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ORIGINAL ARTICLE

Gemcitabine at fixed dose-rate in patients with advanced soft tissue sarcomas: a mono-institutional phase II study

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Abstract
Purpose To explore the clinical activity and toxicity of gemcitabine infused at the fixed dose of 10 mg/m^2/min over 100 min in patients with soft tissue sarcomas (STSs).
Patients and methods Fourteen patients with advanced locally unresectable and/or metastatic, pretreated STSs (seven leiomyosarcoma, three malignant schwannoma, one synovialsarcoma, one malignant fibrous histiocytoma, one endometrial stromal cell sarcoma, one undifferentiated) were treated with gemcitabine 10 mg/m^2/min/week over 100 min given for 3 weeks out of 4. The median age was 52 years (range 27–77), male/female ratio was 3/11, and the median WHO performance status was 0 (range 0–1). The median number of previous medical treatments for advanced disease was 1 (range 1–2).
Results A median number of three cycles (range 1–10 cycles) and a total of 151 weekly administrations (median 9, range 3–27) of gemcitabine were administered. Treatment was well tolerated and the main causes of dose-reduction or omission/delay were hematological and liver toxicities. One patient (7%; 95% confidence interval: 0.2–33.9%) with a metastatic uterine leiomyosarcoma obtained a partial response that lasted for 6.5 months. Three patients (two leiomyosarcoma and one schwannoma) (21%) obtained a stabilization of disease. The median time to progression was 3.1 months (range 1.0–9.5). The median overall survival was 11.8 months (range 1.0–54.5+).
Conclusions Gemcitabine infused at the fixed dose of 10 mg/m^2/min over 100 min shows a good tolerability but an overall modest activity in unselected STSs histotypes. Nevertheless, an interesting tumor growth control rate was observed in specific histological variants (i.e., leiomyosarcoma), thus confirming data from recent controlled clinical trials.

Keywords Soft tissue sarcoma · Chemotherapy · Gemcitabine · Antitumor activity · Toxicity

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Introduction

Soft-tissue sarcomas (STSs) are rare tumors with an annual incidence of approximately 1% of all cancer [1]. Local control of disease can be, generally, obtained through the use of surgery and radiotherapy. In terms of prognosis, the histological grade of the tumor (low, intermediate, or high) is still the most important factor related to the occurrence of distant metastases. In metastatic disease the treatment is often palliative; however, in young patients with good performance status poly-chemotherapy regimens including anthracyclines and ifosfamide allows a temporary control of disease in 50–70% of the cases [2]. In previously treated patients, there is a need to identify effective new regimens.

2′,2′-Difluorodeoxycytidine (dFdC, Gemcitabine), is an analogue of deoxycytidine which, after phosphorylation to the 5′-di- and 5′-triphosphate (dFdCTP), induces inhibition of DNA synthesis and cell death [3]. Gemcitabine has

proven to be active in a wide variety of solid tumors, including pretreated advanced STSs [4–9]. The most extensively employed schedule is a weekly 30-min infusion with doses ranging between 800 and 1,200 mg/m^2. However, several phase I trials demonstrated that the accumulation of its active metabolite (gemcitabine triphosphate) was saturated by dose rates of 10 mg/m^2/min [10–12].

The aim of this mono-institutional study was to evaluate the activity and the toxicity of gemcitabine at a fixed dose-rate of 10 mg/m^2/min over 100 min in patients with advanced pretreated STSs. A review of the trials investigating the activity of gemcitabine as single agent has also been conducted.

Patients and methods

Patient selection

All consecutive patients afferent to the "Division of Medical Oncology A" with the following eligibility criteria were enrolled in the study: histologically confirmed diagnosis of STS with locally unresectable and/or metastatic disease; age 18–75 years; World Health Organization (WHO) performance status $\leq$2; expectancy of life $\geq$12 weeks; measurable or evaluable disease; at least one previous chemotherapy for advanced disease containing anthracyclines and/or ifosfamide; adequate bone marrow and liver/kidney function (leukocyte count $\geq$3,000/μL, absolute neutrophil count [ANC] $\geq$ 1,500/μL, platelet count $\geq$100,000/μL, total bilirubin $\leq$ 1.25 [$\leq$1.5 in case of liver metastases] $\times$ upper limit of normal [ULN], aspartate/alanine aminotransferase [ASAT/ALAT] levels $\leq$ 1.25 [$\leq$2.5 in case of liver metastases] $\times$ UNL, and serum creatinine concentration <1.25 $\times$ UNL); females who were non pregnant or non lactating at the moment of study entry; not evidence of uncontrolled infections; no prior history of malignancy except for previously completely resected non melanoma skin cancer and in situ squamous cell carcinoma of the cervix; no active central nervous system metastases. Signed informed consent was obtained from all patients. The study was approved by the local Ethical Committee of the Regina Elena Cancer Institute.

