PERGAMON

European Journal of Cancer 37 (2001) 1316–1319

European Journal of Cancer

www.ejconline.com

AIDS and cancer in the era of highly active antiretroviral therapy (HAART)

C.S. Rabkin *

Viral Epidemiology Branch, National Cancer Institute, Bethesda, MD 20892 USA

Received 5 February 2001; accepted 7 March 2001

Abstract

Combination therapy with protease inhibitors and nucleoside analogues dramatically suppresses plasma HIV-1 RNA and delays progression to AIDS, but the impact on HIV-associated malignancy remains to be established. Observational and time–trend data indicate that the incidence of Kaposi's sarcoma (KS) and primary brain lymphoma have decreased, but suggest that current therapies have not had a proportionate effect on systemic non-Hodgkin's lymphomas (NHL). As opportunistic infection and mortality are yielding to advances in antiretroviral therapy, lymphoma may increase in importance as a cause of AIDS-related morbidity and mortality. Further improvements in the long-term consequences of HIV infection will depend on better prevention and treatment of this serious malignant complication. © 2001 Published by Elsevier Science Ltd.

Keywords: Kaposi's sarcoma; Non-Hodgkin's lymphoma; HAART; AIDS-related malignancy; Epstein–Barr virus; Human herpesvirus-8

Combination therapies with protease inhibitors and reverse transcriptase inhibitors potently suppress plasma levels of human immunodeficiency virus type 1 (HIV-1) RNA in infected individuals [1]. While these treatments have resulted in dramatic decreases in the progression of HIV infection to AIDS and death [2], the long-term consequences of prolonged survival under such therapy are still being determined. Alteration of cancer risk is of particular concern, and HIV-associated cancers have already emerged as a leading cause of death among patients with AIDS [3].

The major AIDS-associated cancers, Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL), have differing patterns of increased risk in studies on the natural history of AIDS. NHL incidence increases markedly with the progression of HIV infection, although the association with the level of CD4-lymphopenia is somewhat less pronounced than for many other opportunistic infections [4,5]. In contrast, KS may occur early, as well as late following HIV infection. Thus, the restoration of the immune system using current antiretroviral therapy might be expected to differentially affect the risk of AIDS-related KS and NHL. Unlike the relatively uniform NHL risk, KS risk varies among demographic and geographical groups, in part reflecting the varying prevalence of HHV-8 co-infection.

1. Effect of HAART on KS

Three recent studies have reported observational data documenting a decreased risk of KS associated with HAART therapy (as defined as triple drug therapy ±protease inhibitors). The US Centers for Disease Control and Prevention (CDC) reported on HIV-associated disease incidence between 1990 and 1998 for 37 303 subjects in the Adult/Adolescent Spectrum of Disease surveillance project [6]. Receipt of three-drug antiretroviral therapy was associated with a 50% reduction in KS (95% confidence interval (CI) 20–70%). Moreover, annual KS incidence declined from 4.1 to 0.7% over the study period, for an adjusted relative risk (RR) of 0.5.

There are similar findings from a study in Europe. Among 7331 patients in the EuroSIDA cohort studied through to 1998, annual KS incidence averaged 0.7% with three-drug antiretroviral therapy versus 1.8% without [7]. This effect was in addition to any improve-

* Tel.: +1-301-496-8115; fax: +1-301-402-0817.
E-mail address: rabkinc@mail.nih.gov (C.S. Rabkin).

0959-8049/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0959-8049(01)00104-6

ment in CD4 lymphocyte count, as similar decreases were noted in the subgroups of low (<50 cells/ul), intermediate (50–200), and high (>200) CD4 counts.

The Swiss HIV Cohort Study documented a decline in KS incidence among 2410 subjects who initiated protease inhibitor-containing triple drug therapy from 2% per year preceding therapy to 0.14% thereafter (Fig. 1) [8]. Correspondingly, time trends among 6636 subjects

