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Original article

Weekly Paclitaxel and Carboplatin as First Line Treatment in Patients with Recurrent or Metastatic Bladder Carcinoma

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Background: Paclitaxel is one of the most active drugs in several solid tumors as breast, lung, ovary and bladder. Weekly paclitaxel seems less toxic and more efficient compared with paclitaxel every three weeks (possibly because of the proapoptotic and antiangiogenic activity), the dose intensity is quiet higher with less toxicity. The purpose of this study is to evaluate the efficacy of weekly paclitaxel and paraplatin as a first line treatment in patients with recurrent or metastatic bladder cancer

Patients and Methods: Thirty patients with recurrent or metastatic bladder carcinoma were enrolled; between September 2007 to September 2009. All patients had measurable disease. ECOG PS 0-2, adequate renal, liver and bone marrow functions. Patients received no prior chemotherapy for recurrence or metastasis. Patients were treated with 6-8 cycles of weekly paclitaxel 80 mg/m^2 (one hour IV infusion) and paraplatin AUC 5 (IV infusion over half an hour) for three weeks followed by one week rest, response was assessed every 2 cycles. Patients showed an objective response (CR, PR or SD) had continued to 8 cycles.

Results: All patients were evaluable for response, toxicity, and survival. The median age was 52 years (range 48-65), Male/Female 22/8. Twenty patients were transitional cell carcinoma and ten patients were squamous cell carcinoma. The main location of disease was local recurrence in 7 patients (23.3%) liver metastasis in 8 Patients (26.7%), lung metastasis in 6 patients (20%), bone metastasis in 4 patients (13.3%), and nodes in 9 patients (30%). A total of 227 cycles were administrated with a median of seven cycles per patient, with no dose reduction. The overall response rate was 66.7% (CR 20%, PR 46.7%), 6 patients had stable disease (20%), and 4 patients had PD. Median time to progression and median survival were 10 months (95% CI, 9.81-15.16) and 14.5 months (95% CI, 12.59-20.52) respectively.

Conclusion: Weekly paclitaxel and paraplatin is an active, feasible and well tolerated regimen as first line chemotherapy for patients with recurrent or metastatic cancer bladder with overall response rate 66.7%.

Key words: paclitaxel, paraplatin, metastatic bladder cancer.
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INTRODUCTION

Bladder cancer is common worldwide and its incidence continues to increase. Bladder cancer is the 4th most common malignancy in American men & the 9th most common cancer in women leading to 14,330 new deaths annually[1]. In Egypt, bladder cancer is the most common malignancy among males and previously has been attributed to schistosoma infection, a major risk factor for squamous cell carcinoma (SCC). Recently, transitional cell carcinoma (TCC) incidence has been increasing while SCC has declined[2]. Although only 20 % of bladder cancer cases clinically advanced at presentation, many patients with superficial or locally invasive disease eventually recur or develop metastasis. Thus, the management of advanced and metastatic bladder cancer is a frequent problem in clinical practice[3]. However, 25 % of patients will have muscle invasive disease and either present with or later develop metastasis. The prognosis for patients with metastatic disease is poor[4]. Bladder tumors are chemosensitive and a substantial number of agents with different mechanisms of action are active against this disease. Platinum based combination chemotherapy regimens have become standard first line treatment for patients with advanced bladder cancer. The combination of methotrexate, vinblastine, doxorubicine and cisplatin (MVAC) has been considered the standard chemotherapeutic regimen up to late 1990s, MVAC demonstrated ORR of 40-72% with 13-28% of patients achieving a complete response[5]. Due to the high toxicity of MVAC regimen, gemcitabine in combination with cisplatin (GC) was developed for first line treatment of advanced or metastatic bladder carcinoma[6]. A randomized trial of MAVC versus gemcitabine & cisplatin demonstrated that the doublet resulted in similar survival as MVAC but an improved

toxicity profile (response rate of 49% with GC versus 46% with MAVC and a median survival of 13.8 months compared to 14.8 months), while producing less toxicity[7]. However, the median overall survival for patients treated with cisplatin based combination chemotherapy remains approximately 12-14 months, and with few patients will become long term disease free survival[4]. Because most patients with advanced bladder cancer will eventually fail first line chemotherapy, effective salvage regimens are needed. Because platinum is the most active agent for bladder cancer, salvage therapy often includes a platinum agent as a component of combination chemotherapy regimens such as paclitaxel, cisplatin & MXT[8]. These regimens are active not only against platinum sensitive disease but also platinum resistant disease. Although these combinations yielded a higher response rate, the toxicities they induced were severe, especially in previously treated patients[9]. Paclitaxel is an active microtubule inhibitors agent in bladder cancer; paclitaxel yielded a 42% response rate in patients with advanced bladder cancer[10]. Carboplatin is less nephrotoxic and less emetogenic platinum compound and it is more suitable for use in renal impaired or heavily treated patients. Against bladder cancer, carboplatin has shown modest activity (14% response rate) but whether carboplatin is inferior to cisplatin is unclear, especially when combined with paclitaxel[4].

