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Front-line Treatment with Gemcitabine, Paclitaxel and Doxorubicin for Patients with Unresectable or Metastatic Urothelial Cancer and Poor Renal Function: Final Results from a Phase II Study

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Abstract

Objectives—To estimate the response rate to gemcitabine, paclitaxel, and doxorubicin in patients with advanced urothelial carcinoma, we conducted a phase II clinical trial. Patients with renal insufficiency cannot receive standard cisplatin-based chemotherapy for urothelial carcinoma, and carboplatin-based regimens have proved unsatisfactory. Secondary end points for this study included overall survival, safety of the regimen, and safety of same-day pegfilgrastim dosing.

Methods—A two-stage design was chosen with target response rate of 40%. Key inclusion criteria were metastatic or unresectable urothelial carcinoma, no prior chemotherapy, glomerular filtration rate <60 mL/min, and no dialysis. Gemcitabine (900 mg/m²), paclitaxel (135 mg/m²), and doxorubicin (40 mg/m²) were administered on day 1 of each 14-day cycle. Pegfilgrastim was given with every cycle on either day 1 or optionally day 2.

Results—Forty patients were enrolled and 39 were treated. Median age was 72 years (range, 51–89). There were 7 complete and 15 partial responses, for a response rate of 56.4% (95% CI, 39.6–72.2). Most (82.8%) cycles were given with same-day pegfilgrastim. Notable grade 3 and 4 non-hematologic toxicities were fatigue and mucositis (10.3% each). There were 4 episodes of neutropenic fever (4/198 cycles [2%]; 4/39 patients [10.3%]) and no treatment related deaths. Median overall survival was 14.4 months.

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Conflicts of interest: none

Conclusions—The combination of gemcitabine, paclitaxel, and doxorubicin is effective first-line chemotherapy for patients with advanced urothelial carcinoma and renal insufficiency. Neutropenic prophylaxis was acceptable whether pegfilgrastim was given immediately or 24 hours after chemotherapy.

Keywords

Renal insufficiency; urinary bladder neoplasms; combination drug therapy; treatment outcome; phase II clinical trial

INTRODUCTION

There currently is no standard systemic treatment for patients with metastatic or surgically unresectable urothelial carcinoma (UC) and poor renal function. This unmet need is also quite common, owing to the loss of nephrons with advancing age, the renal impairment occurring from malignancy directly obstructing the urinary system, and the impact of comorbid medical conditions associated with this smoking-related malignancy. It is estimated that 40% of patients over age 70 do not have adequate renal function to receive standard cisplatin-based chemotherapy, such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) or gemcitabine/cisplatin.¹

Attempting to improve upon the nephrotoxic profile of chemotherapy for UC, investigators have substituted carboplatin for cisplatin. Unfortunately, non-standard carboplatin-based combinations have been less effective with respect to overall response rate and overall survival (OS) when compared with cisplatin-based chemotherapy. Small randomized trials have shown trends in favor of cisplatin when comparing gemcitabine/cisplatin with gemcitabine/carboplatin², and M-VAC with paclitaxel/carboplatin.³ Several phase II trials of carboplatin plus gemcitabine or a taxane have shown only modest benefit, with median OS of 8-10 months being typical.⁴⁻⁶ It should be noted that carboplatin also can potentially cause renal impairment, despite dose reduction based upon area under the curve (AUC).² Studies in patients with poor baseline renal function have suggested that AUC dosing of carboplatin is not always safe, and that it should not be given when the glomerular filtration rate (GFR) falls below 30 mL/min.⁷ Therefore, there remains a pressing need to develop alternate systemic therapy for patients with advanced UC and poor renal function.

The combination of gemcitabine plus paclitaxel has shown activity in advanced UC with several phase II trials showing response rates of 40-60%.⁸⁻¹⁰ These agents do not require dose adjustment for renal function. Doxorubicin is another drug with proven activity in UC (e.g., M-VAC), is not nephrotoxic and has a toxicity profile substantially different from gemcitabine or paclitaxel. At The University of Texas MD Anderson Cancer Center, 20 patients were retrospectively analyzed who had received the triplet of gemcitabine, paclitaxel, and doxorubicin (GTA) for advanced UC complicated by impaired renal function. The most frequently dosing (12 patients) was 135 mg/m² of paclitaxel, 900 mg/m² of gemcitabine, and 30-35 mg/m² of doxorubicin. This regimen did not compromise renal function and appeared to be otherwise well tolerated. Myelosuppression was observed,

requiring growth factor support. Based on these preliminary results, we designed a phase II clinical trial of GTA given every 2 weeks with pegfilgrastim for neutropenic prophylaxis.

