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Epidoxorubicin plus ifosfamide in advanced and/or metastatic soft-tissue sarcomas

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Summary. We undertook this phase II study to evaluate the efficacy and toxicity of epidoxorubicin and ifosfamide in the treatment of locally advanced and/or metastatic soft-tissue sarcomas. We used escalating doses of epidoxorubicin (from 60 to 75 mg/m^2) on day 1 and 1.2 g/m^2 ifosfamide on days 1–5. Chemotherapy courses were repeated every 3–4 weeks. A total of 16 patients – 13 who had not previously been treated and 3 who had undergone prior therapy with anthracyclines – entered the study. In all, 15 patients were evaluable for response and 16, for toxicity. At least two courses of chemotherapy were given. A complete remission (CR) was seen in 1 patient, a partial remission (PR) in 5, and a minor response (MR) in 1, for an objective response rate (CR+PR) of 40% (6/15); this value reached 50% in non-pretreated patients (6/12). Stable disease (SD) was observed in 40% (6/15) of patients. The relative dose intensity of epidoxorubicin ranged from 10 to 23.3 mg/m^2 (median, 16.6 mg/m^2). The time to objective response ranged from 4 to 12 weeks (median, 8.5 weeks). The duration of response was 4 months for the single CR, and that for the five PRs was 6+ months (range, 4–18 months). Toxicity was evaluated according to WHO criteria in 16 patients; it was mild and consisted mainly of alopecia, nausea and vomiting, and leucopenia. In only three patients did we observe grade 3 leucopenia. In one case an ifosfamide-associated encephalopathy occurred, but it regressed after 24 h. Neither chronic nor acute cardiac toxicity was reported. In this preliminary analysis, the response rate obtained with the combination of epidoxorubicin and ifosfamide was encouraging and the toxicity was acceptable.

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Doxorubicin is the most effective drug used in single-agent or combination chemotherapy of locally advanced and/or metastatic soft-tissue sarcomas. In single-agent therapy its response rate ranges from 9% to 70% [1, 2, 5, 9, 16]; in polychemotherapy it has been associated with DTIC, cyclophosphamide, and vincristine on several therapeutic schedules, obtaining a response rate of 11%–60% [8, 21]. Ifosfamide has recently been introduced in the management of soft-tissue sarcomas. As a single agent, it has a 20%–40% response rate [3, 19]. The association of doxorubicin with ifosfamide has resulted in a response rate of 24%–71% [17, 18, 20]. Epidoxorubicin has been compared with doxorubicin in a randomized study for the treatment of soft-tissue sarcomas and the response rates were comparable; however, haematological toxicity was lower for the epidoxorubicin arm [15]. Therefore, we evaluated the efficacy and toxicity of the combination of epidoxorubicin and ifosfamide, using escalating doses of the former.

Patients and methods

From September 1987 to January 1989, 16 patients with histologically demonstrated, locally advanced and/or metastatic soft-tissue sarcomas entered this study; 15 were evaluable for response and 16, for toxicity. One patient was not evaluable because treatment was given in the presence of minimal disease after surgery for a retroperitoneal sarcoma. Criteria for the selection of patients included an age of 16–75 years, normal renal and hepatic functions (bilirubin, <1.5 mg%; creatinine, <1.5 mg%), a normal ECG, and the absence of clinical cardiac alterations. Patients' performance status according to WHO classification ranged from 0 to 4 (median, 1). All but two patients had not previously been treated with radiotherapy, and three subjects had undergone prior anthracycline chemotherapy. Our patients' characteristics are reported in Table 1.

A total of 16 consecutive patients received 6 g/m^2 i.v. ifosfamide and were given mesna (uromitexan) p.o. (40% of the ifosfamide dose), with concomitant doses of epidoxorubicin escalating from 60 to 75 mg/m^2. Ifosfamide was given over 5 days (1.2 g/m^2 daily) as a 2-h infusion in 1,000 ml Ringer's lactate solution. Mesna was given p.o. with an acidic drink at the beginning of ifosfamide administration and 4 and 8 h later. Epidoxorubicin was given by bolus i.v. The first five patients were treated every 4 weeks with 60 mg/m^2 epidoxorubicin; then,

