

# Liposomal Doxorubicin in the Treatment of Advanced AIDS-Related Kaposi Sarcoma

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**Summary:** Neither single-agent therapy nor any combination treatment has been satisfactory enough to be regarded as standard in systemic advanced Kaposi sarcoma. In an attempt to achieve high efficacy in combination with low toxicity, we used a new liposomal formulation of doxorubicin. Pharmacologic data had established a long plasma half-life, an increased accumulation in tumor tissue, and a decrease in uptake by tissues such as liver, spleen, and bone marrow. In a phase I/II open-label, dose-escalating trial 40 male AIDS patients with advanced Kaposi sarcoma were enrolled to receive intravenous "stealth" liposomal doxorubicin biweekly at doses of 10 mg/m<sup>2</sup> (n = 10), 20 mg/m<sup>2</sup> (n = 27), and 40 mg/m<sup>2</sup> (n = 3). The median CD4 count at baseline was 25/μL. After six cycles (12 weeks), 39 patients were evaluable. Three patients (7.5%) showed a complete response, which was histologically confirmed. A partial response was documented in 33 patients (85%). Stable disease was observed in three patients (7.5%). During a median treatment duration of 25 weeks, four patients developed stomatitis (10%), and four patients (10%) experienced alopecia. The most frequent hematologic toxicity was neutropenia. Grade 4 neutropenia was seen in 42.5%, and grade 3 toxicity was seen in 30%. Toxicity was dose-dependent and more frequent in the 40 mg/m<sup>2</sup> stratum. During a median observation period of 25 weeks, opportunistic infections occurred in 57.5% of the patient population. We conclude that liposomal doxorubicin at dose levels of 10 and 20 mg/m<sup>2</sup> is safe and effective for treatment of advanced Kaposi sarcoma in AIDS. A controlled trial comparing liposomal doxorubicin to conventional combination therapy is underway. **Key Words:** HIV—AIDS—Kaposi sarcoma—Doxorubicin—Liposomes—Visceral Kaposi sarcoma.

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Epidemic Kaposi sarcoma (KS) is one of the most frequent opportunistic manifestations of the acquired immunodeficiency syndrome (AIDS). As many as 18% of HIV-infected homosexual men present with KS (1,2) as an index diagnosis of

AIDS. For patients with AIDS-KS, their clinical course, complications, and survival depend on the extent of a preexisting immunodeficiency. Gastrointestinal and pulmonary KS are potentially life-threatening. Possible complications are bleeding, ileus, and respiratory failure. Edema of the face or limbs is a complication of more severe categories of KS. At least eight different antitumor chemotherapeutic agents have been used for systemic intervention when chemotherapy was indicated (3).

Vinca alkaloids, doxorubicin, and bleomycin have been administered in several trials, either as a single agent or in different combinations (3–8). Nei-

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ther single-agent therapy nor any combination treatment has been satisfactory enough to be regarded as standard in systemic advanced KS. Although combinations such as doxorubicin, bleomycin, and vincristine lead to comparably high response rates, they also result in considerable toxicity and complication rates (7). Nineteen of 31 patients developed opportunistic infection following this kind of therapy, as reported by Gelmann et al. (9). On the other hand, only 10% of patients on doxorubicin monotherapy (15 mg/m<sup>2</sup> weekly) showed even a partial response and no complete remission could be achieved with this course (10).

In an attempt to achieve high efficacy in combination with low toxicity, we used a new liposomal formulation of doxorubicin in an open, dose-escalating trial. Long-circulating "stealth" liposomes are composed of hydrogenated soy phosphatidylcholine/cholesterol/polyethyleneglycol/distearol-phosphatidylethanolamine (11). One report of an animal model showed that the prolonged circulation time of "stealth" liposomal doxorubicin leads to superior therapeutic effectiveness (11). Pharmacologic data have shown a long plasma half-life, an increased accumulation of the drug in tumor tissue, and a decrease in uptake by tissues such as liver, spleen, and bone marrow (11-13). Our objective was to evaluate whether the efficacy and toxicity of this kind of liposomal doxorubicin warrant further randomized trials comparing it to the usual combination regimens.

