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Original article

Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin In Advanced and or Metastatic Bilharzial Urothelial Carcinoma of the Bladder in Egypt.

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Purpose: Gemcitabine plus cisplatin (GC) and methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) were compared in patients with locally advanced or metastatic bilharzial urothelial carcinoma.
Patients and Methods: Patients with with locally advanced or metastatic bilharzial urothelial carcinoma (no prior systemic chemotherapy) were randomized to GC (gemcitabine 1,000 mg/m^2 days 1, 8, 15, cisplatin 70 mg/m^2 day 2) or standard MVAC every 28 days for a maximum of six cycles (Methotrexate = 30 mg/m^2 on days 1, 15 and 22, Vinblastine = 3 mg/m^2 on days 2, 15 and 22,Doxorubicin = 30 mg/m^2 on day 2 and Cisplatin = 70 mg/m^2 on day 2 (1-2 h infusion).
Results: forty-one patients were randomized, twenty-one to the GC arm and twenty to the MVAC arm. Overall survival was similar(13 months) on both arms. Time to progressive disease was 7 months with GC group and 6 months with MVAC group and response rate (GC, 47.6% vs MVAC 45%). Significant prognostic factors correlating with better overall survival were Karnofsky performance status ≥ 70, TNM staging (Mo vs.M1) and the absence of visceral metastasis. Hematologic toxicities were significantly higher with GC therapy. More GC patients, compared with MVAC patients had grade 3/4 anemia (28.5% vs 15%) and thrombocytopenia (47.6% vs 25%). More MVAC patients, compared with GC patients had grade 3/4 neutropenia (80% vs 67.6% $P = 0.001$), grade 3/4 mucositis (20% v 9.5%) and alopecia (25% v 14.3%)
Conclusion: GC provides a similar survival advantage to MVAC with a better tolerability. These results strengthen the role of GC as a standard of care in patients with locally advanced or metastatic bilharzial-related urothelial carcinoma.

Key words: Gl, M-Vac, Bladden Carcinoma
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INTRODUCTION

Carcinoma of the bladder is the most prevalent cancer in Egypt. At the National Cancer Institute (NCI), Cairo University, it constitutes 10.1% of all cancers for both sexes together[1]. In addition to the unique biological, epidemiological, pathological and clinical characteristics of bilharzial bladder cancer compared with the conventional transitional cell carcinoma seen in Western countries[2], the disease also has a different chemoresponsiveness profile, as reported in a series of phase II single-agent and combination chemotherapy trials[3,4].

The standard chemotherapy regimen for advanced bladder cancer for more than a decade was methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)[5,6]. Compared with cisplatin alone, M-VAC is the only treatment that has a better overall response rate (39% vs. 12%), progression-free time (10 vs. 4.3 months), and survival (12.5 vs. 8.2 months)[7]. The significant toxicity associated with M-VAC regimen, including thrombocytopenia, neutropenia with neutropenic fever and significant mucositis, in addition to nausea and vomiting, renal, cardiac, and neurologic toxicities, limits its use as a palliative treatment[5]. In an attempt to identify treatment regimen with better toxicity profile, many new cytotoxic agents have been introduced. Gemcitabine (Gemzar), a pyrimidine antimetabolite, has been studied as a single agent for treatment of metastatic bladder cancer with promising results[8] then, combination of Gemcitabine with cisplatin (GC) against transitional cell bladder cancer with promising results[9-11]. Based on these encouraging results, GC is generally considered the current standard of care for metastatic urothelial bladder cancer. However, it has not been sufficiently tested yet against MVAC in advanced bilharzial-related bladder cancer[12].

The aim of this study was to compare the efficacy and toxicity of GC with MVAC in advanced bilharzial-related urothelial carcinoma of the bladder.

PATIENTS AND METHODS

Between May 2002 till January 2005, 41 patients with advanced bilharzial urothelial carcinoma of the bladder presenting at Assiut University Oncology Department were enrolled in this prospective randomized trial.

Eligibility Criteria:

Patients included on this study had these criteria:

1. Histologically proven locally advanced (T4, N2, N3), inoperable recurrent or metastatic (M1) transitional cell carcinoma of the bladder.
2. Histologically documented bilharziasis by the presence of bilharzia ova in bladder tumour tissue obtained during primary diagnosis.
3. Measurable or evaluable disease.
4. Age ≥ 18 years.
5. Performance status ≥ 70% Karnofsky scale.
6. Adequate haematological, liver and renal functions with estimated creatinine clearance of at least 60 ml/min.
7. No prior systemic chemotherapy or radiotherapy.

