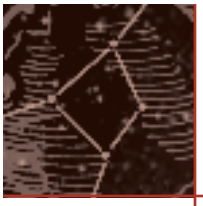

The use of antiretroviral therapy in patients undergoing treatment for HIV-related neoplastic disease

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Introduction

Individuals with HIV infection and cancer are faced with two complex life-threatening diseases. Treatment of such complex illnesses is more straight-forward for the clinician when adequate evidence-based clinical guidelines are available. However, for many patients with AIDS-related (or "AIDS-defining") malignancies, there are no such guidelines and there is in fact little actual clinical science upon which to base dogmatic recommendations. Several important issues remain inadequately studied in this population. Two such issues are whether or not anti-HIV therapy should be administered during anti-neoplastic therapy, and whether anti-neoplastic chemotherapy should be dose-reduced in the setting of HIV-infection. A one-size fits all solution to this dilemma will neither serve the patient well nor promote clinical studies that will be useful in defining the issues. In the absence of evidence-based medicine, various disease elements and biologic principles must be carefully weighed in terms of the realistic therapeutic goals relevant to the affected individual. In this article, we will focus on the first of these issues—the use of HAART during the treatment of AIDS-related malignancies.

Patients with AIDS-related malignancies often present a substantial challenge for the clinical care team because the development of optimal treatment goals and strategies requires a thorough understanding of both HIV and the specific malignancy. The most common tumors that occur in AIDS, AIDS-related Kaposi's sarcoma (KS) and AIDS-related non-Hodgkin's lymphoma (ARL), provide models that illustrate the various issues and highlight the available clinical science findings on which to base a treatment plan for individuals with cancer and HIV/AIDS.

A first step toward developing an appropriate treatment plan is to assess the status of underlying HIV infection and the nature of the tumor. A patient with advanced HIV disease, multidrug-resistant virus, and a tumor that does not respond well to anti-neoplastic therapy clearly presents a separate set of challenges than a patient with well-preserved immune function whose tumor can be easily treated with limited oncologic intervention. Also, a patient with a life-threatening tumor that has some potential to be cured is very different from a patient whose tumor requires long-term palliation. Available clinical data from experiences in KS and ARL are useful for helping consider reasonable approaches, but strict conformity to any given approach is unlikely to be best for all patients. Thus, in the absence of evidence-based practice guidelines, it may be useful to examine the various approaches and to consider the assumptions and data that have been used to support the different approaches. In this way, difficult decisions may at least be made with an understanding of what is known and the relevant biologic principles. Even so, there may be many patients for whom it is hard to identify an optimal approach.

Since the advent of highly active antiretroviral therapy (HAART) for HIV infection, the clinical outcomes for persons living with AIDS have improved substantially, and this includes those affected by neoplastic disease. Drawing on this observation, it has generally been thought that HAART should be used as part of the treatment for all patients with AIDS-related malignancies. However, whether this is correct or not is unclear; in fact, the treatment guidelines for HIV disease provide room for individualiz-