## SUBJECTS AND METHODS

### Study Population

AIDS patients with biopsy-proven advanced KS were eligible for the trial. All patients were recruited from the outpatient clinic of the Medizinische Poliklinik, Klinikum Innenstadt, University of Munich, Germany.

The criteria for eligibility included KS in a severe stage presenting either as visceral KS or progressive disseminated cutaneous disease with edema of face or limbs or with oral lesions. Further inclusion criteria were age  $\geq$  18 years, Karnofsky status  $>$  50%, white blood cell count  $>$  2,000/ $\mu$ L, hemoglobin  $>$  10 g/dl, and platelets of  $>$  50,000/ $\mu$ L. Only patients with a positive HIV antibody status (ELISA and Western blot) were eligible.

Exclusion criteria were acute opportunistic infections or non-Hodgkin's lymphoma, systemic chemotherapy or radiation of KS within 4 weeks prior to entry into the trial, and major psychiatric illness. No subjects with cardiac failure were permitted to participate.

The patients gave written informed consent. The concomitant use of nucleosides with anti-HIV activity was not prohibited, nor was medication for prophylaxis of *Pneumocystis carinii* pneumonia and secondary prophylaxis of oral candidiasis.

### Evaluation and Classification of Participants

The baseline evaluation consisted of a medical history and a physical examination. All visible KS lesions were evaluated for surface area in mm<sup>2</sup> and nodularity. Additional sonographic measurements of tumor volume in a subset of seven patients in the 20-mg stratum were performed according to a method reported previously (14-16).

The following laboratory evaluations were performed: White blood cell count, including a differential count, platelets, hemoglobin, creatinine, blood urea nitrogen, bilirubin, alkaline phosphatase, transaminases, sodium, potassium, calcium, serum albumin and electrophoresis, erythrocyte sedimentation rate, and immunocytology (T cells, B cells, CD4, CD8). Each patient had an electrocardiogram (12 lead), an echocardiogram, a chest roentgenogram, and an abdominal sonography. In patients with symptoms or signs suggestive of gastrointestinal KS, additional endoscopy was performed. Bronchoscopic evaluation was done in patients where pulmonary involvement was suspected by chest roentgenogram or pulmonary computed tomography.

During the course of therapy, the patients were evaluated weekly. The weekly reevaluations consisted of a history and a blood count and, if clinically indicated, further diagnostic procedures were implemented. Biweekly, KS was assessed as stated for the evaluation at baseline. Patients reaching a cumulative dose of 300 mg/m<sup>2</sup> of liposomal doxorubicin were reevaluated by electrocardiogram and echocardiogram.

Classification of HIV disease was carried out according to the definitions of the Centers for Disease Control. KS stages were diagnosed as proposed by the AIDS Clinical Trials Group (ACTG) using the Tumor-Immune system-Systemic illness system (TIS) (17).

At baseline, five target lesions that were representative in terms of size, distribution, and nodularity were selected, documented, and measured. Response criteria were applied as recommended by the ACTG (17). A complete response (CR) was defined as the absence of any detectable residual disease, including tumor-associated edema. In case of remaining macular lesions, a biopsy documenting histological absence of malignant cells was required. The response was only rated complete if it lasted for at least 4 weeks.

A partial response (PR) was defined as either  $\geq$  50% decrease in the sum of the areas of all previously existing lesions (surrogate: target lesions) lasting for  $\geq$  4 weeks or  $\geq$  75% decrease in the nodularity of all previously existing lesions. The rating of PR was only permitted if no new skin or oral lesions appeared and if KS-related edema did not worsen.

Stable disease (SD) was defined as any response not meeting the criteria for CR, PR, or progressive disease.