In this study, our primary objective was to determine the response rate of the GTA triplet in previously untreated patients with metastatic or surgically unresectable UC and renal insufficiency. Secondary end points were OS and safety/tolerance of the regimen. We also report the clinical results of same-day administration of pegfilgrastim in these patients.

MATERIALS AND METHODS

Patients were consented on this IRB approved protocol, done in collaboration with the Community Clinical Oncology Program. Eligible patients were 18 years or older and had histological confirmation of unresectable or metastatic UC of the urethra, bladder, or upper urinary tracts. All patients had measurable disease and an estimated GFR less than 60 mL/min as measured by the Cockcroft-Gault method (not adjusted for body surface area). Patients with localized disease that was potentially resectable after neoadjuvant chemotherapy were eligible only if the renal insufficiency was not reversible by percutaneous nephrostomy or ureteral stenting. Other inclusion criteria were an ECOG performance status 2, an absolute neutrophil count $>1500/\text{mm}^3$ and platelet count $>100,000/\text{mm}^3$, a total bilirubin ≤ 2.0 mg/dL and aspartate aminotransferase or alanine aminotransferase less than twice the upper limit of normal, and left ventricular ejection fraction $\geq 40\%$; or, if no history of coronary artery disease, a normal electrocardiogram. Patients were excluded for brain metastasis, end-stage kidney disease requiring hemodialysis, any prior chemotherapy with gemcitabine, paclitaxel, or doxorubicin, or other systemic chemotherapy for UC. Prior treatment with any intravesical chemotherapy was allowed. Additional exclusion criteria were: Uncontrolled or severe infection; New York Heart Association grade III or IV congestive heart failure, or history of unstable angina/myocardial infarction within six months prior to study entry; grade 2 or worse peripheral neuropathy; uncontrolled hypertension; chronic liver disease; known human immunodeficiency virus infection; second malignancy (excluding non-melanoma skin cancer) unless disease free for greater than 3 years; overt psychosis, mental disability, or inability to give informed consent; pregnancy or current lactation; and known sickle cell disease.

The treatment regimen consisted of doxorubicin (40 mg/m^2) intravenous over 20 minutes, paclitaxel (135 mg/m^2) intravenous over 60 minutes, and gemcitabine (900 mg/m^2) intravenous over 90 minutes, repeating every 14 days. Patients were pre-medicated with antiemetics, corticosteroid, and antihistamines. Pegfilgrastim 6 mg was given subcutaneous on day 1 immediately after chemotherapy administration was complete, although day-2 administration was permitted depending on third party (insurance) payment restriction, patient preference, or physician preference. Treatment was continued until a maximum of 9 cycles, or tumor progression, or unacceptable toxicity.

Response assessment included computerized tomography or magnetic resonance imaging of the abdomen and pelvis, chest x-ray, and any additional imaging as required every 6 weeks (3 cycles) while on therapy.

Statistical Analysis

This Simon two stage phase II design used a target response rate of 40% by Response Evaluation Criteria in Solid Tumors, version 1.1.¹¹ In the event that there were 7 or fewer responses among the first 29 patients treated, the study was to be stopped early due to futility. Because accrual was slower than expected, the original maximum trial size of 72 patients was revised to 40 patients allowing the objective response rate to be estimated with a 95% confidence bound of at most 0.16. Toxicity was defined by the NCI Common Terminology Criteria for Adverse Events 3.0, OS was calculated using the Kaplan-Meier method, and the frequency of neutropenic fever and treatment delay caused by neutropenia were recorded as a measure of growth factor treatment effect. We used summary statistics to describe the demographic and clinical characteristics of patients. We estimated the response rate with an exact 95% binomial confidence interval. A Cox (1972) proportional hazards regression model was used to evaluate OS as a function of potential prognostic factors. All statistical analyses were performed using SAS 9.3 for Windows (Copyright © 2002-2010 by SAS Institute Inc., Cary, NC).

