Phase II study of gemcitabine in children with solid tumors of mesenchymal and embryonic origin

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The therapeutic benefit and side-effect profile of gemcitabine in adults with relapsed solid tumors is well known. So far, few data are available about its significance in pediatric relapsed solid tumors. To determine the efficacy and tolerability of gemcitabine in children, the drug was administered by intravenous short-term infusion over 30 min at a dose of 1200 mg/m^2 weekly for 3 weeks as one cycle in children with relapsed solid tumor of embryonic or mesenchymal origin. From May 2003 to September 2004, 14 male and six female patients (2–23, median 15.8 years) were recruited for this prospective open-label phase II study (two-step Simon design). The patients suffered from rhabdomyosarcoma ($n=8$), Ewing's sarcoma ($n=4$), osteosarcoma ($n=2$), neuroblastoma ($n=3$), hepatoblastoma ($n=2$) and nephroblastoma ($n=1$). Median duration of therapy was 27.5 days (7–99), corresponding to 4.0 (2–11) infusions of gemcitabine. Two patients (neuroblastoma and Ewing) had stable disease documented for 69 and 70 days, whereas no objective responses were observed. In 34/94 administered infusions; doses had to be reduced or omitted for grade 3–4 hematotoxicity. Minimal activity was observed in this cohort of children with a wide spectrum of mesenchymal and embryonic tumors. Given the relatively low dose of gemcitabine administered, this study does not exclude the possibility of activity at higher doses. Secondly, the tolerability of gemcitabine in children was consistent with that expected in adults. For further studies in this population, we recommend the use of gemcitabine in combination with other agents. *Anti-Cancer Drugs* **17:859–864 © 2006 Lippincott Williams & Wilkins.**

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Introduction

The nucleoside analog gemcitabine (2′,2′-difluoro-2′-deoxycytidine) demonstrates efficacy in many types of adult malignancies, including previously untreatable cases of pancreatic cancer [1]. After uptake by nucleoside transporters and metabolism by intracellular enzymes, nucleoside analog is incorporated into newly synthesized DNA, leading to chain termination and inhibition of DNA synthesis. Due to its pharmacologic properties, gemcitabine has been shown to have probably greater membrane permeability, enzyme affinity and more prolonged intracellular retention than cytarabine. The drug has been postulated to generate self-potentiating mechanisms that act to increase the concentrations of the drug and prolong the retention of its active nucleotides in cancer cells [2]. The relatively mild toxicity profile makes gemcitabine an alternative option for patients unable to tolerate more toxic cytostatics [3]. Due to the benefit for the patient's quality of life, gemcitabine is the second most commonly used palliative anticancer drug in Germany. Currently, gemcitabine is approved for a wide spectrum of tumors such as pancreatic carcinoma, non-small cell lung cancer, bladder carcinoma, breast cancer and ovarian cancer [4–8]. The therapeutic benefit and side-effect profile in adult patients has largely been studied in relapsed cancers. [9–11]. In adult phase I and II studies, gemcitabine was primarily administered as weekly infusion schedules [12].

The conduct of systematic clinical trials in palliative situations is usually difficult in terms of a lack of evaluable patients. Either the attending physician is not able to accept the hopelessness of any curative therapy or the patients themselves are not willing to be treated within a further study [13–16].

With a limited number of patients treated in the palliative setting, pediatric oncology trials often combine multiple refractory malignancies in phase II trials. [17]. Tumors can, however, be stratified by histology with certain 'signal' malignancies (e.g. neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma) that are used to predict overall antitumor activity [18]. These trials prioritize new drug entities for further development in specific tumor entities or in combination regimens. According to the meta-analysis data of 45 phase II trials in

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pediatric oncology, the overall response rate was 19.6% [complete response (CR) + partial response (PR)] for children with the whole spectrum of different tumor entities [17]. The maximum tolerated dose (MTD) of gemcitabine was 3600/m^2/dose, weekly for 3 consecutive weeks [19]. Gemcitabine's pharmacokinetics in this group of pediatric patients was similar to those reported for adults and fit a two-compartment open model in almost all 14 patients.

