

Letter to the Editor

Efficacy of paclitaxel in the treatment of Kaposi sarcoma

Dear Editor,

The Kaposi sarcoma (KS) may be considered a model of both malignancy and chronic inflammation. The development depends upon infection with Kaposi's sarcoma herpesvirus/human herpesvirus-8 (KSHV/HHV8) a gamma-herpesvirus from the Rhadinovirus genus strongly associated with all subtypes of KS (Classical, Endemic, post organ transplant or HIV/AIDS related), multicentric Castlemann's disease and a rare form of B-cell lymphoma called Primary Effusion Lymphoma or PEL. KSHV/HHV8 has two modes of replications (lytic and latent phase) that play significant roles in the pathogenesis of KS. In fact during the lytic and latent phase KSHV encodes an arsenal of gene products that induce cellular proliferation, transformation (JNK/SAPK, PLC/PKC, PL3K/Akt), cell signalling (NF- κ B), cytokine production (vCCL-1, vCCL-2, vCCL3, vGPCR, Kaposin B), immune evasion (KCP, K3, K5), antiapoptosis (Bcl-2, vFLIP, K1, Lana-1, vIRF-1, vIRF-3, K8) and angiogenesis (VEGF, IL-6, vCCLs, K1, Angiopoietin-1). However KSHV alone is insufficient to give rise to KS. The presence of admixed immune infiltrate in the lesions suggests that KS is the result of reactive hyper-proliferation induced by chronic inflammation and it is therefore, not a true neoplasm. The chronic inflammation plays a role in its pathogenesis. KSHV excites a down-regulation of the Th1-mediated responses (cellular immunity) through suppression of IFNs and MHC-1 down-regulation so that may actively hinder the innate and adaptive antiviral responses. At the same time the virus excites a hyper-activation of the Th2-mediated responses (immune system) through the secretion of pro-inflammatory cytokines, the activation of signalling molecules and chemotaxis and extravasation of Th2 lymphocytes to the site of infection¹⁻⁵. KS ranges from an indolent to an aggressive disease with significant morbidity and mortality. Typically the disease presents with disseminated and pigmented skin lesions, in size from a few millimetres to several centimetres with a characteristic appearance ranging from pink to purple or brown often associated, according to the different types, with oedema and lymph node and visceral involvement^{1,2}. In the pre-HAART era the AIDS Clinical Trials group (ACTG) devised a staging system based upon the extent of tumour (T), the status of the immune system in terms of CD4 cell count (I), and the presence of systemic illness (S). This classification identified two different risk categories: patients with skin \pm lung \pm minimal oral disease, CD4 > 150, no OI/b-symptoms and PS > 70 were scored as a good risk (T0I0S0), and those with oedema or ulcerations or extensive oral KS and visceral involvement, CD4 < 150, OI and/or B-symptoms and PS < 70 as poor risk (T1I1S1). In 2003, Nasti et al⁶ assessed new potential prognostic factors and validated the ACTG staging system in the HAART era. They showed that while tumour extension and systemic disease maintained their correlation with survival, CD4 cell count above or below 100 as predictive of survival was excluded. The analysis of interaction between tumour stage and systemic disease and its correlation with survival identified two major risk categories: a good-risk group (T0S0-T1S0-T0S1) and a poor-risk group (T1S1). Survival analysis of patients with pulmonary involvement indicated that within the T1 risk category pulmonary disease was associated with a significantly poorer survival rate than other T1 features. These data differ substantially from the results of the pre-HAART Krown study in which CD4 count gave independent predictive information, and tumour stage provided additional predictive information in patients with good immune system status. cART may be responsible for altering the ACTG classification prognostic value^{1,7}. Treatment decisions must be made taking into consideration the extent and the rate of tumour growth, patient's symptom, immune system conditions and concurrent complications. Local therapy is reserved only for patients with minimal cutaneous disease for cosmesis, and for non-responders to systemic therapy who have rapidly progressive disease as palliative therapy. Radiotherapy is effective and often represents the best local treatment for palliation of pain, bleeding or oedema, with response and complete remission rates of over 90% and 70%, respectively. Intralesional vinblastine, oral etoposide, 9-cis-retinoic acid gel, cryotherapy and excisional surgery may be feasible options. The overall response rates range between 35% and 50% with topic skin reac-