RESULTS

Between January 2008 and November 2011, 40 patients were enrolled: 39 at the lead center and one at a CCOP center. Their median age at enrollment was 72 years, with range 51 to 89 years. The baseline demographics and clinical characteristics of the patients are shown in Table 1. One patient withdrew from the study without receiving treatment. A total of 198 cycles were given to 39 patients, of whom 84.6% (33/39) received three cycles or more and 7.7% (3/39) received the maximum allowed number of 9 cycles. One patient received 2 cycles and 5/39 patients (12.8%) received one cycle only.

Response

Thirty-nine patients received at least 1 cycle of chemotherapy and were evaluable for response. Four patients who did not undergo imaging for response assessment because of declining performance status (3 patients) or personal choice (one patient) were considered to be non-responders. The objective response rate was 56.4% (95% CI, 39.6-72.2), including 15/39 patients (38.5%) with partial response and 7/39 (17.9%) with a complete response.

Eight responding patients underwent surgical consolidation for their initially unresectable primary tumor or node-only metastatic disease. Five of these patients had received only GTA in the preoperative period and were found to have residual viable tumor in lymph nodes (3 patients) or primary site alone (ypT1, 2 patients). The other 3 patients had clinical evidence of lymph node metastasis at baseline and were able to receive a cisplatin-based regimen after GTA, before surgery, owing to improvement in GFR. One of these patients had persistent ypT2, node-positive disease, one was down-staged to ypT2 ypN0, and one was found to have a pathologic complete response (ypT0 ypN0).

Survival

The median OS for all patients was 14.4 months (Figure 1). Eight patients remain alive as of their last study contact. The median OS for patients experiencing a complete response was

33.2 months (HR=0.25, 95% CI 0.07-0.95, p=0.04), and for those with a partial response or stable disease it was 14.4 months (HR=1.09, 95% CI 0.44-2.70, p=0.85) and 9.2 months (reference group), respectively (Figure 2).

Univariate Analysis

Previous studies have suggested that performance status and the presence/absence of visceral metastases are prognosticators of clinical outcome.¹² In this trial, the presence of visceral metastases and poor performance status was associated with adverse outcomes (Table 2). When patients were assigned a prognostic score by accumulating a point each for the presence of visceral metastases and poor performance status, those with 0 points had median OS of 20.7 months, 1 point median OS 12.7 months (HR=2.07, 95% CI 0.96-4.45, p = 0.062), and 2 points median OS 10.8 months (HR=3.72, 95% CI 1.14-12.10, p= 0.029).

Timing of Pegfilgrastim

One of our secondary aims was to estimate the safety and efficacy of pegfilgrastim administered on the day of chemotherapy. Thirty-two of 39 patients (82.1%) received pegfilgrastim immediately after chemotherapy on day 1 of the cycle. A total of 198 cycles were provided on study, of which 164 cycles (82.8%) were followed by same-day administration of pegfilgrastim, 15/198 cycles (7.6%) were with next-day pegfilgrastim, and in 19 cycles (9.6%) the timing of the dose was not documented. Four patients (10.3%) experienced neutropenic fever, including 3/32 patients (9.4%) who received same-day pegfilgrastim and 1/7 patients (14.3%) who did not. The same-day schedule was otherwise well tolerated and no patient had a change of pegfilgrastim schedule (e.g., from same-day to next-day) attributed to complications.

Toxicity

The most common adverse events were related to myelosuppression, which was anticipated. In total, 33.3% (13/39) of patients experienced grade 3 or grade 4 neutropenia. Grade 3 thrombocytopenia occurred in 6/39 patients (15.4%) with no grade 4 events recorded. In terms of non-hematologic events, the most common were fatigue and mucositis, each encountered in 4/39 patients (10.3%). Only 3 patients on study required a chemotherapy dose reduction. There were no treatment-related deaths and there were no dose reductions for nephrotoxicity.

Renal Function

In a post hoc analysis, the estimated GFR was calculated before each cycle and after completing therapy. Improvements in GFR were seen, with a mean increase of 8.5 mL/min (p=0.0027) for the 35 patients who had an available post treatment laboratory evaluation within three months of completion and prior to receiving additional treatment (i.e. chemotherapy, consolidation surgery). We grouped patients into GFR (mL/min) groups of less than 40, 40 to 49, and 50 or greater. Using the Fisher's exact test, testing change across these groups, there was a meaningful improvement in the estimated GFR over the course of treatment (p=0.0114).

