

REVIEW ARTICLE

Systemic Management of Bladder Cancer in Egypt: Revisited

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ABSTRACT

Bladder cancer is still the most frequent malignant tumor among Egyptian males. It has a peculiar biologic, clinico-pathologic features and responsiveness to chemotherapy profile than that observed in Western countries. The current review aims to demonstrate the present state-of-art in using systemic therapy as part of the management options available to treat such patients at different stages of their disease. Individualizing therapy for these patients based on more rationale basis is the challenge that oncologists must face in the near future.

INTRODUCTION

Urinary bladder cancer is one of the most common cancers worldwide, with the highest incidence in industrialized countries. In most European countries, the United States, and Canada, rates are between 20 and 30 per 100 000 normal population [1]. Two main histological types of bladder cancer are identified: the transitional cell carcinomas (TCC), related to cigarette smoking and most prevalent in Western and industrialized countries, and the squamous cell carcinomas (SCC), which are more frequently seen in some Middle Eastern and African countries, where urinary bilharziasis is an endemic disease [2].

Despite the marked decrease in prevalence of endemic bilharziasis over the last 2 decades, Egypt is still paying the toll of the previously high prevalence of the disease. However, it could be anticipated that in the near future, there will be a marked decrease in bladder cancer in Egypt as a sequel to schistosomiasis control. Currently, it ranks first in males, repre-

senting 16.2% of male cancers. Among Egyptian females, its frequency is 4.0. For both sexes together, the frequency of bladder cancer is 10.1% [3].

In this review, the role of systemic chemotherapy in bladder cancer in Egypt will be revisited. As the disease is biologically, pathologically and clinically different from that encountered in western countries, response to chemotherapy is also different.

ADVANCED DISEASE

In addition to patients with recurrent, and/or metastatic disease after their primary therapy, about 25% of patients at first presentation also have inoperable tumors. They are all potential candidates for chemotherapy.

SINGLE AGENTS CHEMOTHERAPY

So, in the absence of any information on chemotherapy responsiveness of patients with bilharzial associated bladder cancer, a series of phase II trials, beginning in 1976, and crudely screening about 15 drugs over a period of 10 years, were conducted at the National Cancer Institute, Cairo University. Various drugs were screened in groups of 20-25 patients with advanced (inoperable) or recurrent bilharzial bladder cancer.

Drugs known to be the most active in non-bilharzial transitional cell carcinoma e.g. methotrexate, cisplatin derivatives, and doxorubicin were found to be relatively ineffective for bil-

harzial bladder cancer [4]. The alkylating agents dibromodulcitol, cyclophosphamide, pentamethylmelamine, and hexamethylmelamine yielded response rates of 18% -38%. The vinca alkaloids, vincristine and vindesine, proved very effective and vindesine seemed to be especially effective in transitional cell carcinoma. Ifosfamide gave similar response rates (about 40%) in transitional and squamous cell carcinoma. The most effective agent was epidoxorubicin with response rates of 50-60%. In general, the

drugs seemed to be more effective in metastatic than in locally advanced disease. The vast majority of responses were partial, while complete remissions were rather infrequent. These results are summarized in table (1). Lastly, an encouraging phase II trial has evaluated the role of single agent taxotere in a cohort of 13 patients with advanced disease. All cases had squamous cell carcinoma. Responses (3 partial and 1 complete) were observed in 4 out of the 8 evaluable cases [5].

Table (1): Results of single agent chemotherapy in advanced bilharzial bladder cancer.

