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Phase II Trial of Pemetrexed Disodium and Gemcitabine in Advanced Urothelial Cancer (E4802):

A Trial of the Eastern Cooperative Oncology Group

Robert Dreicer, M.D.¹, Hailun Li, M.S.², Matthew M. Cooney, M.D.³, George Wilding, M.D.⁴, and Bruce J. Roth, M.D.⁵

¹Department of Solid Tumor Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

²Department of Biostatistical Sciences, Dana Farber Cancer Institute, Boston, MA ³University Hospitals Case Medical Center, University Hospitals of Cleveland ⁴University of Wisconsin Clinical Cancer Center, Madison, WI ⁵Vanderbilt-Ingram Cancer Center, 777 Preston Research Building, 2220 Pierce Avenue, Nashville, TN 37232

Abstract

Background—There is a need to identify active new regimens in patients with advanced urothelial cancer. Pemetrexed and gemcitabine are active agents in advanced urothelial cancer. A phase 2 trial of the combination of these two agents was performed in patients with advanced urothelial cancer previously untreated for metastatic disease.

Methods—Forty-six patients with advanced urothelial carcinoma were treated with pemetrexed disodium 500 mg/m² and gemcitabine 1000 mg/m² intravenously on day 1, with gemcitabine repeated on day 8. Cycles were repeated every 3 weeks for a maximum of 6 cycles.

Results—Two patients obtained a complete response (CR) and 12 a partial response (PR) for an overall response rate of 31.8 % (90% confidence interval 20.4%, 45.2%). Median time to progression was 5.8 months and median overall survival was 13.4 months. Thirty-three (75%) of patients experienced grade 3 or greater neutropenia and five (11%) had febrile neutropenia. There were two therapy related deaths.

Conclusions—The combination of pemetrexed and gemcitabine had moderate antitumor activity in previously untreated patients with advanced urothelial cancer at the expense of significant myelosuppression.

Advanced transitional cell carcinoma is a moderately chemosensitive neoplasm. The M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) regimen long considered the standard initial regimen for advanced disease has been replaced by the gemcitabine + cisplatin(GC) doublet based upon a phase III trial comparing M-VAC to GC which demonstrated comparable activity with a somewhat improved toxicity profile favoring GC.¹

Over the last 15 years, a number of new agents and combination regimens have been tested in advanced urothelial cancer. Many of these agents including paclitaxel, pemetrexed and docetaxel have exhibited activity against advanced transitional cell carcinoma, although none of the doublets/triple combinations studied to date have demonstrated improved survival compared to the M-VAC regimen.^{2,3,4, 5} Another therapeutic dilemma is that patients with

advanced urothelial cancer may have impairment in renal function due to age, comorbid conditions and/or disease related factors which limit the utility of cisplatin-based regimens.

Gemcitabine has demonstrated single agent activity in urothelial cancer with response rates in the 24-28% range.^{6, 7} At the time this trial was written pemetrexed disodium was a new, novel multi-targeted antifolate compound that had demonstrated antitumor activity in the preclinical setting against a variety of solid tumors including bladder cancers.⁸ The significant hematologic toxicity associated with the early use of this agent was extensively evaluated and subsequently patients were supplemented with folic acid and vitamin B12 leading to a marked improvement in drug tolerance.⁹ Paz-Ares *et al.* conducted a phase II study of pemetrexed disodium in advanced transitional cell carcinoma of the bladder. Pemetrexed disodium was administered as a 10 minute infusion of 600 mg/m² for the first 6 patients then 500 mg/m² for all additional patients. In the preliminary report of 17 evaluable patients 6 (35%) obtained a partial response. Notably as this trial was performed without prophylactic vitamin supplementation and there were two treatment related deaths.¹⁰

Given the broad antitumor activity of both gemcitabine and pemetrexed disodium and their potential utility in patients with compromised renal function, an evaluation of these agents given in combination was undertaken. Preclinical work demonstrated cytotoxic synergy when gemcitabine exposure preceded pemetrexed disodium in human colon cancer cells and bladder cancer *in vitro*.^{11, 12} Adjei *et al.* performed a phase I trial of the combination using a day 1 and 8 schedule and demonstrated responses in a variety of epithelial cancers.¹¹ Based upon demonstrated single agent activity of these agents, and the potential for developing an active non-platinum containing doublet, we conducted a phase II trial of gemcitabine + pemetrexed in patients with advanced urothelial cancer.

