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# An open label, non-comparative phase II study of gemcitabine as salvage treatment for patients with pretreated adult type soft tissue sarcoma

J. T. Hartmann[1,2], K. Oechsle[1], J. Huober[3], A. Jakob[4], M. Azemar[5], M. Horger[2,6], L. Kanz[1] and C. Bokemeyer[1]

[1]*Department of Medical Oncology, Hematology, Immunology, Rheumatology, Pneumology and;* [2]*Interdisciplinary Sarcoma Center, South West German Cancer Center, Eberhard-Karls-University, Tuebingen;* [3]*Department of Gynaecology and Obstretics, Eberhard-Karls-University, Tuebingen;* [4]*Klinikum, Offenburg;* [5]*Klinik Tumorbiologie, Freiburg;* [6]*Department of Radiology, Eberhard-Karls-University, Tuebingen*

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## Summary

*Background:* The number of effective cytotoxic agents for the treatment of patients with metastatic adult type soft tissue sarcoma (STS) is limited, when patients have failed anthracyline-based chemotherapy. The aim of this trial was to evaluate the efficacy of gemcitabine in this setting. *Methods:* Between August 2001 and March 2003 19 patients were eligible to enter. Gemcitabine was administered as a 30-minutes infusion at a dosage of 1 g/m$^2$ on day 1, 8 and 15 every 4 weeks. All patients had progressive disease during ($n = 12$) or shortly after an anthracycline-based regimen ($n = 3$). *Results:* Four of 19 patients did not start study treatment because of fulminant progression. Fifteen patients with a median age 47 years (32–72) were assessable. All patients had received at least one prior treatment regimen (range, 1–6) for metastatic disease containing anthracyclines ($n = 15$) and ifosfamide ($n = 11$). To date, a total of 72+ cycles have been applied (median; 3, 1–28+). Seven patients (47%) had progressive disease after completion of two cycles at the first response assessment. One patient (6%) attained a partial remission, and 7 patients (47%) achieved disease stabilisations. One patient is still on treatment after more than 2.5 years. The calculated progression-free rate at 3 and 6 months was 46.7% ($CI_{95\%}$, 21.4–71.9) and 13.3% ($CI_{95\%}$, (0–30.5). 95% of the cycles have been applied without any dose modification or treatment delay. *Conclusions:* Considering response and progression-free rate as the primary endpoints for phase II trials in pretreated STS, gemcitabine has moderate efficacy.

## Introduction

Soft tissue sarcoma (STS) are malignant tumors arising from mesodermal tissues. They consist of a wide variety of histological subtypes differing in terms of biological behaviour, prognosis and response to different treatment modalities [1]. The number of effective antitumor drugs in the treatment of advanced adult type STS is limited [2]. Only three drugs have shown significant single-agent activity with response rates of approximately 7 to 27%, ifosfamide and the anthracyclines, doxorubicin and epirubicin [3–6]. The response of epirubicin is approximately 15% [7] in patients with anthracycline refractory STS after failure of first-line treatment only agents with limited efficacy have been identified so far [4, 5, 8–12]. Prospective trials with the nucleoside analogue gemcitabine have revealed various efficacy results on the phase II level in pretreated patients with advanced STS using different dosages and administration types, e.g., prolonged infusion schedules [13–20]. The aim of this open, non-comparative phase II study was to evaluate the efficacy and toxicity of gemcitabine applied as a 30 minutes-infusion in a dosage of 1000 mg/m$^2$ on day 1, 8 and 15 of a four weeks cycle on an outpatient setting in pretreated patients with metastatic STS.

## Patients and methods

### *Eligibility*

Patients with histologically proven STS with evidence of progression during or after anthracycline-based

chemotherapy have been entered into this open-label, non-comparative study. Patients had to be between 18 and 75 years of age, had to have a performance status of 0–2 according to the ECOG-criteria and a life expectancy of at least 3 months. Measurable or evaluable lesions had to be defined by diagnostic studies including computed tomography (CT) or magnet resonance imaging (MRI), ultrasound or chest X-ray. The same diagnostic imaging method had to be used throughout the study to evaluate the lesions. Patients had to have pretreatment neutrophile counts $\geq 1.500/\mu$l, platelet counts $\geq 100.000/\mu$l, haemoglobin $>9$ g/dl, serum creatinine concentration $\leq 2.0$ mg/dl or creatinine clearance $>60$ ml/min and total bilirubin levels $\leq 2.5$ mg/dl. ASAT, ALAT and alkaline phosphatase had to be $<2$ times the upper limit of normal, if liver metastases were absent by abdominal CT or MRI scan, or $<5$ times the upper limit of normal, if liver metastases were present. Patients of reproductive potential had to agree to practice an effective contraceptive method.

