An open-label, multicenter phase II trial of capecitabine in patients with cisplatin-refractory or relapsed germ cell tumors

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The objective of this multicenter phase II trial was to evaluate the efficacy and tolerability of capecitabine in patients with cisplatin-refractory or relapsed germ cell tumors. Between March 2003-June 2004, 14 patients refractory to at least two regimens of cisplatin-based chemotherapy or with relapse after high-dose chemotherapy and autologous peripheral blood stem cell transplantation received 1250 mg/qm capecitabine orally twice daily for 14 days in 3-week cycles. Treatment was continued until tumor progression. All patients were heavily pretreated with a median number of four previous lines of chemotherapy (range, 2–11) and 86% had relapsed after high-dose chemotherapy with peripheral blood stem cell transplantation. No patient responded to study treatment. Nine patients (64%) had progressive disease after two cycles. Two patients already stopped treatment after one cycle, because of a clinically overt tumor progression. One patient died of his tumor progression at the end of the second cycle. Two patients received four cycles of capecitabine, as progression was less than 30%. The median survival time was 4 months (range, 0–10). The toxicity profile was favorable. Eighty-six percent of the cycles could be applied without dose modifications or delay. Grade III/IV toxicities (diarrhea and anorexia in one patient each) occurred in 7% of the cases. No hematotoxicity grade III/IV was observed. Neutropenia grade I/II was documented in 21%, anemia in 35% and thrombocytopenia in 14% of the patients. Capecitabine was well tolerated, but is not effective in heavily pretreated patients with cisplatin-refractory or relapsed germ cell tumors. *Anti-Cancer Drugs* 18:273–276 © 2007 Lippincott Williams & Wilkins.

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Introduction

Today, approximately 70–80% of patients with metastatic germ cell tumors can be cured with cisplatin-based chemotherapy [1,2]. Patients refractory to or relapsed after first-line chemotherapy may still achieve long-term survival after salvage chemotherapy in 10–30% of cases. Prognosis, however, remains extremely poor in patients who progress during or after salvage chemotherapy [3]. Several cytotoxic drugs were evaluated for palliative treatment in this setting, but until now the number of effective treatment options has been limited. Only low-dose oral etoposide, gemcitabine, paclitaxel and oxaliplatin demonstrated single-agent activity in these patients [4–9]. Therefore, the investigation of further cytotoxic agents with potential efficacy appears to be important to increase treatment options and to extend overall survival time.

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate that is enzymatically activated to the cytotoxic 5-fluorouracil (5-FU) after oral application. The phosphorylation by the enzyme thymidilate phosphorylase is one of the main steps of activation of capecitabine to the active metabolite 5-FU. An overexpression of thymidilate phosphorylase has been demonstrated immunhistochemically in germ cell tumor cells in comparison with normal testis tissue [10]. A response to capecitabine has been reported in a single patient with a refractory metastatic germ cell tumor [11].

The objective of this open, multicenter phase II trial was to evaluate the efficacy and tolerability of capecitabine in patients with metastatic germ cell tumors refractory to or relapsed after cisplatin-based chemotherapy with no further established curative treatment option.

Patients and methods

In this phase II trial, patients with histologically confirmed seminomatous or non-seminomatous testicular germ cell tumors and either relapse within 8 weeks after

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cisplatin-based chemotherapy, relapse after salvage high-dose chemotherapy or progression during salvage cisplatin-based chemotherapy were included. Patients who were not able to undergo aggressive platin-based or high-dose chemotherapy owing to severe comorbidities were also eligible for this trial. Patients had to have measurable disease and documented tumor progression with a minimum of $1 \times 1\,cm^2$ at at least one site in physical examination, radiography, ultrasound, computed tomography or magnetic resonance imaging. An elevation of α-fetoprotein or β-human chorionic gonadotropin was accepted as measurable if an increase of at least 25% was documented before study inclusion. Additional radiotherapy was allowed as long as the irradiated field did not contain the only measurable lesion. Patients had to be between 18 and 70 years of age, have a Karnofsky performance status > 60 and a life expectancy of at least 2 months. Further inclusion criteria were an adequate bone marrow function (neutrophils $> 1.500/\mu l$, thrombocytes $> 75.000/\mu l$), liver function (bilirubin < 1.5-fold the upper normal limit) and renal function (creatinine clearance > 50 ml/min). Acute infections, symptomatic cardiovascular or cerebrovascular disease, second malignancy other than basalioma, severe complications owing to tumor disease requiring acute therapeutic intervention, or prior treatment with 5-FU were exclusion criteria. No additional chemotherapy, immunotherapy or hormonal treatment was allowed during study treatment with capecitabine. All patients gave written informed consent. The study has been approved by the ethics committees of the Universities of Tuebingen and Hamburg–Eppendort, Germany, as well as by the local ethics committees of the participating centers.

Pretreatment evaluation consisted of medical history including the assessment of the Karnofsky performance status and pre-existing toxicities, physical examination, routine laboratory including blood cell counts, liver function parameters, creatinine clearance, and electrolytes, tumor markers, electrocardiogram and the documentation of a measurable tumor progression as mentioned above.

