Tumor markers and treatments for Kaposi sarcoma.

Anderson, L., & Goedert, J. J. (2007). Tumor markers and treatments for Kaposi sarcoma. *AIDS (London, England)*, 21(12)(12), 1637-1639. <https://doi.org/10.1097/QAD.0b013e32826fb721>

Published in:
AIDS (London, England)

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Tumor markers and treatments for Kaposi sarcoma

Lesley A. Anderson^{a,b} and James J. Goedert^a

AIDS 2007, **21**:1637–1639

Keywords: Africa, antiviral therapy, cancer chemotherapy, HIV/AIDS, human herpesvirus 8, Kaposi sarcoma, transplantation, virus load

Kaposi sarcoma (KS), in addition to being the most common malignancy among people with AIDS in the USA. [1], has become the most common malignancy overall in entire countries of sub-Saharan Africa [2,3]. AIDS KS prognosis has greatly improved with highly active antiretroviral therapy (HAART) [4], but this tumor is still a major cause of disfigurement, other morbidities, and mortality [4,5].

Shortly after the discovery of human herpesvirus 8 (HHV-8, also known as Kaposi sarcoma-associated herpes virus) [6], which is the primary cause of KS, Whitby *et al.* reported that 52% of AIDS KS patients had HHV-8 DNA detectable in their peripheral blood mononuclear cells (cellular viremia) [7]. Moreover, they showed that HHV-8 cellular viremia was highly predictive of incident KS in patients with untreated HIV infection [7]. During the ensuing 12 years, HHV-8 cellular viremia was shown to be relatively common in non-AIDS KS patients, including those with classical (Mediterranean), endemic (African), and transplant (iatrogenic) KS [8–11]. However, the level of HHV-8 viremia (viral load) is very low and frequently undetectable even in AIDS KS patients [7,12–16]. Thus, cellular viremia is not effective for prediction of KS incidence in a clinical setting [8,17]. In contrast, HHV-8 cellular viremia or viral load may be useful for prediction of KS progression.

In the current issue, Laney *et al.* report the results of a prospective, observational study of 47 AIDS KS patients in Atlanta [18]. Corroborating a study of patients with transplant KS [11], three rather small studies [10,12,19], and their previous report [20], Laney *et al.* found that

HHV-8 cellular viremia and higher viral load were associated with KS disease progression [18]. They propose that monitoring HHV-8 cellular viremia and viral load may help to predict disease progression and potentially prompt treatment with antiherpes medications [18].

Ganciclovir, foscarnet, and cidofovir inhibit in-vitro HHV-8 lytic replication [21–23], and the use of ganciclovir was associated with a reduced incidence of AIDS KS in a randomized clinical trial [24]. Nonetheless, as the vast majority of infected cells are not undergoing lytic replication, antiherpes medications have had little or no effect on established KS or HHV-8 cellular viremia [21,23]. Efforts to induce lytic replication or to attack the episomal (latent) HHV-8 genome are in progress [22].

In contrast to antiherpes medications, HAART is paramount and relatively effective for treatment of AIDS KS. With limited KS (i.e., without visceral involvement, extensive oral involvement, tumor ulceration, or symptomatic lymphedema), complete or partial tumor response may occur in 80% of patients in whom HAART is initiated without specific cancer chemotherapy [25], typically with a drop in HIV load and increase in CD4 cell count [26]. Continuous HAART for at least 12 months may lead to clearance of HHV-8 cellular and plasma viremia [27], and KS responses may correlate with clearance of HHV-8 cellular viremia [28,29]. Such clearance occurs, however, after the tumor responses in many cases [27], negating the use of cellular viremia as a predictive marker.

KS chemotherapy, added to HAART, is necessary and more effective against advanced AIDS KS than is

From the ^aViral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, and the ^bCancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute, Rockville, Maryland, USA. Correspondence to James J. Goedert 6120 Executive Boulevard, Room 7066, Rockville, MD 20852, USA.

E-mail: goedertj@mail.nih.gov

Received: 14 February 2007; revised: 5 March 2007; accepted: 13 March 2007.

HAART alone [25,30]. In many cases, however, KS fails to respond completely or recurs even if HIV itself appears to be well controlled. Thus, there is need to assess combinations of current medications and newer chemotherapies [31,32]. AIDS KS clinical trials in the setting of HAART are, however, hampered on several fronts, including the inherent clinical complexities of AIDS, as well as heterogeneity in the treatment regimens, the staging of KS, and the assessment of outcome [25].