	No. of patients					
	Evaluable	CR	PR (CR+PR)	Imp	SD	PD
Bleomycin	21	0	0 (0%)	2	6	13
Doxorubicin	27	0	0 (0%)	2	4	21
Tenoposide	26	0	1 (4%)	2	6	17
5-fluorouracil	32	0	2 (6%)	3	17	10
Methotrexate	14	0	1 (7%)	0	2	11
Cisplatin	18	1	2 (16%)	0	3	12
Dibromodulcitol	22	1	3 (18%)	0	6	12
Cyclophosphamide	21	1	3 (19%)	2	9	6
Pentamethylmelamine	25	1	7 (32%)	2	9	6
Etoposide	19	0	7 (36%)	3	5	4
Hexamethylmelamine	26	0	10 (38%)	12	0	4
Ifosfamide	20	0	8 (40%)	2	2	8
Vincristine	25	2	9 (44%)	0	8	6
Vindesine	32	3	10 (41%)	0	9	10
Epidoxorubicin	18	0	9 (50%)	0	7	2
	18	0	11 (60%)	0	7	0

Although these data, obtained in consequently different groups of patients, cannot be directly compared as the patients were not randomized nor matched for factors which might have influenced the response rate e.g. age, sex, histologic, type, tumor size, loco-regional recurrence, or metastases, however, the results gave some indications for the drugs that might be most interesting for further clinical studies, and for designing chemotherapeutic combinations.

COMBINATION CHEMOTHERAPY

Based on these data, evaluation of a combination of 4 of the most active agents in bilharzial bladder cancer was then tested. The regimen was designed to consist of epidoxorubicin (120 mg/m² d1) and vincristine (1.4 mg/m² days 1 and 8) alternating with etoposide (100 mg/m² days 1 to 5), and ifosfamide (1800 mg/m² days

1 to 5) with its uroprotector mesna. Courses were repeated every 3-4 weeks.

The trial was conducted on a group of 30 patients with inoperable (20 cases) recurrent (5 cases, 2 of them subsequently developed metastases), or metastatic disease (5 cases). Fourteen patients had squamous cell carcinoma, 12 had transitional cell carcinoma, 2 had adenocarcinoma, and 2 had undifferentiated carcinoma. Among 22 evaluable patients, 8 (36.5%) had PR and 1 (4.5%) had CR giving an overall response rate of 41%. Toxicity was tolerable, mainly myelosuppression. No relation was found between the pathologic subtype of these cases and response to therapy [6].

The relatively low response rate observed in this study (41%) was rather disappointing in view of the noted response rate results of the

same drugs used as single agents (36% to 60%). This could be explained by many factors including unexpected antagonism between these agents when used in combination, lower relative dose intensity of each drug given in combination than in previous studies when these drugs were given alone, and the possibility that accurate assessment of tumor responses in the previous single agents trials was reported to be difficult due to the lack of, at that time of the mid 1970s and early 1980s, advanced radiologic techniques e.g. CT scan. Thus overestimation of responses to therapy in these trials could not be excluded.

At the same time and as a result of the reported encouraging data of the combination gemcitabine and cisplatin in bladder cancer of the transitional cell type, a phase II study was performed in 37 patients with previously untreated advanced bilharzial bladder cancer [7]. Patients received gemcitabine (1000 mg/m²) days 1, 8, and 15 together with cisplatin (70 mg/m²) day 2 of every 28-day cycle. Out of 33 evaluable patients, 8 patients achieved CR (24%), and 10 patients (30%) had PR on therapy with an overall response rate of 54% [8]. Myelosuppression was significant but manageable. Again, response to therapy was not significantly affected by pathologic subtypes although higher response rates were observed in patients with transitional cell carcinoma (60%) when compared to those with squamous cell carcinoma (49.5%).

Although the overall response rate in this study (54%) was not much different from that reported in the study whereby a combination of the drugs epidoxorubicin and vincristine alternating with etoposide and ifosfamide (41%) was used, this is the first study to report on the achievement of a CR rate of 24% (8/33 patients) in advanced bilharzial bladder cancer.