The combination of paclitaxel and carboplatin is a widely used and effective regimen for ovarian cancer & non small cell lung cancer. In a phase II randomized controlled trial of first line therapy for advanced urothelial cancer, the patients who received paclitaxel plus carboplatin had reported a response rate ranging from 21-63% and a median survival of 13.8 months which was similar to the 14.4 months obtained with MAVC. So the combination of paclitaxel and carboplatin might have significant activity against urothelial cancer with less toxicity[8,11]. Furthermore, weekly administration of paclitaxel versus administration every 3 weeks has been reported to have superior activity against metastatic breast cancer, with sustained cumulative exposure and dose dense drug delivery[12]. Weekly paclitaxel plus carboplatin has been reported to have significant activity against recurrent ovarian cancer, advanced non small cell lung carcinoma and advanced breast cancer[13]. Since weekly administration of 135 mg/m^2 of paclitaxel plus the area under the curve (AUC) of carboplatin already has been reported to the intolerable for predominantly chemotherapy-naive patients with advanced urothelial cancer, weekly administration of 80 mg/m^2 of paclitaxel was considered to be more fit for previously treated patients[13].

Aim of the study was to evaluate the efficacy, tolerability and toxicity of weekly paclitaxel and paraplatin as a 1st line treatment in patients with recurrent or metastatic bladder cancer.

PATIENTS AND METHODS

Eligibility criteria:

Between September 2007 and September 2009, 30 patients with recurrent or metastatic bladder cancer were enrolled in the study. Patients aged between 18-65 years with histologically confirmed bidimensionally measurable carcinoma of the bladder were eligible for study. Patients had evidence of progressing regional or metastatic disease. Patients must have received no prior chemotherapy for recurrent or metastatic disease. Prior adjuvant MVAC therapy was eligible. Bone metastasis or malignant pleural effusion as only metastasis was excluded. All patients provided oral informed consent.

Treatment Regimen:

Paclitaxel was administered on an outpatient basis at dose of 80 mg/m^2 D1,8,15 was administered by 1 hour IV infusion followed by paraplatin AUVC 5 IV infusion over 30 minutes on Dl, premedication administered intravenously 30-60 minutes before paclitaxel in the form of dexamethasone 20 mg, diphenhydramine 50 mg and H2 blocker cimetidine 300 mg, cycle repeated every 4 weeks for a maximum of 8 cycles. The protocol treatment was discontinued if 2 weeks elapsed without fulfilling the following criteria: absolute granulocyte count >1000/mm^3, platelet count greater than 7500/mm^3, serum transaminase activity less than 2 times normal level & serum creatinine level of no more than 2 mg/dl.

Response Assessment:

Prestudy evaluation included a complete history & physical examination with performance status assessment, complete blood count with differential, serum chemistry profile. Baseline tumor measurements using appropriate radiographic assessment such as computerized tomography or magnetic resonance imaging. Complete blood counts and toxicity assessment were performed weekly before each treatment. Performance status evaluation and serum chemistry profiles were repeated every 4 weeks. Response and toxicities were evaluated by WHO criteria.

