Long-term response to pegylated liposomal doxorubicin in patients with metastatic soft tissue sarcomas

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Doxorubicin and ifosfamide are currently considered the cornerstones of treatment for advanced soft tissue sarcomas (STSs). Pegylated liposomal doxorubicin (PLD) has been shown to have equivalent activity to doxorubicin and an improved toxicity profile. A review of the medical records of 11 patients with a variety of STSs treated with PLD was performed. The median age of the patients was 54.8 years. Of the 11 patients, seven received no earlier systemic therapy for their sarcoma. The initial dose per course was 40–60 mg/m^2 every 4 weeks with dose reduction to 40 mg/m^2 in the second or third cycle. A median of 11 cycles was given (range, two to 29 cycles). Treatment was generally well tolerated. We did observe some toxic effects as described earlier with PLD, including mild myelosuppression, skin toxicity and fatigue. No cardiotoxicity was observed. Of the 11 treated patients, six had a partial response, two had a best response of stable disease and three had progressive disease. All six patients with a partial response had an extended time to progression. To date, two patients continue on treatment (15 and seven cycles); one patient has stable disease 60 months after withdrawal of PLD (after eight cycles) and one patient had progression of disease 7 months after the withdrawal of therapy after 20 cycles. Of the two patients with stabilization of their disease, one had progression after 29 months and one continues on treatment for 6 months. PLD is active and safe for long-term treatment of metastatic STSs and may be important in maintaining response. *Anti-Cancer Drugs* **20:15–20 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Adult soft tissue sarcomas (STSs) are a heterogeneous group of tumours with many subtypes. In general, treatment is similar in the majority of cases, with the exception of advanced gastrointestinal stromal tumours (GISTs) and Ewing sarcomas [1]. Many patients have a metastatic spread during the course of their illness, and in these patients treatment is primarily palliative.

A large number of agents have been evaluated for the treatment of advanced STSs, but very few have shown definitive activity. The anthracycline, doxorubicin, is one of the few agents for which there is clear evidence of antitumour activity in STS, and this, and ifosfamide, are currently considered the cornerstones of treatment [2,3]. More recently, gemcitabine and docetaxel have also been increasingly used [4]. When any of these treatments are administered in a palliative context, care should be taken to balance the limited benefits, which might be expected to accrue from therapy, with an acceptably low incidence of drug-related toxicity. A randomized study in metastatic STS carried out by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group did not show any significant superiority of combination therapy with doxorubicin and ifosfamide over doxorubicin alone [5]. This has led to the adoption of single agent, doxorubicin, as the standard comparator in studies involving STS. The use of doxorubicin is limited mainly by its tendency to cause myelosuppression and cardiomyopathy. In respect of the latter, doxorubicin effects are cumulative, and more likely to occur with total doses in excess of 450 mg/m^2 [6].

Pegylated liposomal doxorubicin (PLD), marketed under the names of Doxil or Caelyx, is a form of liposomal doxorubicin in which the liposomes are coated with the hydrophilic polymer, polyethylene glycol. This coating results in reduced uptake of the liposomes by the reticuloendothelial system and, consequently, in a substantially increased half-life in the circulation (50–60 h), and a modified, and generally less problematic toxicity profile [7,8]. In particular, PLD seems to be associated with a lower incidence of myelosuppression, alopecia and cardiac side effects than conventional doxorubicin, although a higher incidence of skin toxicity has been found. In addition, long-term therapy with PLD has been shown to be well tolerated and without cumulative cardiotoxicity [6].

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PLD has been shown to localize in implanted tumours in animals because of the increased vascular permeability of tumours, an observation confirmed in cancer patients [9]. This tumour-homing effect of PLD results in a higher tumour concentration of drug as compared with free doxorubicin. For instance, drug levels in Kaposi's sarcoma lesions of patients treated with PLD were four-fold to 55-fold greater than in patients treated with free doxorubicin [10]. PLD is currently indicated in the therapy of breast cancer, ovarian cancer and Kaposi's sarcoma and has also been recently approved for the treatment of multiple myeloma [11].

A randomized phase IIB study carried out by the EORTC Soft Tissue and Bone Sarcoma Group compared PLD with conventional doxorubicin in the treatment of 94 patients with advanced or metastatic STS. In this study, both treatments demonstrated equivalent antitumour activity as determined by response rate and progression-free survival. Regarding median survival there was a nonsignificant advantage of approximately 3 months in the PLD arm. As expected, the toxicity profile was milder than that of doxorubicin [12].

