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Assessment of Outcomes of Maintenance Gemcitabine after Standard Chemotherapy in Metastatic Bladder Transitional Cell Carcinoma Patients

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ABSTRACT

Background: Gemcitabine as a maintenance therapy is cell cycle-specific with activity in the S-phase; it is used successfully in managing metastatic bladder cancer. **Objective:** The aim of the current study was to evaluate outcomes of maintenance gemcitabine monotherapy in metastatic bladder cancer patients after standard platinum-based chemotherapy. **Patients and methods**: A total of 36 patients were included in a randomized controlled clinical trial at Zagazig University Hospitals' Clinical Oncology and Nuclear Medicine Department; 18 patients as a maintenance group (group A) and 18 patients as a control group (group B), who had metastatic cancer of bladder and gave response to 1st line platinum-based chemotherapy. **Results:** The visceral metastasis was not statistically significant prognostic parameter (P=0.137). Our study the "6 and 12 months" Progression Free Survival (PFS) in maintenance group (Group A) was 77.8% and 66.7% respectively versus 42.9% and 0% in control group (Group B) with mean PFS 10.16 months for maintenance group (Group A) and 5.12 months in control group (Group B) which was highly statistically significant different (P-value <0.001). Also "12 and 15 months" Overall survival (OS) was 77.8% and 75.7% respectively in maintenance cases versus 33.3% for both in control group with mean OS (16.05) months among maintenance group and (11.22) months among control subjects which was statistically significant different (P-value 0.008).

Conclusion: Gemcitabine as a maintenance treatment showed good results in delaying disease progression and increased overall survival rate among cases who had metastatic transitional cell carcinoma of the bladder received standard platinum-based chemotherapy.

Keywords: Gemcitabine, Chemotherapy, Bladder Transitional Cell Carcinoma, Metastasis.

INTRODUCTION

Urinary bladder cancer ranks ninth among malignancies and thirteenth among cancer-related deaths worldwide [1,2].

The average age of onset is Sixth to seventh decade. The incidence doubles in men more than 75 years of versus younger men. The risk of developing malignancy of the bladder before age 75 years is 2-4% for men and 0.5-1% for women [3,4]. However, because of delays in referring women to urologists, their tumors are more advanced by the time they are diagnosed. The incidence is three times higher in men than in women. The gender gap in cancer mortality is also evident, with women having a greater rate of death from the disease [5,6].

In Egypt, the incidence of bladder cancer has decreased significantly compared to that of other malignancies over the previous three decades (from 27.6 to 11.7%) [7,8].

Death from bladder cancer is more common in Egypt (65 per 1,000,000 people), than in Turkey (6.6 per 100,000), Iraq (6.3 per 100,000), Lebanon (6.3 per 100,000), or Mali (5.2 per 100,000), when adjusted for age [9].

In places where Schistosoma haematobium is not widespread, as the West, >90% of bladder cancers are transitional cell carcinomas (TCCs). Squamous cell carcinoma (SQCC), adenocarcinoma (AD), and small cell carcinoma (SCC) each make up less than 5%, 2%, and 1% of all cases of cancer, respectively, yet these are all distinct histological subtypes [10,11].

The current study aimed to evaluate outcomes of maintenance gemcitabine monotherapy in metastatic bladder cancer patients after standard platinum-based chemotherapy.

PATIENTS AND METHODS

Patients with metastatic bladder cancer who had responded to first-line platinum-based chemotherapy were included in this randomized controlled clinical trial, which included 36 individuals, and in a random way they were assigned; 18 to a maintenance group (group A) and 18 to a control group (group B).

Patients were recruited from Zagazig University Hospitals' Clinical Oncology and Nuclear Medicine Department;

Inclusion criteria:

1. Patients with histopathology confirmation of transitional cell carcinoma (TCC) of the bladder.
2. Patients who had metastatic bladder cancer to at least one site.
3. Patients who responded to systemic platinum-based chemotherapy [complete remission (CR), partial response (PR), stationary disease (SD)] include those who underwent MVAC (methotrexate, vinblastine, Adriamycin and Cisplatin), GEM+CBDCA (Gemcitabine and Carboplatin), or GC (Gemcitabine and Cisplatin) within the parameters of the RECIST.
4. When the ECOG Performance Status equal or lower than 2.

