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REVIEW

Safety and efficacy of pegylated liposomal doxorubicin in HIV-associated Kaposi's sarcoma

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Abstract: Kaposi's sarcoma is a vascular tumor linked to the presence of Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8) and the incidence of which has increased considerably the world over after the onset of the human immunodeficiency virus (HIV) pandemic. Antiretroviral therapy combined with cytotoxic agents has been established as the treatment of choice in the past 10 years. Among chemotherapeutic agents, pegylated liposomal doxorubicin has become the preferred one for patients with HIV-associated Kaposi's sarcoma in Western countries. The drug in this formulation localizes better to the tumor and has higher efficacy. Skin toxicity, mucositis, and leukopenia/neutropenia are the main side effects. Hepatotoxicity and mild cardiotoxicity are observed less frequently. Pegylated liposomal doxorubicin impacts favorably on quality of life. Although cost effective in Western countries, the drug is less so in developing countries.

Keywords: pegylated liposomal doxorubicin, Kaposi's sarcoma, HIV infection

Pegylated liposomal doxorubicin is the treatment of choice for serious cases of Kaposi's sarcoma in human immunodeficiency virus (HIV)-infected patients. Before reviewing its properties, results of clinical trials, indications, and side effects, we will review briefly the main features of Kaposi's sarcoma in people with HIV-1 infection.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is linked to the Kaposi's sarcoma-associated herpesvirus (KSHV),[1] also known as human herpesvirus-8 (HHV-8) and identified for the first time in 1994 from KS tissue samples.[2] The virus is most closely homologous to the gamma-herpesvirus family,[3] and has also been identified in samples from patients with primary effusion lymphoma and HIV-associated multicentric Castleman disease.[4,5]

Infection with KSHV appears to be necessary for the development of KS, but only a small proportion of KSHV-infected people ever develop the tumor. Although the risk of KS appearance increases significantly with declining immune function, as measured by CD4 T cell counts, the tumor can appear at any stage of HIV infection.[6,7]

As a result of the HIV epidemic, there has been a global increase in the incidence of KS. During the 1990s, a 20-fold increase was observed in African areas with a high co-occurrence of HIV and KSHV[8,9] and the incidence has also increased in countries where KS was rare before the HIV epidemic.[9] In spite of the impact of modern antiretrovirals that have considerably reduced its incidence, KS continues to be the most common neoplasm in patients with HIV-1 infection.

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HIV-associated KS presents with cutaneous lesions. Different degrees of lymphedema of variable size may occur, particularly in the lower extremities, genitalia, and face.[10] Extracutaneous spread is a common manifestation. Although any organ can be affected, including lymph nodes, liver, pancreas, heart, testes, bone marrow, spleen, heart and pericardium,[11] KS mainly affects the oral cavity, palate, gingiva, gastrointestinal tract, larynx, and lungs.[12–14]

The clinical course of HIV-associated KS can be minimal or aggressive and even fulminant.[15] If untreated, the disease is usually progressive and only rarely and temporarily spontaneous regressions can occur.[16]

Pegylated liposomal doxorubicin

Pharmacology

Polyethylene glycol (PEG) liposomal doxorubicin is a formulation of doxorubicin in which the drug is encapsulated in PEG-coated liposomes. It differs greatly from the free drug in pharmacokinetics, toxicity profile, and therapeutic values. It consists of a liquid suspension of liposomes (vesicles with an approximate mean diameter in the range of 80–90 nm) composed of a lipid bilayer membrane made up of hydrogenated soy phosphatidylcholine and cholesterol. Doxorubicin, which is a cytotoxic antibiotic, is an anthracycline contained in the internal aqueous compartment of the liposome.[17] Each individual liposome contains 10,000–15,000 molecules.[18,19] The liposome surface is coated with a PEG polymer layer. This hydrophobic coating protects the liposome from opsonization and rapid reticuloendothelial system-mediated clearance.[20]

The antitumor activity of doxorubicin can be mainly explained through the inhibition of DNA synthesis. Doxorubicin, lodging between adjacent DNA base pairs, deforms and fragments the DNA, causing cell death.[17,21–23]

The drug also acts indirectly through the activity of free radicals, which are formed during its metabolization and can cause damage to mitochondrial, cellular, and nuclear membranes, sarcoplasmic reticulum, DNA, and various other intracellular components.[24]