On the basis of the advantageous toxicity profile of PLD and on the apparent noninferiority of PLD when compared with doxorubicin in the EORTC study, the use of PLD in patients with metastatic STS seems to be a rational approach to therapy, which deserves to be investigated further. We therefore decided to review our own institutional experience with PLD in metastatic STS. This report is a retrospective evaluation of 11 patients with STS treated with PLD at the Shaare Zedek Medical Center.

Materials and methods

An analysis of the medical records of 11 patients (four males/seven females) with a variety of STS treated with PLD at the Shaare Zedek Medical Center between January 2002 and June 2008 was performed. The median age was 54.8 years (range, 32–75 years). Five pleomorphic (malignant fibrous histiocytoma) sarcomas, three uterine leyomiosarcomas, one angiosarcoma, one malignant hemangioendothelioma and one synovial sarcoma were found. All diagnoses were biopsy-proven and all patients had metastatic disease. Of the 11 patients, eight had received no earlier systemic therapy for their sarcoma; one patient had previously received adriamycin in a cumulative dose of 480 mg/m^2; one patient had previously received ifosfamide and gemcitabine as first-line therapy and one patient had previously received sorafenib for their sarcoma (Table 1). In addition, two more patients had received 360 mg/m^2 and 240 mg/m^2 of doxorubicin as adjuvant therapy for breast cancer, 10 and 9 years previously, respectively.

The initial dose per course was 40–60 mg/m^2 every 4 weeks with dose reduction to 40–45 mg/m^2 in the second or third cycle. This lower dose was then maintained for the duration of treatment with PLD. In every case, the PLD was administered by intravenous infusion over a period of 1–2 h.

To assess disease status, radiographic studies and/or reports were reevaluated and responses to therapy were based on computed tomography (CT) scans carried out on a regular basis and generally every 3 months in each patient. The responses were then classified according to the Response Evaluation Criteria in Solid Tumors criteria [13].

Results

A median of 11 cycles was given (range, 2–29 cycles). The median cumulative dose of PLD received was 432 mg/m^2 (range, 80–1212 mg/m^2). Of the 11 treated patients, six

Table 1 Diagnosis, treatment and responses of STS patients treated with PLD

Patient number	Age (years)	Sex	Histology	Response	Time to progression[a] (months)	Number of courses	Cumulative dose (mg/m^2)	Previous chemotherapy
1	40	M	Malignant hemangio-endothelioma	PR	66[d]	7	190	
2	75	M	MFH	PR	15	15	662	
3	58	F	Uterine leiomyosarcoma	SD	29	29	1212	
4	61	F	Pleomorphic sarcoma	PR	14 (include doxorubicin)	8	350	Doxorubicin (480 mg/m^2) for STS
5	54	F	High-grade sarcoma	PR	15[b]	15[b]	615	Doxorubicin (360 mg/m^2) for breast cancer, 10 years before
6	32	F	Pleomorphic sarcoma	PD	3	3	130	
7	59	F	Uterine leiomyosarcoma	PD	2	2	80	
8	42	M	Synovial sarcoma	PD	3	3	140	
9	71	F	Uterine leiomyosarcoma	PR	37[c]	20	788	Ifosfamide and gemcitabine
10	49	F	Angiosarcoma of liver	PR	7[b]	7[b]	280	Sorafenib
11	62	M	Low-grade mixoid MFH	SD	6[b]	6[b]	300	