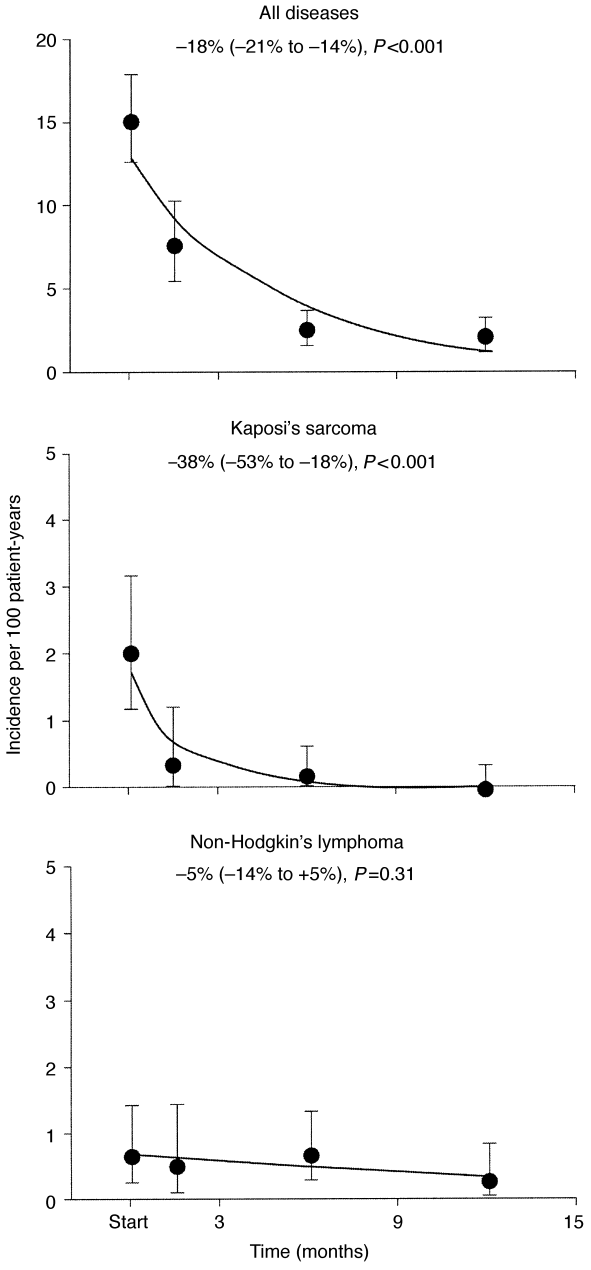

Fig. 1. Incidence per 100 person-years (with 95% confidence intervals (CI)) of KS, NHL, and all opportunistic illnesses combined in Swiss HIV Cohort Study participants before and after introduction of HAART. Incidences given at the Start represent the 6 months prior to initiation of HAART; percentages (with 95% CI) in each graph indicate the reduction in incidence per month and correspond to the slopes of the log linear regression lines (adapted with permission from Ref. [8] *JAMA* 1999, **282**, 2220–2226, © 1999 American Medical Association).

in this cohort showed a KS incidence ratio of 0.08 comparing July 1997–June 1998 with 1992–1994 [9].

Apart from these three studies with individual data on HAART exposure, numerous other studies have reported declining time trends in KS incidence following the introduction and dissemination of HAART therapy. KS incidence in 1813 HIV-positive subjects of the Multicenter AIDS Cohort Study declined from 2.6% per year in the early 1990s to 0.8% in 1996–1997 [10]. Among 1806 patients from the Royal Free Hospital, annual KS incidence declined from 3% in 1992–1993 to 1% in 1997 [11]. There were no KS cases in 1996 versus 3.5% annual incidence in 1993–1995 ($P=0.07$) in 622 subjects of the San Francisco City Clinic Cohort [12]. Among 6587 AIDS Clinical Trial Group study participants, annual incidence declined from 2.7% in the early 1990s to 0.3% in 1996–1997 (Fig. 2) [13]. Among the 387 HIV-positive subjects in the Italian Seroconversion Study, annual KS incidence declined from 3% in 1993–1995 to 1.0% in 1996–1997 [14]. In a meta-analysis of data on 47 936 subjects (which included several of the studies already cited), the KS rate ratio for 1997–1999 versus 1992–1996 was 0.3 [15]. A relative exception, however, is the 3211 patients of the Johns Hopkins AIDS Service, among whom KS incidence was 1.4% in 1994 and 1.1% in 1998 [16].

