A phase II trial of pemetrexed plus gemcitabine in locally advanced and/or metastatic transitional cell carcinoma of the urothelium

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Background: Both pemetrexed and gemcitabine have single-agent activity in bladder cancer, but the combination of these two drugs has not been previously evaluated for safety and efficacy in this disease. Thus, the objectives in the current study were to determine overall response rate (ORR), progression-free survival, overall survival and safety and toxicity in chemonaive patients with locally advanced and/or metastatic transitional cell carcinoma of the urothelium.

Patients and methods: Gemcitabine 1250 mg/m² was administered over 30 min i.v. on days 1 and 8, and pemetrexed 500 mg/m² over 10 min i.v. on day 8 after gemcitabine, every 21 days.

Results: Sixty-four patients were enrolled, 11 female and 53 male, median age 65 years (range 38–81), median WHO performance status of 1. Visceral metastases were present in 55% of patients. ORR among 47 patients evaluable for response was 28% (95% CI 16% to 43%) and ORR for the intention-to-treat population was 20% (95% CI 11% to 32%) with three CR and 10 PR. Median response duration was 11.2 months and median overall survival 10.3 months (95% CI 8.1–14.6 months). CTC grade 3/4 hematologic toxicities included anemia (19%), thrombocytopenia (9%), neutropenia (38%), febrile neutropenia (17%) and neutropenic sepsis (3%). Grade 3/4 non-hematologic toxicities included elevated transaminases (12%), dyspnea (8%), fatigue (8%) and stomatitis (5%). There was one toxic death due to neutropenic sepsis.

Conclusions: The combination of pemetrexed and gemcitabine had a manageable safety profile. However, efficacy was apparently not superior to that of single-agent gemcitabine.

Key words: bladder cancer, gemcitabine, pemetrexed, urothelial cancer

Introduction

Transitional cell carcinoma (TCC) of the bladder globally affects 356 000 men and women annually with 145 000 deaths resulting from the disease [1]. Treatment options for patients with locally advanced and metastatic disease include combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) [2, 3] or gemcitabine plus cisplatin (GC) [4, 5]. Both are effective regimens but have substantial cisplatin-induced toxicities. While cisplatin-based regimens comprise the mainstay of treatment in advanced bladder cancer, many patients with this disease are elderly and often present with significant co-morbidities rendering them especially vulnerable to the toxicities associated with these current regimens. Thus, there is a considerable need to develop effective treatment for patients with advanced bladder cancer who are not suited for cisplatin-containing chemotherapy.

Pemetrexed, a multitargeted antifolate, has shown activity in two phase II trials for locally advanced and metastatic bladder cancer [6–8]. Overall response rates in these two trials ranged from 13% to 29%. The combination of pemetrexed with gemcitabine, a well-studied pyrimidine analog of deoxycytidine, has demonstrated potent antitumor activity in different tumor types [9] and gemcitabine is known as an effective drug by itself in bladder cancer [10]. In preclinical models, a synergistic effect of the combination of pemetrexed and gemcitabine has been indicated [9].

In the light of these observations, we conducted a single-arm phase II study to determine the efficacy and tolerability of the combination of pemetrexed and gemcitabine in patients with locally advanced and/or metastatic TCC of the urothelium who had not received prior chemotherapy for locally advanced or metastatic disease. Secondary objectives included...
progression-free and overall survival, duration of response, time to treatment failure and toxicity. The combination of pemetrexed and gemcitabine has, to our knowledge, not previously been investigated in bladder cancer.

patients and methods

eligibility criteria

 Patients with histologically or cytologically confirmed diagnosis of stage IV TCC of the urothelium were eligible for this study. Eligibility criteria also included the following: (1) no prior chemotherapy for locally advanced or metastatic disease (prior chemotherapeutic agents used for intravesical therapy were permitted). Prior adjuvant or neoadjuvant therapy was allowed, but therapy must have been completed at least 16 weeks prior to enrollment; (2) prior radiation therapy was allowed as long as the irradiated area was not the sole source of measurable disease and radiotherapy was completed with recovery from toxicity at least 3 weeks prior to enrollment; (3) performance status of 0–2 on the World Health Organization (WHO) scale; (4) presence of bidimensionally measurable lesions [11]; (5) a life expectancy of at least 12 weeks; (6) adequate bone marrow function defined as absolute neutrophil count (ANC) ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L and hemoglobin ≥9 g/dL; (7) adequate hepatic function defined as serum bilirubin ≤1.5 × the upper limit of normal (ULN), alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤3 × ULN (ALP, AST and ALT ≤5 × ULN acceptable if liver metastases were present); (8) adequate renal function defined as calculated creatinine clearance ≥25 ml/min; (9) age ≥18 years.

