Table 1. Patients' characteristics

Patient	IL2 dose before TIL	Delay IL2 TIL (weeks)	Cells injected ($\times 10^{10}$)	Phenotype (%) CD3/ CD4/CD8/ CD56	Cytotoxicity (E/T25/1) (%) K562/Raji/ autologous	Status after IL2	Status 1 month after TIL	Status at 6 months	Status at 12 months
1	$48\times10^6/m^2/w\times5w$	5	3.7	99/8/91/1	1/9/14	PD	PD	Dead	Dead
2	$48\times10^6/m^2/w\times5w$	5	7.6	88/64/37/1	16/10/1	PR	CR	CR	CR
3	$48\times10^6/m^2/w\times5w$	6	0.23	95/65/29/27	23/4/0	SD	PR	CR	CR
4	$48\times10^6/m^2/w\times5w$	10	0.56	90/89/4/7	4.6/2/13	PD	SD	SD	SD
5	$9\times10^6/d\times5w$	10	0.02	85/83/5/22	25/10/10	PD	SD	Dead	Dead
6	$9\times10^6/d\times5w$	8	1.1	90/65/41/19	7/2/0	PD	SD	SD	NE

PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; NE, non-evaluable; d, day; w, weeks; IL2, interleukin-2; TIL, tumour-infiltrating lymphocytes.

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Feasibility and Compliance of Epirubicin Plus Ambulatory Continuous Infusion Ifosfamide at Escalating Doses in Advanced Soft Tissue Sarcomas: a Phase I Study

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ANTHRACYCLINES (doxorubicin or epirubicin) plus ifosfamide is the most widely used and effective combination in advanced and/or metastatic soft tissue sarcomas (STS). In determining the ideal combination of the two drugs, consideration has to be given to their specific toxicities, the need to use the maximum tolerable dose, and the dose–response relationship for anthracyclines [1–4]; and, more recently, for ifosfamide [5, 6]. The use of continuous infusion (CI) has been confirmed as a valid option to avoid renal and neurological side effects, which appear to be the dose-limiting factors when high doses of ifosfamide are given [7–10]. Ambulatory CI has been shown to be feasible for patients with advanced, pre-treated disease, with good patient compliance [10].

In view of the above, we conducted a phase I–II study to define the maximum tolerated dose (MTD) of ifosfamide when given in association with a fixed dose of epirubicin, and the dose-limiting toxicities of the combination with at least two cycles of therapy, in a day-hospital regimen.

From December 1993 to July 1994, 17 adult patients with histologically confirmed advanced STS were studied. Epirubicin was given at a fixed dose of 110 mg/m^2/course (55 mg/m^2, intravenously bolus, days 1 and 2) combined with ifosfamide administered by CI over 4 consecutive days, through a portable infusion pump connected to a subcutaneous port system. Total ifosfamide dose/course was escalated by 1 g/m^2, starting from 9 g/m^2/course, in cohorts of 3–5 patients until the MTD of the combination was determined. Equidose mesna uroprotection (by CI, days 1–5), and granulocyte-colony stimulating factor support (200 μg/m^2/day, subcutaneously, days 6–13) were provided in all patients; courses were repeated every 3 weeks. Toxicity was strictly monitored, as previously described [4, 10].

If 2 or more patients at any dose level developed grade 3 non-haematological or grade 4 haematological toxicity requiring treatment delay, or if 2 of the 3–5 patients did not complete the planned two courses of treatment due to poor compliance, the immediately preceding ifosfamide dose level was considered the MTD of the combination.

All patients completed the planned two courses of treatment; 2 patients received a third cycle and one had four courses. The toxicities observed during the total 37 courses are summarised for ifosfamide dose level in Table 1. No toxic death occurred and no patient required hospitalisation for treatment-related side effects.

At the 11 g/m^2 ifosfamide dose level, haematological toxicity precluded further dose escalation, with 5/5 patients developing grade 4 leucopenia, that required a treatment delay of 1–2 weeks and transfusion support.

