Docetaxel and gemcitabine in patients with advanced urinary bladder cancer: A Phase II study

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Abstract: The work aimed: To evaluate the efficacy and tolerability of a combination of docetaxel and gemcitabine in patients with locally advanced recurrent, and/or metastatic urinary bladder cancer. **Patients and methods**: An outpatient regimen of gemcitabine and docetaxel combination was tried in thirty-three patients with locally advanced,recurrent,and/or metastatic urinary bladder cancer.Study treatment consisted of gemcitabine1000 mg m^{-2} (days 1+8), and docetaxel 75 mg m^{-2} (day 8) every 21 days for a total of six to nine cycles. **Results:** Among the 33 patients, 17 patients (51.5%) had transitional cell carcinoma, 7patients (21.2%) had squamous cell carcinoma and 9 patients (27.3%) had transitional cell carcinoma with squamous metaplasia. Two patients (6.1%) had complete remission (CR), and 14 patients (42.4%) had partial remission (PR), for an overall response rate of 48.5%. Disease stabilization (SD) occurred in 7 patients (21.2%), while 10 patients (30.3%) had disease progression (PD). Analysis of response rate according to prognostic features known to predict response; Patients with PS 0&1 had an overall response rate of 55.6% (15/27), and patients with PS 2 had an overall response rate of 16.7%(1/6), and this difference was statistically insignificant (P =0.1). As regard to the site of disease, the overall response rate of patients with soft tissue and locally advanced disease was 58.3% (7/12) and 42.9% for patients with visceral metastasis (9/21), and this difference was statistically insignificant (p=0.4). The response rates for patients with risk index of 0, 1, or 2 were100% (2/2), 66.7% (10/15), and25% (4/16), respectively (P = 0.006).With a median follow-up of 10 months (range, 2-20 months), the median survival time was 11 months, the median time to progression was 7 months , 1-year survival rate was 40.3% and1-year progression free survival rate was 28.3%.Both haematologic and non haematologic toxicity were treatable and not severe. **Conclusion:** This schedule of docetaxel and gemcitabine is active and well tolerated as a first-line treatment for locally advanced, recurrent, and metastatic bladder carcinoma. The favourable toxicity profile of this regimen may offer an interesting alternative, particularly in patients with compromised renal function or cardiovascular disease.

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1. Introduction

Carcinoma of the bladder(BC)is the fifth most common cancer in adults[1].It is an oncologic problem especially in certain areas in the world[2]. Although many patients have localized disease at diagnosis and are cured with definitive local therapies, about half of them will relapse after radical cystectomy. Local recurrence accounts for about 30% of relapses and distant metastases are more common. Furthermore, a considerable number of patients are already metastatic at the time of diagnosis [3]. The prognosis of patients with advanced or metastatic BC remains poor, with the 5-year survival estimated to be <5% [4]. Systemic combination chemotherapy is the only treatment that may result in long term survival in some patients [5].Platinum-based chemotherapy like the combination of methotrexate, vinblastine, Doxorubicin and cisplatin (M-VAC) and the combination of gemcitabine and cisplatin are considered standard treatments. Although these regimens have an overall response rate ranging from 50% to 70%, disease recurrence has been reported in nearly all patients within the first year. The median survival time is approximately 12–14 months [6]. During the last decade, several new chemotherapeutic agents have shown activity against advanced BC, including taxanes [7]. Studies have indicated that docetaxel and paclitaxel have significant antitumour activity as single agents [8], or when administered in combination with other drugs [9]. Similarly, gemcitabine has a single-agent response rate of approximately 24–50% as both first and second-line therapy [10].

The current Phase II study was conducted to evaluate the efficacy and tolerability of a combination of docetaxel and gemcitabine in locally advanced, recurrent, and/or metastatic urinary bladder cancer.