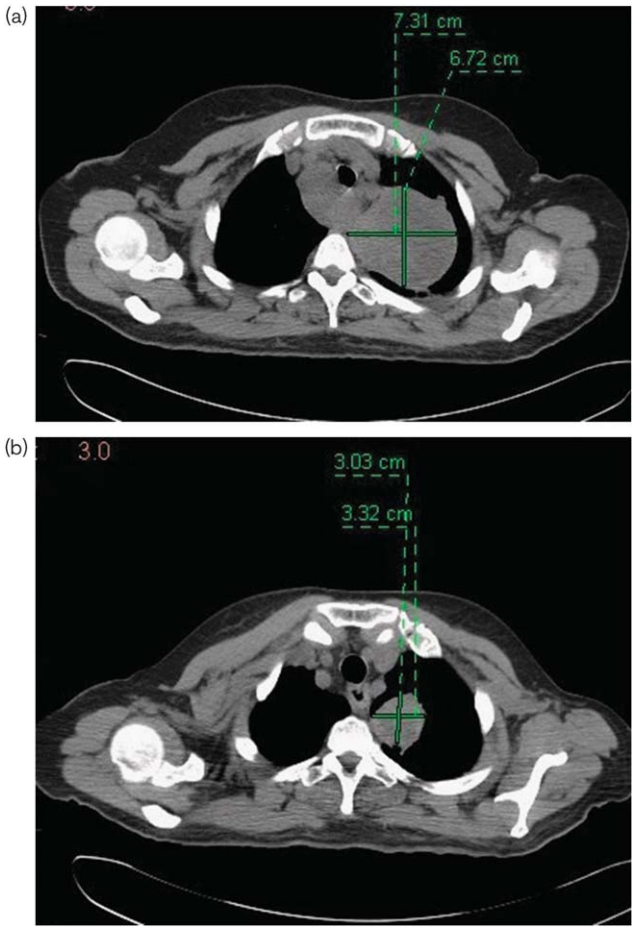
PD, progressive disease; PLD, pegylated liposomal doxorubicin; PR, partial response; SD, stable disease; STS, soft tissue sarcoma.
[a]Patients 1, 5, 9, 10 and 11 continue to be progression-free.
[b]Continues treatment with PLD.
[c]Disease recurrence 7 months after discontinuing PLD.
[d]Continues to be progression free 60 months after stopping PLD.

had a partial response, two had a best response of stable disease and three had progressive disease.

All six patients demonstrating a partial response had an extended time to progression (66 + , 36, 16, 15 + , 15 and 7 + months, respectively) (Figs 1 and 2). One patient who had received doxorubicin in a cumulative dose of 480 mg/m^2 with partial response, received eight additional courses of PLD with further response, and no reduction in left ventricular ejection fraction. Of the two patients with a best response of stabilization of disease, one had progression after 29 cycles of PLD and one continues on treatment after six cycles.

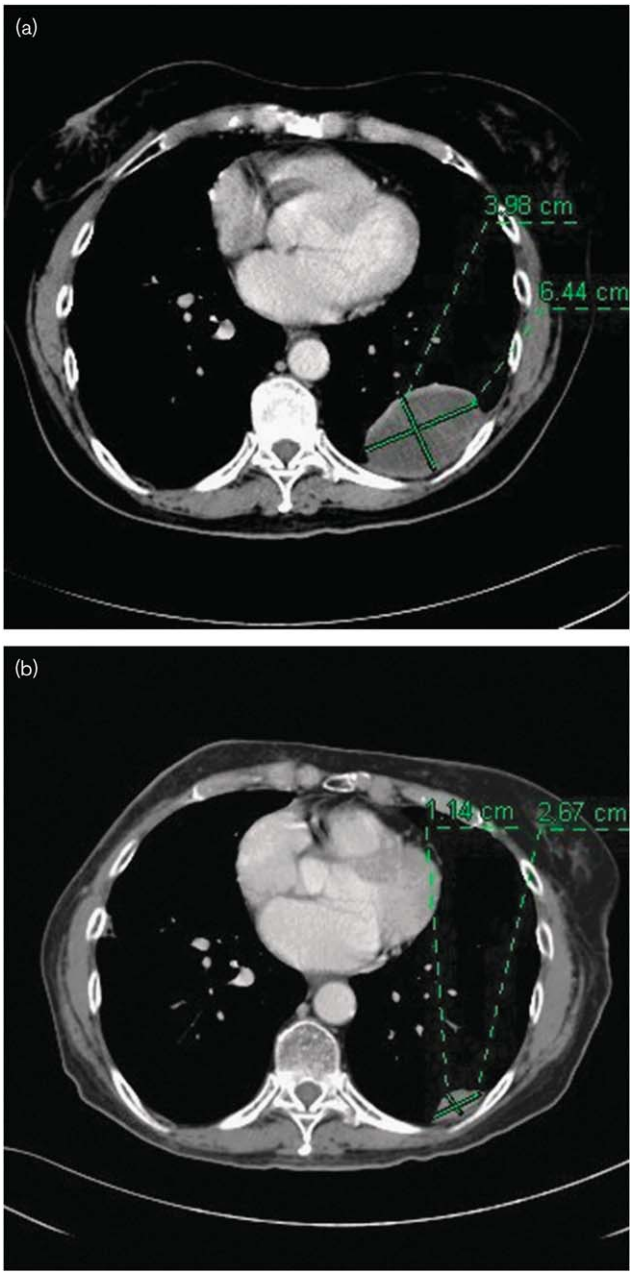
To date, three patients continue on treatment (15, seven and six cycles) and one patient with metastatic malignant hemangio-endothelioma is progression-free 60 months after withdrawal of PLD after seven cycles. One patient received 20 cycles of treatment over a 30-month period with dramatic improvement (Fig. 2), after which treatment was discontinued following a traumatic hip fracture. A CT scan 3 months later showed no progression of disease, but at 7 months she complained of chest pain

