Treatment of HIV-1-Associated Kaposi’s Sarcoma with Pegylated Liposomal Doxorubicin and HAART Simultaneously Induces Effective Tumor Remission and CD4+ T Cell Recovery

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Abstract

Background: The combination of highly active antiretroviral therapy (HAART) and liposomal doxorubicin is a promising approach for the treatment of progressive HIV-related Kaposi’s sarcoma (KS). Here, we determined the safety, tolerability, and efficacy of liposomal doxorubicin and HAART as a combined treatment approach for advanced KS, and assessed the impact of liposomal doxorubicin on HAART-mediated immune reconstitution and viral suppression.

Patients and Methods: In an uncontrolled observational trial, KS treatment responses were assessed in 54 HIV-1-infected patients with advanced KS according to ACTG criteria. Immunological and virological treatment responses were compared to 54 non-KS-affected HIV-1 patients who were individually matched to the study participants according to sex, age (± 5 years), CD4+ T cell count (± 25%), HIV RNA load (± 25%) and previous antiretroviral therapy exposure.

Results: In 81.5% of the study patients, complete or partial responses were observed within a median of 8 weeks. Treatment-related side effects were predominantly confined to leukopenia (44.4% of patients) and mild-to-moderate liver enzyme elevation (22.3% of patients). Relative CD4+ T cell counts increased to a similar degree both in study patients and matched pairs (7% vs 6%, respectively), yet, absolute CD4+ T cell counts augmented considerably stronger in chemotherapy-naïve matched pairs than in the study patients.

Conclusion: The simultaneous administration of HAART and liposomal doxorubicin is a safe and effective treatment approach for advanced KS and HAART-mediated recovery of relative CD4+ T cell counts does not seem to be impaired by concomitant treatment with liposomal doxorubicin.

Introduction

Kaposi’s sarcoma (KS) is the most prevalent malignancy in patients infected with the human immunodeficiency virus-1 (HIV-1). It primarily affects the skin and mucous membranes, but may also involve the lungs, lymph nodes, and the alimentary tract.

Although KS may affect HIV-1 patients with virtually any degree of cellular immune deficiency, KS is strongly regarded as an opportunistic neoplasm that becomes increasingly frequent once the cellular immune system deteriorates. The striking impact of HIV-1-mediated cellular immune suppression on KS disease emergence has been highlighted by the sharp decline in HIV-1 patients with KS following the widespread introduction of highly active antiretroviral therapy (HAART) [1, 2]. In addition to its preventive effect on KS emergence, the administration of HAART has an apparent therapeutical benefit for KS patients and can result in complete disappearance of KS lesions, obviating the need for any additional treatment intervention [3–7]. Thus, potent antiretroviral therapy is considered an obligatory treatment strategy for HIV-1-associated KS that should be offered to any patient affected.

In the subset of HIV-1 patients with severely advanced, recurrent or persistent KS despite HAART, current strategies for the treatment will continue to rely at least temporarily on the use of cytotoxic chemotherapy. Among the many chemotherapeutical agents with pharmacological...
activity against HIV-1-associated KS, the liposomal formulation of pegylated anthracyclins, such as doxorubicin or daunorubicin, has emerged as a first-choice treatment option [8, 9]. The liposomal encapsulation of this drug seems to maximize its delivery to KS cells while reducing certain anthracyclin-specific toxicities, such as cardiac dysfunction or hair loss. Furthermore, this compound is largely resistant to metabolism by the reticulo-endothelial system, resulting in an advantageous pharmacokinetic profile with a prolonged circulation time [10]. Still, in the pre-HAART era, KS treatment responses to liposomal doxorubicin were often unsatisfactory, with a high proportion of patients having incomplete and/or short-lasting treatment responses [8, 9].

The integration of antiviral and antineoplastic treatment strategies simultaneously targeting malignant KS cells and the underlying HIV-1 infection is a promising, yet challenging approach for the management of KS in individuals with widespread and rapidly progressive disease [11]. Notably, the concurrent administration of antiretroviral drugs and chemotherapeutical agents in HIV-1 patients is faced with a variety of practical and theoretical concerns, particularly in terms of overlapping drug toxicities as well as drug-drug interactions. Strikingly, chemotherapy-associated neutropenia might expose HIV-1 patients to a higher susceptibility to opportunistic infections, while potentially delaying CD4+ T cell recovery and cellular immune reconstitution. Here, we determined the safety, tolerability, and efficacy of HAART and liposomal doxorubicin as a combined treatment approach for HIV-1-associated KS.