Treatment plan and dose adjustments

Each cycle of the investigational treatment consisted of gemcitabine at the dose of 10 mg/m^2/min administered over a period of 100 min weekly for three consecutive weeks, followed by 1 week of rest. Gemcitabine (Gemzar) was supplied by Eli Lilly Italia S.p.A. A concomitant medication with antiemetics was administered before each dose of gemcitabine. Weekly complete blood cell (CBC) with differential and platelet count and liver function (ASAT/ALAT) were monitored. Before each cycle CBC and serum chemistries with electrolytes were performed. Treatment toxicities were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0 [13]. Dose-adjustment during the treatment were based on hematological and extra-hematological toxicities. On day 1, if neutrophil count was <1.5 $\times$ 10^9/L and/or platelet count was <100 $\times$ 10^9/L, chemotherapy doses were delayed (for up to 2 weeks). On days 8 and 15, patients having a neutrophil count between 0.5 and 0.999 $\times$ 10^9/L, or platelet count between 50 and 99 $\times$ 10^9/L had their gemcitabine doses reduced by 25% at re-treatment. Gemcitabine was held in cases of patients having ANC $\leq$0.5 $\times$ 10^9/L or platelet count $\leq$50 $\times$ 10^9/L until resolved and then gemcitabine dose was resumed at a 25% reduction. In the event of serious extra-hematological toxicity, gemcitabine was withheld until toxicity decreased to $\leq$grade 2, with subsequent treatment at a 25% dose-reduction. The individual doses of gemcitabine omitted due to toxicity were subsequently not administered for that given course. A delay in recycling superior to 2 weeks due to toxicity led the patient to be withdrawn from the study.

Baseline and treatment assessments

Before study enrolment, patients were submitted to a computed tomography scan and/or a magnetic resonance imaging for baseline evaluation of tumor lesions. Clinical and radiological response assessment was performed every three cycles using the same methods employed for baseline evaluations. RECIST (Response Evaluation Criteria in Solid Tumors) criteria were used to determine best overall response [14]. A complete response (CR) was defined as disappearance of all measurable and evaluable disease and no new lesions. A partial response (PR) is a 30% decrease of the sum of the major diameters of the target lesions; CR and PR were to be confirmed after at least 4 weeks. Progression (P) is a 20% increase of the sum of the major diameters of the target lesions or the appearance of new lesions. Stable disease (SD) is defined as measurement not qualifying for CR, PR or P.

Statistical analysis

The study was conducted using a two-stage study design [15]. With an alpha-error of 5% and a power of 80%, the sample size was 14 patients for the first stage and additional 14 patients for the second stage. The accrual was stopped if less than two responses were observed in the first 14 assessable patients (<14%). Duration of response was defined as the interval from the onset of response until evidence of disease progression. Time to progression and overall

survival were defined as intervals from date on study until progression or death of any cause and were estimated by the method of Kaplan and Meier.

Results

Patient characteristics

From November 2002 until September 2006, 14 patients with advanced pretreated STSs were enrolled in the study. Patients' characteristics are illustrated in Table 1. There were 3 males and 11 females with a median age of 52 years (range 27–77). The most common histology was leiomyosarcoma (50% of patients) of uterine (one patient), gastrointestinal (one patient), and extra-gastrointestinal origin (five patients). The sites of metastases were lung (11 patients), liver (2 patients), other (11 patients). Five patients presented with metastatic disease at the time of first diagnosis. Among patients who underwent surgical excision of primary tumor, three patients received an adjuvant treatment with anthracyclines and ifosfamide. The median number of previous medical treatments for advanced disease was 1 (range 1–2). Nine patients had previously received anthracyclines and ifosfamide, two patients epirubicin alone, two patients ifosfamide alone, and one patient the MAID (mesna, adriamicin, ifosfamide, dacarbazine) regimen. One patient received a second-line chemotherapy with dacarbazine.