MATERIALS AND METHODS

Eligible patients had histologically confirmed transitional cell carcinoma (or mixed histologies containing a component of transitional cell carcinoma) of the urothelium with evidence of progressive, bidimensionally measurable regional or metastatic disease. Patients with a history of prior malignancy were eligible provided they were treated with curative intent and had been disease free for the time period considered appropriate for cure of the specific cancer. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 at entry and must not have received prior systemic chemotherapy for metastatic disease. Patients may have received prior neoadjuvant or adjuvant chemotherapy if treatment ended greater than 1 year prior to registration and must have been at least 4 weeks out from major surgery. Adequate renal and hepatic function was required with a calculated creatinine clearance (CrCl) ≥ 45 mL/min based on the standard Cockcroft and Gault formula, aspartate aminotransferase (AST) ≤ 3.0 and bilirubin ≤ 1.5 times the upper limit of normal. Adequate bone marrow reserve was mandated with a requirement for granulocytes $\geq 1,500$ mm³ and a platelet count $\geq 100,000$ mm³ at entry. Patients with uncontrolled cardiac dysrhythmias or American Heart Association class III or IV disease were excluded as were patients with evidence of clinically significant (by physical exam or plain film) third-space fluid collections (pleural effusions, ascites). Each site was required to have approval of this clinical trial by a local Human Investigations Committee in accord with an assurance filed with and approved by the Department of Health and Human Services. All patients provided written informed consent prior to registration onto this study.

Patients received 1000 mcg of vitamin B 12 intramuscularly and started folic acid 400 mcg daily within 7 days prior to protocol therapy. Injections of vitamin B 12 were repeated every 9 weeks and folic acid 400 mcg /day were both administered until 3 weeks post protocol therapy.

Doses of chemotherapy were based upon actual weights and body surface area was capped empirically at 2.2 m². On day 1 of therapy pemetrexed disodium 500 mg/m² administered IV over 10 minutes followed 60 minutes later by gemcitabine 1000 mg/m² V over 30 minutes. The dose of gemcitabine was repeated on day 8 and therapy was repeated every 3 weeks for a maximum of 6 cycles.

Standard dose modifications for hematologic and non-hematologic toxicity for both regimens were stipulated. Growth factor support usage was in accord with the American Society of Clinical Oncology guidelines.¹³

Prior to study entry, all patients underwent physical examination and standard laboratories and computed tomograms (CT) of chest, abdomen and pelvis. Tumor measurements were performed every other cycle.

Tumor responses were analyzed using RECIST criteria. National Cancer Institute (NCI) common toxicity criteria (Version 2) were used to analyze toxicity. Patients with objective responses or stable disease were continued on therapy for a maximum of 6 cycles.

The study was designed to assess the objective response rate and toxicity of the combination of pemetrexed disodium and gemcitabine. The primary endpoint was the proportion of patients responding to treatment, as measured using RECIST solid tumor response criteria. The trial was designed with the assumption that this doublet would be worthy of further study if the combination had a true response rate of 65%. Alternatively, a response rate of 45% would not be of interest. A two-stage accrual plan was used with the first stage planned for 21 eligible patients although accrual was planned to continue while response assessment of patients in the first stage was ongoing. If 10 or more of 21 eligible patients in the first stage responded, accrual would continue to 41 eligible patients.

RESULTS

Forty-six patients from 18 ECOG institutions were enrolled from April 2004 until October 2005. Two patients never started protocol therapy, the remaining 44 were eligible and evaluable for response and toxicity. The decision rule regarding early stopping was not employed because study accrual was complete before response information was available for the first 21 patients.

Patient characteristics are detailed in Table 1. All 44 eligible patients had tumors that were pure or predominantly transitional cell carcinoma. The bladder was the primary site of disease in 34 patients. Eighteen patients underwent prior cystectomy and 12 nephroureterectomy. Three patients (7%) had received perioperative (adjuvant or neoadjuvant chemotherapy). Using the risk factor status defined by Bajorin et al, 22 patients (50%) were good risk, 21 (48%) intermediate risk and 1 patient (2%) poor risk.¹⁴

The median number of pemetrexed/gemcitabine cycles administered was 4.5 (range 1-6). Twenty-seven percent of patients came off treated for progressive disease, 23% for toxicity, 39% of patients completed all 6 planned cycles of therapy. Forty of 44 patients required at least one modification of their therapy regimen.

Toxicity

Toxicity data were available for all 44 patients. There were two therapy related deaths, one patient died of febrile neutropenia related sepsis, and a second patient of an infection in a non-neutropenic setting. Thirty-three (75%) of patients experienced grade 3 or greater neutropenia five (11%) with febrile neutropenia, 3 (7%) and 6 (14%) patients experience grade 3 thrombocytopenia and anemia respectively. Clinically significant (grades 3 and 4) non-

hematologic toxicity included 7 patients with fatigue, 3 each with transaminitis, anorexia, dehydration and nausea, and 2 each with hyperglycemia and hypotension.

Response

Thirty-eight patients were assessable for response to therapy, with 6 deemed unevaluable (two patients died before evaluation, 1 refused evaluation, 1 received non-protocol therapy prior to evaluation and 2 had incomplete baseline or follow-up information). Two patients obtained a complete response (CR) and 12 a partial response (PR) for an overall response rate of 31.8 % (90% confidence interval 20.4%, 45.2%). At the time of this report 34 patients (77%) had progressed with 6 (14%) alive and progression-free. Median time to progression was 5.8 months (95% confidence interval 3.0 months to 7.7 months) (Figure 1). Median overall survival was 13.4 months (95 % confidence interval 8.8 months to 16.1 months) (Figure 2).

