Malignancy-Related Deaths among HIV-Infected Patients

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(See the article by Bonnet et al. on pages 633–9)

Bonnet et al. [1] have recently published a study on malignancy-related deaths among human immunodeficiency virus (HIV)–infected subjects, comparing data from 2 surveys on deaths conducted in France in 2000 and 2005 (Mortalité 2000 and Mortalité 2005). Globally, in their analysis, malignancies represented the second most common cause of death in 2005, after AIDS-related diseases, and accounted for more than one-third of deaths in the same period. Comparing the 2 surveys, the authors demonstrated an increase in the proportion of malignancy-related deaths and a decrease in the proportion of AIDS-related deaths.

In detail, they outline the increasing prevalence of deaths attributable to non–AIDS-related, non–liver-related, and liver-related cancers between 2000 and 2005, whereas deaths attributable to AIDS-related cancers remained constant. Lung cancer represented the first most common cause of death among non–AIDS-related, non–liver-related cancers in both 2000 and 2005, whereas the relative role of hepatitis B virus (HBV) infection in deaths attributable to liver-related cancers decreased concomitant with an increase in the role of hepatitis C virus (HCV) infection. It was not possible to examine the roles of immunodepression and combination antiretroviral therapy (cART) in this study; the only observation that Bonnet et al. [1] underline is that, despite the increasing percentage of patients receiving cART, the proportion of non-Hodgkin lymphoma did not substantially decrease between 2000 and 2005.

The data from the 2 Mortalité surveys must be compared with those from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study recently published elsewhere [2]. There are several important differences between the 2 studies. First, the Mortalité study is a nationwide survey of deaths among the HIV-infected population, whereas the D:A:D study is a prospective, observational study with very stringent criteria for inclusion, follow-up, and monitoring of endpoints. Second, deaths were recorded differently in the 2 studies; the Mortalité study used the International Classification of Diseases, 10th revision, and the D:A:D study used the Code system, a detailed information system that has been validated in HIV-infected individuals [3]. Finally, the geographical areas observed in the 2 studies are different; the Mortalité surveys were limited to France, whereas the D:A:D study extended to different European and non-European countries. Moreover, the primary objective of the Mortalité surveys was to detect any differences in the distribution of the underlying causes of death attributable to malignancies observed in 2 different calendar years, whereas the primary objective of the D:A:D analysis regarding malignancies was to investigate the relationship between immunodeficiency and death attributable to AIDS-defining and non–AIDS-defining malignancies.

Indeed, the D:A:D study demonstrated that severe immunodepression is a strong independent risk factor of death attributable not only to AIDS-defining but also to non–AIDS-defining malignancies. The D:A:D study further demonstrated that long term cART is associated with an increased risk of death attributable to non–AIDS-defining malignancies but not of death attributable to AIDS-defining malignancies.

Among the different non–AIDS-defining cancers, lung cancer was most common tumor in both the Mortalité and D:A:D studies, which emphasizes the need for preventive campaigns in the HIV-infected population. With regard to liver cancers, the 2 studies had partially different results. The Mortalité surveys demonstrated a decreased frequency of HBV-related liver cancer in 2005, compared with 2000, and an opposite trend for HCV. However, HBV-positive serostatus was an independent predictor of death attributable to liver cancer in the D:A:D study, but HCV serostatus did not demonstrate any predictive value. Bonnet et al. [1]
speculate that this might be related to the extended use of antiretroviral drugs that also act against HBV (i.e., lamivudine and tenofovir), which may have reduced the proportion of HBV-related deaths. On the other hand, the findings of the D:A:D analysis might be interpreted according to the different natural history of chronic hepatitis due to HBV versus HCV, because HCV-related chronic hepatitis has demonstrated a more rapid progression to death attributable to decompensated liver cirrhosis rather than to hepatocellular carcinoma, as reported elsewhere by the D:A:D group [4].

Globally, the main limitations of both studies are that only events with fatal outcomes are taken into account and that a real picture of the incidence of cancers in the late HAART era is not available. The increased survival of HIV-infected patients because of effective cART has resulted in long-term survival and an increased probability of death attributable to non–HIV-related events. In the case of cancers, their occurrence might be caused by traditional risk factors present in the general population, such as smoking for lung cancer, HBV and HCV infection for liver cancer, or human papillomavirus infection for anal and cervical cancers. The role of a long-term compromised immune system that, despite being adequate in terms of CD4 counts and function in preventing opportunistic events, may be not completely adequate in preventing the growth of malignant cells, should be further investigated.

In conclusion, prospective data on the incidence of malignancies among HIV-infected patients, with stringent follow-up and end point criteria are needed, to better elucidate possible complex interactions between immunodeficiency, HIV, and cART in HIV-infected subjects, who also have traditional risk factors.

Acknowledgment


References