2. Patients and Methods

Inclusion and exclusion criteria: Patients with locally advanced, recurrent and/or metastatic urinary

bladder cancer were enrolled into this prospective study. The study was conducted from May 2008 to April 2010 at oncology department, Assiut University hospital. Eligible patients were required to have an Eastern Cooperative Oncology Group performance status(ECPOG p.s) of 0 to 2, age 18 years or older; life expectancy of at least 12 weeks, adequate haematological [white blood cell count (WBC) ≥4000 cells/µl, absolute neutrophil count (ANC) ≥2000 cells/µl, platelet≥100.000/ µl, haemoglobin ≥10 g/dl], renal (serum creatinine <1.5 mg/dl, creatinine clearance ≥60 ml/min) and liver functions [bilirubin <1.5fold the upper normal limit (UNL) and AST <2fold the UNL, unless liver metastases were present, in which case <5fold the UNL was allowed. Previous neoadjuvant or adjuvant treatment was allowed as long as there was at least a 6-months treatment-free interval .Patients who had previously been treated with radiotherapy were entered into the study, provided that the course was completed more than 6 weeks before enrollment. Patients aged >75 years were excluded, as were patients with severe chronic obstructive lung disease, known CNS metastases and patients who were pregnant. Furthermore, patients with active infections or other serious underlying medical or mental conditions, which would impair their ability to receive protocol treatment. Informed consent was obtained from all patients before enrolment. Before entering the study, all patients underwent a physical examination, complete blood count (CBC), blood chemistry, chest X-ray, bone scan and abdominal computed tomography (CT) scan. A thoracic CT scan and other specific tests were performed when indicated. Cystoscopic evaluation was performed only when necessary for local recurrence.

Treatment schedule and toxicity monitoring:

Treatment was administered on an outpatient basis. Gemcitabine(1000 mg m^{-2})was administered by an intravenous infusion over 30 min on days 1 and 8,while docetaxel(75 mg m^{-2}) was administered as an intravenous infusion over 1 hour on day 8. Courses of docetaxel and gemcitabine were scheduled to be repeated every 21 days, but were not initiated until the ANC was ≥ 1500/ µL, the platelet count was ≥ 75,000 / µL, and the serum creatinine was < 1.8 mg/dL. Dose modifications of up to 50% of both agents were mandated for febrile neutropenia, or a bleeding episode with a platelet count <40,000 / µL, any platelet nadir< 20,000 / µL, or if Day 8 therapy could not be delivered secondary to neutropenia or thrombocytopenia.

Premedication included dexamethasone, 8 mg orally b.i.d., the day before and four consecutive days following chemotherapy. Antiemetic treatment consisted of intravenous ondansetron in combination with dexamethasone 20 mg on day 1. Prophylactic use of growth factors (G-CSF) was not routinely recommended. However, if grade 4 granulocytopenia or febrile neutropenia was present, prophylactic filgrastim was administered in subsequent cycles. During treatment, renal and liver function tests were carried out before each cycle on day 1, and complete blood count was carried out on days 1 and 8 of each cycle. Complete blood counts were also obtained on day 14 of the first course in order to assess nadir WBC and PLT. Toxicity was assessed with the use of the Common Toxicity Criteria version 3.0 [11]. Patients were treated with at least six cycles of chemotherapy unless there was evidence of disease progression or unacceptable toxicity occurred during treatment. After completing six cycles of treatment, patients were followed up. Patients who were stable after six cycles were considered to have completed protocol therapy and went off treatment. Patients who achieved either a complete or partial response after six cycles were scheduled to receive the same regimen for up to nine full chemotherapy cycles.

Evaluation of response

Response was assessed every two cycles of treatment according to WHO criteria [12]. Follow-up disease evaluation was performed regularly at 3 monthly intervals after treatment completion till death.

Complete response was defined as the complete disappearance of all measurable disease for at least 4 weeks. Partial response was defined as a more than 50% reduction in all measurable disease for at least 4 weeks. Stable disease was defined as a 50% or less reduction of all measurable lesions. Progressive disease was defined as an increase in any lesion or the appearance of new lesions. All responses were confirmed 4 weeks later.

Statistical analysis:

Data were recorded on specialized forms and all statistical tests were performed using SPSS version 16 for windows (SPSS Inc, Chicago, IL, USA) and Microsoft Excell (Realmond, W.A,USA) software. Descriptive analysis (e.g., mean, standard deviation, frequencies, percentage) were calculated and analysis was performed using the student's t-test and Fisher ExactT- Test, P value ≤0.05 was considered significant. Survival was calculated from the day of commencement of chemotherapy to the day of death using the Kaplan–Meier method [13]. Time to tumour progression (TTP) was defined as the time elapsed from the start of treatment to renewed disease progression.

