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Activity and Safety of Pegylated Liposomal Doxorubicin as First-Line Therapy in the Treatment of Non-Visceral Classic Kaposi's Sarcoma: A Multicenter Study

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TO THE EDITOR

While several studies have been published regarding AIDS-related Kaposi's sarcoma (KS), and standard first- and second-line treatments exist for those patients (Di Lorenzo *et al.*, 2007), no such standard treatment has been established for Classic KS (CKS). Two randomized trials showed that pegylated liposomal doxorubicin (PLD) is more effective than the doxorubicin–bleomycin–vincristine combination (Northfelt *et al.*, 1998) and the bleomycin–vincristine combination (Stewart *et al.*, 1998). Although PLD has been approved for use in patients with AIDS-associated KS, only a few case reports and small retrospective studies have described the use of PLD in CKS (Gottlieb *et al.*, 1997; Kreuter *et al.*, 2005; Di Trolio *et al.*, 2006; Ezquerra *et al.*, 2006; Di Lorenzo *et al.*, 2008). We conducted an international multicenter retrospective analysis to evaluate the activity and safety of PLD in patients with CKS who had not received previous systemic chemotherapy.

Between 1998 and 2007, eight institutions treated 55 patients with CKS with PLD, as first-line chemotherapy. Median age was 70 years and 15 patients (27%) were older than 75 years (Table 1). A total of 610 cycles of PLD were administered. The schedule of every 3 weeks resulted in a mean received dose intensity of 19.2 mg m^{-2}, or 96% of the planned dose intensity. A dose reduction of 20% was made in 70 cycles (12%) because of grade 3 neutropenia, anemia, or thrombocytopenia. The median number of cycles administered was nine (range, 3–30).

Complete and major responses were observed in 16 (29%) and 23 (42%) patients, respectively, giving an overall response rate of 71%. Minor response was observed in 6 (11%), whereas stable disease and disease progression occurred in six (11%) and four (7%) patients, respectively. Median time to response was 4 months (range, 1.4–7 months) and median duration of response was 25 months (range, 1–55 months). There was a statistically significant correlation between complete response and baseline stage. In fact,

Abbreviations: CKS, Classic KS; KS, Kaposi's sarcoma; PLD, pegylated liposomal doxorubicin

Table 1. Patient characteristics

No. of patients	55
Age (years)	70 (31–88)
<75 years	40 (73%)
>75 years	15 (27%)
WHO performance status	
0	30 (55%)
1	25 (45%)
Sex	
Male	38 (69%)
Female	17 (31%)
Ethnic background	
South/Mediterranean European	27 (49%)
Eastern European	12 (22%)
North European	6 (11%)
Western European	10 (18%)
Race	
White	55 (100%)
Black	0
Cutaneous stage	
II	24 (44%)
III	20 (36%)
IV	11 (20%)
Previous therapy	
Intralesional vinblastine	13 (24%)
Radiotherapy	2 (4%)
Surgery	2 (4%)
Cryotherapy	3 (5%)
Complications	30 (55%)
Pain	20 (36%)
Edema	17 (31%)
Hemorrhage	14 (25%)
Functional impairment	9 (16%)
Ulcerations	8 (15%)
Lymphorrhea	5 (9%)
Type of pain medication administered (20 pts)	
Minor analgesics	12 (60%)
Mild narcotics	4 (20%)
Strong narcotics	4 (20%)

Data are expressed as median (range).
WHO: World Health Organization. Pain medication recorded according to WHO ladder.
Cutaneous staging system based on objective criteria (Brambilla, 2003).

54% of the complete responses were observed in stage II, whereas only 15% were in stage III, and none in stage IV ($P<0.05$). The median progression-free survival was 30 months (95% confidence interval, 4–60 months). At a median follow-up of 50 months (95% confidence interval, range 7–108 months), 43 patients were alive and 12 had died (four KS-related and eight non-KS-related deaths). Remission of pain and lymphedema were recorded in eight (40%) and nine (53%) patients after six cycles, respectively. Hemorrhage, functional impairment, ulceration, and lymphorrhea resolved in 43, 78, 63, and 40% of patients, respectively.