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ing therapy based on consideration of these complex issues. The Department of Health and Human Services guidelines for treatment of HIV infection[1] recommend that patients with symptomatic HIV infection be treated with anti-HIV therapy, but that the physician should consider clinical problems such as drug toxicity, ability to adhere to treatment regimens, and drug interactions when determining the time to initiate antiretroviral therapy. The guidelines further note that patients with advanced disease should be maintained on antiretroviral therapy unless drug toxicity, intolerance, or drug interactions are of concern. Many patients with an AIDS-related malignancy do, in fact, have problems with overlapping drug toxicity, drug interactions, and difficulty adhering to drug regimens. Thus, there is no clear answer provided as how to best apply such guidelines in the patient with an AIDS-related malignancy. Also, the guidelines do allow for interruption of antiretroviral therapy in certain situations. With this overview in mind, we will discuss concepts of antiretroviral therapy and anti-neoplastic therapy in KS and ARL as models for principles and practice in AIDS-related malignancies.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is a multicentric, angioproliferative disorder primarily affecting the skin, but also with a predilection for the lungs and gastrointestinal tract. KS can also involve other visceral organs. This disease is caused by a gammaherpesvirus called either Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8). KS is not curable, but advances in the treatment of KS have included the development of several mono-chemotherapy agents as well as advances in the treatment of HIV (for HIV-associated KS). Also, a number of novel pathogenesis-based therapies are currently in development, including those based on inhibition of angiogenesis. Clearly, many cases of KS improve substantially in patients with initiation of HAART alone. This is most likely the case if there is a significant virologic and immunologic response to HAART. Patients with greatest benefit are usually those with relatively low tumor burden who are naïve to antiretroviral therapy and KS therapy in whom HIV viral load decreases to undetectable levels and CD4 T cells increase by 150 cells/mm^3 or more above pretreatment levels.[2] In further support of the protective and therapeutic effect of HAART in KS is the marked decrease in KS incidence since the advent of HAART.[3]

The positive clinical benefit and epidemiologic observation that HAART is active in KS have a sound biologic basis. KSHV encodes for a major immunoreactive latency-associated nuclear antigen (LANA-1), analogous to the Epstein-Barr virus latency-associated nuclear antigens.[4] KSHV evades immune responses in part through its intrinsic ability to downregulate major histocompatibility complex (MHC)-1 surface molecules, an effect that may be decreased if T-helper depletion is prevented or restored with HAART.[5] Evidence exists that HIV-encoded or -induced proteins can activate KSHV and can promote KS growth.[6] KSHV viral load, response to HAART, and KS clinical course are all strongly related, suggesting that the immunologic and virologic features of HIV are important in KS.[7] Also, there is no evidence that either KS or the underlying KSHV infection is curable—rather, oncologic therapy is considered palliative and frequently must be continued for a long period of time (although some patients can later be maintained on HAART alone). These clinical and biologic observations have established HAART as part of the fundamental oncologic therapy in KS.[8] Because treatment advances for KS have included a variety of well-tolerated mono-chemotherapy drugs, combining HAART with anti-KS chemotherapy is relatively straightforward.

Clinicians should be aware that the 3 approved mono-chemotherapy agents for KS (2 liposomal anthracyclines and paclitaxel) have predictable overlapping toxicities with the various antiretroviral drugs. The liposomal anthracyclines (liposomal daunorubicin and pegylated liposomal doxorubicin) have mild myelotoxicity at the doses used in KS, and

in general can be used even with myelotoxic antiretroviral drugs such a zidovudine, when necessary. Bone-marrow stimulating agents such as filgrastim and erythropoietin are often effective in overcoming treatment-related myelotoxicity, and can be used in conjunction with HAART and chemotherapy when needed. Overlapping neurotoxicity between agents such as stavudine, didanosine, zalcitabine, and paclitaxel can at times become problematic, but in general, neurotoxicity is relatively mild in the short run and usually reversible when paclitaxel is suspended. Pharmacokinetic interactions may be somewhat unpredictable, and increases in the plasma levels of these cytotoxic drugs may occur, particularly with inhibition of cytochrome P450 enzymes from antiretroviral drugs such a ritonavir. Generally, in clinical practice this does not seem to be a major issue.[9] Moreover, because the goal of KS treatment is palliative and not curative, optimization of the antitumor and antiretroviral therapies is likely to provide for the best longer-term palliation and quality of life for affected persons. Experience has demonstrated, both anecdotally and in clinical trials work, that this approach represents a valuable advance in AIDS-related KS.[10]

AIDS-related lymphoma (ARL)

