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ORIGINAL ARTICLE

Ambulatory administration of 5-day infusion ifosfamide + mesna: a pilot study in sarcoma patients

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Abstract
Purpose Ifosfamide is a cornerstone of chemotherapy in bone and soft-tissue sarcoma. Results of pharmacokinetic studies indicate that the optimal schedule of ifosfamide should be repeated doses over several days. With the development of 5-day infusion devices, we developed and evaluated a 5-day infusion regimen of ifosfamide in sarcoma patients in the outpatient setting.
Methods Sarcoma patients requiring chemotherapy after at least one doxorubicin-based line were enrolled in this study. Ifosfamide + mesna was administered as 1:1 concentration for a total of 6 g/m^2 of each over 5 days (i.e. 1.2 g/m^2 per day as continuous infusion) every 3 weeks. Patients were treated until progression or limiting toxicity, and salvage surgery was attempted when possible. An economic study was run comparing ifosfamide plus mesna as a 5-day infusion regimen and conventional Ifosfamide regimen.
Results Thirteen sarcoma patients were evaluable. The median number of cycles per patient was 6 (range, 1–8), for a total of 69 cycles. No acute encephalopathy or aggravation of renal function was noted. Acute grade 3 and 4 haematological toxicities were observed in 11.6 and 1.4% of patients, respectively without febrile neutropenia. Median time to progression survival and overall survival were 8.7 and 21.5 months, respectively. Total cost per cycle for a 2-m² patient body surface area was ambulatory infusion = 1,891 € and conventional ifosfamide = 6,256 €.
Conclusion The combination of ifosfamide and mesna as a continuous infusion over 5 days is feasible and well tolerated in the outpatient setting using infusion device. Its very favourable cost-effectiveness invites to further develop this approach.

Keywords Ifosfamide · Mesna · Chemotherapy · Sarcoma · Ambulatory · Outpatient chemotherapy

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Introduction

Ifosfamide is a bi-functional alkylating agent (oxazaphosphorine) that displays clinical activity against a broad spectrum of malignancies, including bone and soft-tissue sarcomas. Ifosfamide is a pro-drug that is metabolized by the P450 cytochrome system (CYP3A4 and CYP2B6) into its active compound, ifosforamide mustard [1].

Ifosfamide is recognized as one of the few active drugs in advanced sarcoma. It is used in first line therapy in association with doxorubicin or as a single agent in patients' relapsing after anthracyclin-based chemotherapy. Doses of 5–12 g/m² per cycle have been used in monotherapy but the optimal schedule remains to be determined in terms of therapeutic index and cost.

Central nervous system (CNS) toxicity of ifosfamide was reported during phase I studies [2]. Acute encephalopathy occurs in 5–30% of all patients treated with ifosfamide, and represents an acute dose-limiting toxicity [3]. Ifosfamide administered by bolus or rapid infusions causes a higher rate of CNS complications than do continuous infusions [4].

Other common toxicities associated with ifosfamide include haemorrhagic cystitis (secondary to elevated urinary concentrations of acrolein, a metabolite toxic to the bladder mucosa), and gastro-intestinal toxicity. Haemorrhagic cystitis can virtually be abolished by the simultaneous administration of mesna, an antidote to acrolein [5, 6].

Fractionation of the dose over 3–5 days is common in clinical practice and has been found to be a safe and effective schedule [7]. The length of infusion is not exactly defined. Ifosfamide is usually freshly prepared within 8 h before infusion, hence requiring inpatient stay for up to 1 week. Radford et al. [8] demonstrated that neither in daylight at room temperature nor at 27°C in a dark environment does a loss of ifosfamide occur from solutions of either ifosfamide alone or ifosfamide plus mesna over a 9-day period. Ifosfamide doses of 5–14 g/m^2 have been used. Continuous infusion ifosfamide regimens are an attractive option for many patients [9–13] However, it is usually performed in hospitalized patients, altering patient's quality of life and increasing related costs.

The aim of the present study was to evaluate the feasibility of continuous infusion of ifosfamide plus mesna for 5 days administered through a multi-day infusion device in the outpatient setting.

Patients and methods

Thirteen patients with a diagnosis of sarcoma were discussed at the multidisciplinary staff of Sarcoma Oncology of our institution, and were assigned to receive ifosfamide plus mesna as a 5-day infusion regimen, every 3 weeks, on a namely basis. Ifosfamide (Holoxan™, Baxter Oncology, Frankfurt am Main, Germany) was given at a fixed dose of 6 g/m² plus 6 g/m² mesna (Uromitexan™, Baxter Oncology, Frankfurt am Main, Germany) for 5 days as a 120-h infusion, every 21 days. Both drugs were administered with an infusional device. Maximum volume of this device was 275 ml.