Table 1. Patients' characteristics

Patients (*n*)	16
Men	6
Women	10
Median age (range)	60 (28–73) years
Median performance status (range)	1 (0–4)
Histological diagnosis:	
Malignant fibrous histiocytoma	4
Liposarcoma	4
Leiomyosarcoma	4
Rhabdomyosarcoma	1
Schwannoma	1
Extraosteal Ewing's sarcoma	1
Mammary stromal sarcoma	1
Site of primary disease:	
Lower limbs	5
Trunk	3
Retroperitoneum	3
Viscera	4
Breast	1
Previous non-surgical treatment:	
Radiotherapy	2
Chemotherapy	3
Locally advanced disease	4
Metastases	5
Locally advanced disease + metastases	7

we treated four subjects with 70 mg/m^2 every 4 weeks, and three others received 70 mg/m^2 every 3 weeks. Three patients received only 50 mg/m^2: one had a performance status of 2 and was 72 years old, one had been pretreated with chemotherapy and had an atrioventricular (AV) block, and one had been pretreated with radiotherapy. One patient received 75 mg/m^2 epidoxorubicin every 4 weeks.

Antiemetics were given routinely; 1 mg/kg metoclopramide was given before chemotherapy and was repeated approx. every 6 h thereafter in cases of persistent nausea and vomiting, and 40 mg methylprednisolone was injected i.m. at two different times after chemotherapy. At least two courses of chemotherapy were given before the response rate was evaluated according to WHO criteria. No progression of disease was observed during the first cycle.

Results

The results obtained with this regimen in 15 evaluable patients are shown in Table 2. Objective responses were observed in 6/15 cases (40%), with 1 achieving a complete remission (CR), 5 attaining a partial remission (PR), and 1 showing a minor response (MR). Six patients (40%) had stable disease (SD), and only two cases of progressive disease (PD) were observed.

Table 2. Response to chemotherapy and duration of response

Response	Patients (*n*)	Duration of response (months)
CR	1	4
PR	5	6 + (range, 4–18)
MR	1	6
SD	6	3.5 (range, 1–10+)
PD	2	–
OR	7/15 (46.6%)	

CR, complete remission; PR, partial remission; MR, minor response; SD, stable disease; PD, progressive disease; OR, objective response

The duration of responses ranged from 4 to 18 months, with a median of 6 months from the beginning of chemotherapy. The only CR lasted 4 months, after which time disease progressed into the CNS; two patients achieving PRs (local disease and lung metastases) underwent subsequent local radical excision and thoracotomy. One of two patients who had a history of two local relapses in the trunk at 3 and 8 months after primary surgery, respectively, experienced another relapse 4 months later in the site of the first surgical scar. He therefore underwent a radical resection of the shoulderblade and has to date remained disease-free. The other patient remains disease-free 3 months after radical surgery. The duration of SDs was 1–10+ months, with a median of 3.5 months. Among the non-pretreated patients, 6/12 (50%) had an objective response (1 CR, 5 PRs), 5 had SD, and 1 experienced PD.

The epidoxorubicin dose, percentage of responses, and time to response are reported in Table 3. The dose intensity of epidoxorubicin (mg/m^2 per week) ranged from 10 to 23.3 mg/m^2 (median, 16.6 mg/m^2). The median time to response was 8.5 weeks (range, 4–12 weeks).

Toxicity

Toxicity was evaluated according to WHO criteria [14]. WBC counts immediately prior to each course of chemotherapy are reported, as nadir counts were taken in only a few cases. A summary of toxicities experienced by 16 patients treated with this regimen is reported in Table 4.

Table 3. Responses according to delivered dose of chemotherapy

Dose of EpiDx	Dose intensity (mg/m^2 per week):		Patients (*n*)	Responses		Median time to response (weeks)
	Median	Range		Number	(%)	
50 mg/4 weeks	12	12.0–12.5	3	–	–	–
60 mg/4 weeks	13.5	10–15	5	3	60.0	8
70 mg/4 weeks	16.6	16.6–17.5	3	2	66.7	10.5
70 mg/3 weeks	23.3	23.3	3	2	66.7	5
75 mg/4 weeks	18.7	18.7	1	–	–	–

EpiDx, epidoxorubicin

Table 4. Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	2	5	7	-
Nausea/vomiting	6	4	3	-
Leucopenia	5	2	3	-
Thrombocytopenia	2	-	-	-
Anaemia	1	2	2	-
Fever	2	1	-	-
Encephalopathy	-	1	-	-
Cardiovascular	1	1	-	-