Progressive disease was defined as any occurrence of new lesions, an increase of  $>$  25% in the size of previously existing lesions, or the increase of edema or effusions.

Patients were considered eligible for the evaluation of antitumor response after at least two cycles of therapy (cycle = 2-week period from dosing to physical examination and laboratory reexamination at day 14).

### Treatment Schedule

Liposomal encapsulated doxorubicin was administered biweekly intravenously at doses of 10 mg/m<sup>2</sup> (n = 10), 20 mg/m<sup>2</sup> (n = 27), and 40 mg/m<sup>2</sup> (n = 3). In case of grade 3 or 4 toxicity,

therapy was interrupted until abnormal values or signs returned to at least grade 2 toxicity. In case of grade 3 or 4 neutropenia, the administration of G-CSF was allowed. Patients in the 40-mg/m<sup>2</sup> stratum were scheduled to receive 20 mg/m<sup>2</sup> if a severe treatment-related toxicity occurred. Enrollment began in November 1991. The cutoff date for analysis was December 31, 1992. After completion of the first six cycles, all patients were eligible to continue the treatment in order to prevent relapse.

Liposomal doxorubicin was supplied by Liposome Technology, Menlo Park, CA, U.S.A.

## RESULTS

### Baseline Staging of HIV Infection and KS

The patient population consisted of men with a mean age of 39.3 ± 8.7 years. Thirty-nine patients were Caucasian; one was Hispanic. At baseline, 23 patients (57%) were classified CDC IV C1/D due to a history of an AIDS-defining opportunistic infection. Ten patients (25%) had AIDS-related complex and fulfilled the criteria for classification as CDC IV C2/D. Five patients (12.5%) were classified as CDC IV A/D, and two patients (5%) had CDC IV D ("only" KS).

The classification of KS according to TIS stages (17) is shown in Table 1. Poor risk evaluation (T<sub>1</sub>) was present in 28 patients (70%), and a CD4 count <200/μL at baseline was noted in 38 patients (95%). The median baseline CD4 count was 25/μL.

Oral and gastrointestinal KS was present in 29 (72.5%) and nine (22.5%) patients, respectively. Four patients had proven pulmonary KS (Table 2).

### Efficacy

Thirty-nine patients were eligible for evaluation of the efficacy of the treatment. One patient did not receive more than one cycle of therapy; he was hospitalized for a severe MAI infection that was not

TABLE 1. TIS staging of KS in 40 patients receiving liposomal doxorubicin

TIS stage	Number of patients	%
T <sub>1</sub> I <sub>1</sub> S <sub>1</sub>	25	62.5
T <sub>0</sub> I <sub>1</sub> S <sub>1</sub>	12	30.0
T <sub>1</sub> I <sub>0</sub> S <sub>1</sub>	2	5
T <sub>1</sub> I <sub>1</sub> S <sub>0</sub>	1	2.5

T<sub>0</sub> = good risk (confined to skin and/or lymph nodes and/or minimal oral KS); T<sub>1</sub> = poor risk (tumor-associated edema or ulceration); KS in other viscera; I<sub>0</sub> = CD4 lymphocytes >200/μL; I<sub>1</sub> = CD4 lymphocytes <200/μL; S<sub>0</sub> = no history of opportunistic infection or thrush; no B symptoms; S<sub>1</sub> = history of opportunistic infection or thrush; Karnofsky status <70%; other HIV-related illness.

TABLE 2. Presentation of Kaposi sarcoma at baseline; localization and visceral involvement

	Number of patients	%
Edema	16	40
head	4	10
lower extremity	11	27.5
scrotum	2	5
pectoral region	1	2.5
Oral KS	29	72.5
Gastrointestinal KS	9	22.5
Pulmonary KS	4	10

apparent at baseline. In an intention-to-treat analysis, after six cycles (12 weeks), three patients (7.5%) showed a complete response that was confirmed histologically. A partial response was documented in 33 patients (85%). Stable disease was observed in three patients (7.5%). No patient showed evidence of progressive disease (Table 3) while on continuous therapy.