Anti-emetic prophylaxis consisted of oral 5-hydroxytryptamine-3 receptor antagonist on days 1–5 plus a "one time" injection of corticosteroids (methyl-prednisolone 60 mg) on day 1. No aprepitant was prescribed, given the risk of aprepitant-related induction of CYP3A4 that may favour the onset of ifosfamide-induced encephalopathy [14, 15]. Chemotherapy was administered if, on day 1, the absolute neutrophil count was >1,500 × 10^{6}cells/l, and the platelet count was >100 × 10^9 cells/l. If counts were not adequate, therapy was delayed until recovery. The dose of ifosfamide was administered at 75% of the planned dose if any of the following toxicities occurred: neutropenic fever with hospitalisation and/or IV antibiotics, grade 3 or 4 thrombocytopenia lasting >3 days associated with bleeding, and any grade 3 nonhaematologic toxicity (except nausea/emesis). On completion of mesna, on day 5, granulocyte colony-stimulating factor (G-CSF) was started at 5 μg/kg subcutaneously daily for 5-day period. Tumour evaluation was performed every four cycles of treatment, or before if clinically indicated, according to standard methods; toxicity was assessed according to the NCI-CTC v3.0 criteria [16].

A cost-effectiveness analysis was made considering the ambulatory unit cost (1,301 € per day) and the conventional hospitalisation (1,080 € per day).

Results

Patient characteristics

During the period October 2004–July 2008, 13 sarcoma patients underwent ifosfamide-based chemotherapy according to the above-described schedule, in an outpatient basis. A total of 69 cycles were administered. The median number of cycles per patient was 6 (range, 1–8). Ten patients received more than 3 cycles.

The characteristics of the 13 patients are shown in Table 1. The median age was 50 years (range, 25–67). Patient's comorbidities are listed in Table 2.

Five patients had locally advanced disease, four had lung metastases and four had abdominal metastases. Ten patients had undergone surgery for primary tumour, and all patients received prior chemotherapy with doxorubicin. Eight patients (62%) had received prior chemotherapy with ifosfamide. Increased CRP level, previously associated with increased risk of severe haematologic toxicity [17] was observed in eight patients (62%).

Toxicity

The toxicity results are presented in Table 3. No re-hospitalisation due to acute haematological toxicity was required. One patient was re-hospitalized for infusion device leakage, and

Table 1 Patients' characteristics

Patients	13
Gender (M/F)	5/8
Age (years) median (range)	50 (25–67)
WHO PS 0/1/2/3	7/4/2/0
BMI (kg/m²) ≤ 18/ > 25	2/6
Histological subtypes	
Synovial sarcoma	3
Leimyosarcoma	3
Osteosarcoma	2
Ewing's	2
Alveolar soft-tissue sarcoma	1
Fibrosarcoma	1
Adenosarcoma	1
Sites of disease	
Locally advanced	5
Sites: pelvis/bone/muscle	1/2/2
Metastasic disease	8
Sites	
Lung	5
Liver	1
Peritoneal	1
Retroperitoneal	3
Patients with measurable disease	12
Prior therapy	
Surgery	10
Chemotherapy	13
Number of previous lines 1/2/3	9/2/1

PS performance status, *BMI* body mass index, *ULN* upper limits of normal levels

Table 2 Patients'comorbidities ($n = 13$)

Comorbidity	*n*
None	6
Renal function: creatinine clearance	
>60 ml/min	8
30–60 ml/min	4
<30 ml/min	1
Cardiac comorbidities	
Hypertension	2
Angina pectoris	1
Myocardial infarction	2
Diabetes mellitus	0
Ischemic stroke	2
Baseline haemoglobin <110 g/l	5

macrohematuria. Gross hematuria stopped within 3 days. A 1-week delay was required in five patients due to prolonged neutropenia (ANC < 1,500 × 10^6cells/l). No episode of grade 3–4 non-haematological toxicity was noticed, except one grade 3 diarrhoea. No toxic death occurred. In all patients, underlying renal function remained stable, and no acute CNS toxicity was noticed. Nephrotoxicity as indicated low serum phosphate from renal phosphorous wasting is usually reversible before the next chemotherapy cycle until larger cumulative doses are reached [11, 18].

Anti-tumour activity

Eleven patients had measurable disease. With a median follow-up of 16.2 months (range, 2–40), the median time to progression (TTP) was 8.7 months (range, 1.4–25.4). At the time of analysis, 7 patients were still alive. The median overall survival was 21.5 months (range 2.3–40) (Fig. 1). Ten patients received at least 3 cycles and were evaluable for tumour response. At first assessment, 4 patients (36%) achieved a partial response and no patient achieved a complete response. Four patients had a stable disease, and one had partial response for local disease allowing curative surgery. Two patients (15%) experienced progressive disease at first assessment.

Discussion

This single institution experience with 5-day infusion ifosfamide plus mesna in a multi-day infusion device, found evidence of clinical activity and a favourable toxicity profile in a selected patient's population.