Fig. 1



Patient 5: Computed tomography (CT) scan of the chest (a), before the initiation of treatment, shows a heterogeneous mass, 7.3 × 6.7 cm (maximal size slice) in the left upper lobe of the lung with involvement of the descending aorta. After 15 months of treatment with pegylated liposomal doxorubicin (b), repeat CT scan shows a decrease in the size of the lung mass to 3.0 × 3.3 cm (maximal size slice).

Fig. 2



Patient 9: Computed tomography scan of the chest (a) shows a mass 6.4 × 3.9 cm (maximal size slice) in the left lower lobe of the lung involving chest wall. Patient treated with pegylated liposomal doxorubicin (PLD) for 30 months. (b) Marked decrease in the size of the mass 6 months after the cessation of PLD therapy to 2.6 × 1.1 cm (maximal size slice).

and general weakness and CT scan showed progression of disease in both the lungs and the liver. In two patients (patients 2 and 4, Table 1) progression involved the development of brain metastases.

Treatment was generally well tolerated. Although toxicity data were not collected prospectively in a systematic fashion, we did, nevertheless, observe some toxic effects described previously with PLD, including mild myelosuppression (but no cases of neutropenic fever), skin toxicity and fatigue. One patient experienced a recall phenomenon, which presented as erythema, exfoliation and pain in a region of earlier irradiation. This developed after one course of treatment and responded to locally administered steroids. It did not require interruption of treatment and did not recur. One patient developed an oesophageal ulcer that necessitated temporary withdrawal of PLD. It was treated conservatively and did not recur after subsequent reintroduction of PLD. In particular, there was no evidence of cardiotoxic events including congestive heart failure and no significant reduction in the left ventricular ejection fraction despite the high cumulative doses.

Discussion

All the patients evaluated in this retrospective analysis had advanced STS with evidence of metastatic spread at the time of exposure to therapy with pegylated doxorubicin. Once metastatic spread has occurred, treatment must be regarded as palliative, and thus necessitates a calculated balance between the likelihood of prolonging life while ensuring a low level of treatment-related side effects and improving or maintaining quality of life. Doxorubicin is probably the most effective agent available at this time for the treatment of advanced, metastatic STS. When administered as a single agent therapy in these circumstances, it has been shown to produce response rates of the order of 16–27% with a median overall survival of 7.7–12.0 months [1]. It is becoming increasingly appreciated that stabilization of disease is a realistic end point for metastatic STS, as therapeutic agents that produce a low objective antitumour response may still slow tumour progression and prolong survival. It has further been shown that survival in patients with a stable disease is comparable with that in patients with partial or complete response [14].

The side effect profile of standard doxorubicin is well documented. Commonly reported unwanted effects include myelosupression, mucositis, alopecia and cardiotoxicity. Cardiotoxicity is most frequently related to the total dose of doxorubicin received and may first present as shortness of breath or as congestive cardiac failure. Besides its unique pharmacologic and tumour-homing properties, the particular advantages of PLD include a long dosing interval, minimal and non-life-threatening acute or chronic toxic effects and no need for special requirements, such as premedication or central venous access. These features confer important clinical benefits when PLD is used either as monotherapy or in combination with other agents.

Although no phase III studies have investigated the therapeutic value of PLD in STS, a review of the literature hints at a positive role for PLD, despite the fact that the information is still fragmentary and does not as yet yield a consistent picture.

