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Report

Phase II trial of gemcitabine in patients with pretreated advanced soft tissue sarcomas

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Because of the low number of active cytotoxic drugs and their limited activity, the evaluation of new anti-cancer agents for their activity in soft tissue sarcomas is a continuing need. The objectives of this prospective phase II trial of gemcitabine were to estimate the response rate and to define the toxicities of prolonged infusions of low-dose gemcitabine in patients with pretreated advanced soft tissue sarcomas. Patients were eligible if they had a histologic diagnosis of unresectable, recurrent or metastatic, progressive soft tissue sarcoma, and if they had been treated with at least one prior chemotherapy consisting of an anthracycline- and/or ifosfamide-containing regimen. Gemcitabine was administered as a 360 min infusion on days 1, 8 and 15 of a 28 day cycle. The initial dose of gemcitabine was 200 mg/m^2 in all patients. Dose escalation to 250 mg/m^2 was allowed in the case of stable disease and good tolerability of the drug. All 18 patients (median age 58 years) who enrolled were treated with gemcitabine, and all were assessable for toxicity, response and survival. Only two of these 18 patients had an objective response to a previous palliative chemotherapy. A median of 3 cycles (range 1–7) of gemcitabicin were administered. Two (11%) of the patients had a partial response lasting 5 and 6 months, respectively. Both of these patients had only lung metastases. Whereas one of these patients had a transient partial response to the foregoing chemotherapy (consisting of ifosfamide and doxorubicin), the other patient has been progressive on these drugs. One additional patient, progressive on ifosfamide and doxorubicin, had an objective response of greater than 50% confined to the lungs and stable local recurrence for 6 months. Six patients had stable disease for 3–6 months and nine patients had disease progression. The median survival was 8 months. Treatment generally was well tolerated with six patients having transient grade 3 non-hematologic toxicity, four having grade 3 neutropenia, and one having grade 4 neutropenia and thrombocytopenia. Gemcitabine, given as a prolonged infusion at a low dose level, has a favorable toxicity profile and displays antitumor activity in patients with intensively pretreated, advanced soft tissue sarcomas.

Key words: Chemotherapy, gemcitabine, metastatic disease, soft tissue sarcomas.

Introduction

Adult soft tissue sarcomas are rare mesenchymal neoplasms characterized by a high morphological and clinical heterogeneity, as well as by a limited responsiveness to most cytotoxic agents. Only three drugs (doxorubicin, ifosfamide and dacarbacine) have clear activity, with response rates of around 20%. Combination chemotherapy may be associated with higher objective response rates than single-agent chemotherapy, but toxicity also is greater with combination regimens and no survival advantage for the more aggressive alternatives has been reproducibly reported in advanced disease.[1,2] Therefore, new active agents need to be identified if therapy of this group of diseases is to be improved.

Gemcitabine (2′,2′-difluorodeoxycytidine, dFdC) is a novel nucleoside analog. In phase II studies, gemcitabine has shown significant activity against different tumors including pancreatic, breast, ovarian, urothelial, testicular, and non-small cell and small cell lung cancer.[3–7] Preclinical analysis of the anti-tumor activity of gemcitabine against human xenografts suggested that gemcitabine also may be effective in soft tissue sarcomas.[8,9]

Results from phase I and II trials of gemcitabine suggested that the most favorable therapeutic index was achieved with a 3-weekly schedule followed by a 1 week break.[10] The usually recommended dosing for gemcitabine is 1000 mg/m^2 as a 30 min i.v. infusion.[4] Phase I dose escalation studies failed to demonstrate a

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clear dose–response effect beyond this dose.[11,12] The reason for this lack of dose–response effect may be explained by the pharmacology of gemcitabine.[13] Gemcitabine is activated from the inactive prodrug by intracellular phosphorylation to dFdC 5′-triphosphate. The rate of this metabolic conversion is limited by the activity of deoxycytidine kinase.[14,15] Because this enzyme is saturated at a low dose level, it is highly likely that short infusions of large doses of gemcitabine over 30 min will not result in higher concentrations of the active metabolite.

The postulation was put forth that longer infusion times might be superior to the brief 30 min infusion.[16,17] In fact, preclinical models suggested that prolonged infusion might provide better antitumor effects and less toxicity, and preliminary clinical data using prolonged infusions of gemcitabine at low dose levels were promising.[16–18] In the latter study conducted by Pollera *et al.*, dose-limited toxicity was encountered at 6 h with a dose of 300 mg/m^2.[18] In a phase I dose escalation study at our institution investigating weekly gemcitabine infusions over 6 h the maximum-tolerated dose has been reached at 250 mg/m^2.[19] The present report describes the results of a phase II study of gemcitabine given as a prolonged infusion at a low dose level in intensively pretreated patients with advanced soft tissue sarcomas.

