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Opportunistic infections in HIV-related lymphoma

Human Immunodeficiency virus (HIV)-associated lymphomas has been considered a late manifestation of HIV infection, occurring more likely in the setting of deep immunosuppression (*Grulich, AIDS 2000*), namely CD4 cell count less than 200 cells/mm³, in patients with a prior diagnosis of an AIDS-defining event. Compared with rates in the general population, in HIV-infected people, the relative risk of immunoblastic lymphoma is increased about 600-fold and that of diffuse large cell lymphoma of about 145-fold (*Cotè, Int J Cancer 1997; Biggar Int J Cancer 1996*).

After the introduction of highly active antiretroviral therapy (HAART) in the clinical practice, which significantly reduced morbidity and mortality of HIV infection-related conditions (*Mocroft, Lancet 2000*), a significant decrease in the incidence of AIDS-related lymphoma has been observed, even though this decrease is not as dramatic as that observed in AIDS-related Kaposi's sarcoma (*Ledergerber, BMJ 1999; International Collaboration on HIV and Cancer J Natl Cancer Inst 2000*). Moreover, as a consequence of the very marked decline in Kaposi's sarcoma and opportunistic infections in the HAART era, AIDS-related lymphoma has now become one of the most common of initial AIDS-defining events (*Mocroft, Lancet 2000*). In a study from the French Hospital Database on HIV, the incidence of AIDS-associated lymphoma has been demonstrated to increase with increasing immunodeficiency (*Besson, Blood 2001*). In both the pre and post HAART era, the likelihood of developing AIDS-related lymphoma has been similar in patients at the same level of CD4 count. AIDS-related lymphoma have been always considered as a systemic condition in terms of treatment decision, and systemic chemotherapy is advocated in all the cases, as opposed to local radiation or surgical excision alone, despite what may appear to be a localized disease. In the general population, the use of dose-intensive therapy was considered important for the achievement of complete remission and long term sur-

vival in patients with intermediate or high grade lymphoma. Since the beginning of HIV epidemic, the role of dose intensity in the management of AIDS-associated lymphoma represented a key point, and often a limiting factor to achieve a complete response to treatment. In fact, in the HIV setting, where poor prognostic indicators of disease could be more prevalent, and the risk of chemotherapy-induced toxicity higher, due to the level of immune suppression, different therapeutic trials were undertaken, with poor results, and other chemotherapy strategies were attempted in order to ascertain if lower doses of chemotherapy may be more effective (*Levine, JAMA 2001; Kaplan N Engl J Med 1997*), showing that low dose chemotherapy was certainly equivalent to standard dose therapy in patients with AIDS-related non Hodgkin's lymphoma. Moreover, additional studies showed that with good prognostic indicators more dose-intensive regimen may be tolerated (*Gisselbrecht, Am J Med 1993*). Nevertheless, all these studies were conducted before the introduction of combined antiretroviral therapy, when the only available antiretroviral agents were monotherapy or dual therapy, which demonstrated to not have any impact of HIV-related morbidity and mortality. One of the most important factor limiting the achievement of adequate dose intensity is the hematologic toxicity, particularly neutropenia, associated with the risk of life-threatening infections. Recent surveys indicate that chemotherapy associated neutropenia remains a prevalent problem associated with substantial morbidity, mortality and costs (*Crawford, Cancer 2004*). Infections related to chemotherapy induced neutropenia may be due directly to chemotherapy itself and to a transient increase in immunosuppression during chemotherapy phase of the disease. In the first case the primary anatomic sites of infection often include the alimentary tract, where cancer chemotherapy-induced mucosal damage allows invasion of opportunistic organisms. Similarly, damage to the integument by invasive procedures, such as placement of vascu-

lar access devices, often provides portals of entry for infectious organisms. In this case the most frequent causes of infections are represented by gram positive and gram negative cocci and bacilli and fungi. In the second condition, infections associated to a profound immunosuppression such as cytomegalovirus, non tubercular mycobacteria, and atypical fungi (*Cryptococcus neoformans*) are the most prevalent causes of disease.

Granulocyte-colony stimulating factors (G-CSF) has been used with efficacy in patients with newly diagnosed AIDS-related lymphoma, and may decrease the number of febrile episodes and hospitalizations, although no change in median survival has been reported (Kaplan, *J Clin Oncol* 1991). Of interest, relatively low doses of G-CSF may be required when compared with HIV-negative patients. After the introduction of HAART in the clinical practice a specific role of this combination treatment has been observed in the management of AIDS-related lymphoma. Particularly, even though some concerns regarding the potential toxicity of HAART when concomitantly administered with chemotherapy have been raised (Little, *Acquir Immune Defic Syndr* 2000), in subsequent studies, HAART has been shown to be safe when used concomitantly with combination chemotherapy (Ratner *J Clin Oncol* 2001). Moreover, different studies have confirmed a prolongation of the survival in patients who received concomitantly HAART and chemotherapy (Besson, *Blood* 2001; Kirk, *Blood* 2001; Tam, *Cancer* 2002). The mechanism whereby HAART may prolong survival could be related to an improvement of HIV disease. Moreover, by preventing opportunistic infections and other AIDS-related complications, HAART may allow patients with AIDS-lymphoma to live enough to receive adequate chemotherapy for their disease, avoiding death due to intercurrent infections. Moreover, HAART may ameliorate the bone marrow suppression due to HIV itself, allowing the use of standard dose of chemotherapy without the frequent reduction of doses and delay which strongly influence the achievement of adequate dose intensity. Moreover, the role of the improvement of HIV infection during HAART in terms of achievement of a response to chemotherapy has been evaluated and the only factor associated with achievement of complete response was attainment of complete virologic response to HAART (Antinori, *AIDS* 2001). Nevertheless, according with a beneficial effect of HAART at a clinical level even in patients without a viroimmunologic response, a prolonged survival was observed even in patients with AIDS-related lymphoma treated with HAART, when compared to patients treated in the pre-HAART era. In this case, the precise mechanism of prolongation of survival in HAART-treated patients have yet to be clarified. It is certainly possible that the longer survival of this group of non responder to HAART may be due to fac-

tors such as the appropriate use of supportive therapy (G-CSF), as well as the use of prophylactic agents against infections in the post HAART era. (Ramanarayanan, *Am Society Hematology* 2002). In conclusion, toxicity related to chemotherapy in patients with AIDS-associated lymphoma is a relevant condition leading to different spectrum of infections. The concomitant use of HAART and chemotherapy may allow to reduce the impact of the problem, by improving the HIV condition

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