

ORIGINAL ARTICLE

Phase II clinical trial with pegylated liposomal doxorubicin (CAELYX[®]/Doxil[®]) and quality of life evaluation (EORTC QLQ-C30) in adult patients with advanced soft tissue sarcomas

A study of the Spanish Group for Research in Sarcomas (GEIS)

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Abstract

Background: Pegylated liposomal doxorubicin (PLD), a formulation with pharmacokinetic differences with respect to doxorubicin (DXR), might benefit patients with advanced soft tissue sarcoma (STS) pretreated with DXR.

Patients and methods: Patients with measurable and progressive STS received PLD at 35 mg/m² every 3 weeks. Quality of life before and during treatment was assessed with EORTC QLQ-C30.

Results: Twenty-eight patients, 22 DXR-pretreated, were given 140 cycles (median 3, range 1–18). Activity in 27 patients (5 GIST): one complete and one partial remission (both non-GIST and without prior DXR), 12 stabilizations and 13 progressions (response rate 7.4%, 95% CI: 0–17%). Grade 3 toxicity: palmar-plantar erythrodysesthesia (19% of patients), stomatitis (4%) or cutaneous (4%). Neutropenia grade ≥ 3 was detected in 16% of patients. Median relative dose intensity was 95%. Progression-free rate at 3 and 6 months was, respectively, 48 and 22%, median progression-free survival 5.8 months and median overall survival 8.7 months. QLQ-C30 at baseline and at weeks 6–11 in 23 and 13 patients, respectively, showed good reliability and validity. Quality of life did not seem to worsen during therapy.

Conclusions: PLD did not induce objective remissions in 22 STS patients pretreated with DXR, but progression-free rate figures support the use of this agent in patients who have not progressed under a DXR-containing regimen. The toxicity observed was comparable to that of other PLD schedules.

Keywords: Pegylated liposomal doxorubicin, soft tissue sarcomas, quality of life

Introduction

For advanced soft tissue sarcomas (STS) of the adult, doxorubicin is one of the drugs which has shown a 20–30% objective activity [1], but total dose is limited by the risk of developing myocardopathy, a side effect related to DXR peak plasma concentrations as well as cumulative dose.

Liposomal technology has been applied to achieve a slower DXR liberation, in an attempt to overcome this problem. In pegylated liposomal doxorubicin (PLD), polyethylene glycol provides an outer layer that protects the liposome from uptake by the reticuloendothelial system. This facilitates the distribution of liposomes to the tissues and to the tumor bed, and DXR plasma half-life is considerably

prolonged, total body clearance being reduced 250-fold when compared to equivalent DXR doses, what may influence its antitumor efficacy [2,3]. This pharmacokinetic behavior influences the toxicity profile of PLD, so that palmar-plantar erythrodysesthesia (PPE) or mucositis are usually dose-limiting, hematological toxicity is less accentuated, and cardiotoxicity is lower [3–5]. PLD toxicity is schedule-dependent, and can be modified by reducing the dose or by increasing the dose interval [4,6,7].

In 1997 our Group planned a Phase II study with PLD in STS patients to determine whether this DXR formulation could provide some benefit to patients already exposed to chemotherapy, including DXR. Recommended doses varied from 50 to 60 mg/m² every 4–6 weeks [6–8] and, in an attempt to reduce toxicity, we selected a dose of 35 mg/m² repeated every 3 weeks, which offered a dose-intensity similar to that of previously tested schedules. Another objective of the trial was to assess the quality of life of patients during PLD therapy.

Patients and methods

Patients

Patients should have a histological STS diagnosis; advanced, measurable and unresectable progressive disease after DXR and ifosfamide; performance status ≤ 2 (WHO); adequate bone marrow (haemoglobin > 9 g/dl, granulocytes $> 1.5 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$), liver (serum bilirubin, AST and ALT values < 2 UNL) and renal (serum creatinine < 1.5 UNL) functions; left ventricular ejection fraction (LVEF) $\geq 50\%$; prior cumulative dose of doxorubicin ≤ 300 mg/m². Patients with NYHA class $\geq II$ cardiomyopathy, or radiotherapy over the only measurable lesion, were excluded. Patients progressing ≤ 6 months from any DXR-containing regimen for advanced disease, or < 12 months if adjuvant, were considered resistant to DXR. Ethics Committee of participating institutions approved the study and informed patients signed a consent form.

