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Gemcitabine in advanced adult soft-tissue sarcomas. A phase II study of the EORTC Soft Tissue and Bone Sarcoma Group

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Abstract

Gemcitabine (2′-deoxy-2′-difluorocytidine monohydrochloride) at a dose of 1250 mg/m^2 was given as a 30-min intravenous (i.v.) infusion on days 1 and 8 in a 3-weekly schedule to 32 patients with advanced soft-tissue sarcoma (STS) failing first-line chemotherapy. One patient was ineligible due to a delay between the previous chemotherapy and the start of treatment. Of the eligible patients, median age was 53 years (range 23–73 years). The predominant histological subtype was leiomyosarcoma in 12 patients (38%). The median number of cycles was three (range 1–8 cycles) with a median total dose of gemcitabine of 6.25 g/m^2 (range 1.25–19.97 g/m^2). The relative dose intensity of gemcitabine was 96% (range 50–103%). Treatment was tolerated very well with non-complicated haematological toxicity as the most frequently observed side-effect. Only one partial tumour response was documented, giving a response rate of 3.23% (95% Confidence Interval (CI): 0.08–16.2%). The median overall survival was 268 days (95% CI: 129–377) and the median time to progression was 45 days (95% CI: 41–79). These results indicate that gemcitabine given at this dose and schedule is not active as second-line therapy in advanced STS.

Keywords: Gemcitabine; Chemotherapy; Soft-tissue sarcoma; Leiomyosarcoma; Synovial sarcoma

1. Introduction

At present, chemotherapy for patients with advanced soft-tissue sarcoma (STS) is inadequate [1–3]. Patients given chemotherapy for advanced STS have not yet shown a statistically significant prolongation of overall survival. Cure is achieved in less than 4% of advanced sarcoma patients. Few drugs have significant activity in STS and combination chemotherapy is only slightly more active at the expense of more toxicity [3–5]. It has been shown that drugs showing some activity as second-line treatment are likely to be significantly effective first-line, hence the justification for phase II trials in this setting [5].

Gemcitabine (2′-deoxy-2′-difluorocytidine monohydrochloride/beta isomer) was developed as a new deoxycytidine analogue with reduced potential for catabolism by cytidine deaminase [6–8]. Gemcitabine is an antimetabolite that acts as an inhibitor of DNA synthesis, causing chain termination, and also inhibits other targets including ribonucleotide reductase. It is cell cycle specific for S phase, and blocks the progression of the cell through the G1/S phase boundary.

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Gemcitabine has been evaluated using a variety of dosages and schedules [9]. In phase I studies, short-lived thrombocytopenia was dose-limiting, granulocytopenia was not so pronounced. Some patients observed maculopapular skin rash with pruritus and flu-like symptoms were also reported. Gemcitabine has shown activity in many solid tumours, both as primary and second-line treatment [10–14]. Of particular note is the activity in patients with advanced and metastatic pancreatic cancer that had progressed despite prior therapy with 5-fluorouracil (5-FU) [11].

Gemcitabine has activity against otherwise refractory solid tumours that suggests that clinical trials in sarcomas are warranted. Therefore, the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group has performed the present phase II study on gemcitabine in advanced STSs.

2. Patients and methods

Patients with histologically-confirmed STS at central review or after pathology review at the treating centre and with measurable lesions with evidence of progression within 6 weeks prior to treatment were eligible for the study. Patients with prior malignant disease or other serious medical conditions were excluded. Patients were required to have normal haematological function, serum creatinine $\leqslant 120$ μmol/l or calculated clearance (Cockroft and Gault method) >1.08 ml/s, bilirubin <30 μmol/l, albumin $\geqslant 25$ g/l, World Health Organization (WHO) performance status 0 or 1. One line of previous combination chemotherapy or two single regimens were permitted. This chemotherapy should have been discontinued for more than 4 weeks (6 weeks for nitrosoureas and mitomycin). Patients who have not received any previous chemotherapy were ineligible. The study was performed in accordance with the Declaration of Helsinki and local ethics regulations. Written informed consent was obtained. Gemcitabine was supplied as 200 and 1000 mg vials by Eli Lilly and Company.

Gemcitabine 1250 mg/m^2 on days 1 and 8 in a 3-weekly schedule was given as a 30-min infusion after reconstitution with 0.95% sodium chloride. Antiemetics were given in accordance with local practice. Follow-up studies included assessment of haematology and biochemistry before each cycle of treatment. A total of seven 3-weekly cycles were planned. Response to treatment was assessed every 6 weeks until documented progression by use of WHO criteria. Responses were subject to independent peer-review. Treatment-related side-effects were assessed separately for each cycle of therapy using National Cancer Institute-Common Toxicity Criteria (NCI-CTC) criteria.