Capecitabine was administered at a dosage of 1250 mg/qm twice daily orally, not chewed with an empty stomach or after meals for 14 days of a 3-week cycle. Concomitant treatment other than chemotherapy was left to the decision of the treating physician.

During application of capecitabine, measurements of the blood cell counts and electrolytes were performed weekly. Before every new cycle, medical history including toxicity evaluation, physical examination, routine laboratory, tumor markers and an orienting tumor staging was performed. Exact tumor staging was required before every third cycle. Capecitabine was applied for at least two cycles if no severe toxicities occurred. Patients responding to study treatment were planned to receive two cycles beyond the maximum response.

Study treatment was stopped in case of grade IV hematological or non-hematological toxicities according to the Common Toxicity Criteria (CTC). If CTC grade II or III toxicities occurred, the study treatment was continued until recovery of symptoms to CTC grade 0 or I. In case of grade II toxicities, no dose reduction was required after the first event, but a reduction to 75% after the second and to 50% after the third event was planned. After grade III toxicities, the dosage was reduced to 75% after the first and to 50% after the second event. Study treatment was stopped if a fourth event of grade II or a third event of a grade III toxicity had occurred. In patients with severe neutropenia, the use of hematopoetic growth factors (granulocyte colony-stimulating factor) was upon the decision of the investigator.

Statistical design

A two-stage design according to Gehan [12] was used to determine the number of patients required aiming to detect a 20% response rate with 95% power. The sample size was calculated using a two-stage design. Assuming a response rate of clinical interest of 20% and a probability of 5% for rejecting an active drug combination (type II error, β), 14 patients had to be enrolled into the first cohort. If no response was observed, the study was to be terminated. If more than one objective remission occurred within these first 14 patients, the study was to be continued with a second cohort of patients. The number of additional patients was dependent on the number of responders within the first cohort. Assuming a standard error of 10%, the patient numbers shown in Table 1 were required.

Results

Between March 2003-June 2004, a total of 18 patients were enrolled in this trial. Four patients never received treatment because of rapid tumor progression before the treatment started. A total of 14 patients received capecitabine therapy within this trial and were eligible for study evaluation. The median age at study entry was 38 years (range, 25–62). All patients were refractory to or had relapsed after platinum-based chemotherapy, with a median number of four previous lines of chemotherapy (range, 2–11). Of those, a median of three lines (range, 1–4) was cisplatin-based or carboplatin-based chemotherapy. Twelve patients (86%) had undergone platin-based high-dose chemotherapy, three as first-line treatment at the time of primary diagnosis and nine at the time of first or second relapse. A median number of two (range, 1–7) previous tumor resections had been performed in 11 patients (79%) and five patients (36%) had received previous palliative irradiation (range, 1–3).

Table 1 Statistical analysis: required patient numbers assuming a type I error of 10%

Number of remissions among the first 14 patients	Number of patients within the second cohort
1	1
2	6
3	9
4+	11

At the time of primary diagnosis, 42% of patients were classified as having a good, 29% an intermediate and 29% a poor prognosis according to the International Germ Cell Cancer Collaboration Group (IGCCCG) classification. The most frequent histological findings were a mixed non-seminomatous germ cell tumor in 56% and embryonal carcinoma in 20% of the patients. Only one patient had pure seminoma. Two patients had an extragonadal primary tumor, one in the retroperitoneum and one in the mediastinum.

At the time of study entry, all patients presented with multiple metastases, mostly lung (71%), retroperitoneal lymph node, liver (43%), distant lymph node (36%) or bone metastases (21%). An elevated α-fetoprotein was seen in nine patients (64%), a lactate dehydrogenase elevation in 50% and an elevated β-chorionic gonadotropin in 36% of the patients. For further details of patients' characteristics, see Table 2.

Twenty-four out of a total of 28 cycles of capecitabine were completed in this study (86%). The median number of cycles was two per patient (range, 1–4). No objective responses to study treatment were documented. A total of nine patients (64%) had tumor progression at evaluation after two cycles of capecitabine and stopped study treatment according to protocol. In one patient, study treatment had to be stopped after the first cycle because of a clinically apparent rapid tumor progression. Another patient suffered from a rapid tumor progession already during the first cycle and study treatment was stopped within the first cycle. This patient died of his progressing disease the following day. Another patient died of his rapidly progressive disease in the last days of the second cycle of study treatment. Only two patients showed tumor progression of less than 30% at the first response evaluation after two cycles of chemotherapy and received two further cycles. Both patients showed a significant tumor progression above 30% after four cycles and study treatment was terminated. After a median follow-up time of 3 months (range, 0–9), two patients were still alive and 12 patients had died of their disease with a median overall survival of 4 months (range, 0–9).