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5. Regular results on a complete blood count, liver and kidney function tests, and creatinine clearance.
6. Signed informed consent form

Exclusion criteria:

1. Patients who refused to be included in our study or unable to visit the hospital regularly.
2. Those who did not respond to platinum-based conventional chemotherapy.
3. Anyone who has previously had chemotherapy and experienced a Common Terminology Criteria for Adverse Events (CTCAE)-grade 3 consequence is considered to have a higher risk of developing cancer.
4. Patients who received non platinum based chemotherapy regimens
5. Patients with more than one primer of cancer.

Patients were divided into 2 groups:

- **Group A** (GEM maintenance group) (18 patients): Received gemcitabine 1000mg/M^2/ 30 minutes IV infusion D1 every 4 weeks until progression or appearance adverse events.
- **Group B** (Control group) (18 patients): which had been followed after Platinum-based chemotherapy and received best supportive care.

Subjective, objective and local response had been observed every 4 weeks to all patients (before each chemotherapy cycle for group A).

Evaluation every 4 cycles for **group A** and every 4 months for **group B** by pelvi abdominal CT and/or (MRI), chest CT, urine cytology, cystoscopy. Bone scan and brain MRI were done if indicated.

All patients were subjected to:

A- Pretreatment evaluation:

1. Clinical examination: A thorough physical examination and medical history were done.
2. Lab Investigations: Hematological (complete blood count "including blood cell differentia and platelet count") and biochemical laboratory evaluation.
3. Radiological evaluation: By pelvi-abdominal CT and/or (MRI), Chest CT, urine cytology, cystoscopy. Bone scan and brain MRI were done if indicated.

B- Treatment:

For Group A: (GEM maintenance group) (18 patients).

1- Preparation: Patients were given antiemetic medications and proton pump inhibitors in addition to dexamethasone (10 mg) before each Gemcitabine cycle.

2- Maintenance therapy schedule: All Patients received gemcitabine 1000mg/M^2/ 30 minutes IV infusion D1 every 4 weeks.

3- Treatment evaluation and follow up:

- During the injection, patients were noticed for Nausea, vomiting, dyspnea, fever.
- All patients evaluated every 4 cycles by commutated tomography (CT) or magnetic resonance imaging (MRI), urine cytology and cystoscopy until progression or appearance adverse events.
- -Maintenance Gemcitabine treatment was discontinued in patients whose quality of life declined due to cancer progression and/or adverse effects, or at the patients' choice.

Group B: (Control group) (18 patients).

Standard platinum-based chemotherapy was administered for 6 cycles, after which all patients received the best supportive care possible and were observed with frequent CT/MRI scans, urine cytology tests, and cystoscopies until the study's completion.

Evaluation of best overall response:

From treatment inception until disease progression or recurrence, the best overall response is the response that lasts the longest (taking as reference for PD the smallest measurements recorded since the treatment started). The optimal response classification for a given patient will typically be determined by meeting both measurement and confirmation criteria.

Ethical approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (ZU-IRB#4680/9-7-2018). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test and Chi-Square for Linear Trend were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

Table 1 summarizes age gender and clinical data of the studied groups. Statistical analysis revealed no significant variation in performance status (≤ 2). There was a statistically significant distinction between the groups in terms of the stage of chronic renal disease (P-value 0.006). Differences between the groups were statistically significant when examining the stage of chronic liver disease (P-value 0.001).

Table (1): Comparing maintenance group and control group regarding demographic and clinical data.