ARLs are a heterogeneous group of aggressive non-Hodgkin's lymphomas occurring overall 60 fold more frequently in HIV-infected individuals than expected, compared to the non-HIV-infected population.[11] ARL foreshortens life more than any other commonly occurring malignancy in HIV infection.[12] Some changes in the epidemiology and outcome of ARL have been documented since the advent of HAART. These changes vary among the various forms of ARL. The epidemiology for systemic ARL, however, is extraordinary for what it potentially may be teaching us. While the incidence of ARL in HIV infection has decreased overall since the advent of HAART, there has been no change within any patient grouping defined by CD4 T cell counts.[13] As has been recognized since the beginning of the AIDS epidemic, the risk of lymphoma increases with decreasing CD4 T cell counts,[11] and this has remained a constant finding since HAART.[13] Thus, the changes in the incidence of ARL since the advent of HAART can be explained by the overall increase in CD4 T cell counts in the HIV-infected population brought about by HAART.

Also a consistent finding since the beginning of the AIDS epidemic is a correlation with the histologic lymphoma subtype, prognosis, and CD4 T cells.[11,13] Patients with low CD4 T cells are more likely to develop treatment-refractory immunoblastic lymphomas expressing the anti-apoptosis protein Bcl-2, whereas patients with higher CD4 T cells are more likely to develop treatment-sensitive Burkitt's or centroblastic tumors.[14] Since HAART, there has been a relative decrease in the occurrence of the immunoblastic tumors, with the more favorable Burkitt's and centroblastic tumors representing a relatively larger proportion of lymphomas. Recent DNA microarray analysis has demonstrated that gene expression profiles predict treatment outcome. For example, the poor outcome marker Bcl-2 more likely segregates with immunoblastic tumors of post-germinal center origin and predicts poor prognosis compared to the Burkitt's and centroblastic tumors, both of which are more likely associated with germinal center histogenesis and a better prognosis.[15,16] Thus, although there has been a modest improvement in ARL survival from approximately 11 to 22 months since the advent of HAART, this effect is most likely because of a change in tumor biology resulting from immune preservation that gives rise to an environment in which lymphomas develop from a germinal center origin with greater treatment sensitivity.[13,14] The available data do not document any additional specific treatment effects of HAART plus anti-lymphoma therapy administered with curative intent in patients with systemic ARL.

Multiple studies have shown that combination anti-lymphoma therapy can be safely combined with HAART, but there are no clinical data that have demonstrated an improvement in treatment outcome achieved by combining HAART with chemotherapy. A Phase 2 study by Ratner *et al.* combined either low or standard-dose CHOP

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(cyclophosphamide, doxorubicin, vincristine, and prednisone) with stavudine, lamivudine, and indinavir.[17] Although neither designed nor powered to detect a difference, there was a trend for better outcome among those treated with standard-dose CHOP. This finding in itself was important. In NHL developing outside the setting of HIV infection, adequate doses of chemotherapy are associated with the curative potential of the regimen,[18] and the study by Ratner *et al*. was among the first to suggest that low-dose chemotherapy may not necessarily be the best treatment in all ARL cases. Pharmacokinetic studies suggested a significant decrease in cyclophosphamide clearance, but no obvious affects on the other drugs. The toxicity data should be interpreted with an awareness that there was not a control arm. Also, the study was not designed to assess the effect of HAART on lymphoma outcome. However, the study is important in showing full or standard-dose CHOP could be safely administered with HAART and that standard-dose CHOP may yield a better outcome than low-dose CHOP in this context.

A retrospective analysis of patients treated with CHOP or CHOP-like regimens in the pre-HAART era compared to those in whom the chemotherapy was combined with HAART in the post-HAART era documented considerably more cases of grade 3 or 4 neurotoxicity (17% versus 0%) and anemia (33% versus 7%) in the combined therapy group as compared to the no-HAART group.[19] Opportunistic infections were decreased in the combined therapy group (18%) compared to the no-HAART group (52%). However, this finding may have been linked to the relative CD4 T cells at lymphoma diagnosis and changes in prophylaxis practices, since the two groups were treated at substantially different periods of the AIDS epidemic.