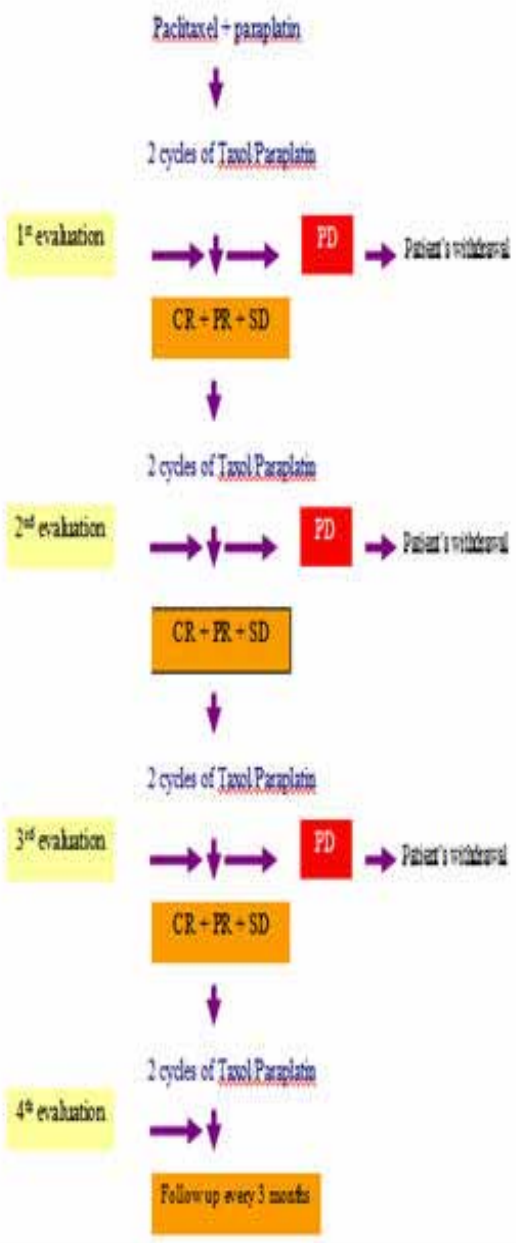
Tumor measurements using the same methods as for the baseline evaluation were repeated every 2 cycles. Response criteria were as follows: complete response was the disappearance of all clinical & radiographic evidence of disease determined on two observation not less than 4 weeks apart an partial response was a decrease of 50% or more in the sum of products of measurable lesions confirmed on two observations not less than 4

weeks apart, along with no simultaneous increase of 25% or greater in any lesion or the appearance of any new lesion.

Statistical Analysis:

The primary end point was response rate, with overall survival & time to progression and toxicity analyzed as secondary end points. Time to progression was calculated from the day of study entry until the day of documented disease progression. Overall survival was calculated from the date of study enrollment until death. Time to progression and overall survival distributions were estimated using the Kaplan Meier Method[14].

Treatment Design



RESULTS

Between September 2007 and September 2009, 30 patients with recurrent or metastatic bladder cancer were enrolled. Patients' characteristics (Table 1); the median age was 52 years (range 48-65 years), 22 patients were male & 8 patients were female, twenty patients (75%) were TCC & 10 patients (25%) were SCC. Fiften patients (50%) had a PS score of 0. Three patients (10%) had PS score 2. The site of recurrence was the bladder in 23% of patients, 30% of patients had nodal meatastasis. Most patients (70%) had visceral metastasis. Twelve patients (40%) had prior surgery. All patients had received no prior chemotherapy regimen for recurrence or metastatic disease.

Toxicities: The median number of cycles delivered per patient was 7 (range 3-8) no dose reduction. Hematologic toxicities consisted of G2 anaemia & neutropenia in 10% & 13% of patients respectively; no grade 3 or 4 toxicities and no febrile neutropenia were noted. The most common non hematologic toxicities were alopecia (Gl 30%, G2 50%), neurotoxicity (Gl 13%, G2 10%) and myalgia (Gl 10%, G2 10%).

Response to treatment: Six (20%) out of the 30 patients had a complete response and 14 (46.7 %) had a partial response. The overall response rate was 66.7% (Table 3). The median time to progression and the median overall survival rates were10 months (95% CI, 9.81-15.16) and 14.5 months (95% CI, 12.59-20.52), respectively. (Fig. 1,2).

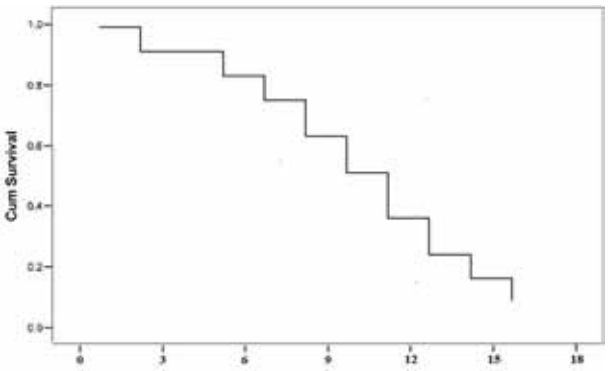


Fig. 1: Time to progression.

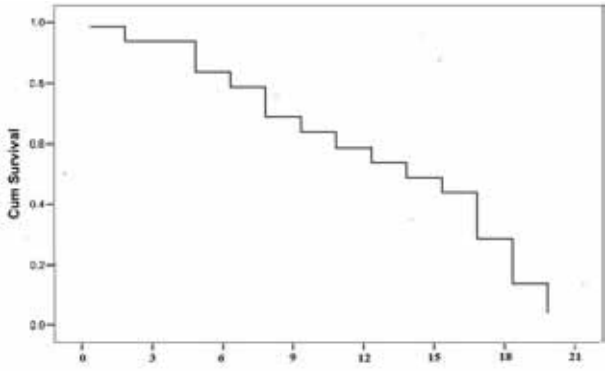


Fig. 2: Overall survival.