Patients and methods

This prospective phase II trial was approved by the Ethics Committee of the University Hospital Charité Berlin. All patients were informed of the investigational nature of the study and were required to provide signed informed consent. Patients with histologically confirmed, advanced soft tissue sarcoma and measurable lesions with documented progression during the previous 6 weeks were eligible for the study, provided that they had received at least one prior palliative chemotherapy consisting of an anthracycline or ifosfamide in the case of contraindications against anthracyclines. Patients were required to have a Karnofsky performance status $\geqslant 50$, a white blood cell count of $> 2.5 \times 10^9$/l (granulocyte count > 1.5) and platelets $> 80 \times 10^9$/l. In addition, the serum creatinine level had to be $\leqslant 2$ mg/dl, the serum bilirubin level had to be $\leqslant 1.5$ mg/dl, and the aspartate transaminase and alanine transaminase < 3 times the upper normal level.

Treatment

Gemcitabine (Eli Lilly, Bad Homburg, Germany) 200 mg/m^2 was given by i.v. infusion over 360 min once weekly for 3 consecutive weeks (days 1, 8 and 15), followed by a 1 week rest. This 4 week schedule defined one cycle of chemotherapy. Patients with stable disease after one cycle of therapy could have their subsequent doses increased to 250 mg/m^2 if hematologic toxicity did not exeed grade 2 and non-hematologic toxicity did not exceed grade 1. On days 1, 8 and 15, full-dose therapy was given if the absolute granulocyte count was $\geqslant 1.5 \times 10^9$/l, the platelet count was $\geqslant 100 \times 10^9$/l and there was no grade $\geqslant 3$ non-hematologic toxicity. If the granulocyte count was $1.0–1.5 \times 10^9$/l or the platelet count was $50–100 \times 10^9$/l, then 75% of the planned dose was given. If the granulocyte count was $< 1.0 \times 10^9$/l, the platelet count was $\leqslant 50 \times 10^9$/l or non-hematologic toxicity was grade $\geqslant 3$, then therapy was held that day and all subsequent doses were reduced by 25%. A cessation of therapy was planned in the case of grade 4 non-hematologic toxicity.

Patients received routine antiemetic treatment consisting of a 5-hydroxytryptamine-3 antagonist. Dexamethasone pretreatment was allowed for patients experiencing a flu-like syndrome after the gemcitabine administration. No other chemotherapy or experimental medication was permitted while patients were on-study.

Response assessment and treatment duration

After every cycle of chemotherapy, response and toxicity were evaluated according to WHO criteria. Only patients receiving at least three doses (one complete cycle) of gemcitabine were considered assessable for response and toxicity. Survival was determined from the first day of treatment until the date of death. For patients with tumor response or at least disease stabilization, gemcitabine was continued until evidence of disease progression or the occurrence of unacceptable toxicity.

Results

Eighteen patients (10 men and eight women) entered into the study, and all were assessable for toxicity and for determination of response. The patient characteristics are listed in Table 1. Patients had advanced disease; all but two patients had more than one site of disease at study entry. Patients were pretreated with doxorubicin- and/or ifosfamide-based chemotherapy. Except for three patients who had been pretreated with single-agent chemotherapy, all patients had received two or more cytostatic agents. Sixteen

Table 1. Characteristics of patients at study entry

	No. of patients	%
Age (years)		
median	58	
range	20–70	
Karnofsky performance status		
median	80	
range	50–100	
Histology		
malignant fibrous hostiocytoma	5	28
leiomyosarcoma (uterine)	6 (3)	33
malignant Schwannoma	4	22
liposarcoma	2	11
clear cell sarcoma	1	6
Sites of disease		
lung	10	56
liver	7	39
nodes	6	33
cutaneous	5	28
other (including local recurrence)	13	72
Previous chemotherapy		
doxorubicin/4-epidoxorubicin	16	89
ifosfamide	15	83
other drugs	9	50

patients never had an objective response to prior chemotherapy.

In this study population of 18 patients, two partial responses (11%) were noted, with a duration of 5 and 6 months, respectively. An additional patient had a reduction (more than 50%) of pulmonary matastases and stable disease of local recurrence lasting 6 months. Two of these responses occurred in patients with uterine leiomyosarcomas. The third response occurred in a patient with malignant fibrous histiocytoma. Of the three patients responding to gemcitabine, two had been refractory to the previous polychemotherapy consisting of doxorubicin and ifosfamide. Remarkably, all responses to gemcitabine occurred in lung metastases. In both of the responding patients who had only pulmonary disease (and who at study entry were considered non-operable), resection of the metastases was attempted upon progression on gemcitabine. However, both patients had disease recurrence shortly after the operation.

Six patients had stable disease for 3–6 months. Median survival was 8 months with five patients were alive at 12 months (Figure 1).

