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Docetaxel as second line after failure of gemcitabine/cisplatin regimen in advanced and/or metastatic urinary bladder cancer patients in Egypt

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Introduction: In Egypt few studies revealed the benefit of docetaxel as second line after failure of Gemcitabine/cisplatin. Given these findings, we conducted a phase II study to evaluate the efficacy and toxicity of docetaxel single agent as second line chemotherapy in bladder cancer after failure of gemcitabine/cisplatin.

Patients and methods: This prospective phase II study included 39 patients. Docetaxel was given as 100 mg/m^2 every 3 weeks.

Results: Patients were collected from the period between September 2009 to October 2012. Median survival time was 9.3 month (95% CI, 6 to 13 month), with 1 year overall survival of 58%. An overall response rate (PR and CR) of 25.6% (CI 17.5-41.2) and stable disease was found in 16 patients (41%), 13 patients (33.3%) progressed and stopped the treatment. Median duration of response was 9.8 months (range 6-15). Median time to progression was 7.2 months. The most frequently recorded adverse events of grade 3 or higher were fatigue (4 of 39, 10.2%) and neutropenia (3 of 39; 7.7%).

Conclusion: This phase II study of docetaxel given every 3 weeks was effective as a second line treatment in Egyptian patients with advanced or metastatic TCC of the bladder after failure of first line gemcitabine/cisplatin or carboplatin. As no systemic agents demonstrated survival benefit as second line treatment in TCC of the bladder carcinoma, a phase III trial comparing docetaxel versus other active agents is recommended in order to support the result of this trial.

Key words: urinary bladder, TCC, Egypt, second line, phase II trial, docetaxel

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INTRODUCTION

Bladder cancer is the ninth most common cancer diagnosed worldwide[1].

There were an estimated 72.570 new cases and 15.210 deaths from bladder cancer in 2013. It represents 4.4% of all new cancer cases in the U.S.[2]. According to NCI Cairo, the leading cancers in Egyptian patients are the urinary bladder (32.67%)[2]. The National cancer registry in Egypt recorded a lower incidence, In Aswan 2008, bladder cancer accounted for 7.6% of total cancer cases. While in El-Minia 2009, 9.2% of total cancer cases, In Damietta 2010, bladder cancer reported a percentage of 5.7% of total cancer cases and it accounted as third most common cancer[3]. In Ain Shams University Hospitals Bladder cancer accounted for 5.2% of total patients and described as the fifth most common cancer[4]. Egyptian males have the highest mortality rates (16.3 per 100,000), which is twice as high as the highest rates in Europe (8.3 in Spain and 8.0 in Poland) and over 4 times higher than that in the United States[5].

Muscle-invasive bladder cancer (clinical stage cT2-cT4a) is an aggressive epithelial tumor with a high rate of early systemic dissemination. Although only one-third of the newly diagnosed bladder cancers are advanced at presentation, another 15-30% of high-grade superficial tumors progress to muscle-invasive tumors, usually within 5 yr. Up to 50% of patients with infiltrating disease develops metastases and ultimately succumbs to their disease. Failure is usually due to occult metastatic disease present at the time of initial diagnosis. Long-term survival remains low, and studies evaluating adjuvant chemotherapy have been limited by inadequate statistical power to detect meaningful clinical answers as well as by experimental arms utilizing inadequate chemotherapy[6].

Because of its high recurrence rate and its propensity to progress and metastasize, thereby requiring long-term follow-up and treatment, bladder cancer (BC) is considered a chronic disease[7].

Very few clinical trials have been conducted in the second-line setting in bladder cancer[8].

In order to limit confusion in the interpretation of data from phase II trials, a strict definition of what is 'second line' is needed. As in bladder cancer, progression within 6 months of first line chemotherapy has a poorer prognosis than those with progression after 6 months[9].

Another difficulty is encountered in the second line research of bladder cancer. It includes the patient's age, poor performance status, comorbidities and impaired renal function. The interpretation of phase II trials was difficult due to the heterogeneity of patients selected[10].