In our series, patients were pre-treated by doxorubicin-based regimens, and had a good performance status (PS ≤ 1) allowing ambulatory therapy. Partial responses were observed in 40% of patients, a finding consistent with previous studies that showed response rates of 18–38% with ifosfamide doses up to 14 g/m² over 6 days [19–21]. In the small cohort of patient described here, we showed the feasibility of this treatment in an outpatient basis.

While the results of pharmacokinetic studies indicate that ifosfamide is probably best administered in divided doses over several days, whether the daily dose should be given in a continuous or in a short infusion remains an unresolved issue [22–24].

Ifosfamide alone displays clinical activity in advanced soft-tissue sarcomas with objective response rates of 22–43% in non-randomized studies [25, 26]. We confirm previously published reports that continuous infusion ifosfamide + mesna without additional hydration is an alternative to inpatient administration of ifosfamide with hydration and mesna [9–13].

Ifosfamide in ringer lactate solution, mixed with mesna in multi-day infusors is stable for 7 days. The mean decrease of ifosfamide concentration, during 7 days storage

Table 3 Acute haematologic toxicities per patient and medical resource assessment (13 patients, 69 cycles)

	Grade 2 toxicity	Grade 3–4 toxicity	Hospitalisation	Transfusion
Haematologic				
Anaemia	4	1[a]	–	3 RBC units[a]
Thrombocytopenia	1[a]	–	–	
Neutropenia	3	–	–	–
Neutropenic fever	–	–	–	–
Nonhaematologic				
Nausea/vomiting	6	–	–	–
Neurological syndrome	1[b]	–	–	
Diarrhoea	7	1[c]	1[c]	
Hematuria	1[d]	–	1[d]	
Leak of infusion	1[d]	–	1[d]	

RBC red blood cells

[a] Same patient

[b] Diplopia without encephalopathy at cycle 1 and normal MRI

[c] Same patient

[d] Same patient

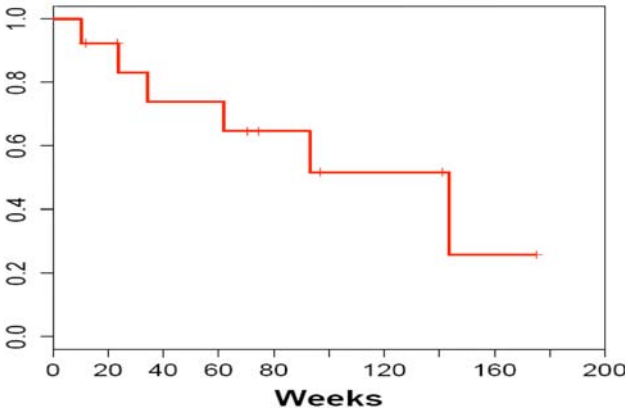

Fig. 1 Overall survival (n = 13)

at 37°C, was estimated as 3.2% [27]. Also, in Leone pharmacological study, neither evaporation nor concentrations of the solution were recorded [27]. Thus infusion ifosfamide plus mesna is a feasible regimen in the outpatient setting. The only factor limiting the dose of ifosfamide administered in this schedule (6 g/m²) is the capacity of multi-day infusion devices, restricted to 275 ml.

Patients following this schedule underwent a unique ambulatory hospitalisation on day 1, instead of a 5-day hospitalisation with conventional ifosfamide regimens.

An economic study was run comparing ifosfamide plus mesna as a 5-day infusion regimen and conventional ifosfamide regimen. Total cycle cost for 2-m² patient body surface area was infusion = 1,891 € and conventional ifosfamide = 6,256 € (Table 4). For a comparable clinical outcome, Ifosfamide can be administered for more than half the cost of conventional regimen.

Conclusion

This study confirms that continuous infusion ifosfamide plus mesna is an interesting schedule, and demonstrates its feasibility in an outpatient basis using a 5-day infusion device. This regimen had clinical activity in sarcoma patients pretreated with doxorubicin- and ifosfamide-based regimens, with a favourable toxicity profile. Its very favourable cost-effectiveness invites to further develop this approach. Finally, provision of dexrazoxane/doxorubicin, then 5-day ifosfamide infusion would be the next logical step as a first line completely outpatient therapy in sarcoma patients.

Table 4 Total cost per cycle for 2 m²-patient body surface area

Cost per cycle	Ifosfamide			
	5-day infusion	Cost (€)	5 days	Cost (€)
Ambulatory unit hospitalisation	1 day	1,301	–	–
Conventional hospitalisation	–	–	5 days	5,402
Ifosfamide dose	6,000 mg/m²	394	2,500 mg/m² × 5 days	820
Mesna dose	6,000 mg/m²	51	800 mg/m² × 5 days	34
Nurse visits at home	5	145	–	–
Total cost per cycle (€)		1,891		6,256

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