Table 1 Patient's characteristics

	Number of patients
Total number	14
Eligible	14
Gender	
Male	3
Female	11
Age (years)	
Median	52
Range	27–77
WHO performance status	
Grade 0	12
Grade 1	2
Histology	
Leiomyosarcoma	7
Malignant schwannoma	3
Synovialsarcoma	1
Malignant fibrous histiocytoma	1
Undifferentiated sarcoma (NOS)	1
Endometrial stromal cell sarcoma	1
Primary tumor site	
Trunk	4
Visceral	3
Uterus	3
Retroperitoneum	2
Lower limb	1
Gastrointestinal tract	1
Prior treatments	
Surgery	14
Radiotherapy	4
Adjuvant	3
Palliative	1
Chemotherapy	14
Neo-adjuvant	1
Adjuvant	3
Advanced	13

Response

All patients were evaluable for response. One PR (7%; 95% confidence interval: 0.2–33.9%) and 3 SD (21%) were observed. The clinical response was observed in a patient with lung metastases from uterine leiomyosarcoma after three cycles of treatment and the duration of the response was 6.5 months. The patient was treated until disease progression and received ten cycles of gemcitabine and 27 weekly administrations of the drug. The patients who obtained a SD had a histological diagnosis of leiomyosarcoma (1 trunk; 1 gastrointestinal) and schwannoma. The duration of the stabilizations was 9 months for one case (leiomyosarcoma of the trunk) and 6 months in the two other cases. A progression of disease occurred in ten patients. One patient with a uterine leiomyosarcoma experienced a rapid deterioration of health status after three cycles and the response to treatment was considered as a clinical P (instrumental reassessment not performed due to the clinical condition of the patient).

The median time to progression was 3.1 months (range 1.0–9.5) and the median overall survival was 11.8 months (range 1.0–54.5+). Two patients are still alive at 54.5+ and 7+ months from the study entry.

Toxicity

A total of 59 cycles of chemotherapy and a median number of 3 cycles (range 1–10) were administered. The complete number of actually delivered weekly infusions of gemcitabine was 151 (median number: 9, range 3–27). Forty-three percent (6 out of 14) of patients completed at least four cycles of study treatment. Table 2 summarizes the hematological and extra-hematological toxicities occurred during the treatment. Severe (grade 3–4) hematological toxicity consisted mainly in neutropenia and thrombocytopenia. A grade 3–4 neutropenia and a grade 3 thrombocytopenia occurred in 14% (2 out of 14) and in 7% (1 out of 14) of

Table 2 Maximum toxicity per patient according to NCI CTC (National Cancer Institute Common Toxicity Criteria) ($n = 14$)

	Grade			
	1	2	3	4
Leucopenia	2 (14%)	7 (50%)	2 (14%)	–
Neutropenia	1 (7%)	6 (43%)	1 (7%)	1 (7%)
Thrombocytopenia	4 (28%)	2 (14%)	1 (7%)	–
Anemia	4 (28%)	5 (36%)	–	–
Asthenia	3 (21%)	1 (7%)	–	–
Nausea and vomiting	1 (7%)	1 (7%)	–	–
Mucositis	2 (14%)	–		–
ASAT/ALAT elevation	2 (14%)	1 (7%)	2 (14%)	–
Bilirubin elevation	2 (14%)	–	–	–
Skin	1 (7%)			
Phlebitis	–	–	2 (14%)	–

patients, respectively. No episode of febrile neutropenia was registered. One patient, despite dose reduction, required a support with prophylactic granulocyte colony stimulating factor (G-CSF) to allow the weekly administrations. Non-hematological toxicity was generally from mild to moderate and included nausea and vomiting, mucositis, ASAT/ALAT and bilirubin elevation, and skin toxicity. Two patients experienced a grade 3 hypertransaminasemia and two patients a grade 3 thrombophlebitis. Thirty-eight (25%) and 23 (15%) out of the 151 weekly administrations of gemcitabine were reduced as per protocol and omitted respectively. The main causes for dose adjustment and/or omission were hematological toxicity (neutropenia and thrombocytopenia) in 24 out of 151 (16%) weekly infusions (8/14 patients, 57%) and hypertransaminasemia in 30 out of 151 (20%) weekly infusions (2/14 patients, 14%). Only one cycle of chemotherapy was delayed and reduced of dose due to persistent thrombocytopenia. No patient withdrew from the study due to toxicity and no toxic deaths were observed.

Discussion

STSs are a heterogeneous group of mesenchymal tumors with different biological and clinical characteristics. Anthracyclines (doxorubicin and epirubicin) and ifosfamide represent the milestone of the treatment and patients affected by chemo-resistant disease have a very poor prognosis.