Demographic data	Maintenance group (Group A) (N=18)			Control group (Group B) (N=18)		Test	P-value (Sig.)
	No.	%		No.	%		
Sex							
Male	12	66.7%		15	83.3%	1.333‡	0.443 (NS)
Female	6	33.3%		3	16.7%		
Age (years)							
Mean±SD	51.55±11.63			62.11±10.72		-2.840•	0.005 (S)
Median (Range)	52.50 (30 – 70)			65 (36 – 75)			
≤ 60 years	13	72.2%		5	27.8%	7.111‡	0.008 (S)
>60 years	5	27.8%		13	72.2%		
Clinical data	**Maintenance group (Group A) (N=18)**			**Control group (Group B) (N=18)**		**Test‡**	**P-value (Sig.)**
	No.	**%**		**No.**	**%**		
ECOG PS							
ECOG 0	6	33.3%		2	11.1%	4.000	0.135 (NS)
ECOG 1	10	55.6%		10	55.6%		
ECOG 2	2	11.1%		6	33.3%		
CKD stage							
Stage o	8	44.4%		0	0%	10.316	0.006 (S)
Stage 1	7	38.9%		12	66.7%		
Stage 2	3	16.7%		6	33.3%		
CLD stage							
Stage o	9	50%		0	0%	13.500	0.001 (S)
Stage 1	9	50%		15	83.3%		
Stage 2	0	0%		3	16.7%		

No statistically significant difference in outcomes was seen between the maintenance group and the control group when comparing the various first-line chemotherapy regimens (P-value 0.195). The response to previous treatment did not differ significantly (P = 0.457) between the maintenance group and the control group (CR, PR.SD) (**Table 2**).

Table (2): Comparing maintenance group and control group regarding prior chemotherapy and response to prior chemotherapy

Prior chemotherapy	Maintenance group (Group A) (N=18)			Control group (Group B) (N=18)		Test‡	P-value (Sig.)
	No.	**%**		**No.**	**%**		
Gem-Cisplatin	7	38.9%		6	33.3%	3.273	0.195 (NS)
Gem-Carbo	10	55.6%		7	38.9%		
MVAC	1	5.6%		5	27.8%		
Response to received chemotherapy	**Maintenance group (Group A) (N=18)**			**Control group (Group B) (N=18)**		**Test‡**	**P-value (Sig.)**
	No.	%		No.	%		
Complete response (CR)	1	5.5%		0	0%		
Stationary disease(SD)	11	61.1%		14	77.8%	0.554	0.457 (NS)
Partial response(PR)	6	33.3%		4	22.2%		

Table 3 shows the outcome of maintenance treatment with progression in 4 (22.2%) patients, stationary disease in 11 (61.1%) patients, partial response in 3 (16.7%) patients with no complete response (0%) (**Figure 1**).

Table (3): Outcome of GEM maintenance treatment (Group A)

Outcome of maintenance treatment	Maintenance group (group A) (N=18)	
	No.	**%**
Response		
Progressive disease	4	22.2%
Stationary disease	11	61.1%
Partial response	3	16.7%
Complete response	0	0%