In a subset of 22 lesions, the tumor volume was determined by ultrasound before and after therapy (n = 7, patients in the 20-mg/m<sup>2</sup> stratum). The average baseline volume of 536 mm<sup>3</sup> ± 690 mm<sup>3</sup> decreased by 90% to 51 mm<sup>3</sup> ± 140 mm<sup>3</sup> (p < 0.01; paired Student's *t* test).

### Toxicity

Adverse events, toxicity, and occurrence of AIDS-defining events were monitored during the study period and follow-up to generate additional information about the long-term feasibility of therapy with liposomal doxorubicin. The median observation period was 25 weeks. The median cumulative dose was 175 mg/m<sup>2</sup>. As expected, at this low dose level no clinical evidence of cardiac toxicity was observed.

TABLE 3. Response of KS in 39 evaluable patients treated with liposomal doxorubicin intravenously every 2 weeks

Response	Dose level			Total n (%)
	10 mg/m <sup>2</sup> (n)	20 mg/m <sup>2</sup> (n)	40 mg/m <sup>2</sup> (n)	
Complete response (CR)	0	3	n.a. <sup>a</sup>	3 (7.5)
Partial response (PR)	7	26	n.a. <sup>a</sup>	33 (84.6)
Stable disease (SD)	3	0	n.a. <sup>a</sup>	3 (7.5)
Progression	0	0	n.a. <sup>a</sup>	0 (0)

<sup>a</sup> Not applicable, because all patients on 40 mg/m<sup>2</sup> had to be switched to 20 mg/m<sup>2</sup> prior to evaluation.

During the whole treatment period (i.e., induction therapy and follow-up; median, 25 weeks), four patients developed stomatitis (10%) and 21 patients (52.5%) reported some degree of alopecia. Four of those 21 developed complete alopecia (Table 4). The most frequent hematologic toxicity was neutropenia. A total of 17 patients (42.5%) experienced grade 4 toxicity. Another 12 patients showed grade 3 toxicity (Table 4). A concomitant use of G-CSF resulted in postponement of only 15% (55 of 368) of scheduled treatment cycles.

#### Dose-related Toxicity and Efficacy

In the high-dose group (40 mg/m<sup>2</sup>), severe toxicity was observed in three of three patients after 6 weeks of treatment. One patient had complete alopecia; two had grade 4 neutropenia. All patients in this group had to be switched to 20 mg/m<sup>2</sup>, which was better tolerated in the subsequent course. Three patients initially allocated to the 10 mg/m<sup>2</sup>-dose group were switched to 20 mg/m<sup>2</sup> because as early as 5 weeks after interruption of chemotherapy new lesions of KS appeared. In two patients, therapy was interrupted due to intercurrent infections. In the third patient, treatment was postponed because he chose to stop therapy temporarily after an initial satisfactory result. However, 6 weeks later, liposomal doxorubicin again was effectively administered at the dose level of 20 mg/m<sup>2</sup>.

Nausea, stomatitis and constipation were the most common adverse events; none of them was severe enough to terminate chemotherapy in the 10 and 20 mg/m<sup>2</sup> groups. The most common toxicity was neutropenia. A total of 72% showed either grade 3 or 4 toxicity at some point during the observation period (Table 5).

TABLE 4. Adverse events during biweekly liposomal doxorubicin therapy (during median observation period of 25 weeks)

Response	Dose level			Total n (%)
	10 mg/m <sup>2</sup> (n)	20 mg/m <sup>2</sup> (n)	40 mg/m <sup>2</sup> (n)	
Nausea	0	1	3	4 (10)
Stomatitis	0	5	2	7 (17.5)
Alopecia (complete)	0	3	1	4 (10)
Constipation	0	3	2	5 (12.5)
Clinical evidence of cardiotoxicity <sup>a</sup>	0	0	0	0

<sup>a</sup> At mean cumulative dosage of 175 mg/m<sup>2</sup>.