DISCUSSION

For fit patients with acceptable renal function, cisplatin-based multi-agent chemotherapy has been the standard of care for more than two decades. The M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) regimen has gradually been replaced by the combination of cisplatin and gemcitabine which has demonstrated similar efficacy with a somewhat better toxicity profile.¹⁵ For unfit patients or those with compromised renal function various agents and combinations have been utilized including paclitaxel, carboplatin and gemcitabine with some evidence of clinical benefit but lingering concerns that these agents failed to provide similar antitumor activity as cisplatin-based treatment.^{16, 17} Given the relatively high percentage of patients with advanced urothelial cancer who are considered unfit or who have some degree of compromised renal function, the need to develop effective alternatives to cisplatin-based chemotherapy remains a priority.

Three trials have evaluated the role of pemetrexed as a single agent in urothelial cancer. The first study, done without use of vitamin supplementation involved 33 previously untreated patients with metastatic urothelial cancer. Patients received pemetrexed 500-600 mg/m² every 21-days. On an intent to treat basis, 29% (95% CI 14-48%) of patients achieved an objective response. There were three early deaths, which the authors felt might be due, in part, to the lack of vitamin supplementation.¹⁰ Two studies evaluated the role of pemetrexed in previously treated patients. Sweeney et al. performed a multi-institutional phase II trial of pemetrexed (500 mg/m² every 21 days) with vitamin replacement in advanced urothelial cancer. All patients had received 1 prior chemotherapy regimen with disease progression following adjuvant/neoadjuvant treatment (disease progression within 12 months) or in the metastatic setting. Of the 45 evaluable patients there was an overall response rate of 28%, 3 patients (6%) achieved a complete response. The reported median overall survival was 9.6 months, and therapy was well tolerated.¹⁸ Galasky et al. treated 13 patients in the second line setting and observed an overall response rate of 8%.¹⁹

The combination of gemcitabine + pemetrexed was evaluated in a multicenter phase II trial in patients with advanced urothelial cancer who had not received chemotherapy in the metastatic setting. Gemcitabine 1250 mg/m² was administered days 1 and 8 of each 21-day cycle. Pemetrexed 500 mg/m² was administered on day 8, 90 min after the gemcitabine administration with all patients receiving vitamin supplementation. Of the 47 evaluable patients three patients obtained a CR, 10 a PR for an overall response rate of 28% (95% CI 16% to 43%) Median response duration was 11.2 months and median overall survival 10.3 months. Febrile neutropenia was seen in 17% of patients, neutropenic sepsis in 3% with 1 patient death secondary to neutropenic sepsis.²⁰ The goal of this study was to evaluate the antitumor activity of the combination of pemetrexed and gemcitabine with the hope of developing an active regimen for patients who are not optimal candidates for cisplatin-based chemotherapy.

Although our dose/schedule was somewhat different than that tested by von der Maase and colleagues²⁰, we observed a similar overall response rate and toxicity profile, with moderate-significant myelosuppression and one patient death secondary to neutropenic sepsis. The observed median survivals from both these trials are in the 10-13 month range which overlaps a large number of other combination regimens described in the phase II setting.

Twenty years of experience with cisplatin-based combination chemotherapy has reinforced our appreciation that advanced transitional cell carcinoma of the bladder is a chemotherapy sensitive neoplasm. Unfortunately despite the introduction of a host of cytotoxic agents with single agent activity, efforts to dose intensify and the use of doublet and triplet regimens, we have made little additional progress in improving patient outcomes. Trials of novel targeted agents have come late to urothelial cancer but are underway. Given that the biology of urothelial carcinoma like that of renal cancer provides many attractive targets amenable to these agents provides a reason for cautious optimism that real progress in the management of this disease may be forthcoming in the near term.

The combination of pemetrexed and gemcitabine has activity in advanced urothelial cancer but at a significant cost in terms of toxicity. Further development of this doublet in urothelial cancer seems unwarranted.

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Figure 1.
Time to Progression for all 44 patients.

Figure 2.
Overall survival for all 44 patients.

Table 1

Baseline Patient Characteristics

Characteristics	No. of patients (%)
Age, yr median (range)	65 (47-87)
Sex	
Men	36 (82)
Women	8 (18)
ECOG performance status	
0	15 (34)
1	26 (59)
2	3 (7)
Sites of metastases	
Distant Nodes	24 (55)
Liver	7 (16)
Bone	3 (7)
Lung	14 (32)
Prognostic factors (MSK)*	
0	22 (50)
1	21 (48)
2	1 (2)

ECOG indicates Eastern Cooperative Oncology Group

MSK Memorial Sloan Kettering, Bajorin et al. ¹⁴