Exclusion criteria were the histology of a gastrointestinal leiomyosarcoma (GIST), active uncontrolled infection, concurrent severe medical problems which would limit full compliance within the study or expose the patient to extreme risk or decreased life expectancy, concomitant or previous malignancies within the last 5 years, except for basal or squamous cell carcinoma or carcinoma in situ of the cervix, history of allergic reaction to compounds chemically related to gemcitabine, pregnancy or lactation. No concurrent other chemotherapy, immunotherapy, investigational therapy or radiotherapy other than prevent the risk of bone fracture in osteolytic lesions were allowed. All patients were informed of the investigational nature of this study and had to provide written informed consent in accordance with institutional and federal guidelines. The study was approved by the local ethical committees of all participating cancer centers.

### *Treatment protocol*

Gemcitabine was administered as an infusion over a maximal time of 30 min with 1000 mg/m$^2$ on day 1, 8 and 15 every 4 weeks on an outpatient basis. All patients were assessed prior to and during treatment by physical examination, routine hematology and biochemistry analysis, 12-lead ECG, and to define the extent of disease chest-X-ray, ultrasound, CT or MRI scans. Complete blood cell counts with platelets and differential counts had to be obtained weekly during chemotherapy and serum chemistry analysis were repeated at least once every course. Subjective symptoms, physical examination, performance status and all adverse reactions were recorded before each treatment cycle. Determination of tumor response followed WHO standard criteria [21].

### *Dose modifications*

Patients were treated within the study protocol until tumor progression, occurrence of unacceptable toxicity or withdrawal of informed consent. The gemcitabine dosage had to be reduced to 750 mg/m$^2$ (75%) in case of occurrence of a neutrophil count $<0.5\times10^9$/l associated with fever or infection or duration of neutropenia IV° $>7$ days, neutrophils ranging between 0.5 and $0.9\times10^9$/l beyond day 28 of the treatment cycle or any non-hematologic toxicity grade III/IV according to CTC-criteria (except nausea and vomiting, alopecia). Patients had to be withdrawn from study if treatment delay was longer than two weeks due to toxicity reasons.

### *Statistical analysis*

The primary objective of the study was to determine the rate of complete or partial remissions (CR/PR) of gemcitabine in advanced pretreated STS. A two-stage study design was used [22]. 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 to stop if less than two remissions 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. Progression-free rate (PFR), progression-free survival (PFS) and overall survival were defined as intervals from date on study until progression or death of any cause and was estimated by the method of Kaplan and Meier [23].

## Results

### *Patients' characteristics*

From August 2001 to March 2003 a total of 19 patients, 11 male and 8 female, with advanced STS with different histologic subtypes progressing during or after anthracycline-based first-line chemotherapy were screened to enter this open-label phase II trial. Four patients had a tumor progression immediately after the first study evaluation or a rapid decrease of their performance status and therefore never started study treatment. The remaining 15 patients, 10 male and 5 female, with a median age of 47 years (range, 32–72) have entered the trial and were assessable within the study protocol. One patient who had undergone allogenic bone marrow transplantation (ABMT) during his treatment for chronic myeloic leukaemia (CML) 6 years prior to study treatment was assessable for response but not for haematological toxicity evaluation.

At study entry 9 patients (60%) had local recurrences. Lung metastases were found in 12 (80%), lymph node involvement in 5 (33%) and liver as well as bone metastases in 3 patients (20%) each.

All patients had undergone at least one (up to 6) previous treatment regimens for advanced disease regimen containing of anthracyclines ($n = 15$, 100%) or ifosfamide in 11 patients (73%). Progressive disease has occurred in 12 of 15 patients while on treatment. The remaining three patients experienced progression within 6, 8 and 19 months after completion of the previous chemotherapy regimen. Best response to pretreatment was a partial remission (PR) in two patients (13%), temporary disease stabilisation in five patients (33%) and progressive disease in 8 patients (53%). A detailed summary of baseline patients' characteristics is given in Table 1.

