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Phase II Trial of Paclitaxel, Carboplatin and Gemcitabine in Patients with Locally Advanced Carcinoma of the Bladder

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Abstract

Purpose—This two-arm phase II multicenter trial was designed to assess the efficacy and toxicity of neoadjuvant paclitaxel, gemcitabine, and carboplatin (PCaG) in patients with invasive bladder cancer.

Methods—Patients in arm I had either clinical stage T2 with hydronephrosis or T3 bladder cancer. They received 3 cycles of chemotherapy (paclitaxel 200mg/m² day 1, carboplatin area under the curve (AUC)= 5 day 1, and gemcitabine 800mg/m² days 1 and 8 of each 21 day cycle). Response was defined as achievement of a pathologic complete response (pT0). Patients on arm II with T4 or lymph node positive disease received up to 6 cycles of PCaG. Response was defined as conversion to surgical resectability.

Results—In arm I, 31 patients were enrolled and 22 were evaluable for response. Seven were pT0 (32% of evaluable patients, 22% by intent to treat). In arm II, 37 patients were enrolled and 29 were evaluable for response with 24 surgically resectable (83% of evaluable and 65% by intent to treat). The most common toxicity was neutropenia with 39 events in arm 1 and 68 in arm 2. There were 7 deaths on study (5 during chemotherapy and 2 post-cystectomy).

Conclusion—Neoadjuvant PCaG resulted in a significant number of responses in both arms but greater than anticipated toxicity. The pT0 rate was modest and overall efficacy difficult to assess due to the toxicity. More studies of novel agents and combinations are needed to improve the efficacy, and reduce the toxicity of neoadjuvant therapy for bladder cancer.

Introduction

Depending on the stage of disease, only 30–50% of patients with locally advanced bladder can be cured by cystectomy alone.¹ Neoadjuvant chemotherapy in this setting is given in an attempt to improve upon this cure rate or to render otherwise unresectable cancers amenable to surgical removal with curative intent. Several studies suggest that this approach has merit. An MRC/EORTC trial using cisplatin, methotrexate, and vinblastine for three cycles prior to either radiotherapy, cystectomy or both, versus cystectomy alone showed an improvement in pathologic complete response rate (pCR) but did not meet its goal of improving survival by 10%.² An Intergroup trial which randomized patients with T2-T4a disease to three cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) followed by cystectomy or cystectomy alone showed an improvement in median survival from 46 to 77 months for the combination group ($p=0.06$ by two-sided stratified log-rank test).³ The majority of this difference was due to a marked increase in pathologic complete response in the combination arm (38% vs. 15%; $p<0.001$) suggesting a significant benefit for chemotherapy. A meta-analysis of neoadjuvant chemotherapy and surgery compared to surgery supported this observation.⁴ A 5% absolute benefit in overall survival for combination platinum-based neoadjuvant therapy was found at 5 years (45% vs. 50%; $p = 0.016$).

Although M-VAC offers a therapeutic benefit, its associated toxicity is significant with patients typically experiencing severe myelosuppression, mucositis and the potential for renal toxicity. Recently, the combination of gemcitabine and cisplatin (GC) was shown to have similar efficacy, but less toxicity in patients with metastatic disease.⁵ The role of GC in other settings remains unproven, and the applicability of either regimen is limited by the need for adequate cardiac and renal function. The combination of paclitaxel, carboplatin, and gemcitabine (PCaG) has demonstrated activity in advanced urothelial malignancies.⁶ A phase II trial in patients with metastatic disease treated with PCaG yielded an overall response rate of 68% and a complete response rate of 32%. The therapy was well tolerated and myelosuppression was the most common toxicity.

Based on the data showing the potential benefits of neoadjuvant therapy and the high response rate of PCaG in metastatic disease, we undertook a phase II trial designed to assess the efficacy of neoadjuvant PCaG in patients with locally advanced bladder cancer.

Patients and Methods

Patient Eligibility

Eligible patients had histologically proven urothelial carcinoma of the bladder, with local disease (T2) with hydronephrosis or locally advanced disease (T3–4 or lymph node positive). Patients had an ECOG performance status of 0–2, life expectancy of ≥ 12 weeks, adequate bone marrow (absolute neutrophil count $\geq 1,500/\text{m}^3$ and platelet count $\geq 100,000/\text{m}^3$), renal (creatinine < 2.0 mg/dl and/or creatinine clearance > 40 ml/min) and hepatic function (total bilirubin < 1.5 mg/dl). Exclusion criteria included evidence of distant metastasis, unresolved bacterial infection, prior systemic or intra-arterial chemotherapy, or prior radiotherapy. The study protocol and informed consent documents were reviewed and approved by the Institutional Review Boards at all participating sites. All patients were informed of the investigational nature of this study and written informed consent was obtained in accordance with institutional and federal guidelines. All patients were registered with the University of Michigan Comprehensive Cancer Center Clinical Trials Office.

