Inhibitor (NNRTI).

Radiation doses ranged between 2000 and 6000 cGy over 4-6 weeks depending on whether they were administered for palliative (∝ 5000 cGy) or curative (≥ 5000 cGy) intent.

Surgery, when performed, included wedge resection, lobectomy and pneumonectomy as a function of the extension of the disease.

In accord with standard ECOG criteria, complete response (CR) was defined as the complete disappearance of all detectable lesions for at least 4 weeks; partial response (PR) as a decrease of 50% in the sum of the products of the longest diameter of all known lesions; stable disease (SD) was defined as a lower reduction than PR. Patients were considered to have progressive disease (PD) whenever a 25% increase was observed without any previous documented CR, PR or SD, or when a new lesion was detected.
Statistical Analysis

Cut-off date for survival analysis was March 2005. Follow-up dates were recorded up to cut-off date or last contact or death. Comparisons were made for pre-HAART and HAART eras. Survival rates were calculated from the date of diagnosis of lung cancer to the date of death or last contact or cut-off and then compared with the values obtained by the Kaplan-Meier method. The differences among the study subgroups were assessed by means of the log-rank test. Statistical significance was claimed for \( p \leq 0.05 \) (two sides). The Chi-square test or Fisher’s exact test were used to compare qualitative parameters. All analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC, USA).

Results

Table I outlines the patients’ demographical and clinical characteristics. Between November 1986 and March 2003, 68 patients were diagnosed as having lung cancer and HIV infection, of whom 34 (50%) in the era before the introduction of HAART into clinical practice (1986-1997) and the remaining 34 (50%) after it became available (1997-2003). The overall median age was 43.5 years (range 31-68), with 40.4 and 46.7 years in the pre- and post-HAART groups, respectively. Most patients – 61 out of 68 (89.7%) – were males.

Risk factors for HIV infection were: pre-HAART: intravenous drug use (23, 68%), homosexual transmission (6, 17%) and heterosexual transmission (5, 14.7%); post-HAART: intravenous drug use was still the predominant risk (17, 50%), followed by homosexual transmission (10, 29.5%) and other factors (7, 20.5%).

Data about the viral load at the time when lung cancer was diagnosed are available only for the post-HAART group of patients; in most cases, namely 20 out of 34 (58.8%), it was undetectable, while in the remaining 14 a median value of 38,020 cp/mL (95-400,000) was detected.

Median CD4 count did not differ significantly in both groups, with 278 cells/μl (range 12-987) in the pre-HAART cohort vs. 339 cells/μl (range 4-761) in the post-HAART group.

All patients were heavy smokers (≥ 20 packs/year), except for one who did not smoke at all. Data were not available for three patients. There was evidence that four patients had been exposed to asbestos in the past.

All patients were diagnosed to have a lung or pleural tumor. Fifty-eight (85.3%) were affected by non-small cell lung cancer (NSCLC); 6 (8.9%) by small cell lung cancer, of whom 5 in the pre-HAART and 1 in the post-HAART peri-

### Table 1. Age and clinical characteristics of 68 HIV-infected patients with lung neoplasia by time of treatment (pre-HAART ≤ 1996 and post-HAART > 1996).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-HAART (n = 34)</th>
<th>Post-HAART (n = 34)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>23 (67.4)</td>
<td>17 (50.0)</td>
<td>ns</td>
</tr>
<tr>
<td>≥ 45</td>
<td>11 (32.3)</td>
<td>17 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>31 (91.2)</td>
<td>30 (88.2)</td>
<td>ns</td>
</tr>
<tr>
<td>F</td>
<td>3 (8.8)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVDU</td>
<td>23 (67.6)</td>
<td>17 (50.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Homosexual</td>
<td>6 (17.6)</td>
<td>10 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (14.7)</td>
<td>7 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Smoke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (94.3)</td>
<td>32 (94.3)</td>
<td>ns</td>
</tr>
<tr>
<td>No</td>
<td>2 (5.7)</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>8 (23.5)</td>
<td>9 (26.5)</td>
<td></td>
</tr>
<tr>
<td>ADK</td>
<td>13 (38.2)</td>
<td>17 (50.0)</td>
<td></td>
</tr>
<tr>
<td>LCC</td>
<td>5 (14.7)</td>
<td>6 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Small cell</td>
<td>5 (14.7)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>3 (8.8)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>7 (21.2)</td>
<td>3 (8.8)</td>
<td>ns</td>
</tr>
<tr>
<td>III-IV</td>
<td>27 (79.4)</td>
<td>31 (91.2)</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>19 (55.9)</td>
<td>24 (70.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥ 2</td>
<td>15 (44.1)</td>
<td>10 (29.4)</td>
<td></td>
</tr>
</tbody>
</table>

HAART: highly active antiretroviral therapy; IVDU: intravenous drug users; SCC: squamous cell carcinoma; ADK: adenocarcinoma; LCC: large cell carcinoma.
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Among the patients affected by NSCLC, the most common histological subtype was adenocarcinoma, with 13 (38.2%) pre-HAART and 17 (50.0%) post-HAART patients, respectively. Advanced (stage III and IV) disease was the most represented, with 27 (79.4%) pre-HAART and 31 (91.2%) post-HAART patients, respectively. ECOG Performance Status (PS) ≥ 2 was significantly more frequent in the pre-HAART than in the post-HAART cohorts, with 15 out of 34 (44%) and 10 out of 34 (29%) respectively, (p = 0.02).