A separate study that analyzed a subset of patients defined as long-term HAART responders compared to HAART-naïve patients and patients failing HAART reported improved lymphoma outcomes in the HAART responders.[20] The overall response rate was 52%, consistent with expected response rates to CHOP and CHOP-like regimens. Among the patients responding to HAART, the response rate to CHOP was 71%, compared to 30% in those who did not have a virologic response to HAART. The use of HAART during therapy for lymphoma has been assumed by some to account for the results. However, another interpretation is that the results are because of an uncontrolled variable (such as more advanced HIV disease, poor compliance, or hindered access to medical care) that led to both HAART failure and poor lymphoma outcome. The study does suggest that individuals who develop lymphoma when their HIV viral load is well controlled are more likely to develop treatment-sensitive tumors, and that administration of concomitant HAART with CHOP or CHOP-like chemotherapy regimens is feasible. Nonetheless, as suggested above, tumor biology is associated with immune status, and this provides a more biologically plausible explanation for the reported findings of this retrospective analysis. Such data do not address the role of concomitant HAART and chemotherapy as beneficially affecting therapy, but rather suggest that it does not substantially adversely affect the outcome.

Early results of a Phase 2 study examining HAART combined with 96-hour infusional CDE (cyclophosphamide, doxorubicin, and etoposide) plus a monoclonal antibody directed against the CD20 antigen suggest that this combination of therapy is feasible and effective. At a short follow-up time of 9 months, the median overall survival had not been reached.[21] The high complete response rate of 86% in this trial is noteworthy.[21] However, it is not clear to what extent the prior HAART, as opposed to the simultaneous use of HAART, may have contributed to these results, and this issue bears further study. In considering this question, it is worth keeping in mind that recent studies of a variety of regimens have shown improving response to ARL and that adding therapeutic agents (such as HAART) to a regimen has the possibility of increasing toxicity. In a recently completed, large, randomized study of CHOP plus HAART, given with or without ritux-

imab, the response rates on the 2 arms (50% and 58% respectively) were similar, but there was an excess of deaths from toxicity in the group randomized to also receive rituximab.[22] Even so, these response rates of 50% and 58% in this large, prospective, randomized trial are typical of what is expected with CHOP and do not demonstrate that HAART added to treatment efficacy in ARL.

Taking a somewhat different approach to this question of whether to combine HAART with therapy for ARL, our group at the National Cancer Institute has explored the use of infusional dose-adjusted EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone) chemotherapy in ARL with HAART temporarily withheld during the period of EPOCH treatment.[14] In considering whether to use HAART during the period of EPOCH therapy, we were concerned that overlapping toxicities and unpredictable pharmacokinetic interactions could lead to impaired curative potential of the EPOCH regimen. In this regard, it is important to keep in mind that unlike the case with KS, chemotherapy for ARL is administered with curative intent and that a number of studies have suggested that failure to achieve a durable complete response with the first regimen portends a poor overall prognosis. Additionally, we were concerned that HAART adherence would be challenged by potential EPOCH side effects such as nausea, vomiting, mucositis, or diarrhea, thus increasing the risk of drug-resistant HIV developing in the setting of suboptimal antiretroviral therapy adherence or absorption. Also, even with very high HIV viral loads during the 15 weeks required to administer 6 cycles of EPOCH, at most approximately 20 CD4 T cells/mm^3 would be lost secondarily to HIV,[23] whereas EPOCH would be expected to profoundly deplete the CD4 T cells whether HAART was present or not.

Thus, we designed the protocol so that antiretroviral therapy was not administered until all cycles of chemotherapy were completed. HIV viral loads increased modestly during chemotherapy, and as expected, CD4 T cells dropped substantially during treatment. Virologic response to subsequent HAART was similar to what is expected in uncomplicated HIV disease, and the time for CD4 T cell recovery to pretreatment levels was similar to that seen in non-HIV-infected individuals receiving similar chemotherapy.[24,25] In fact, the magnitude of the CD4 T cell loss during chemotherapy was clearly in excess of what would be expected from the immune-destructive effects of HIV, but entirely consistent with the effects predicted from lymphocytotoxic chemotherapy.[23,24] HAART would not be expected to prevent the lympholytic effects of chemotherapy, and if it did, would raise concern that it was also protecting against lymphosis of the malignant cells. Thus, there was no evidence that transiently withholding HAART during the period of lymphoma treatment with curative intent compromised HIV disease status or long-term HIV control. Of note, there was no control arm with simultaneous HAART.