COMMENT

In this study we found that GTA is an active regimen for treatment of metastatic or surgically unresectable UC, and is well-tolerated by patients with baseline renal insufficiency. The objective response rate of 56.4% and median OS of 14.4 months compare favorably to historically treated controls who had received cisplatin-containing standard combinations such as M-VAC or gemcitabine and cisplatin. The toxicity profile was manageable for the vast majority of study participants, with no death attributed to the treatment. Growth factor support with same-day pegfilgrastim given with this outpatient regimen every 2 weeks was associated with an acceptably low rate of neutropenic fever and treatment delay.

We optimized the dosing and schedule of GTA by administering gemcitabine at a fixed dose rate of 10 mg/m²/min.¹³⁻¹⁴ The fixed dose rate improves intracellular accumulation of the active triphosphate form of the drug, and was associated with improved outcomes when compared to the standard 30-minute infusion time in several solid tumors, including bladder cancer.¹⁵ We administered doxorubicin as a short infusion and always before paclitaxel to minimize the effect of drug interaction on cardiac toxicity.¹⁶⁻¹⁷ The maximum duration of treatment was capped at 9 cycles to limit the cumulative dose of doxorubicin.

Combinations built on the doublet of gemcitabine and doxorubicin were explored in other clinical trials for the treatment of UC. Milowsky, et al. reported that gemcitabine/doxorubicin was tolerable at all dose levels when given every other week for 6 cycles, but there was no benefit when sequenced with subsequent ifosfamide, paclitaxel and cisplatin as compared to nonsequential cisplatin-based regimens.¹⁸ We developed a combination of gemcitabine/doxorubicin with ifosfamide, which has similar long-term outcomes as cisplatin-based chemotherapy in the neoadjuvant setting.¹⁹ While this regimen avoids cisplatin and is useful in patients with pre-existing peripheral neuropathy or hearing loss, fulfilling another unmet need, the addition of ifosfamide limits its use to patients with excellent renal function. Another example is a phase I clinical trial conducted at MD Anderson, in which gemcitabine and doxorubicin were combined with bortezomib.²⁰ Based upon the experience with these trials and the current study, it seems reasonable to consider gemcitabine/doxorubicin or GTA as a backbone for the addition of novel agents in patients with UC who are cisplatin-ineligible.

The improvement in renal function experienced by a number of the study participants was encouraging, also supporting the lack of any direct nephrotoxicity of the regimen. In the case of tumors obstructing the ureters or bladder outlet, response to chemotherapy helps to decompress the urinary system allowing recovery of kidney function. Of course, whenever possible, this should be done before chemotherapy with a percutaneous nephrostomy or ureteric stent. We excluded patients with localized UC and reversible causes of renal insufficiency such as hydronephrosis from our study. We observed, however, several participants with improvement in their estimated GFR who then went on to receive cisplatin-based regimens followed by surgery. We hypothesize that response to GTA restores patency to a partially obstructed collecting system, even though frank hydronephrosis may not be evident prior to treatment. In 2 of 3 patients who initially had clinically node-positive

disease, sequencing from GTA to cisplatin-based therapy was associated with down-staging to ypN0. Using GTA as a bridge to cisplatin-based regimens may prove to be an attractive treatment strategy in selected patients for whom nephrostomy or stenting is not possible or not sufficient to alleviate renal insufficiency. In this way, more patients with locally advanced UC would be eligible for neoadjuvant chemotherapy, particularly in the upper tract where down-staging is associated with improvement in clinical outcome.²¹

Granulocyte-colony stimulating-factor is typically used when the risk of neutropenic fever with chemotherapy exceeds 20%.²² In our study, pegfilgrastim was routinely administered as part of the protocol treatment. Current guidelines and the approved labeling for pegfilgrastim require that it be given no sooner than 24 hours after the completion of chemotherapy, based on concern that it might otherwise cause exaggerated hematologic toxicity; however, several previous studies demonstrated the feasibility of same-day pegfilgrastim.²³⁻²⁶ Our data suggest that pegfilgrastim was safe and effective when administered immediately after GTA. For the patient, this alternate schedule avoids the cost and inconvenience of a next-day visit. We suggest that it is reasonable to offer UC patients same-day pegfilgrastim with GTA.