tions^{1,2}. In patients with limited cutaneous lesions (T0 early-stage disease and/or slowly-proliferating disease) a HAART regimen including PI may represent the first step of therapy for KS, with an overall response rate of 66%-86% and a complete remission rate of 35%. As virus replication is progressively suppressed and immune restoration begins, KS lesions typically start to decrease in size and many disappear completely within a few weeks or months⁸. Generally systemic chemotherapy is reserved for patients with widespread, symptomatic, rapidly progressive or life-threatening disease with visceral involvement or who do not respond to HAART and/or in IRIS-associated flare (HIV/AIDS related KS). Several single agent therapies have been reported to be active in all subtypes of KS (vincristine, vinblastine, vinorelbine, etoposide, teniposide, adriamycin, epirubicine, bleomycin, docetaxel and paclitaxel) with overall response rate ranges from 30 to 70% although most of them have been partial responses. Liposomal anthracyclines (pegylated liposomal doxorubicin PLD, daunorubicin citrate liposome DNX) are now considered first line therapy in the treatment of patients with advanced KS. Literature data have shown that liposomal anthracyclines had an activity superior to combinations ABV or BV with 76%-82% overall response rate and 26-40% complete remission rate and are associated with less gastrointestinal and neurologic side effects but grade 3-4 myelosuppression compared with BV or ABV. Paclitaxel, a cytotoxic agent which exerts its antitumor activity by polymerizing microtubules and inhibiting of the antiapoptotic effect of Bcl-2, is generally reserved for patients with recurrent or refractory AIDS-related KS after first-line chemotherapy. The intravenous paclitaxel (100 mg/m² given every 2 weeks as a 3 hour infusion) is associated with a response rate of 59% and a duration of sustained response of 10 months, compared to a significant myelosuppression, peripheral neuropathy, renal dysfunction and the inconvenience of a 3-hour infusion^{7,9}. Dose reductions may be required when these drugs are co-administered with PIs or NNRTI, as they are all metabolized by cytochrome P450. Paclitaxel has been associated with a higher incidence of grade 3-4 hematologic toxicity, alopecia and sensory neuropathy. Immunosuppression and infections are the major problem in patients treated with cytotoxic chemotherapy. The use of granulocyte colony-stimulating factor (G-CSF) subcutaneously at the dose of 5 mcg/kg daily is standard practice¹. On the basis of the literature data demonstrating the efficacy of taxanes in the treatment of Kaposi's sarcoma epidemic Ercolak et al¹⁰ aimed to compare efficacy and side effects of paclitaxel compared to free paclitaxel regimens in the treatment of classic KS in a small group of patients with mean age above 63 years not eligible for local therapy. They showed that only three patients receiving chemotherapy (2 treated with paclitaxel and 1 with non-paclitaxel therapy), had recurrence 12 months after the treatment in a percentage of 28.6 and 16.7 respectively in the absence of statistically significant difference between the therapeutic modality and the stage and the recurrence percentage. Also there was no difference in terms of the therapeutic efficacy between paclitaxel and paclitaxel free regimens. Otherwise the authors found significant differences in side effects between paclitaxel and paclitaxel free regimens since the patients receiving paclitaxel developed mainly peripheral neuropathy at the expense of a lower cardiac toxicity more common among regimens paclitaxel free. These results, although observed on a small sample of selected patients, leading the authors to consider paclitaxel a good alternative to anthracycline-containing regimens in patients with mean age above 63 years because not limited by cardiotoxicity although these cases required close monitoring of patients to the increased risk of neuropathy. These findings are in agreement with the data of the literature concerning the therapy of Kaposi's sarcoma AIDS related in which it is shown that paclitaxel associated with a higher incidence of grade 3-4 hematologic toxicity, alopecia and sensory neuropathy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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F. Martellotta, O. Schioppa, E. Vaccher

Department of Medical Oncology, National Cancer Institute of Aviano, Aviano (PN), Italy