A few phase I–II trials demonstrated that gemcitabine, employed at various doses and schedules, exhibits antitumor activity in advanced STSs [4–9]. The activity of gemcitabine, in terms of clinical responses achieved, seems to be more schedule-than dose-related. Laboratory and translational studies have shown that the intracellular accumulation of gemcitabine active metabolite, gemcitabine triphosphate, can be increased by administering a constant dose over progressively longer periods of time. Several phase I trials demonstrated that the accumulation of gemcitabine triphosphate by mononuclear cells and leukemic blasts was saturated by dose rates of 10 mg/m^2/min [10–12]. This dose-rate generates plasmatic levels of gemcitabine of 26 (±9) μmol which maximise intracellular accumulation of its active metabolite allowing in pretreated cancer patients toleration of weekly doses as high as 2,800 mg/m^2 over 280 min [16,17].

In our study we explored the activity and toxicity of gemcitabine administered at the constant dose-rate of 10 mg/m^2/min (1,000 mg/m^2 infused over 100 min) in STSs. The toxicity of the treatment was acceptable, with severe toxicities limited to bone-marrow and liver dysfunctions which led to dose adjustments and/or omissions/delays in 57% and in 14% of patients, respectively, and in 16 and 20% of weekly infusions respectively. We observed one PR that lasted for 6.5 months in a patient with lung metastases from uterine leiomyosarcoma who had been previously treated with epirubicin and ifosfamide for advanced disease. Three patients obtained a SD with an overall tumor control rate of 28% (PR: 7%; SD: 21%).

In Table 3 the results of the published trials exploring the activity of gemcitabine as single agent in advanced STSs are summarized [4–9, 18–24]. In these trials a response rate ranging from 3 to 20.5% was reported.

The differences in response rates observed in these trials may be due to several factors including the schedule utilized and the histological subtypes included in each study. Most of the trials employed a schedule with a short-term infusion (30 min) of gemcitabine ranging from 1,000 to 1,250 mg/m^2 [6, 8, 9, 18, 20–24]. Except for our trial, only two other trials investigated a schedule with a longer duration of infusion (360 min and 72 h, respectively) with gemcitabine doses ranging from 50 to 250 mg/m^2 [5, 7]. Furthermore, sarcoma subtypes seem to have different chemo-sensitivity to gemcitabine, and the different distribution of histological pattern included in the reported studies may contribute to explain the discordances observed. The majority of the responses was observed in patients with uterine or extrauterine leiomyosarcoma and with angiosarcoma, regardless of previous chemotherapy received [4–7, 9, 19, 20, 24]. In a very small experience conducted by Gautam et al. [19] on three patients with angiosarcoma, all the patients achieved a clinical response: one CR and two partial PRs. The Gynecologic Oncology Group has conducted a phase II trial with gemcitabine as second-line chemotherapy in patients affected by uterine leiomyosarcoma, achieving a response rate of 20.5% [9]. In our series of patients the PR and two out of 3 SD were reported in patients affected by leiomyosarcoma, including a gastrointestinal site.

Table 3 Activity of gemcitabine as single agent in patients with advanced adult soft tissue sarcomas

Author	Dose (mg/m^2) and schedule	Infusion duration	Evaluable pts (*n*)	RR (%)	SD (%)	mTTP (mos)	Comments
1st line							
Okuno [22]	1,250/week for 3 weeks q 28d	30′	25	4	32	13[a]	R in epithelial sarcoma
Von Burton [24]	1,000/week for 10 weeks → for 3 weeks q 28d	30′ [d]	46	7	20	2[b]	R in LMS, MFH, and sarcoma NOS
2nd line and over							
Amodio [18]	1,000–1,250/week for 3 weeks q 28d	30′	18	5	39	4	1st line of treatment for 2 pts; R in MFH
Merimsky [4]	1,000/week for 7 weeks q 63d → for 3 weeks q28d	NR	8	13	–	NR	R in uterine LMS/minor R in AS
Spath-Schwalbe [5]	200–250/week for 3 weeks q 28d	360′	18	11	33	NR	R in uterine LMS and MFH
Samuels [7]	50–200/week q14d	72 h	9	11	NR	NR	R in AS
Patel [6]	1,000/week for 7 weeks q 63d → for 3 weeks q 28d	30′	56	12.5	NR	3	1st line of treatment for 20 pts; 17 pts with gastrointestinal LMS. R in uterine/extremities LMS, MFH, and sarcoma NOS
Gautam [19]	1,000/week	NR	3	100	–	NR	All pts with AS
Okuno [20]	1,250/week for 3 weeks q 28d	30′	29	3	7	2.1	1st line of treatment for 10 pts; R in uterine LMS
Švancàrovà [21]	1,250/week for 3 weeks q 28d	30′	31	3	NR	1.5	R in LMS
Bauer [8]	900–1,000/week for 2 weeks	30′	9	11	NA	4.2	R in liposarcoma
Look [9]	1,250/week for 3 weeks q 28d	30′	42	20.5	15.9	4.9[c]	All pts with uterine LMS
Hartmann [23]	1,000/week for 3 weeks q 28d	30′	15	6	47	3	1 SD lasting more than 2.5 years
Ferraresi (current study)	1,000/week for 3 weeks q 28d	100′	14	7	21	3.1	R in uterine LMS