A randomized phase II study carried out by the EORTC Soft Tissue and Bone Sarcoma Group compared PLD with conventional doxorubicin in the treatment of 94 patients with advanced or metastatic STS. In this study, both treatments demonstrated equivalent antitumour activity, although response rates (complete and partial) were lower than expected, at 10 and 9%, respectively. Stable disease was recorded in 40% of patients on doxorubicin and 32% of patients on PLD. If the patients with GIST were excluded, as these are known to be particularly unresponsive to doxorubicin, response rates improved slightly to 14 and 12%, respectively. In terms of toxicity, PLD was significantly less myelosuppressive than doxorubicin (6 vs. 77%), and caused less febrile neutropenia (2 vs. 16%), and less alopecia (6 vs. 86%). More skin toxicity occurred with PLD, with 50% of patients experiencing some level of palmar–plantar–erythrodysesthesia, compared with 0% on doxorubicin. Other toxicities were rare in both groups [12].

Chidiac *et al.* [15] treated 15 patients with metastatic or recurrent STS who had received no earlier chemotherapy for advanced disease. Using doses of 50 mg/m^2 every 4 weeks, they reported that the preparation was well tolerated, but that it had no significant therapeutic activity in this patient population.

Skubitz [16] reported on 47 patients with advanced or metastatic STS treated with initial doses of 55 mg/m^2 every 4 weeks. Two of the 47 patients (4.25%) had a complete response, one (2.13%) a partial response and 11 (23.4%) stable disease. The remaining patients had progressive disease (57.4%), or at best a minor response in a few instances. Fifteen of the 47 patients had GIST. Toxicity was mild, with the most commonly occurring side effects being skin toxicity and mucositis. Skubitz concluded that PLD had clear activity in STS, including some cases refractory to conventional doxorubicin.

A recent study in advanced leiomyosarcoma of the uterus yielded 31 evaluable patients. Complete response was achieved in one patient (3.2%), partial response in four patients (12.9%) and stable disease in 10 patients (32.3%). Fifteen patients (48.4%) had progressive disease

and response could not be assessed in one patient (3.2%). These researchers comment that although the side effects were manageable, they were seen only after two courses of treatment [17].

Combinations of the various agents exhibiting some level of activity in STS have been tried, and there are many reports in the literature of the use of anthracycline–ifosfamide combinations. Although these have often resulted in improved response rates, this has been at the expense of an increased level of toxicity [5]. In addition, no clear benefit in overall survival has been achieved to date, with any of the combinations as compared with single agent therapy [1].

Recently, the Hellenic Cooperative Oncology Group has studied combined therapy with PLD and paclitaxel in advanced STS. Distant metastases were present in 69% of cases. Patients received PLD (45 mg/m^2) and paclitaxel (150 mg/m^2) every 28 days for a total of six cycles. Overall response rate was 16% (complete response, 2%; partial response, 14%), with stable disease in 33%. Median time to progression was 5.7 months and median overall survival 13.2 months [18].

Koukourakis *et al.* treated seven patients with locally advanced or recurrent STS with a combination of PLD and radiotherapy. Radiotherapy was given as a standard fractionation regimen to a total dose of 70 Gy and PLD as a 30-min infusion at a dose of 25 mg/m^2 every 2 weeks. Four of the seven patients (57%) showed a complete response, one patient a partial response and one showed stable disease. The combination was well tolerated and, in this small study, it was highly effective [19].

In this retrospective study, the use of PLD in patients with advanced STS resulted in a partial response, with a prolonged time to disease progression in six of the 11 patients, and the maintenance of stable disease in two patients. One patient who initially responded to doxorubicin in a total dose of 480 mg/m^2 was subsequently transferred to PLD, when additional response was observed over a further 8-month period without the development of cardiotoxicity. Two patients were ultimately found to have brain metastases as a manifestation of their disease progression. It should be noted that brain metastases are uncommon in patients with STS. This may be related to the generally short survival times associated with advanced, metastatic STS, which may not give sufficient time for these lesions to develop. Consistent with this hypothesis, both patients in question showed a prolonged response to PLD and developed brain metastases 38 and 22 months, respectively, from the start of PLD treatment.

In this study, in patients with metastatic STS, PLD was well tolerated. Some toxic effects were noted, and these included mild myelosupression, some skin toxicity and fatigue. No alopecia was observed. In particular, there was no evidence of cardiotoxicity.

On the basis of this small retrospective survey, we conclude that PLD is both active and safe for long-term administration in patients with advanced, metastatic STS. PLD seems to be an improved therapeutic option relative to conventional doxorubicin, especially towards the aims of maintaining response and reducing the risk of cardiotoxicity.

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