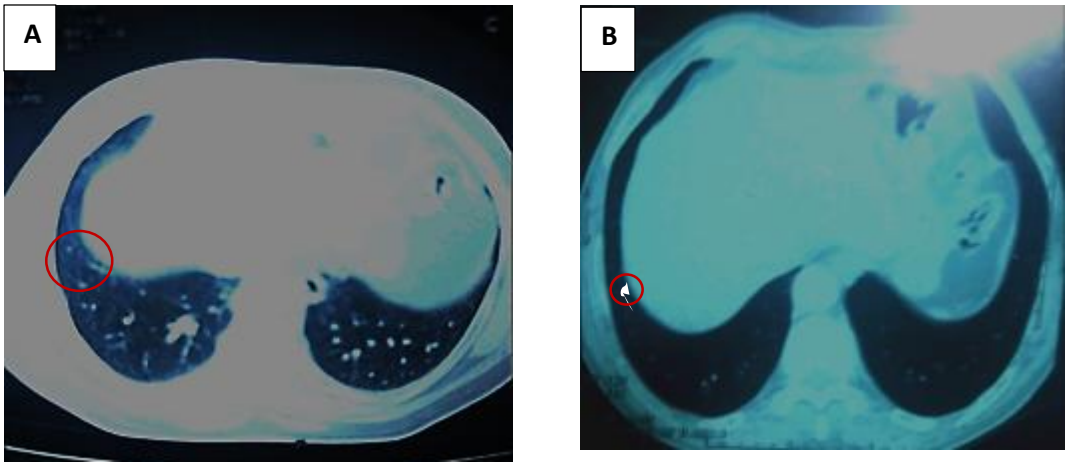

Figure (1): A case of metastatic bladder cancer to the right lung, (A) before GEM maintenance chemotherapy, (B) after GEM maintenance chemotherapy.

A statistically significant difference was found between the rates of progression seen in the maintenance group (4 patients) and the control group (14 patients) (P-value 0.008). In maintenance group 14 (77.8%) patients were alive while in control group 6 (33.3%) patients only which were statistically significant difference (P-value 0.007) (**Table 4**).

Table (4): Comparing maintenance group and control group regarding progression and mortality.

Progression and survival	Maintenance group (Group A) (N=18)			Control group (Group B) (N=18)		Test‡	P-value (Sig.)
	No.	%		No.	%		
Progression							
Absent	14	77.8%		4	22.2%	8.200	0.008 (S)
Present	4	22.2%		14	77.8%		
Mortality							
Alive	14	77.8%		6	33.3%	7.200	0.007 (S)
Died	4	22.2%		12	66.7%		

Table 5 and **Figure 2** show that the mean PFS was 10.16 months in maintenance group and 5.12 months in control group which was highly statistically significant difference (P-value <0.001). **Six month PFS** was in 14 (77.8%) patients in maintenance group and 7 (42.9%) patients in control group. **12 month PFS** was in 12 (66.7%) patients in maintenance with no patients in control group.

Table (5): Comparison maintenance group and control group regarding progression free survival (PFS).

Progression Free Survival (PFS)	Maintenance group (Group A) (N=1ng8)		Control group (Group B) (N=18)	Test†	P-value (Sig.)
Mean PFS (months) (95%CI)	10.16 months (8.95-11.38)		5.12 months (3.06-6.28)	17.098	<0.001 (HS)
6 month PFS	14 (77.8%)		7 (42.9%)		
12 month PFS	12 (66.7%)		0 (0%)		

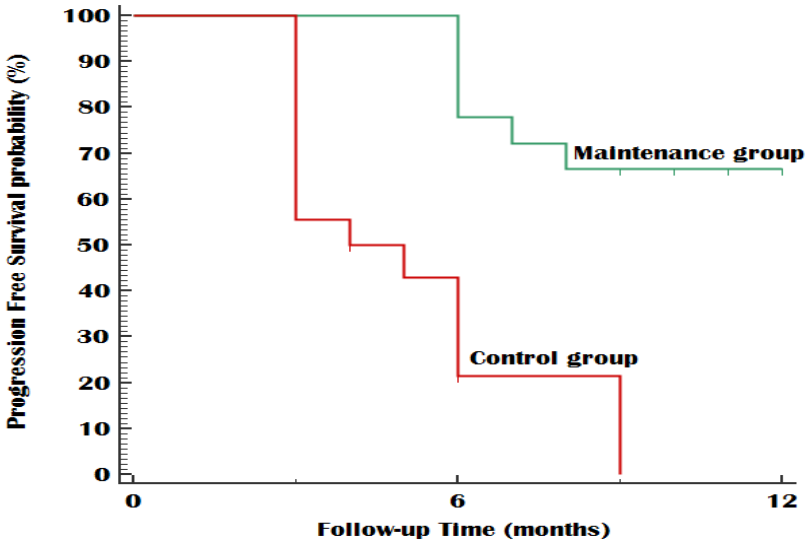

Figure (2): Kaplan Meier plot of progression free survival (PFS) shows comparison between maintenance group and control group.

