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Impact of HAART on the clinical management of AIDS-related cancers

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Abstract

The development of HIV-related disease has changed dramatically since the introduction of highly active antiretroviral therapy (HAART) into clinical practice. Since the use of protease inhibitors became widespread, a 30–50% reduction in Kaposi's sarcoma (KS) has been observed. The results of recent studies indicate that HAART may be a useful alternative both to immune response modifiers during less aggressive stages of KS disease and to systemic cytotoxic drugs in the long-term maintenance therapy of advanced KS. The impact of HAART regimens on the incidence of systemic lymphoma (NHL-HIV) remains unclear, but it can be hypothesised that patients treated with HAART may survive longer with continued B cell stimulation and dysregulation resulting in an increased incidence of lymphoma over time. The impact of HAART on survival in patients affected by NHL-HIV has recently been evaluated and a positive correlation between HAART and outcome in these patients has been found. The spectrum of cancers in patients with HIV infection may develop further since these patients survive longer with HAART and with a better control of opportunistic infections. With the increasing use of HAART, the dilemma is whether to institute or continue protease inhibitors use during chemotherapy. Based on the advances in our understanding of HIV-related disease and the availability of new antiretroviral therapies, the choice for anti-HIV agents in patients receiving chemotherapy is important.

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1. Introduction

The introduction of highly active antiretroviral therapy (HAART) into clinical practice in industrialised countries has dramatically changed the development of HIV-related diseases. Deaths from AIDS-related diseases have been reduced by 75% [1,2] since protease inhibitor (PI) treatment and combination antiretroviral therapy came into use in 1996. This is as a result of the lasting inhibition of viral replication and also due to the immunological recovery induced by the new therapy. Furthermore, the incidence of Kaposi's sarcoma (KS) is declining whereas, the situation for non-Hodgkin's lymphoma (NHL) is more complex, with a reduced incidence of primary central nervous system lymphoma, but with relatively stable levels of patients developing systemic NHL [3,4]. AIDS-related NHL appears not to be markedly decreased by the introduction of HAART and is therefore the greatest challenge as regards therapy in AIDS patients. The general emphasis of therapy has now shifted towards cure, while maintaining vigilance regarding the unique vulnerability of the HIV-infected hosts. It is of note that other non-AIDS defining tumours, such as Hodgkin's disease, anal, head and neck, lung and testicular cancer and melanoma have recently been reported at an increased frequency in patients infected by HIV.

2. Kaposi's sarcoma

KS is the most common malignancy observed in patients with HIV infection. In Western countries, KS is over 200 times more common in HIV-infected individuals than in the general population. The percentage of patients with KS as the index diagnosis for AIDS has been declining since 1996, when HAART became

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available. In particular, since the use of PIs became widespread, a 30–50% reduction of KS has been observed in both the US and Europe [5–7]. The new findings on KS aetiopathogenesis, in particular on the HIV direct and indirect pathogenetic effects and known interactions between HIV and human herpes virus-8 (HHV-8) on the one hand and the advent of HAART on the other have prompted investigators to a new approach, namely to study the anti-KS activity of the new antiretroviral combination therapy.

Regression of KS with HAART has been the subject matter of numerous reports issued worldwide in the last 2 years. The first retrospective study was performed by Bower in 1999 on a group of 78 patients who received antiretroviral combination therapy following chemotherapy [8]. Antiretroviral therapy consisted of a combination of three or more drugs including a PI in 49% of the cases, two PIs in 16% and only reverse transcriptase nucleoside and non-nucleoside inhibitors in the remaining 35% of the cases. After a median time period of 12 months of treatment, 31% of patients showed disease progression. The time to treatment failure was 1.7 years, which is significantly longer than the median time to treatment failure of 0.5 years determined for the controlled group. A significant correlation ($P=0.002$), emerged between KS progression and virological failure to antiretroviral therapy, defined as a viraemia over 5000 copies/μl, but no correlation was observed with immunological failure. This study is very important from a clinical viewpoint as it confirms that HAART has anti-KS activity.

Unfortunately, a correct assessment of the immunological recovery and HHV-8 viraemia after treatment is lacking, which makes it impossible to evaluate the potential factors involved in the anti-neoplastic activity of antiretroviral therapy in these patient populations.