Exclusion criteria:

1. Patients with other histologicsl subtyptes.
2. Performance states < 70% karnofsky scale.
3. Patients with prior chemotherapy or radiotherapy.
4. Patients with inadequate bone marrow reserve.
5. Inadequate renal and liver functions.

All patients had chest X-ray, abdomino-pelvic CT scan, bone scan and echocardiography to assess left ventricular ejection fraction (LVEF) in arm II patients.

Treatment protocol:

Patients were randomized to receive:

- *Arm A = systemic chemotherapy GC:*

Gemcitabine = 1.000 mg/m^2 over 30 to 60 minutes i.v. days 1, 8 and 15 plus.
Cisplatin = 70 mg/m^2 on days 2 (1-2 h infusion).

- *Arm B = systemic chemotherapy MVAC:*

Methotrexate = 30 mg/m^2 on days 1, 15 and 22.
Vinblastine = 3 mg/m^2 on days 2, 15 and 22.
Doxorubicin = 30 mg/m^2 on day 2.
Cisplatin = 70 mg/m^2 on day 2 (1-2 h infusion).

- Cisplatin was administered with adequate pre-and post-hydration.
- During treatment, blood counts and serum chemistries were performed weekly.
- Patients received treatment every 4 weeks for a maximum of six cycles unless they developed progression of disease or unacceptable toxicity.
- On both arms dose was adjusted for hematologic and/or non- hematologic toxicity. If the WBC was lower than 3.0 × 10^9/L or the platelets below 100 × 10^9/L on day 29, the subsequent cycle was delayed for one week. For days 8, 15 and 22, the doses were omitted if these counts were less than 2.0 or 50 × 10^9/L, respectively. For other non-haematological toxicities, the drugs were given at 50% of planned doses or omitted if Common Toxicity Criteria grade 3 or 4 toxicities occurred.
- All patients provided a written informed consent.

Treatment Evaluation

Tumor assessments were done every two cycles radiologically and by physical examinations. Responses were classified according to (World Health Organization) criteria. Complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks. Partial response (PR) was achieved if total tumor size decreased by at least 50% of the measurable lesions without appearance of any new lesions for at least 4 weeks. Stable disease (SD) was reached if reduction of less than 50% or an increase of less than 25% of all measurable disease with no appearance of new lesions for at least 4 weeks. Progressive disease occurred if the size of at least one measurable lesion increased by at least 25% or new lesions appeared[13]. All toxicities were graded using the WHO scale[14].

Overall survival was measured from date of diagnosis until death and time to progressive disease was measured from date of initial treatment until disease progression.

Statistical analysis:

Overall survival and time to progression were estimated by Kaplan Meier methods[8].

The comparison between survivals of the two groups was performed using the log rank test. A *P*-value of ≤ 0.05 was considered significant.

RESULTS

Between May 2002 and January 2005, forty-one patients enrolled the study. Twenty-one patients were randomized to gemcitabine-cisplatin and twenty to MVAC arm. Patients characteristics were generally well balanced between treatment arms as shown in (Table 1). The median length of follow up was 22 months.

Overall survival:

Overall survival was similar on both arms. Median survival was 13 months with GC and MVAC, survival rates at 6 months, 12 months, and 18 months was 85%, 42% and 35%, respectively on GC and 82%, 44%, 37%, respectively on MVAC. Figure 1 provides survival

curves for each treatment arm. Univariate analyses showed that prognostic factors correlating with poorer overall survival were Karnofsky performance status < 70%, TNM staging (M1) and the presence of visceral metastases, (Table 2). When treatment was added to this final model of prognostic factors there was no treatment effect for overall survival.

Tumor response:

Overall response rates were not significant between both arms, most responses were partial. Overall response rate was 47.6% with GC (14.3% CR and 33.3% PR) and 45% with MVAC (10% CR and 35% PR), (P = 0.48). Disease stabilization was reached in 28.6% and 30% of patients and disease progressed in 23.8% and 25% of patients in GC and MVAC, respectively.

Time to progressive disease:

Time to progressive disease was comparable on both arms. Median time to progressive disease was 7 months with CG (6.4 to 8.4 months) and 6 months with MVAC (5.3 to 7.4 months). Figure 2 provides time to progressive curves for each treatment arms. At the time of analysis 10 patients had progressed (CG, n = 5 MVAC, n = 5). Summary of efficacy outcomes are provided in (Table 4).

Toxicity:

On GC arm, 12 patients (57%) were given cycles without any dose adjustments or treatment delays compared with 6 patients (30%) on the MVAC arm. The most common cause for adjustments on GC arm was thrombocytopenia, while on the MVAC arm, the most common causes for adjustments were leucopenia, and mucositis.