The toxicity profile of capecitabine was favorable in these heavily pretreated patients. No dose reductions had to be performed. The only toxicities grade III/IV according to CTC were diarrhea and anorexia in one patient each (7%). No hematotoxicity grade III/IV occurred within this trial. Neutropenia grade I/II was observed in 21%, anemia grade I/II in 35% and thrombocytopenia in 14% of neutropenia grade I/II. Non-hematologic toxicities grade I/II were also tolerable, with nausea and vomiting occurring in 21% of the patients, mucositis in 14%, and diarrhea and anorexia in 7% each. Cases of pre-existing peripheral neuropathia and hypacusis were registered, but did not aggravate. For further details of the toxicity analysis, see Table 3.

Table 2 Patients' characteristics: $n=14$ patients

	Number of patients	%
Age (median)	38 years	(25–62)
IGCCCG prognosis at primary diagnosis		
Good	6	42%
Intermediate	4	29%
Poor risk	4	29%
Primary tumor		
Gonadal	12	86%
Extragonadal	2	14%
Histology		
Pure seminoma	1	8%
Embryonal carcinoma	3	20%
York sack tumor	1	8%
Mixed non-seminomatous	9	64%
Previous lines of chemotherapy (median)	4	(2–11)
Platin-based	3	(1–4)
Non-platin-based	2	(0–7)
Previous high-dose chemotherapy (median)	12	86%
At primary diagnosis	3	25%
At first relapse	7	58%
At second relapse	2	17%
Site of metastases at study entry		
Lung	10	71%
Liver	6	43%
Bone	3	21%
CNS	1	8%
Retroperitoneal lymph nodes	8	57%
Distant lymph nodes	5	36%
Other	4	29%
Tumor marker elevation at study entry		
AFP	9	64% 4428 kU/l (24.8–252754)
β-HCG	5	36% 444 U/l (88–3660)
LDH	7	50% 456 U/l (194–1011)

CNS, central nervous system; AFP, α-fetoprotein; β-HCG, β-human chorionic gonadotropin; LDH, lactate dehydrogenase.

Discussion

Despite the high cure rate in patients with metastatic germ cell tumors treated with platin-based combination chemotherapy, long-term survival rates in patients progressing during or after standard or high-dose salvage chemotherapy is less than 5% [1]. Thus, the evaluation of further cytotoxic agents with potential efficacy is indicated to explore palliative treatment options. Several agents have been studied in these patients, but to date

Table 3 Toxicities per patient ($n=14$)

	Grade I	Grade II	Grade III	Grade IV
Leukopenia	1 (7%)	2 (14%)	0	0
Anemia	3 (21%)	2 (14%)	0	0
Thrombocytopenia	2 (14%)	0	0	0
Elevation of bilirubin	0	0	0	0
Elevation of transaminases	1 (7%)	0	0	0
Elevation of creatinine	0	0	0	0
Febrile neutropenia	0	0	0	0
Mucositis	1 (7%)	1 (7%)	0	0
Nausea	2 (14%)	1 (7%)	0	0
Vomiting	2 (14%)	1 (7%)	0	0
Diarrhea	1 (7%)	0	0	1 (7%)
Anorexia	1 (7%)	0	1 (7%)	0
Obstipation	0	0	0	0
Polyneuropathia	4 (28%)	3 (21%)	0	0
Myalgia	1 (7%)	0	0	0

only low-dose oral etoposide, gemcitabine, paclitaxel and oxaliplatin have demonstrated single-agent efficacy with response rates of 10–20% [4–9]. Recently, thalidomide has been reported with single-agent activity in heavily pretreated germ cell tumor patients with marker-positive partial remissions in 33% of 15 patients [13]. Different drug combinations of the substances mentioned above have been investigated in clinical trials in the last few years and demonstrated the feasibility of combination chemotherapy in this situation [14–17].

Here, we report the results of a phase II trial of capecitabine in 14 patients with relapsed or refractory germ cell cancer. The rationale for the evaluation of this agent was based on a positive case report [11] and the observation that thymidilate phosphorylase, which represents an important enzyme in the activation of capecitabine to the cytotoxic metabolite 5-FU, is overexpressed in germ cell tumor cells compared with normal testicular tissue [10]. In the present study, only patients with very unfavorable prognostic features and extensive previous therapy, including treatment with newer agents with proven activity like paclitaxel, oxaliplatin and gemcitabine, were included (Table 1). Capecitabine did not show activity in these 14 patients with refractory germ cell tumors, as no objective response occurred in these patients during the first two cycles of capecitabine treatment. With the statistical design used in this study after the incluson of 14 patients without any clinical response, the probability that capecitabine is effective in patients with refractory germ cell tumors remains less than 5%.

Overall, the toxicity profile of capecitabine was favorable in these heavily pretreated patients with only one patient each suffering from CTC grade III/IV diarrhea and anorexia.

This is simultaneous to another phase II trial, that had tested capecitabine after high-dose chemotherapy in breast cancer patients, and found capecitabine to be well tolerated and tolerable in this situation [17].

In conclusion, capecitabine has no clinically relevant antitumoral activity with refractory or relapsed germ cell tumors and should not be further evaluated in this situation. Therefore, investigation of other agents, possibly including targeted therapies, remains a priority.

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