Table 1: Patient characteristics.

	No. of patients	Percentage (%)
No. of patients	30	
Median Age [Range]	52 years [48-65]	
Gender		
-Male	22	73.3%
- Female	8	26.7%
Pathology		
-T.C.C	20	75%
-Sq.C.C	10	25%
Performance status		
-0	15	50%
-1	15	50%
Main location of disease		
- Local recurrence	7	23%
- Liver	8	27%
-Lung	6	20%
- Bone	4	13.3%
- Nodes	9	30%

Table 2: Safety profile.

	Grade 1	Grade 2	Grade3	Grade 4
Hematologic:				
Anaemia	2 (6.7%)	3 (10%)	-	-
Neutropenia	3 (10%)	4 (13%)	-	-
Non Hematologic:				
Neurotoxixity	4 (13%)	3 (10%)	-	-
Oral stomatitis	6 (20%)	3 (10%)	-	-
Alopecia	10 (30%)	15 (50%)	-	-
Myalgia	3 (10%)	3 (10%)	-	-
Fatigue	10 (30%)	3 (10%)	-	-

Table 3: Response Rate (n=30).

Response	No. of patients	Percentage (%)
Complete response (CR)	6	20%
Partial response (PR)	14	46.7%
Overall response (OR)	20	66.7%
Stable disease (SD)	6	20%
Progressive disease (PD)	4	13.3%

DISCUSSION

Cisplatin based regimens such as the combination of methotrexate, vinblastine, doxorubicin & Cisplatin (MVAC) and the combination of gemcitabine & Cisplatin (GC) are considered standard treatment for advanced bladder cancer[6,15], but there is no standard treatment for patients who fail such as cisplatin based regimen. Among newer active agents for bladder cancer, paclitaxel yielded a 42% response rate as 1st line therapy. Weekly paclitaxel and paraplatin regimen are active not only against platinum sensitive disease but platinum resistant disease, although toxicity. Since weekly administration of 135 mg/m^2 of paclitaxel plus the area under the curve (AUC) 5 of carboplatin already has been reported to be intolerable for predominantly chemotherapy naive patients with advanced urothelial cancer. Weekly administration of 80 mg/m^2 of paclitaxel and paraplatin were considered to be fit for previously treated patients[13]. Paclitaxel alone yielded a 42% response rate against bladder cancer in the first line setting. The combination of carboplatin & paclitaxel might have significant activity against bladder cancer with less toxicity and median survival of 13.8 months[9,11]. Furthermore weekly administration of paclitaxel has been reported to have significant activity with less toxicity compared to paclitaxel every 3 weeks (possibly because of the proapoptotic and antiangiogenic activity)[12].

In this study, the overall response rate was 66.7% though many of the response were partial, these results are higher than those (32-63%) reported by Kouno *et al*.[16,17], Redman *et al*.[18], Small *et al*.[19] and Yafi *et al*.[20], this may be because all the patients in these trials received weekly paclitaxel and carboplatin as second line treatment after failure of MAVC but in our study only 9 patients had received MVAC as adjuvant treatment.

In the present study, the median time to progression and median survival were 10 and 14 months respectively, our results are comparable to, that obtained by Kouno *et al*.[16,17]. Shinohara *et al*.[21] reported a distinguished result for the paclitaxel, ifosfamide & nedaplatin combination as a second line treatment which provided a 75% response rate, and median PFS & median overall survival of 8 and 22 months respectively. These data strengthen our rationale of a combination including paclitaxel and a platinum compound (carboplatin) for treatment of advanced bladder cancer.

The toxicities of weekly paclitaxel plus paraplatin were all manageable. No patients experienced grade 3 or 4 neurotoxicities and no febrile neutropenia and only 10% experienced grade 2 neurotoxicity & 13% experienced grade 2 neutropenia. These results are similar to that obtained by Kouno *et al*.[16,17].

CONCLUSIONS

Weekly paclitaxel plus paraplatin is active, feasible and well tolerated regimen as a first line chemotherapy for patients with recurrent or metastatic cancer bladder with overall response rate 66.7%. Paclitaxel plus paraplatin was also effective against platinum resistant disease and paclitaxel and paraplatin may act synergistically.

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