3. Results

3.1. Patient characteristics

32 patients were enrolled in the study by eight centres between June and September 1998. One patient was ineligible because of an interval between their previous chemotherapy and the start of the gemcitabine treatment of less than the prescribed 4 weeks. All 31 patients were included in the treatment and toxicity analyses. The median age of the eligible patients was 53 years (range 23–73) Their characteristics are shown in Table 1.

Table 1
Patient characteristics

	Number of patients
Total number	32
Eligible	31
Gender	
Male	15
Female	16
WHO performance status	
Grade 0	10
Grade 1	21
Histology	
Leiomyosarcoma	12
Synovial sarcoma	6
High grade sarcoma (NOS)	4
Liposarcoma	3
Malignant peripheral nerve sheath tumour	2
Angiosarcoma	1
Rhabdomyosarcoma	1
Endometrium stroma cell sarcoma	1
Gastrointestinal stroma cell sarcoma	1
Localisation	
Visceral (intra-abdominal)	9
Other front trunk	2
Shoulder	2
Knee	1
Thigh	3
Uterus	5
Breast	1
Retroperitoneal	2
Lower arm	2
Upper arm	1
Foot	1
Lower leg	2
Prior treatments ($n=31$ eligible pts)	
Surgery	
Curative	21
Palliative	7
Both	3
Radiotherapy	
None	11
Excluding haematopoietic sites	16
Inclusive of haematopoietic sites	4
Chemotherapy	
Adjuvant	4
Advanced	27

WHO, World Health Organization; NOS, not otherwise specified; pts, patients.

Table 2
Haematological toxicity of gemcitabine treatment

Nadir (NCI-CTC)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WBC	10	8	10	3	–
Granulocytes	13	5	9	3	1
Platelets	25	2	1	2	1
Haemoglobin	9	7	12	1	2

WHO, World Health Organization; WBC, white blood cells.

Table 3
Non-haematological toxicity of gemcitabine treatment

NCI-CTC grade	0	1	2	3	4
Vomiting	16	7	5	1	
Other gastrointestinal	28	2			
Dysuria	30	1			
Other genitourinary	29		1		
Infection	24		1		
Headache	24	2	3		
Sensory toxicity	29	2			
Other neurotoxicity	24	2	2		
Cough	26	1			
Shortness of breath	25	1			
Other pulmonary	29	1			
Alopecia	23	2	1		
Local toxicity	30	1			
Other skin	27	1	2		
Weight loss	23	3			
Haemorrhage	29		1		
Other	22	1	3	1	

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

3.2. Gemcitabine treatment and toxicity

31 evaluated patients received a median of three cycles (range 1–8 cycles) with a median total dose of gemcitabine 6.25 g/m^2 (range 1.25–19.97 g/m^2). The relative dose intensity of gemcitabine was 96% (range 50–103%). Haematological toxicity is shown in Table 2 and non-haematological toxicity in Table 3. The treatment was tolerated very well with only a few grade 3 and 4 toxicities. Non-complicated haematological toxicity was the most frequently observed toxicity. The most commonly reported non-haematological toxicity was vomiting which was usually controlled with antiemetics. Many of the other reported non-haematological toxicities were classified as not related to the drug treatment. There was no episode of febrile neutropenia.

3.3. Response

Among the 31 eligible patients, one partial response was documented in a patient with a high-grade leiomyosarcoma relapsing in the pleura and mediastinum. Thus, the overall response rate was 3.23% (95% Confidence Interval (CI): 0.08–16.2%). The median time to progression was 45 days and the median survival was 268 days (95% CI: 129–377).

4. Discussion

STSs are rare tumours accounting for approximately 1% of all malignancies. Despite an optimal primary therapy many patients will fail and develop distant metastasis [1,2,5]. In addition, many patients have locally advanced disease at the time of diagnosis. Only a few drugs have significant activity in STS. Treatment with doxorubicin, ifosfamide and dacarbazine (DTIC) has been reported to result in response rates of approximately 20% [2,4,5,15]. New classes of drugs and more effective modifications of older drugs continue to be tested against STS [5,15–17].

Gemcitabine with its novel mode of action and already proven activity in several other solid tumours was evaluated in this open non-randomised multicentre phase II trial. The drug, given at the above described dosage and schedule, is not very effective in the treatment of patients with advanced STS. However, the activity of gemcitabine in histological subtypes of STSs cannot be excluded. Other reports have indicated that occasional patients do respond to gemcitabine and may experience a prolonged disease stabilisation [18–21]. However, with the present knowledge gemcitabine cannot be recommended as a routine second-line therapy for patients with this disease.

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