#### AIDS-defining Events and Infections

AIDS-defining events observed while patients were on therapy (induction therapy and follow-up) were opportunistic infections (n = 23) and non-Hodgkin's lymphoma (NHL) (n = 1). Six patients developed ulcerating oral or genitoanal herpes. Four had a relapse or first episode of candida-esophagitis; in seven patients, MAI infection was detected; seven others developed CMV manifestations (n = 4, CMV retinitis; n = 3, other CMV localizations). One patient developed cerebral toxoplasmosis. In two patients, more than one of those infections were diagnosed.

Non-AIDS-defining events included oral thrush (nine episodes), herpes simplex (eight episodes), pyomyositis (four patients), and otitis media (one patient). Nineteen of the original 40 subjects died during the (median) observation period of 25 weeks (n = 18) or were lost to follow up (n = 1). Causes of death included MAI infection, wasting syndrome, NHL, and cerebral toxoplasmosis.

#### DISCUSSION

The results of our open, dose-escalating study clearly demonstrate a high response rate after a single-agent course of liposomal doxorubicin. The overall response rate (CR + PR) was 92.5%. Complete response is a rare event in chemotherapy of advanced KS. However, after the administration of 20 mg/m<sup>2</sup> of single-agent liposomal doxorubicin, a histologically proven CR was achieved in three patients (7.5%). Moreover, an exceptionally high percentage of patients had a partial response, and in a substantial number of patients, long-term treatment (median duration, 25 weeks) was feasible.

The results of an ACTG protocol on single-agent conventional doxorubicin have been reported for 26 patients with a comparable tumor burden and staging of HIV disease (10). Doxorubicin was applied at a weekly dose of 15 mg/m<sup>2</sup>. In the group of patients with advanced disease, no CR was achieved. There was also no partial response as judged by the same criteria employed in our study. Eighteen patients (69%) showed a "minor" response; "minor" was defined essentially as any flattening of the nodular indicator lesions. However, comparison of our data with the results of other trials depends on the comparability of response criteria. The dose levels established for the conventional therapy were higher than for liposomal doxorubicin therapy: A monthly

TABLE 5. Hematologic toxicity in patients receiving biweekly liposomal doxorubicin (during median observation period of 25 weeks)

Response	Dose level			Total n (%)
	10 mg/m <sup>2</sup> (n)	20 mg/m <sup>2</sup> (n)	40 mg/m <sup>2</sup> (n)	
Neutropenia				
grade 4 <500/ $\mu$ L	2	13	2	17 (42.5)
grade 3 500-999/ $\mu$ L	3	9	0	12 (30)
grade 2 1,000-1,499/ $\mu$ L	3	4	0	7 (17.5) <sup>a</sup>
grade 1 1,500-2,000/ $\mu$ L	2	1	0	3 (7.5) <sup>a</sup>
Thrombocytopenia				
grade 4 <25,000/ $\mu$ L	0	2	0	2 (5)
grade 3 25,000-49,999/ $\mu$ L	0	3	1	4 (10)
grade 2 50,000-74,999/ $\mu$ L	1	2	0	3 (7.5) <sup>b</sup>
grade 1 75,000-100,000/ $\mu$ L	0	1	0	(2.5) <sup>b</sup>

<sup>a</sup> Patients with baseline count >2,000/ $\mu$ L.

<sup>b</sup> Patients with baseline >100,000/ $\mu$ L.

dose of 40 mg/m<sup>2</sup> of liposomal doxorubicin (20 mg/m<sup>2</sup> biweekly) was used in our trial. This is 20 mg/m<sup>2</sup> less than the dose in the trial reported by Fischl et al. (10) (i.e., 60 mg/m<sup>2</sup> per month).