All 55 patients were assessable for treatment safety. In general, treatment was well tolerated and no toxic deaths occurred. The most important grade 3 toxicities included neutropenia in nine cases (16%), nausea/vomiting (5.5%), thrombocytopenia (3.6%), and hand–foot syndrome (5.5%). Grade 4 toxicity was limited to neutropenia (5.5%) requiring granulocyte-colony stimulating factor and anemia (3.6%) requiring transfusions (Table 2).

This study of 55 patients with CKS represents the largest study of PLD in CKS, as well as the largest study of any cytotoxic agent in this setting. Our overall response rate (71%) in previously untreated CKS compares favorably with that observed in a PLD study in AIDS–KS (45.9%) (Northfelt *et al.*, 1998). Two other studies investigated the role of PLD in CKS. In a retrospective study by Kreuter *et al.* (2005), PLD was compared with IFN-α as second-line therapy for CKS, and in an analysis by Di Lorenzo, PLD was administered to patients with previously treated CKS (Di Lorenzo *et al.*, 2008). Eight of 12 (67%) CKS patients treated with PLD by Kreuter achieved a complete or major response. In that trial, six patients were treated with IFN-α, with major response in 17%. The difference in response to treatment between PLD and IFN-α was significant ($P<0.05$). In the Di Lorenzo study, 20 men with previously treated CKS received PLD. Complete and partial responses were observed in two (10%) and 14 (70%) patients, respectively. Fourteen patients (70%) achieved remission of tumor-associated pain/edema after six cycles.

To our knowledge, long follow-up of patients with CKS has not been previously reported. In our study, we demonstrate that PLD can control disease for more than 2 years. We did not observe cardiac side effects. Our

Table 2. Toxicity for 55 patients (%)

Toxicity	Grades 1–2	Grade 3	Grade 4
Neutropenia	26%	16%	5.5%
Anemia	7.2%	1.8%	3.6%
Thrombocytopenia	11%	3.6%	0
Nausea/vomiting	20%	5.5%	0
Hand-foot syndrome	18%	5.5%	0
Fatigue	9%	3.6%	0
Peripheral neuropathy	13%	1.8%	0
Stomatitis	13%	3.6%	0
Liver dysfunction	5.5%	1.8%	0
Alopecia	15%	2%	0
Constipation	9%	0	0
Diarrhea	7.2%	0	0
Nephrotoxicity	3.6%	0	0

findings need to be confirmed in a prospective study, which, owing to the rarity of the disease, would require the participation of many more centers. It would be interesting to evaluate the action of PLD, comparing it with active and well-tolerated strategies such as vinblastine alone, vinblastine/bleomycin, or taxanes.

The eligibility criteria for this study included the following: histologically confirmed KS, age $\leqslant$90 years, World Health Organization performance status 0 or 1, negative HIV serology, and no immunosuppressive therapy. Patients were excluded if there was evidence of visceral involvement, previous systemic chemotherapy, uncontrolled chronic disease not related to KS, or history of previous cancer.

Patients with the following stages (Brambilla *et al.*, 2003) were eligible: stage II A (infiltrating) slow variant if tumor-related complications were present (lymphedema, hemorrhage, pain, functional impairment, ulcerations); stage II B rapid variant; stage III (florid); and stage IV (disseminated). Patients were treated with PLD ($20\,mg\,m^{-2}$) (Caelyx, Schering-Plough, Milan, Italy; Doxil, OrthoBiotech, New Jersey) every 3 weeks intravenously until disease progression or irreversible toxicity was observed.

The primary end point was objective response rate. Secondary end points were toxicity, improvement in tumor-related symptoms, time to progression, and overall survival. Complete response was the absence of detectable lesions lasting for at least 8 weeks. Major response was $\geqslant$50% decrease in the number of measurable lesions and absence of new cutaneous lesions. The sum of complete and major responses represented overall response rate. Minor response was 25–50% decrease in the number of lesions. Progressive disease was the appearance of new lesions, >25% increase in previous lesions, or worsening of tumor-associated complications. Stable disease was defined as any response that did not fulfilling the criteria described above. We also evaluated reductions in tumor-associated complications (including pain, edema, ulceration, hemorrhage, functional impairment, and lymphorrhea). Treatment-related toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria (version 3.0). Patient consent was deemed not necessary, as the authors were reviewing their own patients' charts.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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