The antitumor activity of doxorubicin may also be due to its ability to increase the numbers of phagocytic cells in KS lesions.[25]

The pharmacokinetic profile of PEG liposomal doxorubicin is linear over a dose range of 10 to 20 mg/m^2, while an increase in dose to 50 mg/m^2 is associated with a nonlinear profile.[26]

The AUC for doxorubicin is large and equal to 564 and 902 mg per h/L, after administration of PEG liposomal doxorubicin 20 and 50 mg/m^2, respectively.[26]

The prolonged circulation time allows PEG liposomal doxorubicin to preferentially accumulate in tumor tissue. The liposomes, once trapped in the tumor interstitial fluid, slowly release doxorubicin. Most of doxorubicin that circulates in plasma is encapsulated in liposomes, whereas very little doxorubicin circulates as free drug.

After PEG liposomal doxorubicin administration, the drug accumulates in KS tissues and its concentrations are about 10 to 20 times higher than in normal tissues.[26]

Bile is the major route of doxorubicin excretion. Doxorubicin metabolites are detected at low concentrations in urines, and are not detected or detected in low concentrations in plasma.[26]

Efficacy

Initially, two phase II studies indicated that pegylated liposomal doxorubicin was a highly potent and well-tolerated agent in acquired immunodeficiency syndrome (AIDS)-related KS when relatively low doses (20 mg/m^2) were used every three weeks (Table 1).[27,28]

Subsequently, two phase III studies compared pegylated liposomal doxorubicin to adriamycin–bleomycin–vincristine (ABV), and bleomycin–vincristine (BV), two of the most common regimens used to treat KS, and found that PEG liposomal doxorubicin was significantly more effective than the previously used standard regimens.[29,30]

Pegylated liposomal doxorubicin was also found to have antitumor activity against KS patients who experienced disease progression during ABV chemotherapy.[31]

The Caelyx/KS Spanish Study Group was a randomized, open-label, multicenter study where HIV-infected patients with KS were randomly selected to receive highly active antiretroviral therapy (HAART) plus pegylated liposomal doxorubicin from the beginning of the study (group A) or to receive HAART alone (group B).[32] The inclusion criteria were adult HIV–KS-affected patients (biopsy confirmed) with positive HIV-RNA because they were naïve, or not on HAART, or failing treatment. Patients had to have at least 10 cutaneous lesions or mucosal or visceral involvement to be included. Patients with life-threatening KS were excluded. Intravenous PEG liposomal doxorubicin was administered at doses of 20 mg/m^2 every three weeks. The total number of cycles was decided by each investigator. Patients in group B who had KS progression or did not respond to HAART alone were considered as nonresponders and allowed to receive pegylated liposomal doxorubicin. Twenty-eight patients were included in the study (13 in group A, 15 in group B). Overall five patients had visceral involvement (three with

Table 1 Summary of trials of pegylated liposomal doxorubicin in patients with HIV-related Kaposi's sarcoma. The drug was administered intravenously once during each cycle

Reference (Author, study design)	Patients no.	Dosage regimen (no. of cycles)	HAART	Response rate	Median duration of response (weeks)
27 (Simpson, open label)	16	20 mg/m^2 every 2–3 weeks (1–3)	No	68.7	14
28 (Harrison, open label)	34	20 mg/m^2 every three weeks (2–4)	No	73.5	9
29 (Northfelt, randomized, nonblind, multicenter)	133	20 mg/m^2 every two weeks (6)	No	45.9	13
30 (Stewart, randomized, nonblind, multicenter)	121	20 mg/m^2 every three weeks (6)	No	58.7	20
32 (Martın-Carbonero, randomized, open-label, multicenter)	13	20 mg/m^2 every three weeks (7–14)	Yes	76.0	Not reported
33 (Lichterfeld, uncontrolled, observational)	54	20 mg/m^2 every two weeks (10–100)	Yes	81.5	52
36 (Cooley, prospective, randomized, double-blind, multicenter)	60	20 mg/m^2 every two weeks (6)	Yes	55.0	22

Abbreviation: HAART, highly active antiretroviral therapy.

lung and two with gastric disease). Complete or partial remission in intent-to-treat analysis was 76% versus 20% for groups A and B, respectively, and in on-treatment analysis, 91% versus 23%, respectively. Ten patients in group B had to be rescued with PEG liposomal doxorubicin.[32] The only factor related to response in multivariate logistic regression analysis was the use of pegylated liposomal doxorubicin. The median number of cycles received was 11. This study showed a good response rate (76%) and tolerance of the combination of HAART plus PEG liposomal doxorubicin.[32]