The toxicities seen in both treatment arms were expected. World health organisation grades 3 and 4 toxicities for hematological and non hematological toxicties are shown in (Table 5). Grade 3 and 4 anaemia was seen more often on the GC arm than on MVAC arm(GC = 28.56%, MVAC = 15%. P = 0.02). Grade 3 and 4 thrombocytopenia was seen more often on GC on (GC: 47.64%, MVAC: 25% P = 0.03) but with no grade 4 bleeding on either arm.

Grade 3 and 4 Neutropenia was significantly more common in MVAC arm (MVAC: 80%, GC = 67.6% P = .001). More patients on MVAC developed febrile neutropenia (20% vs. 4.8% P = 0.04).

For non hematologic toxicities, patients on MVAC experienced more grades 3&4 mucositis (MVAC = 20% GC" 9.5% P = 0.03). Gastrointestinal toxicities like nausea, vomiting, diarrhea, and constipation are more or less the same between both arms., alopecia was more in MVAC patients (25% Vs 14.3% P = 0.02).

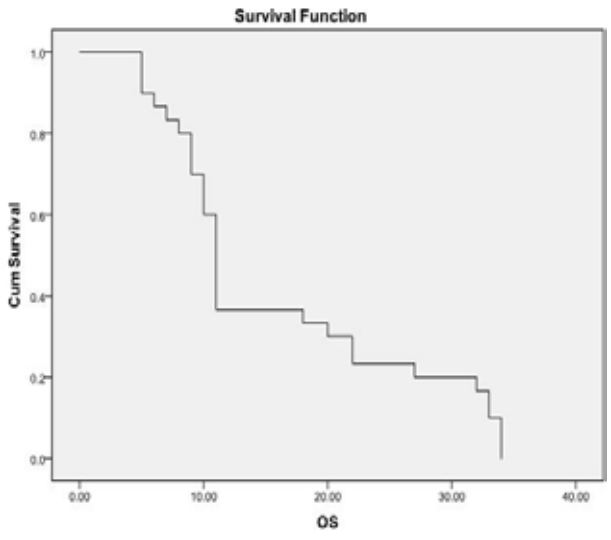

Figure 1: Overall survival

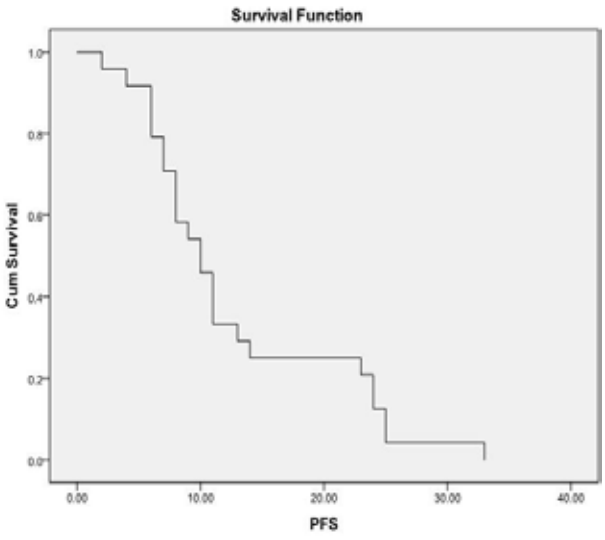

Figure 2: Time to progressive disease.

Table 1: Patient characteristics (41 patients).

Parameter	Arm A = 21 patients GC No (%)	Arm B = 20 patients MVAC No (%)
Age, median, years	63	63
Male	18 (86)	15 (75)
Performance status ≥70%	11(52)	8(40)
Pathological grade		
1	3 (14)	4 (20)
2	8 (38)	7 (35)
3	10 (48)	9 (45)
Locally advanced	12 (57)	10 (50)
Metastatic disease	9 (43)	10 (50)
Bone	5 (23)	5 (25)
Liver	2 (10)	2 (10)
Lung	2 (10)	3 (15)

Abbreviation: GC = gemcitabine, cisplatin, MVAC = methotrexate, vinblastine, doxorubicin, cisplatin, PS = performance status.

Table 2: Univariate analysis of prognostic factors.