For another phase I trial of gemcitabine, published in 2004, 40 pediatric patients with a wide range of advanced solid tumors were recruited [20]. The MTD of gemcitabine given weekly for 3 consecutive weeks was 1200 mg/m^2, a lower dose than used in leukemia patients. Consistent with adult phase I studies, the major toxicity was myelosuppression. Some patients with osteogenic sarcoma, Ewings's sarcoma and soft tissue sarcoma had stable disease despite extensive prior chemotherapy; one patient with pancreatic tumor showed a PR.

To determine the efficacy of gemcitabine in pediatric patients with refractory solid tumors and to evaluate the tolerability in pretreated children, we conducted a prospective open-label multicenter phase II study.

Materials and methods

Enrollment

Patients were enrolled between May 2003 and September 2004 in 11 trial centers in Germany and Austria. Children with first or additional recurrence of a solid tumor of embryonic or mesenchymal origin were included if standard therapy or a nationwide German Society for Pediatric Oncology and Hematology (GPOH) study failed to offer any curative therapeutic option. Eligibility criteria further included (1) histological documentation of one of the following entities: Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, hepatoblastoma and nephroblastoma, (2) radiological documentation of one-dimensional progression, (3) no age limit, (4) life expectancy of more than 4 weeks, (5) adequate hematological function, and (6) adequate renal and hepatic function. Exclusion criteria were (1) previous chemotherapy within 2 weeks, (2) other experimental treatment during or within 6 weeks before this study, (3) other previous malignancies, previous psychiatric or other severe illness that may hamper the patient's treatment per protocol, (4) brain metastases not treated with standard chemotherapy, (5) current participation in another study relating to the underlying disease and (6) any other condition or therapy that may pose a risk for the patient or may affect the study objective (e.g. pregnant or lactating patients).

Informed consent was obtained from patients and/or guardians in accordance with the ethics policy of the institute, and the study was performed in line with the Declaration of Helsinki.

Requirements according to good clinical practice

The University of Muenster served as sponsor of the study, and was represented by the Coordinating Centre for Clinical Trials and the author J.B. In order to fulfill the main requirements of the Good Clinical Practice Guidelines of the International Conference of Harmonization as implemented by the EU-directive quality assurance procedures such as the management of drug accountability, monitoring of data including source data verification accomplished by an external contract research organization (SKM Oncology, Wiesbaden, Germany), organization of audits in trial centers, surveillance by an independent data and safety monitoring board, implementation of a serious adverse event (SAE)-reporting system, double data entry before analysis, etc., were realized.

Study design

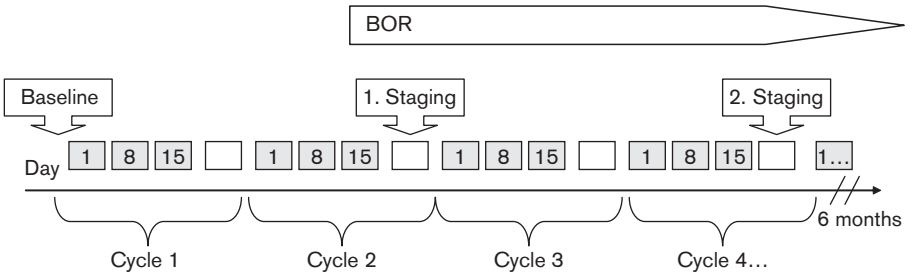
Gemcitabine hydrochloride (Gemzar; Eli Lilly, Bad Homburg for Germany and Vienna for Austria) was supplied as a freeze-dried powder. The drug was diluted in normal saline and administered intravenously with an infusion pump over 30 min. Gemcitabine was given on days 1, 8 and 15 of a 28-day schedule at a dose of 1200 mg/m^2 for at least 6 months or until tumor progression occured or other reasons led to termination, respectively. Almost all infusions were delivered in an outpatient setting.