pts patients, *RR* response rate, *SD* stable disease, *mTTP* median time to progression, *mos* months, *R* response, *NR* not reported, *NA* not available, *LMS* leiomyosarcoma, *MFH* malignant fibrous histiocytoma, *AS* angiosarcoma, *NOS* not otherwise specified

[a] Estimated progression-free survival

[b] Median time to treatment failure

[c] Median duration of responsed

[d] Author's communication

The overall rates of responses (3–20%) and stabilizations (7–47%) showed in all reported trials, including the present, confirm that gemcitabine as single agent has moderate activity and allows an appreciable control of tumor growth, even in patients with pretreated advanced disease. The role of longer durations of infusion (i.e. superior to 30 min) of gemcitabine in combination with other active agents in STSs, as well as in other tumor types (non-small cell lung cancer, pancreatic cancer, urothelial tract cancer, etc.), has been tested in recently published controlled clinical trials [25–35]. In STSs patients, interesting results in terms of clinical benefit have been reported in phase II trials with gemcitabine at fixed dose-rate in combination with either docetaxel or dacarbazine and vinorelbine [25, 26, 28, 30].

In the experience of the Memorial Sloan-Kettering Cancer Center, the combination of gemcitabine (900 mg/m^2 infused over 30 or 90 min on days 1 and 8) and docetaxel (100 mg/m^2 infused on day 8) in a mixed population of 34 untreated and pretreated patients with leiomyosarcoma (mainly of uterine origin) obtained a high overall response rate of 53% [25]. The results of this study seems to suggest that this association may represent a potentially valid therapeutic option in STSs. In a randomized phase II trials by Maki et al of fixed dose-rate infusion of gemcitabine (1,200 mg/m^2 infused over 120 min given for 3 weeks out of 4) compared to a lower dose of gemcitabine (900 mg/m^2 infused over 90 min on days 1 and 8) with docetaxel (100 mg/m^2 infused on day 8) in patients with unselected STSs histotypes, the combination showed a superior progression-free (median: 6.2 vs. 3 months) and overall (median: 17.9 vs. 11.5 months) survival respect to gemcitabine alone but with increased toxicity [26]. The combination of fixed dose-rate gemcitabine 1,800 mg/m^2 delivered over 180 min and dacarbazine 500 mg/m^2 both administered every 2 weeks in 26 patients with advanced STSs yielded a low remission rate (4%) but appreciable progression-free rates at 3 and 6 months (48 and 28%, respectively) with clinical benefit particularly in patients with leiomyosarcomas and malignant fibrous histiocytomas [27, 28]. Finally, Dileo et al. [30] reported an acceptable toxicity and a clinically meaningful rate of disease control (CRs plus PRs plus SD superior to 4 months) of 25% in a phase II study on 40 patients with advanced STSs treated with fixed dose-rate gemcitabine 800 mg/m^2 infused over 90 min in association with vinorelbine 25 mg/m^2, both drugs administered on day 1 and 8 of a 21-day cycle.

To conclude, the schedule of gemcitabine tested in our study showed a good tolerability but an overall modest activity in unselected STSs histotypes. Nevertheless, an interesting tumor growth control rate (PR plus SD superior to 4 months) was observed in specific histological figures such as leiomyosarcoma, thus confirming data from the literature. Higher response rates and better progression-free survival have been reported with gemcitabine-containing combinations, even though further investigations on dose-rate of infusion and sequence of drugs administration are warranted.

Conflict of interest The study had no sponsorship. The authors declare non conflicts of interest.

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