In this trial, like in many other gemcitabine-containing regimens, the drug was given over one hour infusion. For gemcitabine to act, the enzyme deoxycytidine kinase must catalyze its phosphorylation into the active metabolite gemcitabine triphosphate. Usually after an infusion over 30 minutes, this enzyme will be saturated, at conventional drug doses and the action of the drug will be limited. Therefore accumulation of higher intracellular concentrations of the active gemcitabine triphosphate could be achieved by prolonging the infusion time of

gemcitabine. This new gemcitabine schedule was proved to be safe in some recently published phase I trials. Based on these data, the efficacy and safety of a combination of cisplatin and gemcitabine given as prolonged infusion was then tried in a phase II study of 57 untreated patients with stage III/IV disease [9]. Patients received gemcitabine (250 mg/m² over 6 hour infusion) on days 1 and 8, and cisplatin (70 mg/m²) on day 2 every 21-day cycle. Thirty seven cases had transitional cell carcinoma, 15 had squamous cell carcinoma, 2 had adenocarcinoma and 3 had undifferentiated carcinoma. Of 54 evaluable patients 5 (9%) achieved CR, and 27 (50%) PR, for an overall response rate of 59%. The median survival time was 11.5 months, while the one-year overall survival rate was 28% (Fig. 1). These results are comparable to those of the previously published phase II study of the same combination but with gemcitabine given in the standard dose and schedule. Responses were observed at all disease sites. Both hematologic and non-hematologic toxicities were minimal and tolerable. This trial also addresses the cost-benefit of giving a reduced dose of gemcitabine in treating patients with such a common tumor in a country with limited resources.

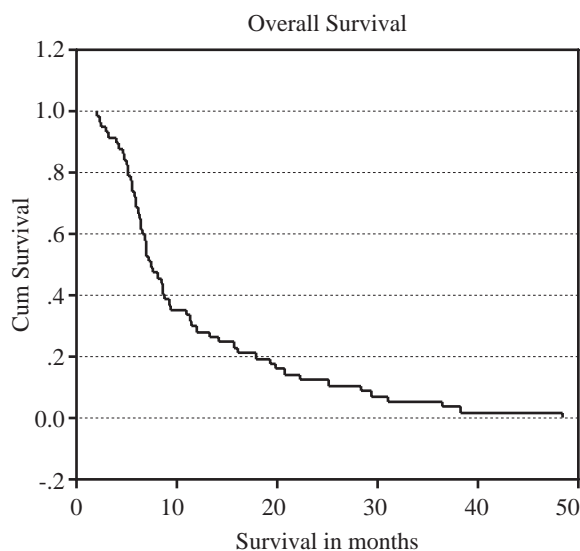


Fig. (1): One-year overall survival rate of the 54 bladder cancer cases included in the low dose prolonged infusion gemcitabine-cisplatin trial.

A summary of the results on combination chemotherapy regimens in bilharzial related bladder cancer is shown in table (2).

Table (2): Results of combination chemotherapy in advanced bilharzial bladder cancer.

No. of patients	Evaluable	CR	PR (CR+PR)
Epidx-VCR Alternating with VP16-Ifos.	22	1	8 (41%)
Gemcitabine – Cisplatin (Standard dose)	33	8	10 (54%)
Gemcitabine – Cisplatin (Low dose - prolonged infusion)	54	5	27 (59%)

NEOADJUVANT AND ADJUVANT THERAPY

Radical cystectomy with urinary diversion is the only curative modality so far identified for patients with bilharzial bladder cancer. Operable patients have overall 5-year survival rates between 27% - 39%. In an effort to improve these unsatisfactory survival figures of patients with respectable disease, many adjuvant and neoadjuvant studies have been conducted over the last 15 years. The first trial was a randomized study evaluating neoadjuvant epidoxorubicin, the most active single agent identified at that time. Seventy-one patients with T2-T3 lesions were randomized to receive either 2 courses of epidoxorubicin (120 mg/m² every 3 weeks) preoperatively and 4 additional courses after radical cystectomy or radical cystectomy alone. In the neoadjuvant chemotherapy arm, necrosis was found in 95% of patients with SCC and in 57% of patients with TCC [10]. The estimated disease-free survival rates for chemotherapy-treated patients vs. cystectomy alone were 74% and 38% respectively ($p=0.05$). This higher survival figure for the neoadjuvant arm patients was then confirmed in a larger series including about 170 patients and using the same schedule for drug epidoxorubicin. Another study, reported from Mansoura, has assessed the value of cisplatin-based neoadjuvant chemotherapy in 194 patients with respectable disease [8]. However, no overall survival information was provided.