Patients with clinically significant effusions, serum calcium ≥1.2 × ULN, or inability to take folic acid or vitamin B12 supplementation were excluded. No aspirin or non-steroidal anti-inflammatory agent ingestion was allowed within 2 days of treatment with pemetrexed (5 days for long-acting agents such as piroxicam). This class of agents has the potential to reduce pemetrexed clearance and increase the risk of toxicity.

The study was conducted in accordance with the Helsinki declaration and the guidelines on good clinical practice. In addition, the study protocol was approved by the appropriate ethical review boards and each patient provided written consent prior to study entry.

treatment plan

Gemcitabine 1250 mg/m² was administered i.v. over 30 min on days 1 and 8 of each 21-day cycle. Pemetrexed 500 mg/m² was administered i.v. over 10 min on day 8, 90 min after the gemcitabine administration. All patients received vitamin supplementation; oral folic acid (350–600 mg) was given daily 1–2 weeks before cycle 1 until discontinuation from study therapy, and vitamin B12 (1000 mg) was injected intramuscularly 1–2 weeks before cycle 1 and repeated every 9 weeks until the discontinuation from study therapy. Dexamethasone 4 mg (or an equivalent corticosteroid) was taken orally twice daily on the day before, the day of, and the day after each dose of pemetrexed. Patients received a maximum of six cycles of therapy. Patients remained on study until disease progression or unacceptable toxicity was noted.

If a patient experienced a platelet count of 25.0 × 10^9/L to 49.9 × 10^9/L, grade 3 neutropenia or grade 3 non-hematologic toxicity (excluding grade 3 transaminase elevations, alopecia, nausea and vomiting) after the day 1 gemcitabine dose, then the day 8 gemcitabine and pemetrexed doses were withheld until resolution of this toxicity or a return to that patient’s baseline levels. At that time, both the gemcitabine dose and the pemetrexed dose were given at full intensity. If a patient experienced grade 4 neutropenia or thrombocytopenia (≤25 × 10^9/L) or grade 4 non-hematologic toxicity after the day 1 gemcitabine dose, then the day 8 gemcitabine and pemetrexed doses were withheld until resolution of this toxicity or a return to that patient’s baseline levels. At that time, both the gemcitabine dose and the pemetrexed dose were given at 50% intensity. If hematological toxicity caused a delay in administration of the day 8 gemcitabine and pemetrexed doses, the next cycle was not begun until 14 days after the delayed doses were given.

baseline and treatment assessments

Each patient underwent radiological imaging (including computerized tomography (CT), magnetic resonance imaging (MRI) scan or X-ray) at baseline for tumor measurement. Measurable and evaluable disease was defined according to the modified Southwest Oncology Group (SWOG) criteria [11] as follows. Measurable disease status was defined as bidimensionally measurable lesions with clearly defined margins. Evaluable disease was defined as unidimensionally measurable lesions, masses without clearly defined margins, lesions with both diameters <0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter <2 cm, or bone metastases documented by CT or MRI. Ultrasound was not permitted as a method of tumor measurement. The same method used at baseline was used consistently for all follow-up tumor assessments. Additional assessments included medical history and physical examination, evaluation of the WHO performance status, hematology and blood chemistries.

All enrolled patients who met the following criteria were evaluated for tumor response and time to event variables: (1) histologic or cytologic diagnosis of TCC of the urothelium; (2) no concurrent systemic chemotherapy; (3) presence of bidimensionally measurable disease; (4) treatment with at least one cycle of gemcitabine and pemetrexed combination; (5) a CT scan performed within 3 weeks of beginning therapy and one or more subsequent tumor response assessment. Efficacy was assessed in patients prior to every cycle via measurement of palpable or visible lesions by physical examination and prior to every other cycle by radiological imaging. Tumor responses were classified according to modified SWOG criteria [11]. Evaluation for tumor response was performed within 3 weeks of study enrollment and then prior to every other cycle for patients with objective response or stable disease up to disease progression.

A complete response (CR) required disappearance of all measurable and evaluable disease on two study visits separated by a minimum of 4 weeks. A partial response (PR) required a decrease of at least 50% in the sum of products of perpendicular diameters of all measurable lesions without evidence of progression of any lesion documented in visits separated by at least 4 weeks. A 50% increase in the size or an increase of 10 cm² in the sum of products of all measurable lesions over the smallest sum observed or the appearance of any new lesion was considered disease progression (PD). Lesions not qualifying for CR, PR, or PD were characterized as stable disease (SD). Response was confirmed with a second assessment scheduled at least 3 weeks after the first documentation of response.