Haematuria and renal toxicity were not observed, and no patient required reduction of the ifosfamide dose. CNS toxicity was seen in only one patient with a performance status of 4, who experienced temporary drowsiness. Gastro-intestinal toxicity was tolerable even with increasing epidoxorubicin dose intensity. We observed two cases of grade 3 anaemia that required blood transfusions; these patients had received relatively low doses of epidoxorubicin (15 and 12 mg/m^2 per week), but one subject had a performance status of 4 and the other experienced blood loss due to advanced pelvic disease. Of the three patients who developed leucopenia of grade 3 at nadir, two also suffered from grade 3 anaemia and the other had received an epidoxorubicin dose of 23.2 mg/m^2 per week. We delayed chemotherapy for 1 week in these patients, with no dose reduction; none of these patients experienced septic fever, and leucopenia regressed in all cases. Cardiac toxicity resulted in two cases of tachycardia (grade 1) and ventricular extrasystole (grade 2); one patient had a performance status of 4 and the other had been pretreated with doxorubicin. In neither case did we observe heart failure, nor did chemotherapy have to be discontinued.

Discussion

Chemotherapeutic regimens based on ifosfamide and doxorubicin have resulted in various response rates in different studies, and these median response rates seem to be superior to those obtained with single drugs [10, 17, 20]. A dose-response relationship has been well defined for doxorubicin, and when the latter is used in combination with ifosfamide, an increase in the response rate seems to be observed in patients treated at the highest doxorubicin doses [12, 20]. Unfortunately, an increase in toxicity for this combination is inevitable at higher doses, particularly myelosuppression. To date, the combination of ifosfamide and doxorubicin has not offered better results in terms of complete remission and survival than those achieved using single drugs at optimal doses [12].

In the present study we used epidoxorubicin, which has previously been shown to achieve response rates comparable with those obtained with doxorubicin. For the treatment of breast cancer and soft-tissue sarcomas, equimolar doses of doxorubicin and epidoxorubicin have been used, with no significant difference in the therapeutic results but with minor myelo- and cardiotoxicity being reported for epirubicin [6, 15]. The lower toxicity and equivalent effectiveness of the latter drug prompted us to increase the dose to obtain a greater number of responses. We report an objective response rate of 40%. After 4–18 months in patients achieving PRs, disease progressed in primary or distant sites. Nevertheless, it is noteworthy that the two patients with PRs who underwent radical surgery are alive and show no evidence of disease at 9 months after the beginning of chemotherapy. However, the number of patients was small and the follow-up was too brief to enable us to draw firm conclusions. Other studies confirm the possibility of increasing survival rates by using combination treatments in metastatic patients [11].

The effective dose intensity for each week was calculated for all patients treated. Numerous studies of different neoplasias indicate a relationship between the dose of active drug and the response; rather than the established dose, the cumulative dose is related to response and survival in both metastatic therapy and adjuvant treatment. In the present study the time to response seemed to be shorter at higher injected doses; however, additional studies using a larger patient population are needed to establish exactly the influence of drug dose intensity on the time to response.

Toxicity results reported by different authors using regimens based on doxorubicin and ifosfamide have varied according to the number of patients and their differing performance status. Alopecia and nausea and vomiting (grade, >2) are frequent, and grade 3 leucopenia occurs in 14.2%–32% of cases [12, 14, 20]. With ifosfamide, cerebral effects (from disturbances of consciousness to motor disturbances) are often described [13, 19]. Mansi et al. [12] have reported reversible CNS toxicity in three patients who developed either drowsiness or epileptiform crisis. In other studies, encephalopathy has been reported in 5%–12.5% of cases [4]. In the present study, grade 2 encephalopathy occurred in one patient with a performance status of 4.

We observed limited gastro-intestinal toxicity (pharmacologically resolvable), and grade 3 leucopenia occurred in only three patients. The absence of haematuria may indicate the importance of mesna as a uroprotector, although other investigators report that it is not sufficient to prevent renal injury in patients with tubular damage [7]. We cannot say with certainty that this regimen is better than epidoxorubicin or ifosfamide given alone; a randomized study comparing epidoxorubicin and ifosfamide vs epidoxorubicin or ifosfamide alone is necessary before a conclusion can be drawn. Meanwhile, we believe that this regimen can be used for the treatment of advanced and/or metastatic soft-tissue sarcomas, as well as in radical surgery carried out in patients who relapse after achieving a PR, especially due to its low toxicity. We are continuing the use of this well-tolerated regimen and the evaluation of its efficacy.

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