Most prospective studies on HAART anti-KS activity have enrolled a low number of patients, who cannot be evaluated and compared with one another because the selection criteria were heterogeneous and the mode of administration different, since HAART has been given either as first-line therapy or as post-chemotherapy maintenance treatment [9–13]. The preliminary results obtained from these small groups, even though the response rates are different, are nevertheless very interesting since the existence of a complex (and still rather unexplained) interaction between the anti-neoplastic response and virological and/or immunological response to HAART is shown for the first time. A study from the Italian Cooperative Group on AIDS and Tumors (GICAT) on 53 patients with a slowly proliferating disease at onset, stages I–III according to New York University and HAART-naïve, treated with HAART as first-line treatment for KS, concluded that slowly proliferating KS with skin and/or slight visceral involvement is responsive to first-line antineoplastic treatment with HAART in a high percentage of cases [14]. The clinical follow-up of some patients with advanced KS who have shown a complete response to HAART after partial remission following chemotherapy has convinced the GICAT investigators to perform a new prospective study on the role of HAART as postchemotherapy maintenance treatment. The results of this study indicate that HAART is active as postchemotherapy maintenance treatment in patients with an advanced disease stage, above all in the cases in which the tumour mass has been reduced significantly as a result of conventional antineoplastic treatment (E. Vaccher, data not shown). At present, the correlation between the anti-KS response and virological/immunological response markers are being evaluated. The results of these trials can be used to give some guidelines on the treatment of KS. HAART is a major treatment for all KS patients. It is often the only anti-neoplastic therapy in the early stages of the disease (T0) and/or for slowly-proliferating disease, that is when the tumour load is low and/or the tumour growth is consistent with a long time interval to the development of HAART anti-KS activity. In patients with T1 and rapidly-proliferating disease, the first-line treatment is chemotherapy with or without antiretroviral therapy (depending on the patient's tolerance) followed by maintenance therapy with HAART. HAART may be a useful alternative both to immune response modifiers during the less aggressive stages of KS disease and to systemic cytotoxic drugs in long-term maintenance therapy of advanced KS. The management of KS with HAART is very interesting as it targets both tumour cells and the underlying HIV infection. The likelihood of long-term treatment, with lower adverse effects makes this approach very attractive.

3. Non-Hodgkin's lymphomas

Since the beginning of the AIDS epidemic, the incidence of NHL in the USA among HIV-infected individuals is approximately 60 times greater than that expected in the general population [15]. The impact of HAART regimens on the incidence of systemic lymphoma remains unclear, but it can be hypothesised that improved immune function and reduced B cell stimulation in patients receiving HAART may reduce the risk of developing lymphoma. By contrast, however, it is possible that patients treated with HAART may survive longer, with continued B cells stimulation and dysregulation resulting in an increased incidence of lymphoma over time. Grulich [16] concludes that the incidence rate of AIDS-related NHL has decreased with the use of HAART, but the magnitude of the decrease appears to be less than that for other AIDS-associated opportunistic infections and KS. Possible reasons include the fact that NHL is due to a variety of causes rather than a

specific infective agent. NHL also occurs in patients that are more immune competent than those in which most other opportunistic infections occur. The favourable impact of HAART therapy may thus be smaller for NHL than for other AIDS-defining illnesses [17,18]. The same conclusion is drawn by Rabkin from the AIDS Clinical Trial Group (ACTG) [19], who suggests that while the incidence of the KS has decreased with the improved therapy for HIV infection, the smaller change in the incidence of NHL may be due to the fact that current strategies do not eliminate the risks for lymphoma. If HAART remains only partly effective in the reconstruction of the immune system it is likely that NHL will become proportionally more important as a cause of morbidity and mortality in people with HIV-NHL. This emphasises the need for HIV treatment strategies that will more completely reverse the immune deficiency. Some authors [20] have underlined that in contrast to patients affected by KS, who cease to be at risk for KS once immune function has been improved by HAART, patients with a history of severe immune deficiency continue to be at risk for NHL despite antiretroviral combination therapy. Although the initiation of carcinogenesis may require an immunodeficient state, the factors promoting the development of NHL further along the causal chain do not seem to be related to immune function, or are related to aspects not affected by any antiretroviral combination therapy. NHL will thus remain a relatively common complication among patients treated with antiretroviral combination therapy.

The treatment of HIV infection has evolved very rapidly over recent years, and there are reasons to believe that these advances may also benefit cancer treatment in HIV-infected patients. Indeed, there is rather compelling evidence that the incidence and natural history of epidemic KS have substantially improved coincident with better HIV treatment [3]. Remissions of lymphomas have also been attributed to HAART [21]; thus, an important work has been initiated in an attempt to better define the role of combined antiretroviral therapy and cytotoxic chemotherapy for AIDS-NHL. HAART can suppress HIV viraemia for prolonged periods to levels below polymerase chain reaction (PCR) detection limits in most antiretroviral-naive patients and even some patients previously treated with antiretrovirals. Low viral burden is associated with an increased CD4 count and improved prognosis in HIV patients [22,23]. The development of HAART has resulted in substantial improvements in the survival of patients with AIDS. Upon starting HAART, extremely ill and terminally-ill patients often have a marked improvement in their health status. More recently, the optimism resulting from these observations has been tempered by the fact that prolonged viral suppression does not appear to be achievable in a substantial number of patients for a variety of reasons, including the difficulty of complying with such complex regimens, drug tolerance, and ultimately the development of HIV genomic mutations that confer resistance [24]. HIV eradication using current therapy is now considered by many researchers to be very unlikely, because ongoing localised HIV replication occurs even during HAART therapy [25] and the viral reservoir is likely persist for a lifetime [26].