Our study has a number of limitations, including the small number of patients and single-arm design. Further evaluation of response rate and OS associated with GTA will require randomized controlled trials. Our methodology for calculating the estimated GFR was not the most accurate by today's standards. The Cockcroft-Gault formula was designed to estimate creatinine clearance, which is higher than GFR owing to tubular excretion of creatinine. Estimated GFR is now more commonly expressed as mL/min per 1.73 m² of body surface area and calculated by the Modification of Diet in Renal Disease (MDRD) formula.^{27, 28} The MDRD was reexpressed in 2005 to be compatible with the isotope dilution mass spectrometry (IDMS)-traceable serum creatinine assay, which gives results about 5% lower than non-IDMS creatinine concentrations. We used the Cockcroft-Gault formula, which is based on non-IDMS creatinine, and unlike MDRD it does not adjust for body surface area or race. Indexing GFR to body surface area becomes less informative in very large or very small individuals. One proposed solution for obese individuals was to use ideal body weight plus 30% in the Cockcroft-Gault formula (mL/min) for patients weighing >30% over their ideal body weight.²⁹ We used the actual weight and did not adjust the Cockcroft-Gault formula for body mass index or ideal body weight. With these limitations in mind, the only practical implication for our study is that we may have underestimated the GFR and misclassified some patients as having GFR < 60 mL/min.

Conclusions

Gemcitabine, paclitaxel, and doxorubicin given every 2 weeks is a highly effective first-line chemotherapy regimen with acceptable toxicity for patients with advanced UC who are unable to receive cisplatin. Until there has been a randomized trial to establish one evidence-based standard of care, GTA should be considered as one of the treatment options for this patient subgroup.

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Figure 1.
Kaplan-Meier estimate of OS.

Figure 2.
Kaplan-Meier estimate of OS for patients with stable disease or better, grouped by response; complete response (black), partial response (blue) and stable disease (red).

Table 1

Demographic and Clinical Characteristics

	N	%
Race		
Caucasian	35	89.7
African American	3	7.7
Unknown	1	2.6
Gender		
Female	11	28.2
Male	28	71.8
Prognostic Score		
0	20	51.3
1	15	38.5
2	4	10.3
Visceral Metastasis		
No	22	56.4
Yes	17	43.6
ECOG Performance Status		
0	11	28.2
1	22	56.4
2	6	15.4
Baseline GFR (mL/min)		
< 40	19	50.0
40 to < 50	9	23.7
50	10	26.3
Primary Site		
Bladder	26	66.7
Prostate	1	2.6
Renal pelvis	5	12.8
Ureter	4	10.3
Urethra	3	7.7

Table 2

Univariate Analysis

	N (deaths)	Median OS (Months)	p-value	HR	95% CI	
Age	39 (31)	14.4	0.5598	1.012	0.973	1.051
Race						
Caucasian	35 (28)	14.4	---	Ref	---	---
African American	3 (2)	14.9	0.6146	0.691	0.164	2.916
Unknown	1 (1)	---	---	---	---	---
Sex						
Female	11 (8)	20.7	---	Ref	---	---
Male	28 (23)	13.8	0.3366	1.487	0.662	3.339
Prognostic Score						
0	20 (13)	20.7	---	Ref	---	---
1	15 (14)	12.7	0.0622	2.070	0.964	4.448
2	4 (4)	10.8	0.0292	3.719	1.142	12.104
Visceral Metastasis						
No	22 (15)	20.7	---	Ref	---	---
Yes	17 (16)	12.6	0.0172	2.427	1.170	5.034
Performance Status						
0	11 (5)	30.5	---	Ref	---	---
1	22 (20)	13.8	0.0091	3.777	1.391	10.259
2	6 (6)	11.4	0.0211	4.101	1.236	13.607
GFR (Baseline, in mL/min)						
< 40	19 (15)	16.4	---	Ref	---	---
40 to < 50	9 (7)	12.7	0.7398	1.165	0.472	2.874
50	10 (8)	17.2	0.8597	0.926	0.395	2.173
Subsequent Cisplatin						
No	21 (17)	14.4	---	Ref	---	---
Yes	16 (12)	17.2	0.4268	0.739	0.351	1.557
Primary Site						
Other	13 (10)	12.7	---	Ref	---	---
Bladder	26 (21)	14.6	0.9962	1.002	0.471	2.132
Response						
SD	11 (9)	9.2	---	Ref	---	---
PR	15 (13)	14.4	0.8488	1.092	0.442	2.700
CR	7 (3)	33.2	0.0409	0.254	0.068	0.945

Ref = Reference, SD = Stable disease, PR = Partial response

CR = Complete response.