Whether HHV-8 cellular load or viremia is clinically useful could be more clearly determined among patients with classical KS, as they have fewer co-morbidities and require fewer treatments than those with AIDS KS [18]. Results from the classical KS population probably would be replicated in the AIDS KS population. Classical KS is rare, but this need not be an impediment. Sensitive, specific, reproducible, and accurate tumor markers have been defined and have improved treatments for patients with an equally rare malignancy, nonseminomatous germ cell tumors of the testis [33–35]. The current and previous studies provide evidence that HHV-8 cellular viremia and viral load may predict KS progression and potentially provide a systemic measurement of the efficacy of KS treatments [10–12,18–20].

Acknowledgement

We acknowledge the support offered by the Research and Development Office, Northern Ireland who funded L.A.A. in the Cancer Prevention Fellowship Program at the National Cancer Institute.

References

- Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS* 2006; **20**:1645–1654.
- Wabinga HR, Parkin DM, Wabwire-Mangen F, Mugerwa JW. Cancer in Kampala, Uganda, in 1989–91: changes in incidence in the era of AIDS. *Int J Cancer* 1993; **54**:26–36.
- Chokunonga E, Levy LM, Bassett MT, Mauchaza BG, Thomas DB, Parkin DM. Cancer incidence in the African population of Harare, Zimbabwe: second results from the cancer registry 1993–1995. *Int J Cancer* 2000; **85**:54–59.
- Nasti G, Martellotta F, Berretta M, Mena M, Fasan M, Di Perri G, et al. Impact of highly active antiretroviral therapy on the presenting features and outcome of patients with acquired immunodeficiency syndrome-related Kaposi sarcoma. *Cancer* 2003; **98**:2440–2446.
- Nasti G, Talamini R, Antinori A, Martellotta F, Jacchetti G, Chiodo F, et al. AIDS-related Kaposi's sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart Era—the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive From Antiretrovirals. *J Clin Oncol* 2003; **21**:2876–2882.
- Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; **266**:1865–1869.
- Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma [see comments]. *Lancet* 1995; **346**:799–802.
- Brown EE, Whitby D, Vitale F, Marshall V, Mbisa G, Gamache C, et al. Virologic, hematologic and immunologic risk factors for classic Kaposi sarcoma. *Cancer* 2006; **107**:2282–2290.
- Boneschi V, Brambilla L, Berti E, Ferrucci S, Corbellino M, Parravicini C, et al. Human herpesvirus 8 DNA in the skin and blood of patients with Mediterranean Kaposi's sarcoma: clinical correlations. *Dermatology* 2001; **203**:19–23.
- Pellet C, Kerob D, Dupuy A, Carmagnat MV, Mourah S, Podgorniak MP, et al. Kaposi's sarcoma-associated herpesvirus viremia is associated with the progression of classic and endemic Kaposi's sarcoma. *J Invest Dermatol* 2006; **126**:621–627.
- Pellet C, Chevret S, Frances C, Euvrard S, Hurault M, Legendre C, et al. Prognostic value of quantitative Kaposi sarcoma-associated herpesvirus load in posttransplantation Kaposi sarcoma. *J Infect Dis* 2002; **186**:110–113.
- Quinlivan EB, Zhang C, Stewart PW, Komoltri C, Davis MG, Wehbie RS. Elevated virus loads of Kaposi's sarcoma-associated human herpesvirus 8 predict Kaposi's sarcoma disease progression, but elevated levels of human immunodeficiency virus type 1 do not. *J Infect Dis* 2002; **185**:1736–1744.
- Martro E, Cannon MJ, Dollard SC, Spira TJ, Laney AS, Ou CY, et al. Evidence for both lytic replication and tightly regulated human herpesvirus 8 latency in circulating mononuclear cells, with virus loads frequently below common thresholds of detection. *J Virol* 2004; **78**:11707–11714.
- Laney AS, Dollard SC, Jaffe HW, Offermann MK, Spira TJ, Gunthel CJ, et al. Repeated measures study of human herpesvirus 8 (HHV-8) DNA and antibodies in men seropositive for both HHV-8 and HIV. *AIDS* 2004; **18**:1819–1826.
- Little RF, Merced-Galindez F, Staskus K, Whitby D, Aoki Y, Humphrey R, et al. A pilot study of cidofovir in patients with Kaposi sarcoma. *J Infect Dis* 2003; **187**:149–153.
- Dupon M, Masquelier B, Cazorla C, Chene G, Dumon B, Ragnaud JM, et al. Acquired immunodeficiency syndrome-associated Kaposi's sarcoma and human herpesvirus 8 DNA detection in serial peripheral blood mononuclear cell samples. *Res Virol* 1997; **148**:417–425.
- Engels EA, Biggar RJ, Marshall VA, Walters MA, Gamache CJ, Whitby D, et al. Detection and quantification of Kaposi's sarcoma-associated herpesvirus to predict AIDS-associated Kaposi's sarcoma. *AIDS* 2003; **17**:1847–1851.
- Laney AS, Cannon MJ, Jaffe HW, Offermann MK, Ou CY, Radford KW, et al. Human herpesvirus 8 (HHV-8) presence and viral load are associated with changes in Kaposi's sarcoma severity among HIV-positive men. *AIDS* 2007; **21**:00–00.
- Pellet C, Chevret S, Blum L, Gauville C, Hurault M, Blanchard G, et al. Virologic and immunologic parameters that predict clinical response of AIDS-associated Kaposi's sarcoma to highly active antiretroviral therapy. *J Invest Dermatol* 2001; **117**:858–863.
- Cannon MJ, Dollard SC, Black JB, Edlin BR, Hannah C, Hogan SE, et al. Risk factors for Kaposi's sarcoma in men seropositive for both human herpesvirus 8 and human immunodeficiency virus. *AIDS* 2003; **17**:215–222.
- Casper C. Defining a role for antiviral drugs in the treatment of persons with HHV-8 infection. *Herpes* 2006; **13**:42–47.
- Klass CM, Offermann MK. Targeting human herpesvirus-8 for treatment of Kaposi's sarcoma and primary effusion lymphoma. *Curr Opin Oncol* 2005; **17**:447–455.
- Krown SE. Therapy of AIDS-associated Kaposi's sarcoma: targeting pathogenetic mechanisms. *Hematol Oncol Clin North Am* 2003; **17**:763–783.
- Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group [see comments]. *N Engl J Med* 1999; **340**:1063–1070.
- Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. *J Clin Oncol* 2004; **22**:399–402.