Cisplatin is considered the cornerstone of combination chemotherapy and the most effective single-agent in treatment of bladder cancer. Gemcitabine/cisplatin regimen has become standard of care for patients with advanced or metastatic TCC of the bladder. But, after failure of this line there is no sufficient data about further management of the disease[11].

Vinflunine (VFL) is a new microtubule inhibitor that has activity against transitional cell carcinoma of urothelial tract (TCCU). So, a randomized phase III study of VFL and best supportive care (BSC) versus BSC alone was conducted in the treatment of patients with advanced TCCU who had experienced progression after a first-line platinum-containing regimen. VFL demonstrates a survival advantage in second-line treatment for advanced TCCU[12].

Docetaxel binds to the β-subunit of tubulin, inhibiting the formation of stable microtubule bundles, which leads to cell death[13]. It also acts through phosphorylation of Bcl-2, which promotes apoptosis[14].

In the early 90's Single-agent docetaxel 100 mg/m^2 has achieved response rates ranging from 31-50% in patients with chemotherapy-naïve metastatic TCC, and 13% in previously treated patients[15-18].

To our knowledge, in Egypt no studies done on docetaxel as second line after failure of Gemcitabine/cisplatin. Given these findings, we conducted a phase II study to evaluate the efficacy and toxicity of docetaxel single agent as second line chemotherapy in bladder cancer after failure of gemcitabine/cisplatin administered on a 3 weeks basis.

PATIENTS AND METHODS

This prospective phase II study to assess docetaxel single agent as second line chemotherapy in bladder cancer after failure of gemcitabine/cisplatin or gemcitabine/carboplatin. Patients were collected from the period between September 2009 to October 2012. It is estimated that 25% response rate of the tumor can submit further evaluation but <7% will not worth further evaluation. A two stage design with a sample size of 39 patients will have a ,022 significance level and a power of 86% to differentiate it from the 7% response rate.

This study included 39 patients aged more 18 years with performance status less than or equal to 2. No history of other malignancies. No currently uncontrolled diseases (e.g., ongoing cardiac dysrhythmias, unstable diabetes) or active infection. Adequate hematological function with:

- Absolute neutrophil count (ANC) ≥ 1500/mm^3
- Platelets ≥ 100,000/ mm3
- Hemoglobin ≥ 10 g/dL

Adequate hepatic and renal function with:
- Serum bilirubin ≤ 1.5×UNL
- Alkaline phosphatase and alanine aminotransferase (ALT) ≤ 2.5 x ULN.
- Serum creatinine ≤ 1.5 mg/dl

All patients had histological proven transitional cell carcinoma of the bladder; patients with metastases, progression or recurrence during or after treatment with a Gemcitabine/cisplatin were eligible.

Patients with previous radical cystectomy surgery were allowed.

Patients with previous second line treatment or radical radiotherapy were not included. Also, patient progressing after bladder preserving approach are not allowed.

Patients received docetaxel 100 mg/m^2 in 500 ml 5% glucose as a 1 hour intravenous (i.v)infusion with oral steroid premedication (dexamethasone 8 mg orally

every 12 h for 3 days beginning 1 day before drug administration) and antiemetic prechemotherapy; every 3 weeks for 6 cycles. Treatment was discontinued if disease progression or unacceptable toxic effects occurred. Palliative radiotherapy for bone and brain metastases was allowed.

G-CSF was given when absolute neutrophil count (ANC) < 1500/mm^3.

The primary endpoint was to evaluate the overall survival and time to progression. The secondary end point was to evaluate tumor response and toxicity.

Overall survival was defined as the time from the day of start of chemotherapy till death using the Kaplan-Meier method. Time to progression was calculated from the start of treatment to disease progression. Duration of response was calculated from the first day response until the date of progression.

RESULTS

Most of the patients were male (74.3% of total patients) with male to female ratio 2.9:1. Above 60 age patients was the most affected age group with median age 67 (range 45-70). patients' characteristic are illustrated in Table (1).

Median follow up was 14 month (range 3-25 month), Median survival time was 9.3 month (95% CI, 6 to 13 month), with 1 year overall survival of 58%, Figure (1).

