Short Communication

Does HIV adversely influence the outcome in advanced non-small-cell lung cancer in the era of HAART?

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HIV is associated with a small, but significant risk of developing lung cancer; particularly non-small-cell lung cancer (NSCLC) (Franceschi et al., 1998; Parker et al., 1998; Frisch et al., 2001). Before the introduction of highly active antiretroviral therapy (HAART), patients with HIV-related NSCLC had a worse outcome compared to age-matched HIV-negative controls (Sridhar et al., 1992; Vyzula and Remick, 1996; Tirelli et al., 2000). It has been suggested that this increased mortality was because the patients were younger, and had both more advanced and more aggressive disease compared to HIV-negative patients (Sridhar et al., 1992; Vyzula and Remick, 1996; Whooley et al., 1999; Skarin et al., 2001).

Others have speculated that individuals with HIV-related lung cancer were offered suboptimal treatment due to concerns surrounding HIV-related comorbidity (Tirelli et al., 2000).

Since the introduction of HAART, the life expectancy of HIV patients has increased (Palella et al., 1998). This is largely due to a decrease in opportunistic infections; however, the outcome of a number of HIV-related malignancies has also improved (Tam et al., 2002). Currently, there are no controlled data regarding the outcome of patients with HIV-related lung cancer in the HAART era, despite reports that the incidence of HIV-related lung cancer may be rising (Bower et al., 2003).

In this study, we compare the treatment and outcome of HIV-positive and age-matched HIV-negative controls with advanced NSCLC in the HAART era.

PATIENTS AND METHODS

The clinical details of patients with HIV-related NSCLC, diagnosed since the introduction of HAART in January 1996, were retrieved from a prospective single-centre lung cancer database. The HIV-negative control group was derived from the same database. For each HIV-positive case patient, three HIV-negative controls were identified who were of the same gender, had the same stage of lung cancer and were within 6 years of age of the case patient.

All patients included had histologically confirmed lung cancer, which, for the cases was diagnosed after testing HIV seropositive. Routine lung cancer staging was undertaken in all patients using the American Joint Committee tumour-node-metastasis (TNM) system. The HIV-positive and control groups were treated in an identical manner using standard chemotherapy regimens (mitomycin, vincristine and cisplatin or gemcitabine and carboplatin, depending on the date of diagnosis). None of the patients had received prior chemotherapy or radiotherapy. The response to treatment was evaluated using the RECIST guidelines (Therasse et al., 2000) and toxicities were recorded according to the National Cancer Institute common toxicity criteria (CTC) version 2.0. Specifically, age, date of cancer diagnosis, treatment, toxicity, response to treatment and survival were recorded. Survival was plotted according to the Kaplan–Meier method (Kaplan and Meier, 1958).

RESULTS

Nine HIV-positive and 27 HIV-negative patients with NSCLC were identified between January 1996 and October 2002. The
HIV-positive patients and HIV-negative controls had similar characteristics in terms of age, percent with stage IV disease and proportion with adenocarcinoma. However, HIV-positive patients appeared to have a worse performance status at presentation (Tables 1 and 2). The HIV patients were relatively asymptomatic with respect to their HIV disease, with a median CD4 cell count at presentation of 160 mm$^{-3}$ (range 136–890 mm$^{-3}$), and a median HIV viral load of 173 copies ml$^{-1}$ (range <50–200 000 copies ml$^{-1}$). Three patients had no detectable HIV viraemia and four had been diagnosed with an AIDS defining illness prior to the development of lung cancer.

The median overall survival in both groups was 4 months (range 2–15+) for HIV positives vs 1–24+ months for HIV negatives). The 1-year survival for the HIV-positive patients was 11% compared to 22% for the HIV-negative group. The two groups received a similar number of cycles of chemotherapy (Table 1). Stable disease or a partial response was achieved in 50% of the patients treated with chemotherapy in both the groups of patients.

Chemotherapy was stopped early in three HIV-positive patients, two due to progression of disease and one due to chemotherapy toxicity. In all, 50% of HIV-positive patients treated with chemotherapy, developed grade 3 or 4 haematological toxicity; however, there were no chemotherapy-related deaths. Seven patients were on HAART at the start of treatment, two stopped due to concern surrounding interaction of chemotherapy and HAART. None of the HIV-positive patients developed an AIDS defining diagnosis or died of HIV-related disease during treatment or follow-up.