26. Cattelan AM, Calabro ML, Gasperini P, Aversa SM, Zanchetta M, Meneghetti F, *et al.* **Acquired immunodeficiency syndrome-related Kaposi's sarcoma regression after highly active antiretroviral therapy: biologic correlates of clinical outcome.** *J Natl Cancer Inst Monogr* 2001; (28):44–49.
27. Bourboulia D, Aldam D, Lagos D, Allen E, Williams I, Cornforth D, *et al.* **Short- and long-term effects of highly active antiretroviral therapy on Kaposi sarcoma-associated herpesvirus immune responses and viraemia.** *AIDS* 2004; **18**:485–493.
28. Gill J, Bourboulia D, Wilkinson J, Hayes P, Cope A, Marcelin AG, *et al.* **Prospective study of the effects of antiretroviral therapy on Kaposi sarcoma-associated herpesvirus infection in patients with and without Kaposi sarcoma.** *J Acquir Immune Defic Syndr* 2002; **31**:384–390.
29. Cattelan AM, Calabro ML, De Rossi A, Aversa SM, Barbierato M, Trevenzoli M, *et al.* **Long-term clinical outcome of AIDS-related Kaposi's sarcoma during highly active antiretroviral therapy.** *Int J Oncol* 2005; **27**:779–785.
30. Martin-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R, *et al.* **Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma.** *AIDS* 2004; **18**:1737–1740.
31. Vaccher E, di Gennaro G, Simonelli C, Schioppa O, Tirelli U. **Evidence of activity of Irinotecan in patients with advanced AIDS-related Kaposi's sarcoma.** *AIDS* 2005; **19**:1915–1916.
32. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, *et al.* **Sirolimus for Kaposi's sarcoma in renal-transplant recipients.** *N Engl J Med* 2005; **352**:1317–1323.
33. International Germ Cell Cancer Collaborative Group. **International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers.** *J Clin Oncol* 1997; **15**:594–603.
34. Fizazi K, Culine S, Kramar A, Amato RJ, Bouzy J, Chen I, *et al.* **Early predicted time to normalization of tumor markers predicts outcome in poor-prognosis nonseminomatous germ cell tumors.** *J Clin Oncol* 2004; **22**:3868–3876.
35. Vaena DA, Abonour R, Einhorn LH. **Long-term survival after high-dose salvage chemotherapy for germ cell malignancies with adverse prognostic variables.** *J Clin Oncol* 2003; **21**:4100–4104.