An overall response (PR and CR) of 25.6% (CI 17.5-41.2) was achieved. One patient (2.56%) had a CR, 9 (23.07%) had PR, and stable disease was found in 16 patients (41%), 13 patients (33.3%) progressed and stopped the treatment. Response rate and relation of response to disease site is shown in Table (2) and (3).

Median duration of response was 9.8 month (range 6-15). Median time to progression 7.2 was month.

The most frequently recorded adverse events of grade 3 or higher were fatigue (4 of 39, 10.2%) and neutropenia (3 of 39; 7.7%), two of them were neutropenic fever, toxicity profile Table (4). Dose reduction was needed in 4 patients (10.2%) due to adverse events.

Table 1: Patient characteristics at presentation.

Characteristic	No. of patients (n = 39)	percentage
Sex		
Male	29	74.3%
Female	10	25.6%
Age (years)		
Median	67	
Range	45-70	
ECOG performance status		
0	4	10.2%
1	16	41%
2	19	48.7%
Surgery (number of radical cystectomy)	32	82%
Stage of the disease		
Locally advanced disease	10	25.6%
Local pelvic recurrence	5	12.8%
Metastatic disease	24	61.5%
Sites of metastatic disease		
Bones	12	30.7%
Lung	6	15.3%
Liver	4	10.2%
Pleural effusion	1	2.5%
Lymph nodes	1	2.5%

ECOG, Eastern Cooperative Oncology Group.

Table 2: Response rates (n = 39).

	n Patients	(%)
Complete response	1	2.5
Partial response	9	23
Stable disease	16	41
Progressive disease	13	33.3

Table 3: Response by disease site.

Disease site	Complete response	Partial response	Stable disease	progression
	No.	No.	No.	No.
Locally advanced		2	3	5
Local pelvic recurrence		1	2	2
Lung	1	1	3	1
Liver		1	1	2
Bones		3	7	2
Lymph nodes		1		
Pleural effusion				1

Table 4: Incidence of toxicity Graded according to CTCAE v4.03.

Incidence of toxicity				
	1	2	3	4
Haematological				
Neutropenia	10(25.6%)	7(17.9%)	2(5%)	1(2.5%)
Anaemia	8(20.5%)	3(7.7%)	0	0
Thrombocytopenia	4(10.2%)	1(2.5%)	0	0
Non-haematological				
Fluid retention	2 (5%)	1(2.5%)	0	0
Skin changes (maculopapular rashes)	3(7.7%)	5(12.8%)	0	0
Fatigue	14(35.9%)	6(15.3%)	4(10.2%)	0
Alopecia	15(38.4%)	3(7.7%)	0	0
Peripheral neuropathy	1(2.5%)	1(2.5%)	0	0
Diarrhoea	14(35.8%)	5(12.8%)	0	0

Table 5: Trial of phase II with single agent docetaxel as second line in urothelial carcinoma.

Study	**Patient population**	**Previous chemotherapy**	**Number of patients**	**Overall response**
McCaffrey et al.[15]	Advanced and metastatic disease	Prior chemotherapy with cisplatin	30	13.3%
deWit et al.[17]	Metastatic disease	No prior chemotherapy	29	31%
Dimopolous et al.[18]	Metastatic disease Patients with renal impairement	No prior chemotherapy	11	45%

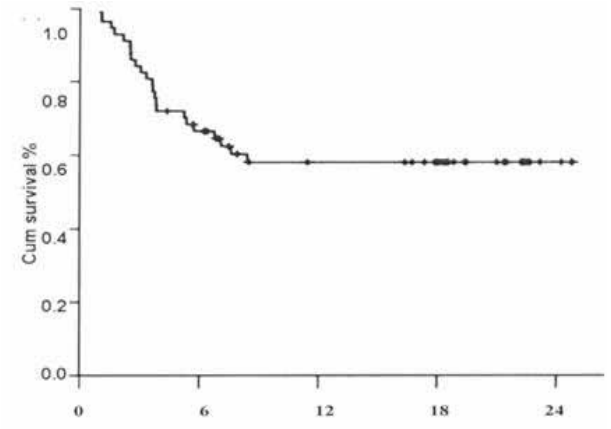

Figure 1: The overall survival of the 39 patients with survival rates at 6 and 12 month were 65 % and 58%, respectively.