Table 6 and **Figure 3** show that the mean OS in maintenance group was 16.05 months and in control group was 11.22 months which was statistically significant difference (P-value 0.008). **12** month OS was in 14 (77.8%) patients in maintenance group, 6 (33.3%) patients in control group. **15** month OS was in 13 (75.7%) patients in maintenance group, 6 (33.3%) patients in control group.

Table (6): Comparing maintenance group and control group regarding overall survival (OS).

Overall Survival (OS)	Maintenance group (Group A) (N=18)		Control group (Group B) (N=18)	Test†	P-value (Sig.)
Mean OS (months) (95%CI)	16.05 months (14.29-17.80)		11.22 months (9.84-12.59)	6.955	0.008
12 month OS	14 (77.8%)		6 (33.3%)		
15 month OS	13 (75.7%)		6 (33.3%)		

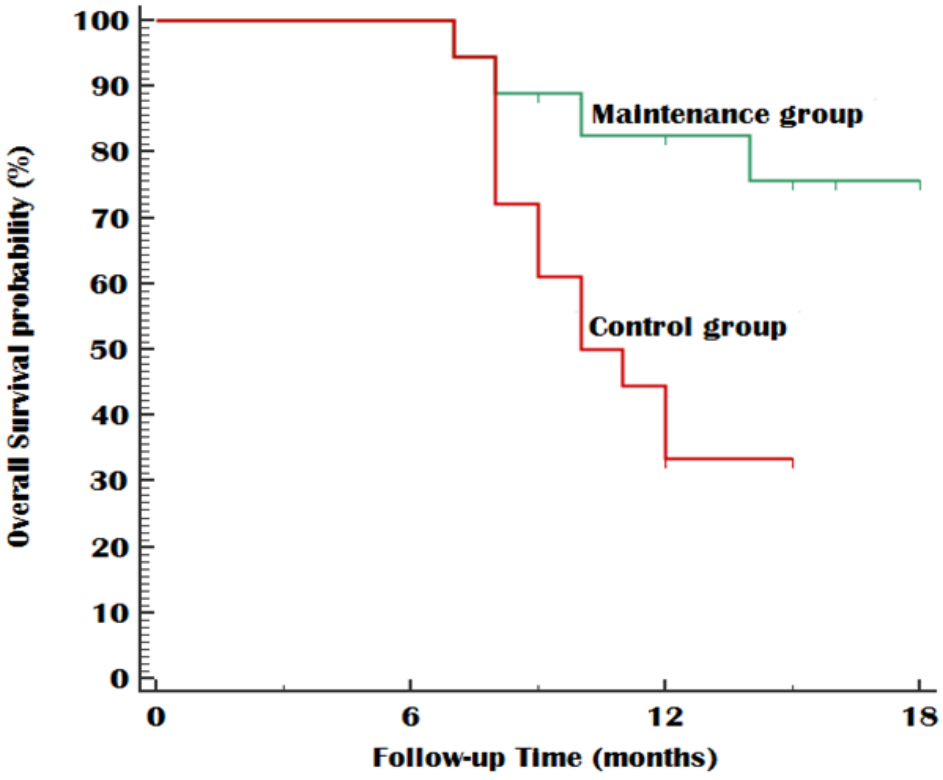

Figure (3): Kaplan Meier plot of overall survival (OS) shows comparison between maintenance group and control group.

Table 7 summarizes the main toxicities of GEM maintenance treatment. Other toxicities occurred in 5 (27.8%) patients such as diarrhea, stomatitis, transient flu-like symptoms, headache, mild fatigue, arthralgia and myalgia, transient and mild proteinuria, hematuria, hair loss, edema ,macular or maculopapular rash affected areas include the trunk and limbs, with lower extremity symptoms include pruritus and peripheral edema that may not cause any discomfort at all.