The duration of response was defined as the time from first objective status assessment of CR or PR to the first date of documented progression or death due to any cause. Duration of response was censored at the date of the last post-therapy follow-up visit for responders who were still alive and who had not progressed. Time-to-treatment failure was defined as the time from study entry to the first observation of early discontinuation of treatment, disease progression or death due to any cause. Time-to-treatment failure was censored at the date of the last post-therapy follow-up visit for patients who did not discontinue treatment early, who were still alive, and who had not progressed. Progression-free survival time was defined as the time from the date of study entry to the first date of documented progression or death from any cause. Progression-free survival time was censored at the date of the last post-therapy follow-up visit for patients who were still alive and who had not progressed. Survival was defined as the time from study entry to the first date of documented progression or death from any cause.
from study entry to time of death due to any cause. Survival time was censored at the time of the last post-therapy follow-up visit for patients who were still alive.

This study employed a two-stage trial design and stopping rules were as follows. Response was analyzed in the first 17 patients. If fewer than five patients responded among these first 17 qualified patients, further accrual would have been halted. If five or more responses were observed, accrual would continue until a total of 44 qualified patients were enrolled.

All patients who received at least one dose of gemcitabine or pemetrexed were evaluated for safety and toxicity. Assessment of toxicity was conducted prior to every cycle using the NCI-CTC (National Cancer Institute Common Toxicity Criteria) investigator guide [12].

Patients were assessed 30 days following completion of the last cycle to evaluate response using the same imaging technique that was used at baseline, and to carry out blood chemistry and hematology assessments and CTC toxicity grading. Long-term assessments were also performed every 4 months for a maximum of 18 months after the patient’s last on-study visit to establish the date of disease progression and to record the type of post-study therapy. Fourteen (22%) of the 64 patients who entered the study failed to undergo the protocol-specified follow-up radiological scans required for response evaluation. Because of this high frequency of non-evaluable patients, both the protocol-qualified and the intent-to-treat populations are presented in the data analyses.

statistical methods
A null hypothesis that the tumor response rate would be less than 25% was tested using an overall one-sided type I error rate equal to 0.1. For the alternative hypothesis that the tumor response rate was 45%, the statistical power was over 90%. All 44 qualified patients were enrolled in a two-stage sequential manner with the possibility of stopping the study early for either lack of efficacy or unacceptable toxicity. All confidence intervals for parameters to be estimated were constructed with a significance level of $\alpha = 0.05$.

Response rates were calculated based on the best response assessments and included 95% confidence intervals (CI). Kaplan–Meier analysis was performed on observed distributions for duration of response, time to disease progression, time to treatment failure and overall survival.

results
patient characteristics
From April 2001 to November 2004, 64 patients with locally advanced and/or metastatic TCC of the urothelium were enrolled. Median age was 65 years (range 38–81 years). Patients presented with a performance status of 0 (29%), 1 (63%) or 2 (8%). Visceral metastases were present in 55% of the patients. Patient characteristics are summarized in Table 1.

tumor response
Of the 64 patients included in the intent-to-treat population, 47 patients were protocol-qualified. Reasons for failure to satisfy protocol criteria included: failure to receive a follow-up imaging assessment (14 patients), not meeting initial inclusion criteria (two patients), and receiving only one study drug (one patient). Of the 47 protocol-qualified patients, there were three CRs (6%) and 10 PRs (21%). This gave an ORR of 28% (95% CI 16% to 43%). The ORR for the intent-to-treat population was 20% (95% CI 11% to 32%). Response data are summarized in Table 2.
The most commonly reported grade 3/4 hematologic toxicity was neutropenia (24 patients, 38%). Eleven patients (17%) developed grade 3/4 febrile neutropenia, which resolved after conventional treatment in 10 patients. One patient died as a result of neutropenic sepsis considered to be related to the chemotherapeutic regimen.

**Chemotherapy administration**

The 64 patients completed a total of 223 cycles of therapy (Table 4). The median number of cycles administered was four (range 1–9 cycles). One patient received nine cycles of therapy and experienced a PR after cycle 4. Mean administered doses were 84% and 84% of planned dose for pemetrexed and gemcitabine, respectively. Pemetrexed doses were omitted in 17 (8%) of the 223 cycles. Out of the 206 doses of pemetrexed administered, 11 (5%) were reduced and 71 (34%) were delayed. Four of the 11 dose reductions of pemetrexed (36%) were due to febrile neutropenia and three (27%) were due to neutropenia without fever. Two of the 17 dose omissions of pemetrexed (12%) were due to decreased creatinine clearance. A gemcitabine dose was omitted in 16 (7%) of the 223 cycles. Out of the 430 doses of gemcitabine administered, 15 (3%) were reduced. Eight of the 15 dose reductions (53%) were due to febrile neutropenia and three (20%) were due to neutropenia without fever. Two of the 16 dose omissions of gemcitabine (12%) were due to decreased creatinine clearance.