Study Design

Patients were stratified into two arms based on extent of disease. In arm I, patients with T3N0 disease or T2N0 with hydronephrosis received 3 cycles of chemotherapy followed by

cystectomy. In arm II, patients with T4 disease or any patient with N1–3 disease received 3 cycles of therapy followed by assessment of response. Patients with evidence of response, received an additional three cycles of therapy. On completion of chemotherapy, those patients deemed resectable by the attending urologist underwent cystectomy. Patients with stable disease or evidence of disease progression were removed from the study.

Response was defined independently for the two arms. The primary endpoint for arm I was complete pathologic response at cystectomy. The endpoint for arm II was conversion to resectable disease. To minimize the number of patients treated in the event that the response rate in either arm was lower than estimated, the Minimax two-stage accrual design was used.⁷ For Arm I, a complete pathologic response rate less than or equal to 33% would be of little interest, but a complete pathologic response rate of 50% or more should be explored in larger studies. For arm II, a conversion rate less than or equal to 20% would be of little interest, however, a conversion rate of 40% or more should be explored in larger trials. The early stopping rules for each arm had 80% power to detect the response rate of interest with a 5% false positive rate.

Treatment Plan

Starting dose levels (dose level 0) were as follows: paclitaxel 200mg/m² on day 1, carboplatin area under the curve (AUC) 5 on day 1, and gemcitabine 800mg/m² over 30 minutes on days 1 and 8 for a 21 day cycle. On day 1, the infusion sequence began with paclitaxel followed by carboplatin and concluded with gemcitabine. All patients were premedicated with dexamethasone 20 mg intravenous (IV) injection, diphenhydramine 50 mg IV, and ranitidine 50 mg IV or famotidine 20 mg IV. Antiemetic therapy was administered at the discretion of the treating physician. Following the first cycle, doses were adjusted for toxicity using the algorithm specified in the phase II trial.⁶

RESULTS

68 patients were enrolled between June 2000 and September 2005. Sixty-three patients had biopsy proven muscle-invasive transitional cell carcinoma of the bladder. Five patients had variant or mixed histologies of urothelial carcinoma (3 with predominant squamous cell carcinoma, 2 with adenocarcinoma). Median age was 61.5 years (range: 29–83), median performance status was 1 (range 0–2), and 90% of participants were Caucasian. The patient characteristics and treatment administered are summarized in Tables 1 and 2 respectively.

Arm I of the study enrolled 31 patients, and 22 were evaluable for response. Nine patients were not evaluable for the primary endpoint. One refused cystectomy, but remains free of disease more than 3 years since completing chemotherapy. Four were removed from study due to toxicity. One developed urinary obstruction from nephrolithiasis resulting in a delay in treatment after one cycle of therapy. One patient suffered a vesicorectal fistula, small bowel obstruction and urosepsis after one cycle. Two additional patients (following 1 and 2 cycles respectively) experienced a >2 week delay in treatment from dehydration, low blood counts and one of the two experienced urosepsis. There were 4 preoperative deaths all occurring during the first cycle of chemotherapy on this arm of the study. One patient suffered a cardiac arrest from previously unrecognized three-vessel coronary artery disease, one had apparent bowel obstruction due to a prior colon resection then became neutropenic, one experienced a bowel obstruction after one cycle and at the time of surgery was found to have peritoneal carcinomatosis not detected by baseline imaging, and the fourth developed a strangulated hernia and suffered complications following his bowel surgery with renal failure and failure to wean from mechanical ventilation. There were two post-cystectomy deaths. One patient suffered multiorgan failure postoperatively in the setting of Crohn's disease and ankylosing spondylitis. A second patient died of pseudomembranous

enterocolitis during his recovery from surgery. Due to the mortality rate during chemotherapy, we elected to close this arm prior to reaching the planned enrollment goal.

Arm II enrolled 37 patients and 29 were evaluable for response. Two patients received only three cycles of therapy before proceeding to radical cystectomy. No significant toxicity was recorded and no reason for a shortened course was provided for either patient. Of the eight patients not evaluable for response, three were found to have metastatic disease which became apparent during their neoadjuvant therapy. This manifested as sclerosis of bone lesions which in retrospect were actually present but not reported on baseline CT scans. One patient had an acute myocardial infarction necessitating coronary bypass surgery during cycle 3, one was removed due to protocol noncompliance and one developed persistent peripheral neuropathy after cycle 3 of therapy and was treated off study with further neoadjuvant therapy. Two patients had a decline in their performance status necessitating > 2 week delay in treatment (one due to dehydration during cycle 3 and another to hematuria from the tumor during cycle 1). An additional patient developed a recurrent arterial femoral thrombus due to a dissection at the site of a prior arterial bypass graft and completed only 4 cycles of therapy. She went on to radical cystectomy. The only death on this arm of the study occurred in a patient who had an intracranial hemorrhage with grade 4 thrombocytopenia following the sixth cycle of therapy. As both of these patients were deemed resectable, they are included in the analysis for response.