Prognostic factor	GC "n = 21"	MVAC "n = 20"	OSHR (95%CI)
1- PS = Good > 70 = Poor < 70	11 (52.4%) 10 (47.6%)	8 (40%) 12 (60%)	1.92 (1.23-2.71) *P* = 0.01*
2- TNM = M1 M0	12 (27.1%) 9 (42.9%)	7 (35%) 13 (65%)	1.78(1.03-2.04) *P* = 0.02*
3- nodal.status= - ve + ve	9 (42.9%) 12 (57.1%)	10 (20%) 10 (20%)	1.13 (0.85-1.41) *P* = 0.442 n.s
4-Visceral metastasis. - ve + ve	 16 (76.2%) 5 (23.8%)	 16 (80%) 4 (20%)	 2.01 (1.72-2.85) *P* = 0.01*
5- Responce: (CR+PR) (SD+PD)	10 (47.6%) 11 (52.4%)	9 (45%) 11 (55%)	1.25 (0.93-201) *P* = 0.981 n.s
6- Sex= male Fcmale	18 (85.7%) 3 (14.3%)	15 (75%) 5 (25%)	1.92 (1.58-2.43) *P* = 0.319 n.s

Table 3: Results of response to gemcitabime plus cisplation (A) and methotrexate, vimblastion, adriamycin and cisplation in advanced urothelial cancer.

Response	Arm A (21 patients) GC No (%)	A rm B= 20 Patients MVAC No (%)
Complete response (CR)	3 (14.3)	2 (10)
Partial response (RR)	7 (33.3)	7 (35)
Stable disease (SD)	6 (28.6)	6 (30)
Progressive disease (PD)	5 (23.8)	5 (35)

Table 4: Summary of efficacy outcomes.

Parameter	GC months	MVAC months	*P* value
Median overall survival	13	13	-
Median TTPD	7	6	0.521 ns
Response rate %	47.6	45	0.483 ns

Abbreviation: TTPD, time to progressive disease,

Table 5: Maximum toxicity grade.

Toxicity	GC % of patients		MVAC % of patients		*P*
	Grade		Grade		
	3	4	3	4	
Hematologic					
Anemia	23.8	4.76	15	0	0.02
Thrombocytopenia	28.6	19.04	10	15	0.03
Neutropenia	42.8	23.8	15	65	0.001
Non hematologic					
Mucositis	9.5	0	15	5	0.03
Nausea/vomiting	23.8	0	20	0	0.237
Diarrhea	9.5	0	10	0	0.653
Infection	4.8	0	10	5	0.04
Pulmonary	4.8	0	5	5	0.673
Haematuria	9.5	0	-	0	0.221
Constipation	4.8	0	5	0	0.591
Hemorrhage	4.8	0	0	0	0.237
Alopecia	14.3	0	25	0	0.02

DISCUSSION

Combination chemotherapy is the treatment of choice for patients with inoperable locally-advanced or metastatic bladder cancer. M-VAC was a frequently used regimen for this disease[6]. Although a survival advantage with noted with MVAC compared with cisplatin alnoe[7], MVAC was associated with significant toxicities with a toxic death rate of 3-4%. Thus, there was a need for other regimens that provide better survival outcome or similar survival with reduced toxicity. Based on encouraging results of phase III studies comparing gemcitabine and cisplatin with MVAC in bladder cancer[8], this regimen is generally considered the current standard of care for metastatic TCC of the urothelium. However, it has not been sufficiently tested yet against MVAC in advanced bilharzial-related bladder cancer[11].

This phase III study comparing, GC with MVAC for efficacy and toxicity in advanced bilharzial-related urothelial carcinoma of the bladder. Our results showed that the combination of gemcitabine and cisplatin obtained a median survival similar to MVAC. In both arms, the overall response rates and the median progression-free survival demonstrated nearly identical results and this indicated nearly similar efficacy of both treatment regimens but GC is more tolerable and safer, so GC has a better risk-benefit ratio than MVAC.

These results were comparable with the results from studies using the same gemcitabine–cisplatin combination against advanced transitional cell carcinoma[8,15,16].

However, the overall response rate (47.6%) and CR (14.3) in the GC therapy in this study is lower than the results reported by Khaled HM, *et al*.[17]. The difference may be due to dose adjustment and frequent omissions of gemcitabine occurred on day 15 in this study.

This study demonstrated that GC is less toxic than MVAC. Patients treated with GC had lower toxicity-related mortality and lower rates of grade 3 or 4 mucositis. This is in accordance with that reported by Von Der Masse H *et al*.[8] and Khaled HM, *et al*.[17].

In this study, overall survival, time to progressive disease and response rates were similar on both arms. The results of our univariate analysis of prognostic factors support the finding of Bajorin *et al*. who define performance status, stage and presence or absence of visceral metastases as important, independent prognostic variables[18].

CONCLUSION

In conclusion, GC therapy is effective for the treatment of advanced or metastatic bilharzial-related

urothelial carcinoma of the bladder, with an acceptable clinical safety profile. This study also indicates that GC therapy may be better tolerated and safer than MVAC therapy. The promising results of using gemcitabine-cisplatin combination in the metastatic setting led to multi-institutional neo-adjuvant trial for organ preservation[1].

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