DISCUSSION

This phase II study of docetaxel given every 3 weeks was effective as a second line treatment in Egyptian patients with advanced or metastatic TCC of the bladder after failure of first line gemcitabine/cisplatin or gemcitabine/carboplatin. It demonstrated an overall response rate (CR and PR) in 25.6% of the total patients, time to progression was 7.2 months, and duration of response was 9.8 months. Median follow up was 13.7 months (range 3-25 months), Median survival time was 9.3 months (95% CI, 6 to 13 months), with 1 year overall survival of 58%.

It was also well tolerated with accepted toxicity; 3 patients (7.6%) experienced neutropenia Grade 3 and 4. Fatigue, alopecia and, diarrhea were the most frequent non hematological toxicity encountered.

The overall response rate is superior to the result shown previously in trial with single agent docetaxel as second line in urothelial carcinoma with prior cisplatin chemotherapy as shown by McCaffrey et al (25.6 % vs 13.3%)[15].

Docetaxel is effective in urothelial carcinoma specially when given as first line, trials using docetaxel single agent as first line showed better overall response (31% and 45%)[17,18].

Several studies assessed the efficacy of different chemotherapeutic agents in second line treatment of TCC of the bladder cancer but till now there is no approved drug. These studies used bortezomib, lapatinib, vinflunine, topotecan, 2′,2′-difluorodeoxycytidine, gemcitabine, paclitaxel, ifosfamide, piritrexim. These trials demonstrated variable response rates ranging from 0% to 29%[19-33].

This variable response rates in these studies may be due to the different drug activities and different patients' characteristics.

A randomized phase III study of Vinflunine and best supportive care (BSC) versus BSC alone as second line treatment after failure of cisplatin based regimen showed a median 2-month survival advantage (6.9 months for VFL + BSC v 4.6 months for BSC) but was not statistically significant (P = .287). Vinflunine showed modest activity in 2 phase II trials, with overall response of 17% and 15.9% respectively and median overall survival of 6.6 months (95% CI 4.8 to 7.6 months) and 7.9 months (95% CI 6.7 to 9.7 months) respectively[12,34,35]. In comparison to these studies docetaxel achieved better response rate and better median survival with acceptable toxicity.

Other trials combined docetaxel with gemcitabine and cisplatin or docetaxel and cisplatin but very few studies evaluating the docetaxel as single agent after failure of gemcitabine and cisplatin.

Another trial combined Vandetanib (an oral once-daily tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptor 2 and epidermal growth factor receptor) with docetaxel in platinum-pretreated population of advanced UC versus docetaxel plus placebo, the addition of vandetanib to docetaxel did not result in a significant improvement in PFS, ORR, or OS. The toxicity of vandetanib plus docetaxel was greater than that for docetaxel plus placebo. Median PFS was 2.56 months for the docetaxel plus vandetanib arm versus 1.58 months for the docetaxel plus placebo arm, and the hazard ratio for PFS was 1.02 (95% CI, 0.69 to 1.49; P = .9). ORR and OS were not different between both arms. Grade 3 or higher toxicities were more commonly seen in the docetaxel plus vandetanib arm and included rash/photosensitivity (11% v 0%) and diarrhea (7% v 0%). Among 37 patients who crossed over to single-agent vandetanib, ORR was 3% and OS was 5.2 months[36].

Although pemetrexed appeared to have an efficacy in these patients group in a Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium, it showed an overall response rate of 27.7% But, the cost effectiveness make us in need to compare Pemetrexed and docetaxel as both have a comparable effective overall response rate (27.7% vs 25.6% respectively) and median overall survival (9.6 vs 9.3 months respectively)[37].

As no agents demonstrated survival benefits as second line treatment in TCC of the bladder carcinoma, a phase III trial comparing docetaxel versus other active agents is recommended in order to support the result of this trial.

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