The German Clinical AIDS Working Group did an uncontrolled, observational trial in 54 patients with a confirmed HIV-1 infection and a proven diagnosis of KS receiving different HAART regimens (two nucleoside reverse transcriptase inhibitors in combination with either 1–2 protease inhibitors or one nonnucleoside reverse transcriptase inhibitor or abacavir) and sequentially included into the study at five different treatment centers from 1997–2002.[33] Patients with all stages of KS were eligible for study participation, and visceral involvement was present in 29.6%. Exclusion criteria were bone marrow depression, renal or hepatic damage, active opportunistic infection, and Karnofsky performance index <50%. Pegylated liposomal doxorubicin was administered intravenously at a dosage of 20 mg/m^2 every two weeks. The patients received a median of 14 cycles of chemotherapy. Overall, 81.5% of study patients developed a response to the combined treatment, with a total of 55.5% and 26% of individuals reaching partial or complete responses, respectively.[33] After the completion of chemotherapy, 81.5% of the patients sustained their treatment responses for more than one year. The treatment outcomes of this study were superior to studies that used liposomal doxorubicin without additional antiretroviral combination therapy, where mostly unsustained treatment responses were obtained in 25%–80% of patients.[30,34,35]

In this study the patients treated with PEG liposomal doxorubicin and HAART maintained stable levels of absolute CD4+ T cell counts while increasing relative CD4+ T cell numbers, and additional opportunistic infections did not occur during the entire study period.[33] This observation was in sharp contrast with the high incidences of opportunistic infections in patients receiving liposomal doxorubicin in the pre-HAART era, when patients' HIV-1-associated susceptibility to opportunistic infections was potentiated by recurrent episodes of chemotherapy-related leucopenia.

One prospective, double-blind, multicenter (seven sites), active control study published in 2007 randomized patients with KS to six cycles of pegylated liposomal doxorubicin (20 mg/m^2, 60 patients) or liposomal daunorubicin (40 mg/m^2, 19 patients) every two weeks.[36] Clinical benefit was observed in 80% of patients receiving pegylated liposomal doxorubicin and in 63.2% of those receiving liposomal daunorubicin. Benefit was maintained for a median of 62 days in PEG liposomal doxorubicin-treated patients and for a median of 55 days in those treated with liposomal daunorubicin.[36] Tumor responses were achieved by 55% of patients receiving

PEG liposomal doxorubicin and 31.6% of those treated with liposomal daunorubicin.[36]

A recent trial evaluated 36 patients with AIDS-associated KS requiring chemotherapy who were treated for six three-week cycles of pegylated liposomal doxorubicin at usual doses (20 mg/m^2) plus interleukin-12 (IL-12; 300 ng/kg subcutaneously twice weekly), followed by 500 ng/kg subcutaneous IL-12 twice weekly for up to three years.[37] All patients also received HAART. Twenty-two patients had poor-prognosis KS (T1S1 stage).[37] Thirty of 36 patients had a major response (including nine with complete response) and responses were sustained on IL-12 maintenance therapy.[37]

Finally, one retrospective analysis of all patients who had received pegylated liposomal doxorubicin in centers belonging to the Caeylix/KS Spanish group study evaluated the long-term efficacy of the drug combined with HAART in preventing KS relapse.[38] A total of 98 HIV-infected patients with KS who had received PEG liposomal doxorubicin as part of two clinical trials[32,39] were evaluated. Of the 75 patients with complete or partial response to initial PEG liposomal doxorubicin, 61 had data included in the study from a control visit after completion of therapy. In a median follow-up of 50 months, eight patients (13%) had experienced relapse, five of whom within the first year after stopping chemotherapy.[38] Hence the overall rate of relapse among patients who responded to therapy was 13.5% per year, with most relapses occurring within the first year after therapy was discontinued.

Toxicity

Skin toxicity, in the form of palmar-plantar erythrodysesthesia (also known as acral erythema or hand-foot syndrome), and mucositis are the two major dose-limiting toxicities of pegylated liposomal doxorubicin, but are rarely observed at the doses used for KS, as they have been described in patients with other tumors treated with higher doses (50 mg/m^2 every four weeks).