In combination with epirubicin at the fixed dose of 110 mg/m^2, ifosfamide at 10 g/m^2 by CI with mesna uroprotection was identified as the MTD. At this dose level, haematological

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Table 1. Toxicity: epirubicin 110 mg/m² course and dose escalation of ifosfamide (first and second cycle)*

	Ifosfamide dose level (g/m²/course)							
	9	10	11	9	10	11	All	
Courses	First cycle			Second cycle			First cycle	Second cycle
No. of patients	$n = 3$	$n = 9$	$n = 5$	$n = 3$	$n = 9$	$n = 5$	$n = 17$	$n = 17$
Grade	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4
Haematological								
WBC	0 1 0 0	4 0 1 1	0 0 0 5	0 2 0 0	4 1 2 1	0 0 0 5	4 1 1 6	4 3 2 6
Haemoglobin	1 0 0 0	2 1 0 0	1 0 1 0	1 1 0 0	3 1 0 0	0 2 1 0	4 1 1 0	4 4 1 0
Platelets	1 0 0 0	2 4 0 0	1 2 0 0	1 0 0 0	1 5 1 0	0 3 1 0	4 6 0 0	2 8 2 0
Gastrointestinal								
Nausea, vomiting	2 0 0 0	5 1 0 0	2 3 0 0	2 2 0 0	5 1 0 0	2 2 0 0	9 4 0 0	9 5 0 0
Mucositis	1 0 0 0	2 1 0 0	2 1 0 0	1 0 0 0	3 1 0 0	2 1 0 0	5 2 0 0	6 2 0 0
Cardiac								
Dysrhythmias	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	1 1 0 0	0 0 0 0	1 1 0 0
Function	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0
Renal								
Creatinine	0 0 0 0	0 0 0 0	1 0 0 0	0 0 0 0	2 0 0 0	1 0 0 0	1 0 0 0	3 0 0 0
Haematuria	0 0 0 0	1 0 0 0	0 0 0 0	0 0 0 0	1 0 0 0	1 0 0 0	1 0 0 0	2 0 0 0
Proteinuria	0 0 0 0	0 0 0 0	2 0 0 0	0 0 0 0	0 2 0 0	2 0 0 0	2 0 0 0	2 2 0 0
Neurological								
Neurocortical	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	2 0 0 0	2 0 0 0	0 0 0 0	4 0 0 0
Neuro-mood	1 0 0 0	2 0 0 0	0 0 0 0	1 0 0 0	0 0 0 0	0 0 0 0	3 0 0 0	1 0 0 0

* Number of episodes of each specified toxicity which occurred in the first and second course of treatment (according to the "Common Toxicity Criteria from the Cancer Therapy Evaluation Program", NCI, 1988).

recovery was sufficient to begin the following cycle on day 21, and no significant non-haematological toxicity was observed. As expected, the non-haematological toxicities of epirubicin and ifosfamide in combination were non-overlapping. The treatment was well tolerated and the adopted system, by using portable infusion pumps, allowed good patient compliance.

Compared with our previous scheduling of treatment, in which ifosfamide was given as an intravenously bolus of 1.2 g/m²/day for 5 consecutive days [4], the use of CI with mesna uroprotection and growth factor support permitted the administration of higher doses of the drug in combination with high-dose anthracycline, without overall increased toxicity. The possibility of combining the two drugs at optimum doses is important in view of the suggested dose–response relationship. In addition, the feasibility and the manageability of the adopted ambulatory scheduling may be of a significant advantage, when patients with advanced disease are treated.

In the present series, an overall response rate of 47% was achieved (8/17), with 2 complete responses, 6 partial responses, 7 stable disease and 2 progressive disease. We are now testing the effectiveness of this combination in phase II studies on anthracycline/ifosfamide-responsive tumours.

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