The overall responses reported in other single-agent studies were as follows: 26% with vinblastine (18), 48% with bleomycin (5), and 48% with vincristine (19). Any comparison of those trials to our results may not be valid because the study populations and response criteria are not identical.

The rationale behind combining several chemotherapeutic agents to treat AIDS-KS was that this regimen would enhance efficacy while keeping toxicity at an acceptable level. Using a combination of doxorubicin, bleomycin, and vinblastine, Gelmann et al. reported an overall response (CR + PR) of 84% (9). In another study, two different dosages of doxorubicin, vincristine, and bleomycin were tested (20). The overall response rate was 79%. In yet another series, combining bleomycin with vincristine in patients with neutropenia resulted in a 72% response rate (8). The frequency of opportunistic infections that occurred in association with these three combination regimens ranged from 61% to 89% of all treated patients (4-8, 10,18).

Liposomal doxorubicin, as shown in our results, achieved the same range of efficacy as these combination therapies. The rate of opportunistic infections was 57.5%. Whether these data indicate that single-agent liposomal doxorubicin at a dose level of 20 mg/m<sup>2</sup> is superior to combination chemotherapy for AIDS-KS patients with advanced disease has yet to be determined. We are now addressing this hypothesis in an ongoing randomized multicenter trial comparing the relative efficacy and tox-

icity of liposomal doxorubicin to the combination of bleomycin and vincristine.

In a patient population with advanced AIDS-KS and severe immunodeficiency (median baseline CD4 count, 25/ $\mu$ L), a certain number of opportunistic infections is to be expected, even if there is no chemotherapeutic intervention for KS. A concomitant antiretroviral therapy in all patients could further reduce the number of opportunistic infections. In patients with neutropenia who take a combination of liposomal doxorubicin and zidovudine, the use of zalcitabine and didanosine might contribute to an improvement of immunological function and survival.

Initial studies of the pharmacokinetics of these drugs indicated a high degree of drug delivery to KS tumors (12). The long circulation period of liposome formulations that incorporate a synthetic polyethylene glycol-derived phospholipid has a pronounced effect on liposome tissue distribution. A considerable increase in pharmacological efficacy can be expected (12). Liposomes carry polyethylen-glycol on the surface; the high vascularization of KS lesions in combination with an abnormal permeability of capillaries results in a higher proportion of the drug being deposited in tumor tissue rather than other tissues (11,21). Therefore, toxicity levels would be lower than with conventional doxorubicin. Some patients experienced adverse events like those seen with free doxorubicin. Nausea, stomatitis, and constipation were the most common of these adverse events; none of them was severe enough to require termination of chemotherapy in the 10 and 20 mg/m<sup>2</sup> groups. Alopecia and neutropenia, however, occurred in all three patients receiving 40 mg/m<sup>2</sup>, re-

sulting in dose interruption and a switch to 20 mg/m<sup>2</sup>.

The most common toxicity was neutropenia, but the concomitant use of G-CSF was not prohibited by the protocol. Thus, only 15% of all scheduled cycles had to be postponed. The availability and the use of G-CSF in this open trial may therefore have indirectly contributed to the high overall response rate. Most episodes of neutropenia, on the other hand, occurred late in the course of therapy or during the follow-up treatment. Therefore, only a minor influence on response rates would be expected.

In a mouse model testing the myelosuppressive activity of doxorubicin encapsulated in liposomes of different size and composition, it was demonstrated that delivery of doxorubicin to the bone marrow depends on the size of the liposomes (13). The use of a different formulation, resulting in smaller liposomes, could lead to a reduction in the myelosuppressive action of liposomal doxorubicin.

Overall, liposomal doxorubicin was fairly well tolerated by our patients; the only dose-limiting toxicity was neutropenia. We conclude that at dose levels of 10 and 20 mg/m<sup>2</sup>, liposomal doxorubicin is a safe and effective drug for the treatment of advanced AIDS-KS. A controlled trial comparing liposomal doxorubicin to a conventional combination of bleomycin and vincristine is underway.

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