Before gemcitabine, all patients were staged by computerized tomography, magnetic resonance imaging or other radiological methods including measurements of all tumor masses and hematological and chemical profiles. Chest X-ray had to be performed in patients with pulmonary symptoms or pretreatment with potential pulmonary toxic agents such as busulfan. At the end of each second cycle (infusions on days 1, 8 and 15 are summarized as one cycle), meaning every 8 weeks and every sixth infusion or at least at the time of study termination, response was assessed by the same methods as in the baseline. All patients were followed up until progression (Fig. 1).

Sample size calculation

The calculation of the number of patients required for the study was based on the main target criterion of the study, which is defined by response during study therapy with gemcitabine. Response was assessed by using the objective remission rate to RECIST guidelines, a model by which a combined assessment of all existing lesions, characterized by target lesions and nontarget lesions, is used to extrapolate an overall response to treatment [21].

Fig. 1



Treatment schedule. Gray boxes: weekly infusion of gemcitabine on days 1, 8, 15 are summarized as a cycle; white boxes: week 22 without application of gemcitabine, treatment duration at least 6 months or until progression. Best overall response (BOR) evaluable after first staging.

An optimal two-stage schedule design to Simon was used [22]. As for the patient population defined by inclusion/exclusion criteria, a clinically irrelevant response rate of 3% was assumed for the formal sample size calculation. The study was to show that a minimum remission rate of 15% is attainable with gemcitabine. The clinically relevant rate of 15% or above was regarded as acceptance of therapy and the irrelevant rate below 3% as rejection of therapy.

If there was no responder among the first 18 patients, the study was regarded as ineffective and had to be stopped at this first stage. If at least one responder was observed among 18 patients, the study was to be continued with 29 additional patients. If the total number of responders among $n = 47$ patients did not exceed three, therapy was regarded ineffective as well. If at least four responders were observed among 47 patients, therapy was acceptable for further clinical trials.

Statistical analysis

The primary study objective was response rate.

The 'best overall response' according to RECIST criteria was the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since the treatment started. If the therapy was terminated before the regular restaging was performed, the best overall response (BOR) was not evaluable.

Remission criteria for CR or PR had to be evaluated on two successive staging examinations, and had to be reviewed by external experts of the GPOH study group that was responsible for the respective tumor entity.

All patients with no CR or PR were considered nonresponders. A patient who died from gemcitabine toxicity after receiving all or part of the infusion would have been considered a nonresponder. If other reasons led to termination of therapy, the response was classified as 'not assessable'.

Distributions of continuous variables such as age at study entry were presented with median and range; distributions of qualitative variables such as sex, tumor entity and pretreatment were presented with the number and percentage in each category. Time to tumor progression was calculated as the time from enrollment to the date of documented progress or death. A death, regardless of cause, was considered a progressive event. The median for time to progression was determined using the Kaplan–Meier method [23]. Statistical analyses were performed using software SAS (version 8.2; SAS Institute, Cary, North Carolina, USA).

The toxicity profile for gemcitabine was estimated by recording the cycle-specific grade 3 or 4 toxicity rate. Toxicities were identified and graded using National Cancer Institute Common Toxicity Criteria version 2.0 (National Cancer Institute, Bethesda, Maryland, USA). For each cycle, the highest grade of each toxicity type was reported, and the number of infusions with grade 3 or 4 toxicity type possibly, probably or likely related to gemcitabine was calculated and divided by the total number of cycles reported, to estimate incidence rate of serious toxicity associated with the agent.

Results

Characteristics

Twenty patients were enrolled, 14 men and six women. All patients were evaluable; however, data of one patient have not been monitored by source data verification because of the loss of his clinical file. Patient characteristics are given in Table 1.