3. Results:

Patients characteristics: table (1)

The study included 39 patients of which only 33 patients were eligible for assessment. Their clinicopathologic characteristics are shown in table (1). There were 24 males (72.7%) and 9 females (27.3%). Their age ranged between 35and 80 years (median; 60 years). Most patients (81.8%, 27/33) had a ECPOG p. s of 0 to 1. A total of 17 patients (51.5%) had transitional cell carcinoma, 7 patients (21.2%) had squamous cell carcinoma and 9 patients (27.3%) had mixed elements of transitional cell carcinoma and squamous metaplasia. Of the 33patients included in the present study, 21(63.6%) had not undergone radical cystectomy because of either locally advanced disease (6 /33; 18.2%), locally advanced disease with distant metastases in the liver, bone, lung (15 /33; 45.5%). The other 12 patients (36.4%) had locally recurrent (6 /33; 18.2%), metastatic disease after radical cystectomy (4/33; 12.1%),or both (2/33;6.1%).The treatment protocol was administered in all cases as first line therapy; however while 21(63.6%) had not previously received any therapeutic manipulation, the remaining patients were exposed to prior surgery, adjuvant/neoadjuvant chemotherapy or radiotherapy to the pelvis.
table (2, 3)

There were 2 patients (6.1%) who had a complete response (CR), and 14 (42.4%) had a partial response (PR), for an overall response rate of 48.5%. Disease stabilization (SD) occurred in 7 patients (21.2%), while the remaining 10 patients (30.3%) had disease progression (PD).

As regards the relation between response rate and pathologic Subtype (table 2, 3) it was found that the overall response rates were higher for patients with transitional cell carcinoma (52.9%, 9/17 patients) compared to those for patients with squamous cell carcinoma (42.9%,3/7patients), or transitional cell carcinoma with squamous metaplasia(44.4%,4/9), however, this difference in response rate was statistically insignificant (P =0.6). Patients with ECPOG p.s of 0&1 had an overall response of 55.6%(15/27), and patients with ECPOG p.s of 2 had an overall response rate of 16.7%(1/6), and this difference was statistically insignificant (P =0.1). As regard the site of disease, the overall response rate of patients with soft tissue and locally advanced disease was 58.3% (7/12) and 42.9% for those with visceral metastasis(9/21),and this difference was statistically insignificant,(p=0.4).As regard the number of disease sites, patients with one site had an overall response of 57.9%(11/19) ,patients with two sites had an overall response of 45.5%(5/11), and those with ≥3site had an overall response of 0%(0/3) ,(p=0.08). Based on Bellmunt et al [14], the ECOG p.s and the presence of visceral metastases are two pretreatment risk factors. In the current study the number of patients with zero-risk (ECOG p.s 0 and no visceral metastasis), one-risk (ECOG p.s > 0 or visceral metastasis), and two-risk factors (ECOG p.s > 0 and visceral metastasis) was 2 patients (6.1%), 15 patients (45.5%), and 16 patients (48.5%), respectively. The response rate for 0, 1, or 2 risk index were 100% (2/2), 66.7% (10/15), and 25% (4/16), respectively (P = 0.006). Response rates in different patients subgroups are detailed in table (3).

After a median follow-up of 10 months (range, 2–20 months), the median overall survival of all patients was11 months (95% CI = 9.46–12.54 months) and the 1-year survival rate was 40.3% (Figure, 1). The median time to disease progression (TTP) was7 months (95% CI = 3.75–10.25 months) and the 1-year progression free survival rate was 28.3% (Figure,2).

The toxicity pattern was generally tolerable, and no toxic deaths occurred among the 33 patients (table 4)

Toxicity was primarily haematologic with neutropenia being the most prominent. Ten patients experienced grade 3 or 4 granulocytopenia; however, only 2 patients experienced neutropenic fever Also, 3patients had grade 3 anemia. Non haematological toxicities were mild and can be managed.

4. Discussion

Treatment of patients with advanced carcinoma of the urinary bladder is difficult. Advanced age, concomitant diseases, poor performance status, frequent deterioration of renal function, and frequent palliative treatment underscore the need to search for a treatment scheme with a good efficacy/toxicity profile [15]. The dismal long-term outcome with currently available regimens and the finding that at least one-third of patients with inoperable bladder cancer are unfit to receive cisplatin-based chemotherapy has led to the search of new treatment approaches and trials were conducted using platinum-free agents. [15,16,17]. The taxanes are primarily being studied in previously pretreated patients. Incorporation of taxanes as first-line treatment for advanced bladder carcinoma may not only offer an alternative to gemcitabine/cisplatin but may eventually be indicated as a first-line treatment, if equivalence to M-VAC or gemcitabine/cisplatin regimens can be confirmed [18].In addition, they can be administered safely to patients with impaired renal function, a condition frequently associated with bladder carcinoma [19].