Treatment and evaluation criteria

The drug for this study was kindly provided by Schering-Plough España S.A. All patients received PLD (Caelyx[®], Doxil[®]) at 35 mg/m² over 1 h, every 3 weeks.

Toxicity was evaluated according to NCI Common Toxicity Criteria, version 1.0. Cycles were repeated on day 21 if granulocytes $> 1.0 \times 10^9/l$ and any other toxicity had reached grade ≤ 1 . If granulocyte nadir was $< 0.5 \times 10^9/l$, the dose was reduced by 25%. Patients with grade 1 PPE, stomatitis, esophagitis or cutaneous toxicity on day

21, who had not suffered a similar episode of grade 3–4, repeated the cycle on schedule; otherwise, cycle was delayed until complete recovery, and the dose reduced by 25% if a 2-week delay was necessary. Patients were removed from study if grade 3–4 toxicity was still present at day 35 or if > 2 dose reductions were necessary. Patients with a confirmed LVEF $< 45\%$ abandoned the study.

Patients were controlled weekly for toxicity. LVEF was measured every 6 weeks. Only cycles with weekly BCC were analyzed for hematological toxicity, and patients receiving one PLD dose were assessed for toxicity. Target lesions were evaluated every two cycles (or 6 weeks). WHO criteria for activity were applied [9] and patients continued on study until disease progression or excessive toxicity occurred. Time to progression, progression-free survival and overall survival were estimated by actuarial methods.

Authorization to utilize the quality of life questionnaire C30 (QLQ-C30), version 1.0 [10], was obtained from the EORTC Quality of Life Unit. It was to be administered to patients before treatment and every other cycle. Scoring was performed according to the EORTC QLQ-C30 Scoring Manual recommendations [11].

Statistics

Sample size was calculated according to a minimax-design [12]. For $P_0 = 10\%$ and $P_1 = 25\%$ DXR activity in first line, and α and β errors equal to 0.1, the initial sample size was 27 patients. If two or less responses were observed in the first 27 patients, the study would be considered not worth expanding.

Evaluation of QLQ-C30 results were performed as recommended [10]. The internal consistency of QLQ-C30 was assessed by Cronbach's α coefficient, with values > 0.70 considered acceptable [13]. Pearson's r was calculated to check the validity of the questionnaire, and values > 0.40 indicated substantial correlations among the different scales.

Results

Patient characteristics

From June 1998 to June 1999, 28 patients entered this study (Table I). One of the six patients with a retrospective GIST diagnosis died of tumor-related complications 2 weeks after the first cycle and was not evaluable. Another patient received only one cycle due to rapid disease progression. In total, 140 PLD cycles were delivered, (median 3, range 1–18). All patients had received one prior chemotherapy regimen (24 for advanced disease, four adjuvant) that in 23 had included DXR. Median cumulative dose of doxorubicin per patient was 200 mg/m² (range 50–300). Eleven out of 18

Table I. Patient characteristics.

<i>Number</i>	28
Male/Female	15/13
Age (median, range)	54.4 (28–74)
<i>Performance status</i>	
0	10
1	14
2	4
<i>Histological type of sarcoma</i>	
GIST	6
Leiomyosarcoma	4
Malignant fibrous histiocytoma	3
Synovial sarcoma	3
Liposarcoma	2
Neurogenic sarcoma	2
Other	8
<i>Grade of malignancy</i>	
1	2
2	10
3	16
<i>Primary site</i>	
Extremities and trunk wall	18
Gastrointestinal	5
Uterine	3
Other	2
<i>Sites of disease</i>	
Lung	19
Primary tumor	6
Liver	6
Intra-abdominal	4
Lymph node	5
Soft-tissues	2
<i>Prior chemotherapy</i>	
Doxorubicin ± ifosfamide	23
High-dose ifosfamide	3
Ifosfamide ± cis-platinum	2
Treatment-free interval (months) (median, range)	4.6 (0.83–37)

non-GIST patients were resistant and seven were potentially sensitive to DXR, with all GIST patients being resistant.

