

Editorial – Non AIDS-defining malignancies: a new epidemic in HIV-infected population for the upcoming decades?

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Dramatic improvements in HIV-infected patient survival and morbidity has followed the expanded use of highly active antiretroviral therapy (HAART), opening a new era in which HIV disease has become a chronic disease. However, the increased survival has turned in a substantial number of HIV-infected patient to age-related diseases that now have a significant impact on morbidity^{1,2}. Furthermore, in the last decade, a significant decline in the incidence of virus-related AIDS-defining malignancies (Kaposi's sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer) has been accompanied by a dramatic increase in the incidence of non-AIDS defining malignancies (NADMs)³. Among these, an increasing role is played by HPV-related cancer such anal cancer⁴. Among hematological NADMs an increasing impact is attributable to Hodgkin lymphoma (HL) which displays several peculiarities when compared with HL of the general population. In fact, HIV-HL exhibits an unusually aggressive clinical behavior, which mandates the use of specific therapeutic strategies and is associated with a poor prognosis⁵. The availability of direct-acting antiviral agents (DAAs) for the treatment of HCV infection has substantially improved the probability of sustained virologic response even in HIV-infected patients. These successes have led the World Health Organization to call for the eradication of HCV infection by 2030. However, despite the projected reduction in the occurrence of HCV-related hepatocellular carcinoma (HCC) due to the eradication of patients with early fibrosis stages, HIV patients with cirrhosis remain at substantial risk of HCC⁶. Therefore, they should be considered for liver transplantation given their improved survival with regards to HIV-infection⁷. Among not virus-related NADMs colorectal cancer shows different characteristics in respect of HIV negative patients. Berretta et al⁸, in a case-control study, compared the clinical characteristics of HIV-positive patients with colorectal cancer (CRC) with the uninfected patients. They found that HIV-infected patients were younger compared to the general population, 72% of HIV-positive patients are younger than 50 years at the time of CRC diagnosis (median age 41 years). They also that found 90% of patients had advanced stages (III-IV) at diagnosis compared to 57% in the general population. At multivariate analysis, the only characteristics that significantly reduced the survival of the CRC patients were: HIV-positive status (hazard ratio (HR): 2.4; 95% CI: 1.1-5.2) and Dukes' stage D (HR: 3.7; 95% CI: 1.9-7.1). Although FOLFOX4 (Folinic acid/5 Fluorouracil/Oxaliplatin) is considered the standard chemotherapy regimen for CRC, few data are available on its results in HIV-related CRC. Berretta et al⁹ described 24 patients that were selected among the HIV-infected patients with CRC treated with FOLFOX4 and concomitant HAART within the Italian Cooperative Group on AIDS and Tumors (GICAT). An overall response rate of 50% was observed, 4.2% of patients achieved a complete response and 45.8% partial response. Interestingly, no opportunistic infections occurred during or immediately after chemotherapy. These results suggest that FOLFOX4 associated with HAART is a feasible option in HIV-infected patients with CRC. Recently, Robbins et al studied excess cancer rates in the United States. They found that among NADMs the most common excess cancers were anal cancer (n = 740, 97% excess) and lung cancer (n = 440, 52% excess)^{10,11}. Furthermore, HIV-related lung cancer seems to be associated with a poorer prognosis when compared to the general population. Taken together, the results of the more recent studies on NADMs in HIV-infected patients highlight an occurrence increase over

time despite fully suppressive HAART. In this scenario, there is a clear need to identify prevention strategies specifically tailored for the HIV-infected population in the absence of which there could be a loss in the HAART associated mortality and morbidity benefits.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) MADEDDU G, SPANU A, SOLINAS P, CALIA GM, LOVIGU C, CHESSA F, MANNAZZU M, FALCHI A, MURA MS, MADEDDU G. Bone mineral loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. *Q J Nucl Med Mol Imaging* 2004; 48: 39-48.
- 2) MADEDDU G, FOIS AG, CALIA GM, BABUDIERI S, SODDU V, BECCIU F, FIORI ML, SPADA V, LOVIGU C, MANNAZZU M, CADDEO A, PIRAS B, PIRINA P, MURA MS. Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era? *Infection* 2013; 41: 347-353.
- 3) PINZONE MR, FIORICA F, DI ROSA M, MALAGUARNERA G, MALAGUARNERA L, CACOPARDO B, ZANGHÌ G, NUNNARI G. Non-AIDS-defining cancers among HIV-infected people. *Eur Rev Med Pharmacol Sci* 2012; 16: 1377-1388.
- 4) ZANET E, BERRETTA M, MARTELOTTA F, CACOPARDO B, FISICHELLA R, TAVIO M, BERRETTA S, TIRELLI U. Anal cancer: Focus on HIV-positive patients in the HAART-era. *Curr HIV Res* 2011; 9: 70-81.
- 5) SPINA M, CARBONE A, GLOGHINI A, SERRAINO D, BERRETTA M, TIRELLI U. Hodgkin's disease in patients with HIV infection. *Adv Hematol* 2011; 2011. pii: 402682
- 6) FIORE V, VIDILI G, BAGELLA P, LOBRANO G, MUREDDA AA, CARUANA G, BABUDIERI S, MADEDDU G. Hepatocellular carcinoma development in a patients with HCV infection after eradication with direct-acting antiviral agents. *WCRJ* 2017; 4: e833.
- 7) DI BENEDETTO F, DE RUVO N, BERRETTA M, MASETTI M, MONTALTI R, DI SANDRO S, QUINTINI C, CODELUPPI M, TIRELLI U, GERUNDA GE. Don't deny liver transplantation to HIV patients with hepatocellular carcinoma in the highly active antiretroviral therapy era. *J Clin Oncol* 2006; 24: e26-27.
- 8) BERRETTA M, CAPPELLANI A, DI BENEDETTO F, LLESHI A, TALAMINI R, CANZONIERI V, ZANET E, BEARZ A, NASTI G, LACCHIN T, BERRETTA S, FISICHELLA R, BALESTRERI L, TORRESIN A, IZZI I, ORTOLANI P, TIRELLI U. Clinical presentation and outcome of colorectal cancer in HIV-positive patients: a clinical case-control study. *Onkologie* 2009; 32: 319-324.
- 9) BERRETTA M, LLESHI A, CAPPELLANI A, BEARZ A, SPINA M, TALAMINI R, CACOPARDO B, NUNNARI G, MONTESARCHIO V, IZZI I, LANZAFAME M, NASTI G, BASILE F, BERRETTA S, FISICHELLA R, SCHIANTARELLI CC, GARLASSI E, RIDOLFO A, GUELLA L, TIRELLI U. Oxaliplatin based chemotherapy and concomitant highly active antiretroviral therapy in the treatment of 24 patients with colorectal cancer and HIV infection. *Curr HIV Res* 2010; 8: 218-222.
- 10) ROBBINS HA, PFEIFFER RM, SHIELS MS, LI J, HALL HI, ENGELS EA. Excess cancers among HIV-infected people in the United States. *J Natl Cancer Inst* 2015; 107. pii: dju503.
- 11) BERRETTA M, MARTELOTTA F, DI FRANCA R, SPINA M, VACCHER E, BALESTRERI L, BORSATTI E, BEARZ A, DE PAOLI P, TIRELLI U. Clinical presentation and outcome of non-AIDS defining cancers, in HIV-infected patients in the ART-era: the Italian Cooperative Group on AIDS and tumors activity. *Eur Rev Med Pharmacol Sci* 2015; 19: 3619-3634.