Treatment data are summarized in Table II. Some patients with poor performance status (PS), most of whom were in the pre-HAART group (13, 38.2% vs. 2, 5.9%), did not receive any treatment.

Sixteen pre-HAART (47%) and 27 (79.4%) post-HAART patients had chemotherapy, either alone or combined with radiotherapy; the difference is significative (p = 0.04). In the pre-HAART group, 10 out of 16 patients (62.5%) were treated with Cisplatin, mostly associated with Etoposide; 6 out of 16 patients (37.5%) were given Platin-free mono- or polichemotherapy based on either Cyclophosphamide, Anthracyclines or Etoposide.

During the post-HAART era, 13 out of 27 patients (48.1%) received a Platinum-based association, mostly including Gemcitabine; 10 out of 27 patients (37%) were given a Platin-free association, namely Vinorelbine and Gemcitabine, and 4 out of 27 patients (14.8%) were administered a single-agent regimen, namely Vinorelbine or Etoposide or Gemcitabine.

The median number of chemotherapy cycles was 3 for the pre-HAART group vs. 2.7 for the post-HAART group. Treatment toxicity was never serious: the greatest hematological toxicity was G3 in 15% and 25% of the patients in the pre- and post-HAART groups, respectively. No non-hematological toxicity greater than 2 and no chemotherapy-related deaths were recorded.

Response was the following; among the pre-HAART patients, 13 were not treated at all and censored by response analysis. The disease progressed in all of them. Among the 21 patients who did receive treatment, disease progression was evidenced in 11 (52.4%) cases, while in 10 (47.6%) a clinical benefit was shown either as partial/complete response or stable disease.

Among the post-HAART patients, we censored the data related to 2 patients who did not get any treatment; among the remaining 32 patients, 16 (50%) obtained some clinical benefit, showing partial/complete response or stable disease, while in 14 (43.7%) the disease progressed; 2 patients were not evaluable for response.

Cancer was the leading cause of death for almost all the patients in both groups, with 29 (85.3%) and 21 (61.8%) patients in the pre- and post-HAART settings, respectively. Infection as a cause of death was almost irrelevant with 2 patients in both groups.

Table II. Treatment, response and cause of death in 68 HIV patients with lung cancer by HAART.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-HAART (n = 34)</th>
<th>Post-HAART (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>No treatment</td>
<td>13 (38.3)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>3 (8.8)</td>
<td>1 (2.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>RT</td>
<td>2 (5.9)</td>
<td>4 (11.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>CT only</td>
<td>10 (29.4)</td>
<td>17 (50.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>CT+RT</td>
<td>6 (17.6)</td>
<td>10 (29.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Response</td>
<td>CR +PR</td>
<td>7/21 (33.3)</td>
<td>9/32 (28.1)</td>
</tr>
<tr>
<td>SD</td>
<td>4/21 (19.0)</td>
<td>7/32 (21.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>PD</td>
<td>10/21 (47.6)</td>
<td>14/32 (43.7)</td>
<td>ns</td>
</tr>
<tr>
<td>NE</td>
<td>0/21</td>
<td>2/32 (6.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Infection</td>
<td>2 (5.9)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Tumor</td>
<td>29 (85.3)</td>
<td>21 (61.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Other</td>
<td>3 (8.5)</td>
<td>1 (2.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Alive</td>
<td>0</td>
<td>6 (17.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lost FU</td>
<td>0</td>
<td>4 (11.8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

HAART: highly active antiretroviral therapy; RT: radiotherapy; CT: chemotherapy; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; NE: not evaluable; FU: follow-up.
The median OS was 3.8 months for the pre-HAART population vs. 7 months for the post-HAART patients, \( p = 0.01 \) (Figure 1).

By analyzing mortality by cause, it was observed that when death was caused by an infection, the OS rates for the study groups overlapped (\( p = 0.78 \); Figure 2), whereas when it was lung cancer, they differed significantly (Figure 3), the median OS being 4.1 and 7 months for the pre- and post-HAART groups, respectively (\( p = 0.02 \)).