These considerations have led some practitioners to question the rationale for early HIV treatment in favour of delayed therapy in certain cases [27]. One potential advantage of antiretroviral treatment is that viral suppression may further limit immune damage by HIV during chemotherapy and may even permit the development of anti-tumour immune responses. It may also reduce the HIV-associated production of proinflammatory cytokines, such as interleukin-6 (IL-6), that have been proposed as potential co-factors in lymphomagenesis in AIDS-NHL [28]. In addition, it is theoretically possible that in the absence of antiretroviral therapy, HIV could transactivate oncogenic viruses, such as HHV-8, that play a role in lymphomagenesis [29]. In contrast, there is concern that overlapping toxicities and the pharmacokinetic interactions between antiretroviral drugs and chemotherapy may affect the therapeutic index of the various drugs. Increased toxicity may lead to a delay in chemotherapy or prompt the reduction of doses, possibly compromising the curative potential of chemotherapy treatment of the lymphoma. Toxicity can also adversely affect compliance with antiretroviral therapy, resulting in the potential danger of resistant HIV emerging. In addition, from a practical standpoint, chemotherapy is lymphocytotoxic and can deplete the CD4 cell count by upwards of 50% independent of HIV infection, limiting the relative CD4 protective effect conferred by HAART.

Ultimately, the relative impact of these various factors must be balanced by considering their contribution to the lethality of the lymphoma and the underlying AIDS condition. The impact of HAART on chemotherapy was recently assessed by our group in a matched case–control retrospective analysis of 24 patients with AIDS-NHL treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and anti-retroviral therapy compared with 18 patients treated with CHOP or CHOP-like regimens without antiretroviral therapy [30]. Antiretroviral regimens were selected based on the patient's prior therapy. Response rates were similar between the two treatment groups. Complete remission occurred in 50% of patients treated with CHOP-HAART and 36% of the evaluable patients treated with CHOP alone. Toxicity, however, was greater in the patients treated with the combined therapy compared with patients treated with the CHOP regimen alone. CHOP-HAART-treated patients had a better survival than the CHOP-treated patients, sug-

gesting that the reduction of opportunistic infections morbidity by HAART other than the good performance status of these patients, may have improved the overall outcome of the combined treatment patients. In fact, in our case series of 235 patients affected by NHL-HIV, the actuarial 3-year disease-free survival for a subgroup of 88 patients achieving complete response after chemotherapy was significantly longer for those who had been treated with HAART than for the HAART-naive patients (86% versus 57%, $P = 0.004$) (E. Vaccher, data not shown). These findings have important implications for the management of patients with AIDS-NHL, since a positive correlation between HAART and lymphoma is demonstrated for the first time. Prospective trials within our group are currently investigating the impact of the combined chemotherapy–HAART treatment on the immune system and HIV viral load in AIDS-NHL patients.

4. Other tumours

As the AIDS epidemic advances, other tumours are being increasingly recognised in HIV-infected individuals including invasive cervical cancer, Hodgkin's disease (HD), anal cancer, basal cell carcinoma of the skin, testicular cancer, lung cancer, oral mucosa and head and neck tumours [31,32]. The spectrum of cancer in patients with HIV infection may further develop, since these patients survive longer with HAART and with a better control of opportunistic infections. Several questions such as feasibility and toxicity and drug–drug interactions face the oncologists using the combination of HAART and chemotherapy for the management of patients with malignancies and HIV infection. With the increasing use of HAART, the dilemma is whether to institute or continue protease inhibitors use during chemotherapy. Most clinicians would recommend continuation of HAART until unacceptable toxicity occurs. On the other hand, discontinuing HAART in a patient undergoing chemotherapy for a tumour that we know is not curable might also be a suitable option if we consider that in this case the overlapping of toxicity from the chemotherapy and HAART should be avoided in order to improve the quality of life of the patient. HAART treatment could be restarted once chemotherapy has been demonstrated to be effective, and a complete response has been achieved. Based on the advances in our understanding of HIV infection-related diseases and the availability of newer antiretroviral therapies, the choice for anti-HIV agents in patients receiving chemotherapy is important [30]. Continuation of HAART with prophylaxis against opportunistic infections in patients receiving chemotherapy may be beneficial in order to improve the treatment outcome of patients with HIV infection and malignancy.

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