Toxicity

Maximum hematological toxicity noted was anemia of grade 3 in 4% of patients, granulocytopenia grade 3–4 in 16% and thrombocytopenia grade 2 in 4%. Toxicity on granulocytes was not cumulative and nadir occurred by day 21 (median). PPE reached grade 3 in five patients, three of whom had to abandon the study for this toxicity (Table II). PPE grade 3 was noted after a median of five cycles (range 3–8), with a cumulative incidence in cycles 3–8 of 1.4, 1.1, 4, 4.6, 5 and 6%, respectively. A patient with persistent grade 2 stomatitis in spite of two dose reductions was also removed from the study. Cutaneous toxicity was described as a psoriasiform eruption in one patient, and as a pruriginous erythema in 10, only in one reaching grade 3 concomitantly with grade 3 PPE. In this patient the lesions had a lichenoid appearance and a diagnosis

Table II. Maximum grade of toxicity observed per patient.

Grade	0	1	2	3
Nausea	61	34	4	–
Vomiting	73	19	8	–
Stomatitis	42	23	31	4
Esophagitis	85	15	–	–
Cardiac	92	8	–	–
Cephalea	84	16	–	–
Asthenia	39	31	19	11
Anorexia	58	19	15	8
Fever	73	27	–	–
Infection	85	11	–	4
Pruritus	85	11	4	–
Cutaneous	62	15	19	4
PPE	34	34	12	19
Alopecia	90	5	5	–

Figures represent percentage of patients.

of neoplastic epidermal toxicity was made upon biopsy [14].

Asthenia of grade 3 was noted in three patients and infection of grade 3, unrelated to therapy, occurred in one patient. No hypersensitivity reactions or episodes of cardiac failure were registered. Median cumulative anthracycline (prior doxorubicin plus PLD) was 350 mg/m² (range 70–577). Two out of 17 patients with serial LFEV showed a transient decrease of 25 and 14%, respectively. PLD was delayed a median of 7 days (range 7–14) in 21 cycles, due to hematological (6), mucocutaneous toxicity (13) or other reasons (2), and it was reduced by 25% in five patients. Cumulative PLD was 141 mg/m² (35–567), dose intensity 11 mg/m²/week (7–12), and relative dose intensity of 95% (0.61–1.03) (median, range).

Response to therapy and survival

Objective activity in 27 evaluable patients included one complete (CR) and one partial remission (PR), 12 stabilizations (NC) and 13 progressions (PD) (response rate 7.4%; 95% CI, 0–17%). One out of five patients with a GIST diagnosis had a <50% reduction of liver metastases, one had disease stabilization and three progressed. If GIST patients are excluded, the remission rate was 9% (95% CI, 0–21%). Objective remissions were noted in two out of five patients without prior DXR exposure after five and 18 PLD cycles, and lasted 6 months. In 22 patients with prior DXR treatment, 12 stabilizations and 10 progressions were noted. Median duration of stable disease was 4.7 months (range 2.7–12 months). Among non-GIST patients, 11 DXR-resistant had three stabilizations and eight progressions, with seven stabilizations noted in seven patients with potentially DXR-sensitive disease (Fisher exact test, $P=0.004$). Progression-free rate (PFR) at 3 and 6 months was, respectively, 48 and 22% for the whole group, 40 and 40% for