The promising results of using the gemcitabine-cisplatin combination in the metastatic setting then led to a multi-institutional neoadjuvant trial that was planned with the primary objectives of organ preservation and/or prolongation of disease-free survival and overall sur-

vival rates. In this randomized phase III trial that accrued patients (stages T2-T4, N0-N2) between Nov 2000 and June 2002, 114 patients were randomized to receive either of 2 regimens: arm I (58 patients): 3 cycles of gemcitabine / cisplatin combination chemotherapy preoperatively, or arm II (56): radical cystectomy only. In arm I, tumor response was assessed after 3 cycles. Patients with a CR received 3 additional chemo cycles followed by radical RT (68 Gy/7 wks). In patients who were down-staged to T2-T3, surgery was performed, followed by 3 more cycles of the same regimen. Those with SD or progression of disease were treated with radical cystectomy. In arm I, an overall response of 56% (28 patients) was achieved (30% CR and 26% PR). Bladder preservation was feasible in 11 patients (22% of patients in arm I) of the group achieving a CR. In arm II, 52 patients underwent radical cystectomy, and 4 were found unresectable on exploration. There was a trend towards increased overall one-year survival for the neoadjuvant chemo group at 69% compared to 54% for patients undergoing cystectomy alone ($p=0.9$). Severe toxicity was observed infrequently. The authors concluded that the combination of gemcitabine and cisplatin is effective and tolerable when used as neoadjuvant therapy in muscle-invasive bladder cancer. This regimen helped achieve organ preservation in a significant sector of patients [11].

The value of combining both post-operative combined chemotherapy and radiotherapy was also tried for patients with high risk factors. The combination gemcitabine - cisplatin given with hyperfractionated postoperative radiotherapy (4500 cGy/3 weeks/ 30 fractions) as an adjuvant combination to surgery proved to be tolerable and the percentage of grade III and IV toxicities were minimal. Preliminary results showed improvement of the one-year DFS in the Gem-Cis group though not reaching the level of significance [12].

Thus it is clear from the previously mentioned data that the efforts investigating the value of adding neoadjuvant or adjuvant radiotherapy and/or chemotherapy to improve treatment outcome of patients with bladder cancer all over the country are ongoing.

Therefore, the need for developing a prognostic model to define high risk groups that are more vulnerable to disease relapse after radical

cystectomy and, thus, may benefit from additional preoperative therapy is highly indicated, and may also explain the controversial data of such therapy. So, a newly designed prognostic index formed of the 3 known independently significant risk factors, namely P stage, tumor grade, and lymph node affection, was recently evaluated in a group of 198 bladder cancer cases at the National Cancer Institute [13]. This simple and easy-to-apply prognostic index (Fig. 2.) may guide for more rationale choice of patients into future clinical trials.

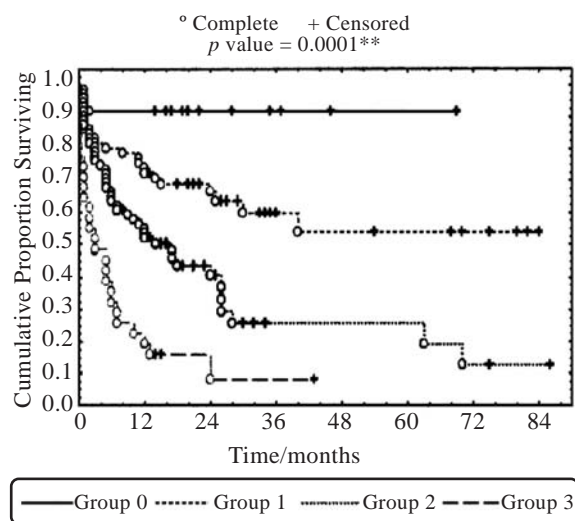


Fig. (2): Disease - free survival in relation to prognostic group of the bladder cancer prognostic index.

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