Gemcitabine and docetaxel have different cellular targets (DNA synthesis and microtubules, respectively) and act at different phases of the cell cycle (S phase and mitosis, respectively) so

combination therapy could possibly be more effective [20].Antagonism was noted when gemcitabine and taxanes were administered concurrently, while additive effects were seen when gemcitabine preceded or followed taxanes[21,22].

In the present study, the 48.5% overall response were higher than that reported by Dreicer et al. (17%), Manola et al, (23%)and Gitlitz et al, (33.3%) but lower than that of Ardavanis et al, (51.6%), Dumez et al, (53%),and Neri et al, (53.1%)[23,24,25,18,26,27].

The combination of the other taxane; paclitaxel and gemcitabine showed response rates of 40%–60% [28, 29,30]. The variability in the response rates between our study and the other studies is likely due to the variability in drug schedules and also confounding factors among the different patient populations where 48.5% of the patients of this study were of non transitional cell histology.

It has been reported that regimens currently in use have limited efficacy against non–transitional-cell histologies, such as squamous cell tumour. If responses in non–transitional-cell components would be confirmed, this regimen could be particularly useful in the therapy of non-transitional histologies, a common occurrence in Egypt and certain areas of the world [32]. In our study,43.8% of the patients who achieved objective response had squamous cell carcinoma and mixd histology of transitional cell carcinoma with squamous metaplasia .The response of non transitional histology to chemotherapy is confirmed by a study of Khaled et al [31, 32], but with a different regimen of low-dose prolonged infusion gemcitabine and cisplatin where 38% of non transitional cell histology had objective response.Further studies are needed for evaluation of this regimen for non–transitional-cell histologies.

Additional studies have evaluated docetaxel in other combinations in the treatment of bladder cancer. Krege et al [33], assessed the association of docetaxel and ifosfamide after failure of cisplatin-based chemotherapy. This combination showed activity with acceptable tolerability. Another attempt were made to combine 3 or more agents to improve the outcomes obtained with dual therapy, where taxanes have demonstrated synergy when used in combination with a platinum salt. There is a trend in favor of the triplet chemotherapy suggesting different patterns of chemosensitivity and favoring primary bladder carcinoma [34, 35]. Pectasides et al [36], evaluated the three-drug combination of docetaxel with cisplatin and epirubicin. The response rate was 66.7% and the median overall survival was 14.5 month. Another study of Weekly chemotherapy with docetaxel, gemcitabine and cisplatin, the objective response rate was 65.6% [37].

Critical for optimal management of patients with advanced disease is the use of pretreatment factors to define treatment objectives. In this study, the performance status and the presence of visceral metastasis were insignificant factors affecting the response rate in contrary to the results of the trials conducted by Bajorin et al.[38], Bellmunt et al[39]. and Pliarchopoulou et al [40]who identified performance status and the sites of metastatic disease as major response parameters. However,this result was parallel to the Egyptian study of Khaled et al [32] ,in which the combination of performance status and the presence of visceral metastasis (Memorial Sloan Kettering Risk Index)was the main factor affecting response rate[38].

The toxicity of this regimen was generally acceptable and manageable. The most common toxicity was haematological,mainly granulocytopenia. However, most episodes of granulocytopenia were brief, easily managed and not associated with the clinically significant event of neutropenic fevers occurring only in (6.1%, 2 /33).

Several conclusions can be drawn. First, this schedule of docetaxel and gemcitabine is active and well tolerated as a first-line treatment for advanced/relapsing or metastatic BC. These results, added to the other studies that included docetaxel in their treatment regimens, indicate the interest in this drug for treatment of BC as an alternative to conventional therapeutic regimens. Second, the favourable toxicity profile of this regimen may offer an interesting alternative, particularly in patients with compromised renal function or cardiovascular disease. Patients with advanced BC often have impaired renal function because of advanced age, prior platinum-containing chemotherapy, prior nephrectomy or disease-related hydronephrosis. Third, this regimen was given on an outpatient basis, so decreasing the costs of treatment. Further studies are needed for future comparisons with M-VAC or other gemcitabine or cisplatin-based regimens and to determine more accurately the potential of docetaxel together with investigation of new strategies that will introduce it into three-drug regimens or in combinations without cisplatin.