## Discussion

To the best of our knowledge the current study is the largest trial on patients with lung cancer and HIV infection ever published in the literature. We compared data before and after the introduction of HAART into clinical practice with an aim to evaluate its impact on treatment and outcome of HIV patients affected by lung cancer. The rationale was that the improvement in clinical conditions, which was experienced after HAART became available, might lead to a more extensive treatment of lung cancer in these patients and perhaps to prolonged survival. We regard lung cancer in HIV patients as a model to study because of the assumed increasing incidence of this disease in HIV-positive individuals as a result of the prolonged survival induced by HAART and the frequent smoking habit.

The HIV patients in our study groups were mostly intravenous drug users, which is in line with the epidemiology of HIV infection in Italy – 68% and 50% in the pre- and post-HAART groups, respectively. The clinical features of HIV infection were quite similar in both groups. Median CD4 counts were similar, too, 278 and 339 cells/µL, respectively. These data show that lung cancer is more common in association with acceptable immune competence than in the more advanced stages of HIV infection. As already pointed out by other investigators, this might suggest that the immune function plays less of a role in the pathogenesis of lung cancer than in Kaposi’s sarcoma or non-Hodgkin’s lymphomas.

Data on the viral load are available only since 1997 and only for the post-HAART cohort; taking account of these limitations, the median viral load at the time when lung cancer was diagnosed was quite low, with an undetectable result in 72% of the patients, which is consistent with the above assumption.

HIV patients with lung cancer were mostly males (87%) and smokers. The overall median age was 43.5 years, 40.4 and 46.7 years for the pre- and post-HAART groups, respectively. HIV-infected patients are still quite young, which may explain why lung cancer occurs at a younger age as compared to HIV-negative lung cancer patients.

NSCLC was the most frequent histological type of lung cancer in both groups, and among these patients, adenocarcinoma was predominant, with 35.3% and 44.1% in the pre- and post-HAART groups, respectively. As previously reported, the adenocarcinoma subtype of NSCLC prevails in young patients affected by lung cancer. As for staging, stages III and IV were the most common, with 79% and 91% in the pre- and post-HAART settings, respectively. The groups differed in performance status (PS) at the time of presentation, being a low PS score (PS \( \geq 2 \)) more frequent in the pre-HAART setting. A larger number of patients in this group received no treatment at all, which may be explained by the poorer performance status at the time of diagnosis. Chemotherapy was much more frequent among post-HAART patients, of whom 27 were treated (79.4%) vs. 16 (48%) in the pre-HAART group, \( p = 0.04 \). In our opinion, this may be due to the improved clinical features of the patients at the time of diagnosis, to the results of the 1995 meta-analysis and to a growing amount of papers confirming that the association of chemotherapy and antiretroviral therapy is feasible and safe.

The overall compliance was poor, however, toxicity was quite mild.

The overall survival (OS) rate was significantly better for the post-HAART group, 3.8 months vs. 7 months, \( p = 0.01 \) (Figure 1). However, the cause of death was comparable between both groups, with lung tumor as the leading cause.

We believe that these results may be attributed to a concomitant synergistic effect by HAART and chemotherapy. Actually, by analyzing data by cause of death, when this was infection (Figure 2) the two curves overlapped (\( p = 0.78 \)). In other words, the infection-related death rate at 1 year was the same across both groups.

When the cause of death was lung cancer, OS (Figure 3) was significantly better for the post-HAART patients with 7 months vs. 4.1 months in the pre-HAART group (\( p = 0.02 \)), e.g. the cancer-related mortality rate at 1-year was 85% vs. 67% during the pre- and post-HAART periods, respectively.
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**Figure 1.** Overall survival by treatment: —— pre-HAART (n. 34 pts) vs. – – – post-HAART (n. 34 pts).

**Figure 2.** Cause-specific survival (infection deaths) of lung cancer by treatment: —— pre (N=34 pts) vs. – – – post-HAART (N = 31 pts).

**Figure 3.** Cause-specific survival (lung deaths) of lung cancer by treatment: —— pre (N = 34 pts) vs. – – – post-HAART (N = 34 pts).
We are aware that the performance status at the time of lung cancer diagnosis is a strong predictor of the overall survival. There is a direct correlation between a better OS in the post-HAART group of patients affected by lung cancer and a higher performance status score at the time of diagnosis; nevertheless, our study shows indirectly that chemotherapy has at least a non-detrimental effect on the survival rate for these patients. It demonstrates that the association of chemotherapy and HAART is feasible, as already stated, and supports its protective effect, which co-induces a significative improvement in the overall survival.

Unfortunately no data regarding cancer fatigue syndrome\textsuperscript{23,35} nutrition during antiflastic treatment and use of new antiemetic drug are evolved\textsuperscript{19,33,49}.

Conclusions

Our study shows that lung cancer does have an impact on the OS of HIV-positive patients suffering from this neoplasia; for this reason, we strongly advice that patients with advanced lung cancer and HIV be treated in accord with the standard policy for HIV-negative patients, that is that they receive an adequate number of Platinum-based combination cycles and/or radiotherapy. Further studies are needed addressing the issue of lung cancer screening in this high risk population and detecting the best treatment schedule.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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