A total of 189 gemcitabine administrations were given, with a median of 9 (range 3–24). Dose reductions were necessary for five patients; two patients had their dose increased to 250 mg/m^2; however, without an objective tumor response.

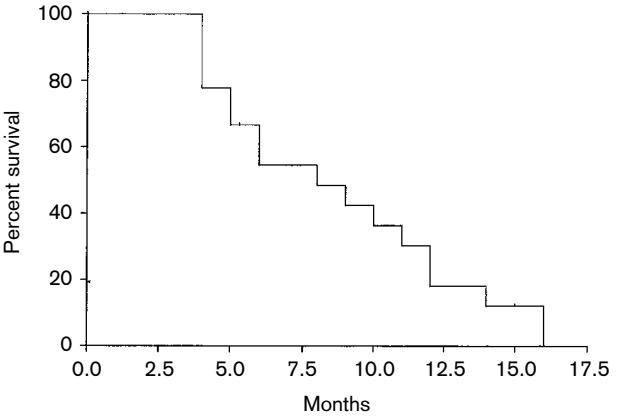

Figure 1. Overall survival of patients with advanced soft tissue sarcomas treated with gemcitabine.

Table 2. Incidence of grade 2 or higher toxicity according to WHO criteria during gemcitabine therapy ($n=18$)

	No. of patients at WHO grade (worst toxicity)		
	2	3	4
Non-hematologic			
nausea and vomiting	3	0	0
fever	4	0	0
edema	3	2	0
liver toxicity	4	3	0
mucositis	1	0	0
Hematologic			
granulocytopenia	4	3	1
thrombocytopenia	2	0	1
anemia	2	0	0

Toxicity is summarized in Table 2. In general, non-hematologic toxicities were transient and mild. Only one patient had to be treated because of neutropenic infection; this patient also required transfusions of platelets. There was no treatment-associated death.

Discussion

Because of the limited number and activity of cytostatic agents in soft tissue sarcomas, testing new drugs for the treatment of soft tissue sarcomas in second-line therapy is appropriate.[2,20] Because of its clinical activity in several different neoplasms and its activity in xenograft models with human soft tissue sarcomas, we evaluated gemcitabine in patients with soft tissue sarcomas. This report summarizes the

results of a small phase II study of gemcitabine in 18 patients with pretreated, advanced soft tissue sarcomas, only two of whom had responded to previous palliative chemotherapy with anthracycline- or ifosfamide-based regimens.

Two patients (11%) showed a partial remission to weekly gemcitabine given at a low dose level as a prolonged infusion. For one additional patient, pulmonary metastases responded to this regimen. Remarkably, all responses occurred in pulmonary disease, and two of these responses occurred in patients who had been refractory to first-line chemotherapy with doxorubicin and ifosfamide. This fact should be considered in conjunction with other unfavorable features of this study population, including the advanced median age, the high frequency of liver metastases (39%) and a reduced performance status (70 or less) in eight patients. The latter features have been identified as unfavorable prognostic factors of response rates in advanced soft tissue sarcoma in a previously published study.[21]

A recent abstract reported preliminary results of a phase II trial of gemcitabine in 30 patients with recurrent or metastatic gastrointestinal leiomyosarcomas and other soft tissue sarcomas.[22] In this trial investigators at the MD Anderson Cancer Center used a 'conventional' schedule of a weekly gemcitabine dose of 1000 mg/m^2 given as a 30 min infusion. The treatment was generally well tolerated with the need for only few delays in therapy due to toxicity. Three of the 30 evaluable patients responded to gemcitabine with one complete response and two partial responses. The results of both that study and ours indicate that gemcitabine has some activity in patients with advanced soft tissue sarcomas.

The optimal schedule of drug administration still needs to be defined for gemcitabine. Currently, it is unclear whether a short infusion of a large dose is superior to a prolonged infusion of gemcitabine at a low dose level. The optimal dose and duration of infusion still remains to be defined, considering the results of a very recent study using gemcitabine by fixed dose rate infusion in patients with metastatic pancreatic adenocarcinoma.[23] In any case, our study corroborates recent findings that gemcitabine retains its antitumor effect when given as a prolonged infusion at a low dose level.[24] Furthermore, the toxicity profile of this regimen in our heavily pretreated patients was reasonably well tolerated. This finding is important because there is a need for well-tolerated agents suitable for palliative therapy in patients with advanced soft tissue sarcomas. Such patients currently have little chance of any long-term disease control.

Conclusion

Gemcitabine, given as a prolonged infusion at a low dose level, has a favorable toxicity profile in heavily pretreated patients. The schedule we used displays some antitumor activity in patients with soft tissue sarcomas, at least in those with pulmonary metastases. In view of the activity and modest toxicity, gemcitabine warrants further investigation in soft tissue sarcomas. Especially, schedules using gemcitabine as prolonged infusions at low dose levels should be further explored.

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