DISCUSSION

Non-small-cell lung cancer occurs more frequently in the HIV population compared to HIV negatives (relative risk 4.5, 95% confidence interval: 4.2–4.8) (Frisch et al, 2001). Moreover, it has been reported that the incidence of NSCLC may be rising in people with HIV (Bower et al, 2003). The reason for the link between these two diseases is not clear; unlike most HIV-associated malignancies, no viral oncogene has been implicated in NSCLC. It has been speculated that the relationship is due to increased tobacco exposure in the HIV-positive population (Parker et al, 1998). In addition, pulmonary opportunistic infections and chronic immune suppression have both been implicated in the disease process; however, there is no clear consensus (Tirelli et al, 2000; Bower et al, 2003).

Before the introduction of HAART, HIV-related lung cancer patients had a worse outcome than HIV-negative age-matched controls (Sridhar et al, 1992; Vyzula and Remick, 1996; Tirelli et al, 2000) (Table 2). It was uncertain whether this was due to more aggressive lung cancer (Sridhar et al, 1992; Vyzula and Remick, 1996) or diagnostic delays and suboptimal treatment compared to HIV-negative controls (Tirelli et al, 2000). This controlled study compares the outcome of these patients since the introduction of HAART. It shows that the survival of the HIV-positive and HIV-negative groups is now the same, suggesting that the outcome of HIV-associated NSCLC has improved (Table 2, Figure 1). Since in this study the groups were matched for NSCLC stage and the treatment protocols used were the same in both the groups, the results support the hypothesis that NSCLC is not more aggressive in the immunocompromised. The prior reports of worse survival in the HIV-positive patients may therefore have reflected excess deaths due to immunodeficiency rather than NSCLC. Indeed, there were fewer HIV-related deaths in this study compared to those in the pre-HAART era (0 vs 16–54%, respectively) (Hoffman et al, 2000; Tirelli et al, 2000) (Table 3). Moreover, in this study, HIV-
positive and -negative patients received equivalent amounts of chemotherapy. This does not appear to be the case for patients in the pre-HAART era, where dosage modifications were common (Sridhar et al., 1992; Hoffman et al., 2000). These two factors may help explain the improved outcome of patients in this study.

Three of the four studies in the pre-HAART era were not well controlled. Two had a significantly older HIV-negative cohort (Hoffman et al., 2000; Tirelli et al., 2000), while the other was not matched for stage of disease (Vyzula and Remick, 1996). It may be that these confounding factors biased the results in favour of HIV negatives; however, there was a high degree of significance in all four studies (see Table 2). It has also been speculated that a smaller proportion of HIV patients with operable disease are offered surgery, resulting in worse outcome (Tirelli et al., 2000). This issue remains unresolved, as all of the patients in this study had advanced disease. The HIV-positive and -negative groups present in this study were remarkably similar, with a similar median age, proportion with adenocarcinoma and a similar amount of chemotherapy given. The HIV-positive patients did appear to have a poorer performance status than the negative group, which is associated with a worse outcome (Schiller et al., 2002).

Advanced HIV-related NSCLC is still associated with a poor outcome in the HAART era (median survival 4 months). However, this may reflect the advanced and aggressive nature of the disease in young people as a whole, rather than exclusively in people with HIV. It has been speculated that the high proportion of adenocarcinomas in the young, which is associated with early metastasis, may be responsible for this poor survival (Hoffman et al., 2000). There are no specific data on the median survival of patients with advanced NSCLC pre-HAART era; however, despite being incomplete, pooled data give a figure of approximately 2 months ($n = 23$) (Sridhar et al., 1992; Vyzula and Remick, 1996; Alshafie et al., 1997).

It is of note that two of the patients in this study stopped HAART during or at the time of chemotherapy. The continuation of HAART is thought to reduce opportunistic infections and preserve immune parameters (Powlès et al., 2002; Bower et al., 2003). However, if interactions between chemotherapy and HAART do occur, it may be worth considering a modification of the antiretroviral regimen rather than stopping the chemotherapy, as long-term prevention of HIV progression may be less of a priority in view of the poor prognosis of these patients. Prophylaxis against opportunistic infection is therefore crucial in this setting.

The data presented here suggest that the introduction of HAART may have improved outcome in advanced NSCLC in HIV-positive individuals. This may be due to decreased HIV-related mortality and an increased ability to tolerate treatment. These individuals may now have a similar outcome to HIV-negative people with the disease, provided that they are treated in a similar manner.

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