PEG liposomal doxorubicin has a mild myelosuppressive effect characterized mainly by leukopenia/neutropenia. The white blood cell count nadir is usually detected 2–3 weeks after infusion. Neutropenia-related fever is very rare.

A cardiac biopsy study in 10 patients with KS treated with cumulative doses of 440–900 mg/m^2 reported a near-normal endomyocardial biopsy score with a median of 0.3 on a seven-point scale previously described by Billingham and colleagues,[40] a score 10 times lower than that for matched historical controls receiving similar cumulative doses of doxorubicin.[41]

In the Caelyx/KS Spanish Study Group, one or more adverse events were identified in 33% of the patients, the most common being anemia and neutropenia, followed by mucositis, enteritis, hepatotoxicity, and fever.[32] There were two deaths during treatment with PEG liposomal doxorubicin, unrelated to therapy or KS.[32] In the German Clinical AIDS Working Group study, although hematological adverse events (especially leucopenia) were the most frequent side effects, severe (World Health Organization stage IV) hematological adverse reactions were seen in only two individuals.[33] Hepatotoxicity and mild cardiotoxicity were the other side effects observed. Six patients died within eight months of the study completion: one died of KS, and the remaining five of causes that were not mentioned.[33]

In the study comparing pegylated liposomal doxorubicin with liposomal daunorubicin, adverse events associated with PEG liposomal doxorubicin were neutropenia (30%), nausea (28.3%), and asthenia (16.7%).[36] No change in median LVEF was observed over the course of the study.[36]

Quality of life

The effect of pegylated liposomal doxorubicin compared with doxorubicin-bleomycin-vincristine on health-related quality of life was assessed in one randomized study.[42] From baseline to the end of treatment (21 days after the last chemotherapy cycle) patients receiving PEG liposomal doxorubicin improved significantly in pain, cognitive functioning, social functioning and health distress, whereas patients receiving doxorubicin-bleomycin-vincristine deteriorated significantly in energy/fatigue.[42]

Cost-effectiveness

In two initial economic analyses comparing chemotherapy regimens for KS that considered the European and American conditions, the cost-effectiveness results (defined as average cost per responder) favored pegylated liposomal doxorubicin when compared to liposomal daunorubicin or to combination chemotherapy.[43,44]

A more recent study from Brazil confirmed that, even though PEG liposomal doxorubicin has a higher acquisition cost compared to liposomal daunorubicin, when the average cost per responder is considered pegylated liposomal doxorubicin has a better cost-effectiveness profile.[45] However, at difference with previous reports, this latter study showed that the doxorubicin-bleomycin-vincristine regimen, which is no longer considered the first choice, was the most rational treatment option in a resource-limited country like Brazil.[45] Indeed the incremental cost per additional responder of using

PEG liposomal doxorubicin instead of ABV was as high as US$20,990.[45]

Long term consequences of treatment

In the retrospective analysis conducted by Caeylix/KS Spanish group, 29 out of 98 patients (30%) died during a median follow up period of 28.7 months.[38] Eight patients died while receiving PEG liposomal doxorubicin cycles, nine died during the first year after stopping chemotherapy, twelve died 11 years after completion of therapy.[38] In nine patients the cause of death was related to the appearance of other tumors (seven lymphomas, one gastrointestinal adenocarcinoma, one tongue epidermoid cancer).[38] Death caused by progression of KS occurred in three cases. The rate of non-Hodgkin's lymphoma in this series was high (2.3% per year).[38] Overall, the mortality rate was 14.6% per year.

The observation that the number of PEG liposomal doxorubicin treatment cycles was not associated with morbidity or mortality seems to be against the idea that the drug was linked to either. It should also be noted that an increasing risk of non-Hodgkin's lymphoma among patients with KS is observed even in HIV-negative individuals,[46] and three of the cases observed in the Caelyx/KS Spanish Study Group study were primary effusion lymphoma,[38] likely linked to HHV-8 similarly to KS.

Conclusions

Treatment of KS in HIV-infected patients has been considerably improved by the use of modern antiretrovirals, which represent the cornerstones of therapy. Pegylated liposomal doxorubicin appears to be the best added treatment available for those cases with life-threatening KS or extensive disease compromising an organ function.[47] Response to therapy must be evaluated carefully and regularly to prevent excessive dosages of chemotherapy and long term negative consequences.

Disclosures

The authors report no conflicts of interest in this work.

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