The complete response rate of 74% (87% for those with greater than 100 CD4 T cells/mm^3) and the disease-free survival of 92% at 52 months of follow-up demonstrated that a desirable outcome in the therapy of ARL is not dependent on concomitant HAART administration during chemotherapy. Furthermore, intensive study of pathobiologic markers provided evidence that the tumor biology was related to outcome. This is important in that, as mentioned above, HAART may affect tumor biology through its effects on the immune environment at the time the lymphoma is developing, but would be irrelevant to tumor biology once the tumor has already developed.

The comments above apply to systemic ARL in which therapy is administered for curative intent. In such cases, it is reasonable to consider that the immediate threat to prolonged survival is the lymphoma and that the primary focus of initial therapy should be achieving cure of the lymphoma. For patients with primary central nervous system lymphoma, a different set of principles may apply—such patients often die of complications of AIDS and administering HAART during lymphoma therapy would seem to be a higher priority. Also, for patients

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whose lymphoma is not likely to be curable and who are receiving palliative therapy, consideration of clinical principles would indicate co-administering HAART if at all possible.

Conclusion

HAART represents a major treatment advance for HIV disease and has affected the bio-epidemiology of certain AIDS-related malignancies, most notably KS and ARL. Through biologically plausible mechanisms, HAART has decreased the incidence of KS and exerts a beneficial treatment effect in KS. HAART should be considered a fundamental component of the oncologic armamentarium in AIDS-related KS. Only in exceptional circumstances should it be omitted from the therapy of AIDS-related KS. HAART should be used either as the only component of anti-tumor therapy or in combination with additional specific anti-KS therapy depending on the extent and aggressiveness of the KS.

HAART has also affected the bio-epidemiology of ARL, though in ways that do not parallel its effect in KS. HAART has not been shown to affect the CD4 T cell count-specific incidence of ARL. However, the histologic subtypes of ARL have shifted, coincident with HAART-related immune preservation or restoration. This shift in histologic types toward more treatment-sensitive tumors is the likely explanation for the modestly improved overall survival in ARL since HAART. Unlike the case with KS, chemotherapy of ARL is undertaken with curative intent and the best chance of cure comes by optimizing the first anti-lymphoma regimen. There are no data proving that concomitant administration of HAART with lymphoma therapy leads to better treatment outcome and no prospective randomized trials specifically addressing this point. Certain regimens for ARL can be safely given with certain HAART regimens, although there are mixed data as to whether the strategy of combining HAART with chemotherapy results in additional toxicity or not. This issue is to some extent dependent on the particular drugs being used. For certain patients or patient populations, optimal treatment may consist of the combined use of HAART plus anti-lymphoma therapy. However, as has been pointed out, the continuously expanding assortment of antiretroviral drugs has created an environment that makes methodical examination of HAART and chemotherapy difficult at best.[26]

In our opinion, the current state of the literature does not provide clear guidance on what approach in systemic lymphoma is best. The appropriate trials have not been conducted, and may be difficult to design. However, in developing a therapeutic plan for a curable tumor (such as lymphoma or germ cell tumors) consideration of whether HAART is to be included should at least include an examination of the potential for increased complications created by overlapping toxicities and potential pharmacokinetic interactions.

In the individual case, the principles of oncology and antiretroviral therapy can be used to help make the decision of whether or not to include HAART during anti-neoplastic therapy. Thus, it is useful to consider the expected effects of chemotherapy on the immune system, whether HAART is likely to protect against such effects, whether HAART has any oncologic role in the specific tumor, and whether HAART may compromise the anti-tumor therapy. The biologic plausibility of any assumed benefits of HAART should be considered. If there is evidence that HAART has specific anti-tumor effects for the tumor under consideration or can provide immune-protection without compromising the oncologic therapy, it may be important to include HAART in the treatment. These considerations must be made in the context of individualizing therapy to tumor type and therapeutic goals.