Toxicity is summarized in table 3. All patients treated were included in the analysis for toxicity. Overall, myelosuppression and neutropenia were the most common grade 3–4 toxicities. Febrile neutropenia was rare with only 3 events (3 events/253 cycles = 1 %) all of which occurred in patients enrolled on arm I. No pretreatment characteristic appeared to predict for development of toxicity.

Response

In arm I, a total of 22 patients were evaluable for response (defined as ability to assess pathologic response). Seven had a pathologic complete response at time of radical cystectomy. Thus the response rate was 32% of evaluable patients and 22% by intent to treat. An additional patient had no residual invasive tumor but was found to have carcinoma in-situ.

In arm II, a total of 29 patients were evaluable for response. 24 were considered resectable following neoadjuvant therapy (83% of evaluable, 65% by intent to treat). Of the 24 patients, 21 underwent cystectomy. Five patients had a pT0, 2 patients had pTis and the remaining 14 patients had residual invasive bladder cancer. Of the three patients deemed resectable that did not proceed to surgery, one was the patient who suffered an intracranial hemorrhage and expired after completing six cycles of chemotherapy. One had an excellent response by radiographic imaging but ultimately was felt to be too obese to proceed with surgery. He received combination chemotherapy and radiation therapy for definitive management in lieu of surgery. Following bariatric surgery and subsequent weight loss, he underwent radical cystectomy due to cytologic evidence of persistent bladder cancer. The third patient refused surgery and received salvage radiation therapy to a minimal residual urethral mass.

Although survival was not the primary endpoint of either arm of the study, data is available for the majority of the patients. Median overall survival in all patients on arm I was 18.8 months (range: 0.5 to 83.2 months). Median progression free survival in the 23 patients with data available was 35.3 months (range: 4.2 – 83.2 months). In arm II the median survival in all patients was 28.5 months (range: 1.5 – 77.6 months). Median progression free survival on arm II was 17 months (range: 2 – 77.6 months) in the 32 patients with available data.

Twenty-one patients (31%) remain alive and disease free (10 in arm I, 11 in arm II) at a median followup of 58.7 months.

DISCUSSION

Based on their documented efficacy, cisplatin-based regimens have long been the mainstay of therapy for urothelial cancer. The major studies demonstrating this benefit have been conducted with M-VAC.⁸ The incorporation of newer agents including gemcitabine and paclitaxel into regimens for advanced disease has shown substantial promise with high response rates and apparently lower rates of toxicity.^{6, 9-11} The recent randomized comparison of M-VAC and GC demonstrated comparable response rates and survival for the two arms with less toxicity associated with GC.⁵ Survival at 5 years was 12–15% with both regimens.

Neoadjuvant chemotherapy with M-VAC is of benefit in the setting of muscle-invasive urothelial carcinoma of the bladder with a reduction in disease-related mortality.³ This study sought to evaluate the activity of one of the newer regimens in the neoadjuvant setting. Using pathologic complete response as an endpoint, 7 patients (32% of evaluable, 22% by intent to treat) with disease clinically confined to the bladder had a positive result. An additional 5 patients with more advanced disease (T4 or node positive) in arm II also had a pathologic complete response. Overall, 12 of 43 evaluable patients (27.9% of evaluable, 17.6% by intent to treat) in both arms had this positive pathologic endpoint. An additional 3 patients (6.9% by evaluable, 4% by intent to treat) had only residual superficial disease. By comparison, in the neoadjuvant M-VAC trial, complete pathologic response was seen in 38% of patients treated with chemotherapy.³ The MRC/EORTC trial using cisplatin, methotrexate, and vinblastine for three cycles prior to either radiotherapy, cystectomy or both, versus cystectomy alone only yielded a complete pCR rate of 32.5%.² Thus, PCaG appears to have a pathologic complete response rate which approaches but does not surpass that of the older regimens. This rate is below the threshold that was established in the prestudy design that would warrant further investigation of this regimen in the neoadjuvant setting.