Response

Gemcitabine was given for at least 6 months or until tumor progression occured. Early progression of tumors led to shortened treatment duration. Median duration of

Table 1 Characteristics of 20 patients enrolled and evaluated

Characteristics	Value ($n=20$)
Age at study entry (years)	
median (range)	15.8 (2–23)
Gender	
male	14 (70)
female	6 (30)
Number of chemotherapy regimens received before enrollment [*n*(%)]	
1	9 (45)
2	5 (25)
3	6 (30)
Was radiation therapy received before enrollment? [*n*(%)]	
yes	6 (30)
no	14 (70)
Did the patient have a bone marrow transplant or stem cell rescue before enrollment? [*n*(%)]	
yes	4 (20)
no	16 (80)
Did the patient have metastases at enrollment? [*n*(%)]	
yes	18 (90)
no	2 (10)
Tumor type [*n*(%)]	
rhabdomyosarcoma	8 (40)
Ewing's sarcoma	4 (20)
neuroblastoma	3 (15)
hepatoblastoma	2 (10)
osteosarcoma	2 (10)
nephroblastoma	1 (5)

therapy was 27, 5 days (7–99) equaling 4, 0 (2–11) infusions of gemcitabine.

Only eight of 20 patients were evaluable for response. The other patients (12/20) left the trial mainly due to early progress ($n = 8$), lost to follow-up after emigration to home country ($n = 1$) and change of treatment ($n = 3$). Reasons for change of treatment were tumor progression (2/3) and realization of a liver transplantation as an anticipated procedure (1/3).

Early progress was defined by clinical symptoms ($n = 3$) or early restaging by ultrasonography ($n = 6$) in deviation of the protocol's suggestions.

In 6/8 patients evaluable for 'BOR' according to RECIST criteria, the first staging after 6 weeks showed progressive disease and resulted in ceasing the study treatment; two patients had stable disease documented for 69 and 70 days followed by ultimate progress, whereas no response to gemcitabine was observed (Table 2).

Tumor progression

We estimated the time to progression to be 47 days (10–105). Reasons for ceasing the study treatment were progressive disease ($n = 18$, and other reasons like a change of medication ($n = 1$) and one patient leaving the country ($n = 1$). Two patients died because of progressive disease during treatment or within 28 days after the last infusion of gemcitabine.

Table 2 Best overall response to gemcitabine

Diagnosis	Duration of treatment (days)	Best overall response (days)
Neuroblastoma	77	SD (69)
Ewing's sarcoma	99	SD (70)
Rhabdomyosarcoma	42	PD
Hepatoblastoma	42	PD
Nephroblastoma	42	PD
Rhabdomyosarcoma	42	PD
Ewing's sarcoma	45	PD
Rhabdomyosarcoma	48	PD

SD, stable disease; PD, progressive disease.

Toxicity

The median dosage per infusion was 1196, 8 mg/m^2. In 34/94 evaluable infusions, dosages had to be reduced for grade 3 toxicity (30/34) or omitted for grade 4 toxicity (4/34). According to the protocol guideline, the dosage had to be reduced for 25% in case of any grade 3 toxicity and had to be omitted after any grade 4 toxicity. No patient died from toxicity possibly associated with gemcitabine. No suspected unexpected serious adverse reactions were reported.

The toxicity most commonly observed was hematological (Table 3). Fever of unknown origin in the absence of neutropenia was observed twice in one patient. Hepatic toxicity was mild (grade I and II) and only observed in 20% of patients.

Discussion

The activity of gemcitabine as a single agent against pediatric relapsed solid tumors of different origin has not been clearly defined. Steinherz *et al.* [19] conducted a phase I single-agent study of gemcitabine in children with relapsed or refractory leukemia and non-Hodgkin's lymphoma. His group identified a MTD of 3600 mg/m^2 in less heavily pretreated patients. No patients had a complete response. However, 1/14 patients went into remission without completely recovering his platelet count sufficient for the study's definition of CR. Hepatotoxicity was the most frequent toxicity observed in this phase I trial and was the major DLT of gemcitabine.