2. Effect of HAART on NHL

In contrast to the observed reductions in KS incidence, these same studies generally indicate disproportionate persistence of NHL risk. In the EuroSIDA study, NHL incidence was 0.9% annually among persons on HAART compared with 1.5% among persons with lesser therapy, but the difference was significant only among the subjects with 50 or less CD4+ T-cells

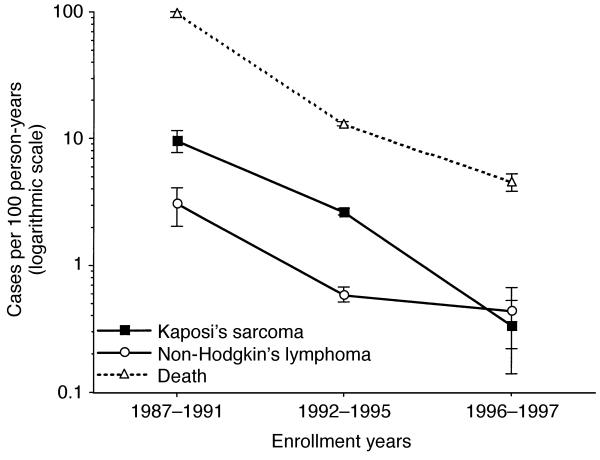

Fig. 2. Incidence per 100 person-years (with standard errors of the mean (SEM)) of Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and death in AIDS Clinical Trial Group studies, by period of accrual (reprinted from Ref. [13]).

[7]. The investigators also noted that except for primary brain lymphoma, other categories of NHL each accounted for an increasing proportion of AIDS-defining illnesses over time. Notably, in the European AIDS surveillance data, primary brain lymphoma as a fraction of all NHL decreased from 14 to 9% in 1997 [17].

In the Swiss HIV Cohort, NHL incidence was 0.7% annually before starting HAART and 0.5% thereafter; the decrease was not statistically significant (Fig. 1) [8]. The corresponding time trend showed an incidence ratio of 0.6 (95% CI 0.3–1.3), comparing the period July 1997–June 1998 with 1992–1994 [9].

The CDC Adult/Adolescent Spectrum of Disease Study has not reported specific associations with HAART therapy for NHL. However, in an analysis of incidence trends among 19 684 subjects from that study, a decline in incidence was noted for primary brain lymphoma, which was 0.5% per year for the overall period 1994–1997 versus 0.2% in 1997 [18]. In contrast, no decreases were seen over the same period for NHL categorised as immunoblastic (0.7% versus 0.7%), Burkitt's lymphoma (0.09% versus 0.04%), or other (0.14% versus 0.5%).

A number of other studies have also reported time trends in NHL. In the data through to 1997 from the Multicenter AIDS Cohort Study, NHL incidence increased progressively to a rate of 0.8% annually in 1996–1997 [10]. Incidence in the Royal Free Hospital patients varied from 1.7% per year in 1992–1993 to 0.3% in 1995 to 0.7% in 1997 [11]. NHL incidence in the San Francisco City Clinic Cohort study was 1.4% per year in 1993–1995, and rose slightly to 1.9% in 1996 [12]. In the AIDS Clinical Trial Group data, annual NHL incidence averaged 0.6% in the early 1990s and declined slightly to 0.4% in 1996–1997 (Fig. 2) [13]. Among 7840 patients followed at the Chelsea and Westminster Hospital, systemic NHL incidence averaged 0.53% per year in 1988–1995 and 0.47% in 1996–1999 [19]. NHL incidence in the Johns Hopkins AIDS Service was 0.7% in 1994 and 0.6% in 1998 [16]. An exception is the meta-analysis, in which the rate ratio for 1997–1999 versus 1992–1996 for systemic NHL (excluding Burkitt's) was 0.57, similar to the rate ratio of 0.42 for primary brain lymphoma; the rate ratio for Burkitt's lymphoma was 1.2 [15]. Overall, the available studies are consistent in indicating a decrease of primary brain lymphoma, whereas an effect on systemic lymphoma to date is unclear.

3. Effects of antiviral therapies

Foscarnet and ganciclovir are anticytomegalovirus (CMV) drugs with *in vitro* activity against human herpesvirus 8 (HHV-8), the KS-associated herpesvirus, and could theoretically impact upon the risk of KS [20]. In observational data from the Chelsea and Westminster Hospital, exposure to either of these anti-herpsesviral drugs was associated with a KS relative hazard of 0.4 (95% CI: 0.2–0.7) [21]. There were similar, but not statistically significant, declines in KS risk with both of these drugs in the Multicenter AIDS Cohort Study [22]. In the CDC Adult/Adolescent Spectrum of Disease project, KS risk was decreased following the use of foscarnet (odds ratio (OR) 0.3; 95% CI: 0.1–0.6), but not following the use of ganciclovir (OR 1.0; 95% CI: 0.8–1.3) [23]. In all three of these studies, acyclovir use was associated with a small increase, rather than decrease, in KS risk. Nevertheless, in the AIDS Clinical Trial Group studies, the incidence of KS was higher in the trials using antivirals foscarnet or ganciclovir in the early 1990s than during the later trials using intensive antiretroviral treatment [13]. Thus, prevention of KS may depend as much on treatment of the underlying cause of immunodeficiency as on specific measures against HHV-8.