The assessment of the efficacy of this regimen is clearly hampered by the number of patients on both arms who are not evaluable for the primary endpoints, primarily due to adverse events occurring during the study. The five pre-operative deaths were surprising based on experience with this regimen in patients with advanced disease in which there were no treatment related deaths.⁶ In a number of the preoperative deaths and the two postoperative deaths it is unclear what role the chemotherapy played in predisposing these patients to these complications. Surprisingly, all but one of the deaths occurred in arm I of the trial. The patients with more advanced disease enrolled on arm II received a median of 2 additional cycles of therapy which would presumably have exposed them to an even greater risk of adverse events. Similarly, a number of patients on both arms were not evaluable due to circumstances (nephrolithiasis, refusal of cystectomy, morbid obesity) which were not related to the chemotherapy. This also suggests the possibility that the chemotherapy may not have had a direct relationship to a number of the adverse events. Ultimately, however, the number of deaths and patients that were removed from study due to toxicity raises questions as to the feasibility of this regimen in this setting.

Future studies will need to consider the duration of neoadjuvant therapy and means to better assess tumor response during treatment. In arm II of the study, additional cycles of therapy appeared to produce an equivalent response rate despite the more advanced disease with lymph node involvement or invasion of other structures. Changing the schedule of administration may improve tolerability and lessen toxicity. PCaG in the setting of

neoadjuvant chemotherapy for bladder cancer has activity. We cannot however, recommend either routine use or further exploration of this regimen based on the toxicity in this setting and the failure to reach a significantly greater level of activity than other available regimens. M-VAC remains the only proven regimen for neoadjuvant therapy and more studies are needed to develop newer agents in this setting.

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References

1. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666. [PubMed: 11157016]
2. Anonymous. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet* 1999;354:533. [comment][erratum appears in *Lancet* 1999 Nov 6;354(9190):1650]. [PubMed: 10470696]
3. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *New England Journal of Medicine* 2003;349:859. [erratum appears in *N Engl J Med*. 2003 Nov 6;349(19):1880]. [PubMed: 12944571]
4. Advanced Bladder Cancer Meta-analysis C. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361:1927. [see comment]. [PubMed: 12801735]
5. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *Journal of Clinical Oncology* 2000;18:3068. [comment]. [PubMed: 11001674]
6. Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *Journal of Clinical Oncology* 2001;19:2527. [PubMed: 11331332]
7. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clin Trials* 1989;10:1. [PubMed: 2702835]
8. Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *Journal of Clinical Oncology* 1997;15:2564. [PubMed: 9215826]
9. Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer* 2001;92:2993. [PubMed: 11753976]
10. Bellmunt J, Guillem V, Paz-Ares L, Gonzalez-Larriba JL, Carles J, Albanell J, et al. Gemcitabine/paclitaxel-based three-drug regimens in advanced urothelial cancer. *European Journal of Cancer* 2000;36:17. [PubMed: 10908844]
11. Meluch AA, Greco FA, Burris HA 3rd, O'Rourke T, Ortega G, Steis RG, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. *J Clin Oncol* 2001;19:3018. [PubMed: 11408496]

Table 1

Patient Characteristics

	Arm I	Arm II
Patients	31	37
Age		
median	65	58
range	39–80	29–83
Gender		
Male	20	25
Female	11	12
Performance Status		
Median	1	0
Range	(0–2)	(0–2)
Initial Stage		
T2	3	3
T3	28	9
T4		25
Node +		17
Baseline Renal Function		
Normal Creatinine	16	27
Elevated Creatinine	15	10
Hydronephrosis	21	
Histology		
TCC	29	34
Squamous	2	1
Adeno	0	2
Grade		
High	31	36
Low (focal high)	0	1

Table 2

Treatment Summary

Treatment Summary		
	Arm I (N = 31)	Arm II (N = 37)
Number of cycles		
Total	78	175
Median/patient	3	5
Range	1–3	1–6
Dose reduction		
Median/patient	1	1
total	18	34
0	15 (48%)	14 (38%)
1	14 (45%)	12 (32%)
2	2 (6%)	11 (30%)
Dose increase	0	1

Table 3

Toxicity during therapy

Toxicity	Number of Events									
	Arm I (N= 31 patients, 78 cycles)					Arm II (N=37 patients, 175 cycles)				
	Grade 3	Grade 4	Grade 5	Total		Grade 3	Grade 4	Grade 5	Total	
WBC	16			19		38	1		39	
ANC	13	26		39		42	26		68	
Febrile Neutropenia	2	1		3						
Anemia	6	1		7		9			9	
Transfusion pRBC	2			2		8			8	
Platelets	6			6		25	2	1	28	
Myocardial infarction			1	1			1		1	
Bowel obstruction			3	3						
Vesorectal fistula		1		1						
Fatigue						3			3	
Anorexia	1			1						
Neuropathy	1			1		3			3	
Myalgias/arthralgias	1			1		1			1	
Infection	3			3		2			2	
Constipation						1			1	
Diarrhea	1			1		1			1	
Hematuria						1			1	
AST/ALT	1			1		1			1	
DVT						1			1	
Urinary Incontinence						1			1	
Bowel Incontinence						1			1	
Nausea	2			2						
Dehydration	1			1		1			1	