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References

1. The Panel on Clinical Practices for Treatment of HIV Infection convened by the US Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. 2003. ***http://www.aidsinfo.nih.gov/guidelines/adult/AA_071403.pdf***
2. Dupont C, Vasseur E, Beauchet A, et al. *AIDS*. 2000;14(8):987-993.
3. Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. *J Natl Cancer Inst*. 2002;94(16):1204-1210.
4. Kellam P, Boshoff C, Whitby D, Matthews S, Weiss RA, Talbot SJ. *J Hum Virol*. 1997;1(1):19-29.
5. Brander C, Suscovich T, Lee Y, et al. *J Immunol*. 2000;165(4):2077-2083.
6. Pati S, Foulke JS, Jr., Barabitskaya O, et al. *J Virol*. 2003;77(10):5759-5773.
7. Boivin G, Gaudreau A, Routy JP. *AIDS*. 2000;14(13):1907-1910.
8. Yarchoan R, Little RF. Immunosuppression-related malignancies. In: DeVita Jr. VT, Hellman S, Rosenberg SA, eds. *Cancer, Principles and Practice of Oncology, 6th Edition*. Philadelphia: Lippincott Williams and Wilkins, 2001;2575-2597.
9. Little RF, Yarchoan R. Considerations in the Management of HIV Infection in Patients Undergoing Antineoplastic Chemotherapy. In: Feigal EG, Levine AM, Biggar RJ, eds. *AIDS-Related Cancers and Their Treatment*. New York-Basel: Marcel Dekker, 2000;281-330.
10. Little RF, Aleman K, Merced, et al. *10th Conference on Retroviruses and Opportunistic Infections*, February 10-14, 2003; Boston. Abstract 816.
11. Beral V, Peterman T, Berkelman R, Jaffe H. *Lancet*. 1991;337:805-809.
12. Little RF, Wilson WH. *Curr Infect Dis Rep*. 2003;5(2):176-184.
13. Besson C, Goubar A, Gabarre J, et al. *Blood*. 2001;98(8):2339-2344.
14. Little RF, Pittaluga S, Grant N, et al. *Blood*. 2003;101(12):4653-4659.
15. Rosenwald A, Wright G, Chan WC, et al. *N Engl J Med*. 2002;346(25):1937-1947.
16. Dalla-Favera R. *7th International Conference on Malignancies in AIDS and Other Immunodeficiencies*, April 28-29, 2003; Bethesda. Presentation S13.
17. Ratner L, Lee J, Tang S, et al. *J Clin Oncol*. 2001;19(8):2171-2178.
18. Kwak LW, Halpern J, Olshen RA, Horning SJ. *J Clin Oncol*. 1990;8(6):963-977.
19. Vaccher E, Spina M, di Gennaro G, et al. *Cancer*. 2001;91(1):155-163.
20. Antinori A, Cingolani A, Alba L, et al. *AIDS*. 2001;15(12):1483-1491.
21. Tirelli U, Spina M, Jaeger U, et al. *Recent Results Cancer Res*. 2002;159:149-153.
22. Kaplan L. *7th International Conference on Malignancies in AIDS and Other Immunodeficiencies*, April 28-29, 2003; Bethesda. Presentation S17.
23. Mellors JW, Rinaldo CR, Jr., Gupta P, White RM, Todd JA, Kingsley LA. *Science*. 1996;272(5265):1167-1170.
24. Mackall CL, Fleisher TA, Brown MR, et al. *Blood*. 1994;84(7):2221-2228.
25. Mackall CL, Fleisher TA, Brown MR, et al. *N Engl J Med*. 1995;332(3):143-149.
26. Scadden DT. *Blood*. 2003;101(12):4647.