In our study, the weekly single dose of gemcitabine was much lower than the identified MTD in leukemia and lymphoma. The applied dosing schedule was recommended for first-line therapy of solid tumors in adults and corresponds exactly to the MTD identified by a phase I study in children with advanced solid tumors [20]. In this study, the major toxicity was myelosuppression; however,

Table 3 Documented grade III/IV toxicity by cycle

Toxicity type	Cycle 1	%	Cycle 2	%	Cycle 3	%	Cycle 4	%
Hemoglobin	5	20			1	50	1	100
Leukocytes (white blood cells)	5	20	3	25	2	100		
Platelets	13	65	3	25	2	100		
Fever in absence of neutropenia	1	5	1	8				
Nausea/vomiting	1	5						
Constitutional symptoms			1	8				
Total patients/cycle	20		12		2		1	

only 1/40 patients received granulocyte colony stimulating factor after grade 4 hematoxicity and hospitalization for fever and neutropenia. One patient with a pancreatic tumor fulfilled the criteria of PR, and 4/13 patients with osteogenic sarcoma had stable disease up to 6 months. Stable disease could be seen in one Ewing's sarcoma and in two patients with rare neoplasms like cervical rhabdoid tumor, for example.

It is generally assumed that the efficacy of low weekly chemotherapeutic dosages within dose-intensified regimens is possibly evaluable after a minimum of six infusions at the earliest. That means the nonevaluability of BOR according to RECIST criteria in 12 patients is at least partly a problem of trial center compliance. With regard to the palliative character of the study and the pretreatment of patients before study entry, the results including two patients with stable disease documented for more than 2 months are not as disappointing as it seems.

The overall toxicity of the substance was approximately as low as in adults. In face of our precautions, hematological toxicity was, however, slightly more pronounced than expected, possibly because of the sustained pretreatment of our patients (Table 1).

No suspected unexpected serious adverse reactions, however, were reported, whereas some SAEs with possible relation to gemcitabine were documented. The SAEs were either tumor progression until death or febrile episodes during neutropenia, both of which may be expected in a clinical situation of relapsed disease and chemotherapy in pretreated patients, respectively.

Due to the lack of any response within the first 18 patients, however, the therapy with gemcitabine as single drug in this dosage and regimen had to be rated as nonacceptable for trial continuation and stopped at this first stage according to the two-step Simon design [21].

Recently, the Children's Oncology Group presented a phase II study of gemcitabine in children with relapsed acute lymphoblastic leukemia or acute myeloic leukemia [24]. One of 30 evaluable patients had complete response to gemcitabine. Only one patient was alive 1 year after entry. Grade 3 or 4 hematological toxicity and hepatotoxicity were common. In childhood relapsed leukemia, with gemcitabine being given as a single dose in a 3-fold higher dose (3600 mg/m^2 weekly for 3 weeks), no effect could be detected either.

Despite the wide spectrum of different tumors in our screening study, the presumption of possible chemosensitivity was similar for each entity.

Meta-analysis data of 45 phase II trials in pediatric oncology show related response rates as for soft tissue sarcoma 17.0%, Ewing's sarcoma 17.6%, osteogenic sarcoma 10.7% and neuroblastoma 21.5% [17].

Our data do not rule out a low level of activity, but in our view further studies with gemcitabine as a single agent are not warranted.

Conclusion

Gemcitabine as a single drug has probably no general relevance in the treatment of refractory childhood solid tumors. As activity in specific entities cannot be precluded and because of the good tolerability, however, inclusion of gemcitabine into a polychemotherapeutic schedule in reasonable synergistic combinations offers interesting perspectives and questions for future trials.

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