Table (1): Clinicopathological characteristics of the 33 patients:

		Frequency	Percent
Sex	Male	24	72.7%
	Female	9	27.3%
Age	Mean ± SD	57.12 ± 12.9	
	Median	60	
	Range	35 - 80	
ECPOG ps	0	10	30.3%
	1	17	51.5%
	2	6	18.2%
histopathology	TCC	17	51.5%
	sq.c.c	7	21.2%
	mixed	9	27.3%
tumour at presentation	locally advanced	6	18.2%
	primary with metastasis	15	45.5%
	metastasis after removal of primary tumour	4	12.1%
	local recurrence	6	18.2%
	metastasis and local recurrence	2	6.1%
No. of sites	1	19	57.6%
	2	11	33.3%
	≥3	3	9.1%
Previous treatment	surgery	12	36.4%
	Chemotherapy	9	27.3%
	Radiotherapy	9	27.3%

- ECOG ps:Eastern Cooperative Oncology Group performance status
-sq.c.c: squamous cell carcinoma -TCC: transitional cell carcinoma -mixed: transitional cell carcinoma with squamous metaplasia-

Table (2): Response rates of the 33 patients:

		Frequency	Percent
response	CR	2	6.1%
	PR	14	42.4%
	Overall response	16	48.5%
	SD	7	21.2%
	PD	10	30.3%

- CR =Complete response - SD =stationary disease - PR = partial response -PD =progressive disease

Table (3): Response rates in selected patients subgroups:

		Overall response		P-value*
		No.	%	
Sex	Male(no.=24)	10	41.7%	0.2
	Female (no.=9)	6	66.7%	
ECPOG ps	0&1 (no.=27)	15	55.6%	0.1
	2(no.=6)	1	16.7%	
site of disease	ST/LA(no.=12)	7	58.3%	0.4
	Visceral(no.=21)	9	42.9%	
Risk Index	Risk 0(no.=2)	2	100%	0.006*
	Risk 1(no.=15)	10	66.7%	
	Risk 2(no.=16)	4	25%	
histopathology	TCC(no.=17)	9	52.9%	0.6
	Sq.c.c (no.=7)	3	42.9%	
	Mixed(no.=9)	4	44.4%	
No. of sites	1 (no.=19)	11	57.9%	0.08
	2 (no.=11)	5	45.5%	
	≥3 (no.=3)	0	0%	

*fisher exact test - pvalue ≤0.05 is significant - ECOG p.s: Eastern Cooperative Oncology Group performance status ST/LA: soft tissue and locally advanced disease- -TCC: transitional cell carcinoma
- sq.c.c: squamous cell carcinoma - mixed: transitional cell carcinoma with squamous metaplasia-

Table (4): toxicity during treatment of the 33 patients:

	Toxicity Grade				
	total	**1**	**2**	**3**	**4**
	N (%)	N (%)	N (%)	N (%)	N (%)
granulocytopenia	15(45.5%)	0(0%)	5(15.2%)	8(24.2%)	2(6.1%)
thrombocytopenia	5(15.2%)	2(6.1%)	3(9.1%)	0(0%)	0(0%)
anaemia	11(33.3%)	2(6.1%)	6(18.2%)	3(9.1%)	0(0%)
diarrhea	6(18.2%)	3(9.1%)	2(6.1%)	1(3%)	0(0%)
Fluid retention	1(3%)	0(0%)	0(0%)	1((3%))	0(0%)
Nausea&vomiting	14(42.4%)	10(30.3%)	4(12.1%)	0(0)	0(0%)
fatigue	14(42.4%)	3(9.1%)	8(24.2%)	3(9.1%)	0(0%)
stomatitis	17(51.5%)	5(15.2%)	7(21.2)	4(12.1%)	1(3%)
alopecia	19(57.6%)	6(18.2%)	5(15.2%)	8(24.2%)	0(0%)