**Discussion**

In this phase II trial, pemetrexed plus gemcitabine was given to patients with locally advanced and/or metastatic transitional cell carcinoma of the urothelium to assess efficacy of this combination and to examine its safety profile in this patient population. The pemetrexed and gemcitabine combination was...
Relative dose intensity

agent pemetrexed 500 mg/m² every 21 days in patients with toxicity. More recently, a phase II study of second-line single drug in bladder cancer [10] might be warranted. However, the suggested that a study addressing the efficacy of pemetrexed in advanced bladder carcinoma found an ORR of 15% [7]. This reduced, toxicity observed in the present study with pemetrexed plus gemcitabine was apparently no better than that seen with single-agent gemcitabine. Thus, gemcitabine administered as first and second-line chemotherapy in patients with metastatic bladder cancer has demonstrated an ORR between 23% and 29% [13–16]. In a pooled analysis, the ORR for gemcitabine as a single agent was 25% with a CR rate of 9% [10]. The reasons for the unexpected low efficacy obtained with the combination of pemetrexed and gemcitabine in the present study remain speculative. One reason may be due to the relative poor prognostic group of patients included in the study, as fit patients and patients with good prognostic features were primarily offered cisplatin-containing chemotherapy. Furthermore, sequence-dependent administration effects of pemetrexed plus gemcitabine have been observed both in vitro and in vivo [17–20] and the applied schedule using gemcitabine before pemetrexed may have been suboptimal.

The toxicity profile of the combination was consistent with what has been previously observed with these two agents. Neutropenia was the major hematologic toxicity observed and one patient died from neutropenic sepsis that was related to the study drugs. It appears likely from these results that patients would probably benefit from the prophylactic use of hematopoietic growth factors with this combination. Non-hematologic toxicity was generally manageable.

In conclusion, the combination of pemetrexed and gemcitabine had a manageable safety profile in this phase II study of patients with locally advanced and/or metastatic bladder cancer. However, efficacy was apparently not better than that of single-agent gemcitabine.

acknowledgements

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Table 3. Maximum NCI-CTC grade 3/4 toxicities (N = 64)\(^a\)

<table>
<thead>
<tr>
<th>Toxicities, n (%)</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (14)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (10)</td>
<td>18 (28)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Non-hematologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6 (9)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>6 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Infection with G3 or G4 neutropenia</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

\(\text{aIncidence} \geq 2\% \text{ of patients are shown.}\)

\(\text{bThere was one toxic death associated with neutropenic sepsis.}\)

NCI-CTC, National Cancer Institute—Common Toxicity Criteria; G3, grade 3; G4, grade 4.

Table 4. Dose modifications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pemetrexed</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles</td>
<td>223</td>
<td>223</td>
</tr>
<tr>
<td>Doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned, n</td>
<td>223</td>
<td>446</td>
</tr>
<tr>
<td>Given, n</td>
<td>206</td>
<td>430</td>
</tr>
<tr>
<td>Delayed, n (%)</td>
<td>71 (34%)</td>
<td>45 (11%) day 1</td>
</tr>
<tr>
<td>Reduced, n (%)</td>
<td>11 (5)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Omitted, n (%)</td>
<td>17 (8)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Dose intensity</td>
<td>N = 59</td>
<td>N = 64</td>
</tr>
<tr>
<td>Planned mean dose, mg/m²/week</td>
<td>167</td>
<td>833</td>
</tr>
<tr>
<td>Actual mean dose, mg/m²/week</td>
<td>140</td>
<td>696</td>
</tr>
<tr>
<td>Relative dose intensity, (actual/planned \times 100)</td>
<td>84%</td>
<td>84%</td>
</tr>
</tbody>
</table>

modestly active in these patients with an ORR of 28% in evaluable patients for response and an ORR of 20% within the intent-to-treat population. The pemetrexed and gemcitabine regimen was moderately well tolerated although there was one toxic death associated with this treatment.

A prior phase II study of pemetrexed as single agent in first-line chemotherapy in advanced TCC at 500 mg/m² every 21 days yielded a response rate of 29% based on an intent-to-treat analysis [6]. The toxicity observed in this study was substantial with 26% of patients experiencing febrile neutropenia and three toxic deaths. These results were obtained, however, in the absence of folate and vitamin B₁₂ supplementation, which has subsequently been shown to dramatically reduce pemetrexed toxicity. More recently, a phase II study of second-line single agent pemetrexed 500 mg/m² every 21 days in patients with advanced bladder carcinoma found an ORR of 15% [7]. This suggested that a study addressing the efficacy of pemetrexed in combination with gemcitabine, a well established and effective drug in bladder cancer [10] might be warranted. However, the