Epstein–Barr virus (EBV) is suspected to play a role in causing some cases of AIDS-associated NHL, although the specific aetiological mechanisms are uncertain. Monoclonal EBV DNA may be detectable in tumour tissue, especially tumours localised to the central nervous system, which are almost always EBV-positive [24]. In addition, EBV in cerebrospinal fluid is highly predictive of central nervous system lymphoma [25]. EBV is less frequently detected in AIDS-related systemic lymphoma, with the prevalence ranging from 28% [26] to 66% [27] in various studies. EBV prevalence varies by histological subtype, and is higher in immunoblastic than in small non-cleaved cell tumours.

Long-term antiviral therapy with acyclovir, ganciclovir or foscarnet may potentially decrease the risk of NHL. Among patients at one hospital and three primary-care HIV medical practices in Toronto, the relative risk of NHL among recipients of these therapies was 0.3 compared with patients never receiving antiviral treatments [28]. There is also anecdotal evidence that antiviral therapy may be useful against HIV-associated NHL after clinical presentation. 4 (80%) of 5 patients with primary central nervous system lymphoma had a partial or complete response to treatment with zidovudine, ganciclovir and interleukin 2 [29], and 2 patients with EBV-associated high-grade NHL had prolonged remission after combined chemotherapy and acyclovir therapy [30].

4. Effect on other cancers

AIDS patients are also at a high risk of developing several other malignancies, including Hodgkin's disease (HD) and cancers of the cervix, anus, liver and lung. With the exception of HD, these other cancers have

generally not been causally associated with HIV infection and/or immunosuppression; rather, the high risk of individuals with HIV infection is due to their increased prevalence of other carcinogenic exposures, such as human papillomavirus infection, hepatitis B and C, and cigarette smoking. While there are, as yet, little data regarding HAART effects on the incidence rates, these cancers may arise in individuals who otherwise would not have survived in the absence of HAART.

Cancer is an increasingly important outcome resulting from HIV infection as opportunistic infection and mortality are yielding to improvements in therapy. The data suggest that current therapeutic strategies for HIV infection have ameliorated KS incidence, but have had a relatively minor impact on NHL risk. Accordingly, NHL may be expected to account for a greater proportion of AIDS morbidity and mortality. Further improvements in the long-term consequences of HIV infection will depend on better prevention and treatment of this serious malignant complication.