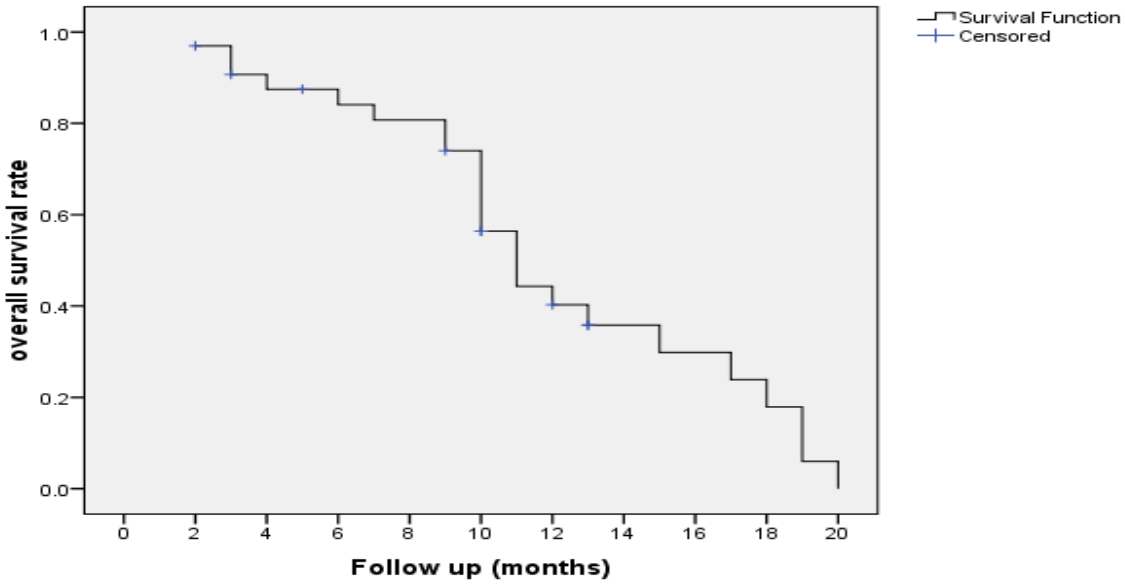

Figure (1): Kaplan–Meier curve for overall survival.

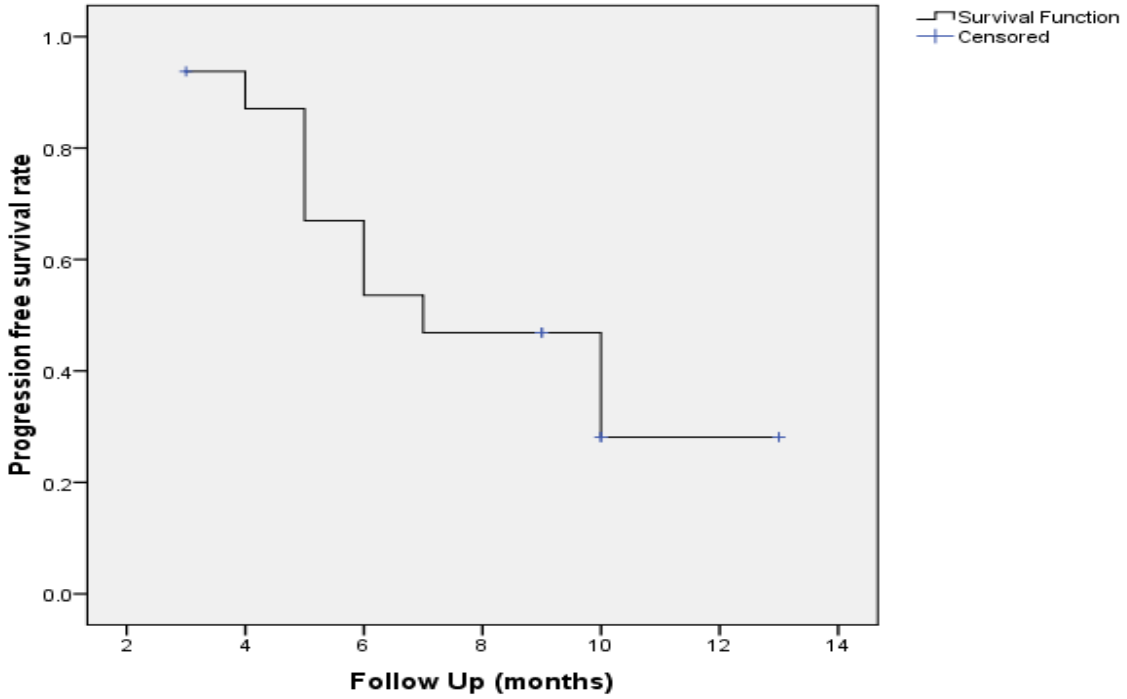

Figure (2): Kaplan–Meier curve for progression free survival.

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