*Table 1.* Patients' characteristics.

| | *N* (pts) | % |
|---|---|---|
| Sex | | |
| Male | 10 | 67 |
| Female | 5 | 33 |
| Median age | 47 years (range, 32–72) | |
| Performance status (ECOG) | | |
| 0 | 11 | 73 |
| 1 | 4 | 27 |
| Primary histology | | |
| Malignant fibrous histiocytoma | 6 | 40 |
| Leiomyosarcoma | 3 | 20 |
| Haemangioendothelioma | 2 | 13 |
| Rhabdomyosarcoma | 1 | 7 |
| Malignant peripheral nerve sheath tumor | 1 | 7 |
| Undifferentiated sarcoma, nos | 2 | 14 |
| Grading of primary tumor | | |
| Grade 1 | 1 | 7 |
| Grade 2 | 6 | 40 |
| Grade 3 | 6 | 40 |
| Not applicable | 2 | 14 |
| Staging at primary diagnosis | | |
| T1 | 8 | 64 |
| T2 | 7 | 46 |
| N0 | 15 | 100 |
| N1 | 0 | |
| M0 | 10 | 67 |
| M1 | 5 | 33 |
| Response to previous chemotherapy | | |
| Complete remission | 0 | 0 |
| Partial remission | 2 | 13 |
| Stable disease | 5 | 33 |
| Progressive disease | 8 | 53 |
| Sites of metastases at study entry | | |
| Local recurrence | 9 | 60 |
| Lung | 12 | 80 |
| Lymph node | 5 | 33 |
| Liver | 3 | 20 |
| Bone | 3 | 20 |

nos = not otherwise specified.

### *Toxicity*

The drug was well tolerated in patients with pretreated STS. In total, 95% of the cycles could be applied without dose reduction. Treatment due to haematotoxicity was delayed in five patients (33%) with thrombocytopenia and/or neutropenia occurring at treatment day 15.

Four dose reduced and time extended cycles have been applied in the ABMT recipient with CML who achieved a disease stabilisation over five cycles of gemcitabine. After the first cycle this patient experienced severe anemia and neutropenia (grade III) as well as thrombocytopenia (grade IV). Therefore, the further four cycles have been applied in a reduced dosage of 750 mg per meter squared every two weeks.

In the other 14 patients haematological toxicity profile was moderate. Anemia grade III/IV was seen in 7% ($n = 1$), severe thrombocytopenia (grade III/IV) in 33% ($n = 5$) and neutropenia (grade III/IV) in 13% ($n = 2$) of the patients. Mild haematologic toxicity (grade I/II) occurred in 66% of the patients during gemcitabine treatment.

The non-haematological side-effects are listed in Table 2. Grade III/IV toxicity consisted of neutropenic fever, alopecia and flulike syndrom in one patient (7%) each. There were no major abnormalities on blood chemistry examinations and no toxicity-related death occurred or any hospitalisation were necessary due to study medication.

### *Response to treatment*

To date, a total of 72+ cycles of gemcitabine have been applied in the 15 patients with a median number of three cycles per patient (range, 1–28+). One patient is still on study treatment having a disease stabilisation for more than 2.5 years while progressive during an adriamycin and ifosfamide combination. The reason for the end of gemcitabine treatment was tumor progression in other 14 patients. At the first response evaluation after 10 weeks 7 patients (47%) had progressive disease. Only one patient (7%) attained a partial response and 7 patients (47%) achieved a temporary disease stabilization.

*Table 2.* Worst toxicity per patient during treatment with gemcitabine (1000 mg/m$^2$ on day 1, 8, 15 every 4 weeks) for advanced soft tissue sarcoma ($n = 15$ pts; $n = 72$ cycles).

| | Grade | | | |
|---|---|---|---|---|
| Toxicity | 1 | 2 | 3 | 4 |
| Alopecia | 0 | 0 | 1 (7%) | 0 |
| Diarrhea | 1 (7%) | 1 (7%) | 0 | 0 |
| Dyspnoea | 0 | 1 (7%) | 0 | 0 |
| Elevation of ASAT/ALAT | 2 (13%) | 0 | 0 | 0 |
| Fever | 2 (13%) | 1 (7%) | 0 | 0 |
| Flulike syndrome | 5 (33%) | 1 (7%) | 1 (7%) | 0 |
| Myalgia/arthralgia | 2 (13%) | 1 (7%) | 0 | 0 |
| Nausea/emesis | 8 (53%) | 1 (7%) | 0 | 0 |
| Neutropenic fever | 3 (20%) | 0 | 1 (7%) | 0 |
| Oedema | 1 (7%) | 0 | 0 | 0 |
| Sweating | 1 (7%) | 0 | 0 | 0 |

ASAT: Aspartat-Amino-Transferase; ALAT: Alanin-Aminotransferase.