Table (7): Toxicity of GEM maintenance treatment (Group A).

Toxicity of maintenance treatment	Maintenance group (Group A) (N=18)	
	No.	%
Hematological toxicity	**18**	**100%**
Neutropenia	**9**	**50%**
Grade 1	4	44%
Grade2	4	44%
Grade3	1	11%
Febrile neutropenia	**3**	**16.7%**
Grade1	2	66.6%
Grade2	1	33.3%
Grade3	0	0%
Thrombocytopenia	**15**	**83.3%**
Grade1	7	46%
Grade2	4	26%
Grade3	4	26%
Anemia	**9**	**50%**
Grade1	4	44%
Grade2	3	33%
Grade3	2	22%
Non-hematological toxicity	**16**	**88.9%**
Elevated kidney function tests	**14**	**77.8%**
Grade1	6	42%
Grade2	7	50%
Grade3	1	7.1%
Elevated liver function tests	**9**	**50%**
Grade1	6	66%
Grade2	3	33%
Grade3	0	0%
Nausea & Vomiting	**12**	**66.7%**
Grade1	9	75%
Grade2	3	25%
Grade3	0	0%
Others	**5**	**27.8%**

DISCUSSION

Systemic chemotherapy is considered the First-line treatment of fit patients with metastatic disease, which must be platinum-based chemotherapy regimens such as MVAC (methotrexate, vinblastine, Adriamycin and cisplatin), GEM+CBDCA (Gemcitabine and Carboplatin) or GC (Gemcitabine and Cisplatin), limits include bone marrow suppression and nephrotoxicity [12, 13].

Patients who have responded to first-line platinum-based combination chemotherapy may benefit minimally from maintenance monotherapy [12].

In our study, patients age in maintenance group ranged from 30 to 70 years (mean 51.55±11.63) and in control group 36 to 75 (mean 62.11±10.72) years which showed a statistically significant difference (P-value 0.005). On the contrary **Muto *et al.*** [12] did not find a significant difference (P-value 0.057).

In our study, chronic kidney disease stage differed significantly between groups (P-value 0.006). Patients with no CKD were 8 patients in maintenance group versus no patients in control group. Stage I, 7 patients in maintenance group versus 12 patients in control group, and Stage II, 3 patients in maintenance group versus 6 patients in control group. While in **Muto *et al.*** [12] they did not find a significant difference (P-value 0.142).

Regarding initial treatment (radical surgery), in our study 11 patients in the maintenance group and just 4 individuals in the control group underwent major surgery, a statistically significant difference (P-value 0.018), while in **Muto *et al.*** [12] they did not find a significant difference, 21 patients in maintenance group versus 21 patients in control group (P-value 0.523).

In our study, the visceral metastasis was not statistically significant prognostic parameter was as in **Kus and Aktas** [14] **study** (P=0.482). On the contrary, **Muto *et al.*** [12] **study** demonstrated that the presence of visceral metastases (P=0.007), the success of initial chemotherapy (P=0.018), and GEM maintenance therapy (P<0.001) were all statistically significant predictors of DSS.

The maintenance treatment in our study, the median (range) of number of cycles was (1-12)cycles with median dose of cycle (1000-1800mg) while **Muto *et al.*** [12] the median was (2-49) cycles with median dose of cycle (500-1795mg), **Kus and Aktas** [14] the Median 7 (3-14) cycles with median dose of cycle (500-1800mg) and **Lehmann *et al.*** [15] reported administrating 41 cycles of GEM maintenance monotherapy with cumulative total dose of gemcitabine 88.500mg.

In our study the "6 and 12 months" PFS in maintenance group (Group A) was 77.8% and 66.7% respectively versus 42.9% and 0% in control group (Group B) with mean PFS 10.16 months for maintenance group (Group A) and 5.12 months in control group (Group B) which was highly statistically significant difference (P-value <0.001).