Patients and Methods
Study Design
This was an uncontrolled, observational trial. All patients agreed to the storage of personal and treatment-related data for the purpose of scientific analysis. The study conformed to the Declaration of Helsinki and was conducted according to the guidelines of the ethics committee and the institutional review board of the University of Bonn.

Study Participants
A total of 54 patients with a confirmed HIV-1 infection and a proven diagnosis of KS were sequentially included into this study at five different treatment centers from 1997–2002. All of these individuals received HAART, the composition of which varied individually according to the choice of the treating physician. Patients with all stages of KS were eligible for study participation; the decision to start treatment with liposomal doxorubicin relied on the treating physician’s judgment, taking into account the dissemination and severity of KS lesions, the patient’s immunological and virological status as well as the likelihood to respond to alternative treatment options.

Patients were not considered eligible for this study if they met any of the following criteria: bone marrow depression (defined as an absolute neutrophil count of < 2,000 cells/µl, thrombocytes < 50,000 cells/µl, hemoglobin < 10 mg/dl), renal or hepatic organ damage (defined as a serum creatinine > 1.5 mg/dl, serum bilirubin > 2 mg/dl and AST/ALT levels exceeding the references values more than 2-fold), evidence of an active opportunistic infection or any other acute illness as determined by vital signs, physical examination and laboratory assessment, a Karnofsky performance index < 50%, preceding cytotoxic chemotherapy or interferon-α treatment within 4 months before study initiation.

Prior to treatment commencement, patients’ complete medical histories were taken, including their regular medication, previous AIDS-defining events and earlier treatment attempts for KS. At baseline, standard hematological and serological parameters were determined in addition to the relative and absolute CD4+ T cell count and the HIV-1 RNA load. A regular 12-lead electrocardiogram (ECG) was performed in patients to rule out cardiac abnormalities. All patients underwent a complete physical examination to evaluate the number of cutaneous and mucocutaneous KS lesions and to characterize their nodularity and color. Endoscopic investigation of the bronchial or alimentary tract and/or computed tomography were performed when visceral KS involvement was clinically suspected. The stage of KS was determined according to the AIDS Clinical Trial Group (ACTG) Oncology Committee staging system [12], classifying patients with regard to tumor burden (T), immunological status (I) and the presence or absence of systemic disease (S).

Treatment and Regimen
Study participants received an intravenous infusion of pegylated liposomal doxorubicin (Caelyx, Essex Pharma, Munich, Germany) at a dosage of 20 mg/m² every 2 weeks. Dosage variations were at the local investigator’s discretion, considering the treatment tolerability as well as the patient’s treatment response. All patients received at least six cycles of chemotherapy, with the option to continue treatment if deemed necessary or beneficial by the treating physician. Every patient simultaneously took HAART with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either 1–2 protease inhibitors (PIs) or 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) or abacavir. Antiretroviral treatment was not modified on the day of chemotherapy administration.

Study Assessment
Standard hematological and serological parameters were determined prior to every chemotherapy cycle. Abnormal laboratory values as well as any side effect possibly related to the study medication were recorded and classified according to WHO criteria.

Patients’ CD4+ T cell counts as well as their HIV-1 RNA were measured at baseline, at the end of chemotherapeutical treatment and at least every 3 months in between. The proportion of patients with controlled viremia (< 400 copies/ml) was determined at the beginning and at the end of chemotherapy. The response to KS treatment was investigated at every chemotherapy cycle by physical examination. In patients with visceral organ involvement, computed tomography or endoscopic examination was conducted at regular intervals. Treatment response evaluation followed the ACTG criteria as described previously [12]. Briefly, complete response was defined as the absence of any detectable residual disease persisting for at least 4 weeks, including tumor-associated edema. Partial response was defined as the absence of new mucocutaneous lesions, new visceral sites of involvement, and a 50% or greater decrease in the number or size of previously existing lesions or complete flattening of more than 50% of previously existing nodular lesions lasting for at least 4 weeks. Progressive disease was defined as a 25% or more increase in the size of previously existing lesions and/or the number of new lesions. Stable