References

1. Hammer SM, Squires KE, Hughes MD, *et al*. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* 1997, **337**, 725–733.
2. Hogg RS, Heath KV, Yip B, *et al*. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* 1998, **279**, 450–454.
3. Selik RM, Rabkin CS. Cancer death rates associated with human immunodeficiency virus infection in the United States. *J Natl Cancer Inst* 1998, **90**, 1300–1302.
4. Rabkin CS, Hilgartner MW, Hedberg KW, *et al*. Incidence of lymphomas and other cancers in HIV-infected and HIV-uninfected patients with hemophilia. *JAMA* 1992, **267**, 1090–1094.
5. Munoz A, Schrager LK, Bacellar H, *et al*. Trends in the incidence of outcomes defining acquired immunodeficiency syndrome (AIDS) in the Multicenter AIDS Cohort Study: 1985–1991. *Am J Epidemiol* 1993, **137**, 423–438.
6. Jones JL, Hanson DL, Dworkin MS, Jaffe HW. Incidence and trends in Kaposi's sarcoma in the era of effective antiretroviral therapy. *J Acquir Immune Defic Syndr* 2000, **24**, 270–274.
7. Mocroft A, Katlama C, Johnson AM, *et al*. AIDS across Europe, 1994–98: the EuroSIDA study. *Lancet* 2000, **356**, 291–296.
8. Ledergerber B, Egger M, Erard V, *et al*. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999, **282**, 2220–2226.
9. Ledergerber B, Telenti A, Egger M. Risk of HIV related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study. Swiss HIV Cohort Study. *BMJ* 1999, **319**, 23–24.
10. Jacobson LP, Yamashita TE, Detels R, *et al*. Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals. Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S34–S41.
11. Mocroft A, Sabin CA, Youle M, *et al*. Changes in AIDS-defining illnesses in a London Clinic, 1987–1998. *J Acquir Immune Defic Syndr* 1999, **21**, 401–407.
12. Buchbinder SP, Holmberg SD, Scheer S, Colfax G, O'Malley P, Vittinghoff E. Combination antiretroviral therapy and incidence of AIDS-related malignancies. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S23–S26.
13. Rabkin CS, Testa MA, Huang J, Von Roenn JH. Kaposi's sarcoma and non-Hodgkin's lymphoma incidence trends in AIDS Clinical Trial Group study participants. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S31–S33.
14. Rezza G, Dorrucci M, Serraino D, *et al*. Incidence of Kaposi's sarcoma and HHV-8 seroprevalence among homosexual men with known dates of HIV seroconversion. Italian Seroconversion Study. *AIDS* 2000, **14**, 1647–1653.
15. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* 2000, **92**, 1823–1830.
16. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS* 1999, **13**, 1933–1942.
17. Franceschi S, Dal Maso L, La Vecchia C. Advances in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer* 1999, **83**, 481–485.
18. Jones JL, Hanson DL, Dworkin MS, Ward JW, Jaffe HW. Effect of antiretroviral therapy on recent trends in selected cancers among HIV-infected persons. Adult/Adolescent Spectrum of HIV Disease Project Group. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S11–S17.
19. Matthews GV, Bower M, Mandalia S, Powles T, Nelson MR, Gazzard BG. Changes in acquired immunodeficiency syndrome-related lymphoma since the introduction of highly active antiretroviral therapy. *Blood* 2000, **96**, 2730–2734.
20. Kedes DH, Ganem D. Sensitivity of Kaposi's sarcoma-associated herpesvirus replication to antiviral drugs. Implications for potential therapy. *J Clin Invest* 1997, **99**, 2082–2086.
21. Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. *AIDS* 1996, **10**, 1101–1105.
22. Glesby MJ, Hoover DR, Weng S, *et al*. Use of antiherpes drugs and the risk of Kaposi's sarcoma: data from the Multicenter AIDS Cohort Study. *J Infect Dis* 1996, **173**, 1477–1480.
23. Jones JL, Hanson DL, Chu SY, Ward JW, Jaffe HW. AIDS-associated Kaposi's sarcoma. *Science* 1995, **267**, 1078–1079.
24. MacMahon EME, Glass JD, Hayward SD, *et al*. Epstein–Barr virus in AIDS-related primary central nervous system lymphoma. *Lancet* 1991, **338**, 969–974.
25. Cinque P, Brytting M, Vago L, *et al*. Epstein–Barr virus DNA in cerebrospinal fluid from patients with AIDS-related primary lymphoma of the central nervous system. *Lancet* 1993, **342**, 398–401.
26. Ernberg I, Altiok E. The role of Epstein–Barr virus in lymphomas of HIV-carriers. *APMIS* 1989, **8**(Suppl.), 58–61.
27. Shibata D, Weiss LM, Hernandez AM, Nathwani BN, Bernstein L, Levine AM. Epstein–Barr virus-associated non-Hodgkin's lymphoma in patients infected with the human immunodeficiency virus. *Blood* 1993, **81**, 2102–2109.
28. Fong IW, Ho J, Toy C, Lo B, Fong MW. Value of long-term administration of acyclovir and similar agents for protecting against AIDS-related lymphoma: case–control and historical cohort studies. *Clin Infect Dis* 2000, **30**, 757–761.
29. Raez L, Cabral L, Cai JP, *et al*. Treatment of AIDS-related primary central nervous system lymphoma with zidovudine, ganciclovir, and interleukin 2. *AIDS Res Hum Retroviruses* 1999, **15**, 713–719.
30. Brockmeyer NH, Pohl G, Mertins L. Combination of chemotherapy and antiviral therapy for Epstein–Barr virus-associated non-Hodgkin's lymphoma of high grade malignancy in cases of HIV infection. *Eur J Med Res* 1997, **2**, 133–135.