Also "12 and 15 months" OS was 77.8% and 75.7% respectively in maintenance group versus 33.3% for both in control group with mean OS 16.05 months in maintenance group and 11.22 months in control group which was statistically significant difference.

In Kus and Aktas [14], patients were retrospectively enrolled from February 2009 through

October 2015. After receiving platinum-based therapy and maintenance gemcitabine monotherapy, the median progression-free survival (PFS) was 46 weeks (range, 30-82 weeks). With just gemcitabine maintenance therapy, median progression-free survival (PFS) was 26 weeks (range, 10-56 weeks) and OS, 73 weeks (range, 30-132 weeks). Patients younger than 65 years old, those without organ metastases, and those with an objective response rate achieved a high median PFS; nevertheless, this was not statistically significant.

Muto *et al.* [(12)] comparison between the maintenance group (median PFS=12 months) and the control group (median PFS=2 months; P<0.001) demonstrated a statistically significant difference in PFS. The statistically significant difference (P<0.001) between the maintenance group's 1-year and 2-year DSS rates and the control group's 11.2% rate is in the maintenance group's favor. In the maintenance group, both DSS and OS were 15.0 months, but in the control group, they were only 4.0 months.

In **Lehmann *et al.* [(15)],** case report of a 74-year-old man with widespread metastatic lung and retroperitoneal transitional cell carcinoma. Having been diagnosed with pT3 G2-3 urothelial cancer of the renal pelvis in 1999, the patient underwent a right nephro-ureterectomy and subsequently underwent adjuvant chemotherapy consisting of three cycles of cisplatin and methotrexate, followed by palliative maintenance gemcitabine monotherapy, with dosing of 1200 mg/m2 body surface on days 1 and 8 of a 21-day cycle. A partial response was observed at both metastatic locations after 23 doses, and no new metastatic sites were detected using CT of the chest and abdomen. The tumor responded once again to gemcitabine monotherapy during a second round of treatment in 2002. A metastatic urothelial carcinoma patient who received a cumulative total dose of gemcitabine 88.500mg over the course of 41 doses was shown in a case study to have survived for over 30 months following diagnosis.

In our study, according to Common Terminology Criteria of Adverse Events (CTCEA), in our study, 18 (100%) patients experienced hematotoxicity and 16 (88.9%) patients experienced non-hematological toxicity. Neutropenia was in 9 (50%) patients, 4 (44%) patients were grade 1, 4 (44%) patients were grade 2 and one patient only grade 3. Febrile neutropenia was in 3 (16.7%) patients, 2 (66.6%) patients were grade1 and only one (33.3%) patient was grade 2. Thrombocytopenia was in 15 (83.3%) patients, 7 (46%) patients suffered from grade1, 4 (26%) patients grade 2 as well as 4 (26%) patients grade 3.

Anemia was in 9 (50%) patients, 4 (44%) patients were grade1, 3 (33%) patients were grade 2 and 2 (22%) patients were grade 3. Non-hematological toxicity was in 16 (88.9%) patients. Elevated kidney function tests were in 14 (77.8%) patients, 6 (42%) patients suffered from grade 1, 7 (50%) patients suffered from grade 2 and only one patient grade 3. Elevated liver function tests were in 9 (50%) patients, 6 (66%) patients were grade 1, 3 (33%) patients were grade 2.

On the other hand, **Muto *et al.* [(12)] study**, There were 9 cases of hematotoxicity (27.3%) and 1 case of non-hematological toxicity (1 patient). There were 3 (9.1%) patients with grade 3 neutropenia, however no patients had grade 2 or higher febrile neutropenia. Only one (3%) patient showed severe thrombocytopenia, with a count of fewer than 100,000. Creatinine elevations of grade 3 or higher were not seen, suggesting normal renal function.

CONCLUSION

Gemcitabine as a maintenance treatment showed good results in delaying disease progression and increased overall survival rate in patients with metastatic transitional cell carcinoma of the bladder received standard platinum-based chemotherapy.

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Conflict of interest: The authors state no conflict of interest.

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