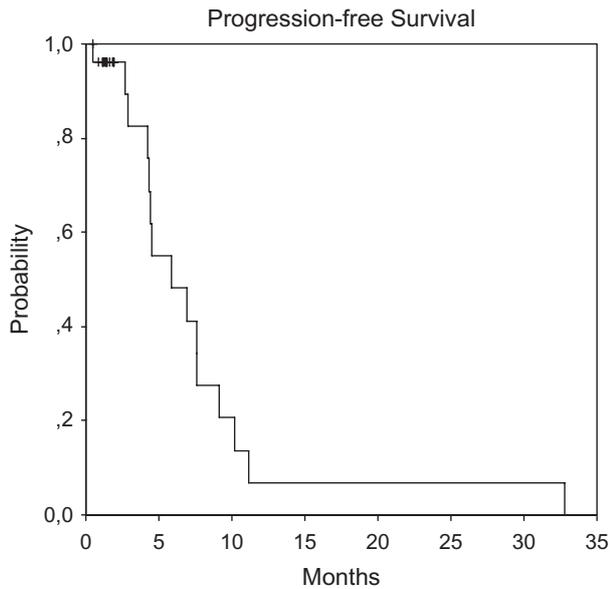


Figure 1. Progression-free survival.

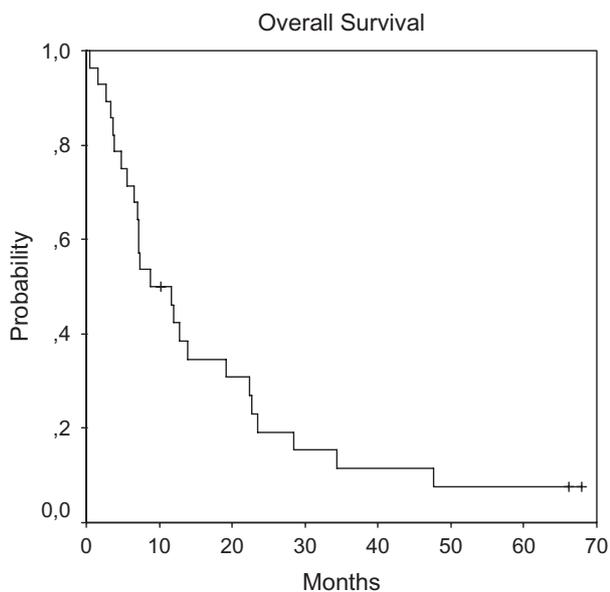


Figure 2. Overall survival.

patients never exposed to DXR, and 45 and 18% for those with prior DXR therapy. Median progression-free survival was 5.8 months (95% CI: 1.4–10 months) (Figure 1), and all but two patients have died with a median overall survival of 8.7 months (95% CI: 2.8–15 months) (Figure 2).

Quality of life

A baseline QLQ-C30 was available from 23 patients, with evaluations obtained from 13 patients at weeks 6–11, and from seven patients at weeks 12–18. In Table III we present mean score values

(\pm standard deviation) of the different scales with the corresponding Cronbach's α coefficients for multi-item scales. All correlations among QLQ-C30 scales before treatment were significant ($P < 0.056$); those same correlations within weeks 6–11 ($n = 13$) were significant, except for the pairs global quality of life–physical ($P = 0.16$), fatigue–social ($P = 0.13$) and nausea and vomiting–role ($P = 0.10$) (data not shown). No significant differences were noted when scores at weeks 6–11 or at week >12 were paired-compared with the respective baseline values. Correlation of the initial WHO performance status and the scale for global quality of life (QLQ-C30) at baseline showed a certain trend for lineal correlation ($V_{\text{Cramer}} = 0.753$ and contingency coefficient = 0.794, both with $P = 0.062$).