The median PFS was 3 months (range, 1–33+) and the median survival 6 months (range, 3–33+). The PFR at 3 months was 46.7% ($CI_{95\%}$, 21.4–71.9) and 13.3% ($CI_{95\%}$, (0–30.5) at 6 months.

## Discussion

Patients with metastatic STS except of GIST still have a dismal prognosis because the number of effective cytotoxic agents is limited. These patients with so called adult type STS-fibro-, lipo-, leiomyo-, pleomorphic and synovial sarcoma-are treated with an anthracycline-based regimens with or without ifosfamide as front-line therapy. Both drugs have produced single-agent activity in the range of 7 to 26% partial remissions [3–6] and therefore are part of currently used first-line treatment regimens.

Active agents for patients progressing during or shortly after first-line chemotherapy are still rare. Potential active groups of cytotoxic drugs have been investigated such as the taxanes—docetaxel and paclitaxel —, patupilone derivates (epothilone B analogues; BMS 247550), vinca alkaloids (vinorelbine), minor groove binders (ecteinascidin, ET-743; brostacillin), alkylating agents such as oxazaphosphorines (trofosfamide) or imidazotetrazine (temozolomide), as well as DNA topoisomerase inhibitors-topo-, rubo-, exa-, irino-and recently becatecarin (NSC 655649), a rebbeccamycin analogue with topo I inhibitory properties [8–12].

The role of the newer agents acting as proteasome inhibitor (PS 341) or restoring the sensitivity to P-glycoprotein (VX 710) is currently not definable. Targeted therapy such as mTOR inhibitors and tyrosine kinase inhibitors to VEGFR, EGFR, c-Kit, Raf or PDGFR are currently being tested in GIST patients refractory to imatinib mesylate and in other sarcoma histological subtypes.

The antimetabolite gemcitabine was evaluated in a various number of phase II trials in patients with advanced STS. These trials were heterogeneous in design, used drug dosage and drug administration. The observed remission rates in those studies, including trials with at least 15 patients, ranged from 3 to 18% [13, 15–20]. The highest response rates have been reported by Patel and coworkers using a fixed dose-rate infusion of 10 ml/min over 2.5 h [18]; however, the median time to progression (TTP) was 3 months in this trial corresponding to other phase II trials using a 30-minutes infusion.

With an objective response rate of 6% and a median TTP of 3 months the results of this trial using a more practical application regimen (dosage of 1000 mg/m$^2$ as a 30 min infusion) are comparable to published data with a pharmacologically guided fixed dose-rate infusion regimen despite a 1.4-fold increase in the concentration of GTP (gemcitabine triphosphate) measured in peripheral-blood mononuclear cells.

By reviewing all trials, activity of gemcitabine was particularly observed in patients with histological subtypes of angio-, non-GI leiomyo-and unclassified sarcomas [13, 16, 18–20].

Gemcitabine is currently tested as first-line treatment in metastatic disease alone [24, 25] or in combination with adriamycin, vinorelbine, dacarbacin and docetaxel [26–29] as well as in phase I trial as a radiosensitizer in the neoadjuvant setting in conjunction to radiation therapy [30].

In conclusion, this trial confirms the considerable number of disease stabilisations during gemcitabine applied as a 30 min-infusion in a dosage of 1000 mg/m$^2$ in pretreated adult STS patients. Considering response and progression-free rate as primary endpoints for phase II trials in STS, gemcitabine has moderate efficacy [31].

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*Address for offprints:* J. T. Hartmann, Department of Medical Oncology/Hematology/Immunology/Rheumatology/Pneumology, UKT-Medical Center II, Interdisciplinary Sarcoma Center, South West German Cancer Center, Eberhard-Karls-University, Tuebingen, Otfried-Mueller-Str. 10, 72076 Tuebingen, Germany. Tel.: +49-7071/29 82127, Fax: +49-7071/29 5689; E-mail: joerg.hartmann@med.uni-tuebingen.de