Discussion

The activity of PLD administered at 35 mg/m² every 3 weeks to patients with STS previously treated with doxorubicin, measured in terms of objective remissions, is negligible. Prior studies have been conducted with PLD doses that varied from 50 to 60 mg/m² repeated every 3–4 weeks. In two trials, where most patients had received DXR, five out of 45 STS patients responded [15, 16], and two small studies conducted in previously untreated patients gave negative results [17, 18]. In a first-line comparative study of the EORTC STBSG, 50 patients received PLD and 45 DXR, with a remission rate, respectively, of 10 and 9%, with no differences detected in time to progression or overall survival [19]. Progression-free rate has been proposed as a parameter to evaluate the activity of new agents in patients with advanced STS. In this trial, progression-free rates at 3 and 6 months were higher than the 39 and 14% encountered, respectively, for active drugs delivered as second-line regimens [20]. Those figures may be explained by a potential DXR sensitivity in our patient population, as 50% of non-GIST patients had either not received DXR or not progressed during a DXR-containing regimen, supporting the administration of PLD to patients who have not progressed under DXR therapy.

Phase II trials conducted with PLD have been usually performed at 50 mg/m² delivered every 4 weeks, with stomatitis grade 3–4 noted in 4–9% of patients and PPE grade 3–4 in 17–20% [19, 21]. In this trial PPE appeared in 65% of patients and stomatitis grade 2–3 was reported by 35%. Intensity and incidence of stomatitis and PPE have been related, respectively, to dose and cycle interval. Grade 2–4 stomatitis occurred in 83% of patients receiving PLD at 70 mg/m² every 6 weeks, and grade 2–3 PPE appeared in 73% of those treated at

Table III. Score of the EORTC QLQ-C30 before and during treatment.

	Before treatment			During treatment (weeks 6–12)			During treatment (week > 12)		
	(n = 23)			(n = 13)			(n = 7)		
	Mean score	SD	α	Mean score	SD	α	Mean score	SD	α
Functioning scales									
Physical	63.5	32.8	0.82	63.8	26.9	0.72	62.8	34.02	0.81
Role	54.3	45	0.74	51.9	41.4	0.50	82.1	37.40	0.93
Cognitive	84	24	0.87	91	12.9	0.04	85.8	17.21	0.90
Emotional	72.4	22.2	0.80	72.4	27	0.89	61.2	22.22	0.87
Social	67.4	33.5	0.80	66.6	35.3	0.91	69.2	26.95	0.79
Global quality of life	50	26.3	0.96	53.8	22.7	0.96	64.6	12.56	0.93
Symptom scales and/or items									
Fatigue	33.8	25.2	0.89	25.2	25.5	0.94	18.7	13.50	0.70
Nausea and vomiting	11.6	29	0.97	11.5	20.8	1	8.3	12.73	0.75
Pain	34	26.3	0.79	19.2	16.4	0.68	30.6	24.57	0.92
Dyspnea	7.2	14		10.2	21		9.5	25.2	
Sleep disturbance	27.5	31.2		30.7	31.8		19	17.8	
Appetite loss	27.5	34.3		25.6	33.7		28.6	30	
Constipation	18.8	30		12.8	21.7		19	37.80	
Diarrhea	2.9	13.9		5.1	12.5		4.7	12.6	
Financial impact	21.7	35.6		38.4	42.7		38.9	44.3	

α = Cronbach's alpha coefficient. Values ≥ 0.70 indicate adequate scale reliability.

35 mg/m² every 3 weeks, both schedules with a dose intensity of 11.6 mg/m² per week, equivalent to ours [22]. Mucositis was also dose-limiting in another trial with 70 mg/m² PLD delivered every 6 weeks [23]. The schedule we tested did not cause a higher PPE incidence than regimens where PLD was delivered every 4 weeks and, in our case, the intensity of stomatitis was lower. Grade 3–4 granulocytopenia (16% of patients) was higher than the 2–6% reported with PLD at 50 mg/m² every 4 weeks [19,21], but in our trial 93% of cycles had weekly BCCs. No episodes of cardiac failure were observed, and the lower cardiac toxicity of PLD with respect to DXR has been confirmed in a recent study [24].

Quality of life before treatment was measured in 23 patients with the EORTC QLQ-C30 (version 1.0). To our knowledge, this questionnaire had not been passed before to STS patients, and the limited data obtained here point to its adequacy to measure the quality of life of sarcoma patients exposed to chemotherapy. In 13 patients with assessable data, quality of life did not seem to worsen during therapy.

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