The Changing Patterns of Bilharzial Bladder Cancer and its Treatment Outcome, NCI, Cairo University Experience

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Abstract
Bilharzial bladder cancer (B.B.C) is a major health problem in Egypt, as well as some African & Asian countries it represents a distinct clinicopathologic disease. Tumors are usually advanced at presentation, they can be either of squamous or transitional cell carcinoma type, on the background of bilharzial cystitis. Bilharzial bladder cancer is a preventable malignancy, through eradication of the schistosomal infestation. Management is mainly surgical, with median 5 years survival about 48%. This article will try to explore clinicopathologic aspects as well as treatment options of such cases.

Key Words: Bilharzial – Bladder – Cancer.

Introduction
BILHARZIAL bladder carcinoma is the most common cancer, particularly in Egyptian males, accounting for 14-30% of all malignant diseases presenting to, NCI, Cairo University. Classically carcinoma in bilharzial bladder is most commonly of squamous cell type. Decline in prevalence of bilharziasis in Egypt during past decade due to success of schistosomaisis control program in Egypt, was associated with significant changes in the pathology of bladder carcinoma, with decline in the frequency of squamous carcinoma and increase in transitional carcinoma [1].

Radical cystectomy with urinary diversion is the only curative modality so far identified with long term survival rate in range of 27 to 39%. Twenty five percent of patients presenting with bladder cancer are inoperable. In addition; the reported overall rate of local recurrence following radical cystectomy ranges from 40-50% most of them occur during the first year following surgery [2].

So, the Aim of this work is to investigate the current status of treatment options available for cases of bilharzial bladder cancer as well as different clinicopathologic factors, that distinguishes it from western type of bladder cancer.

Molecular biologic and genetic changes:
Bilharzial infestation is usually associated with bacterial infection and human papiloma virus infection, bacterial enzymes liberate free carcinogens and also produce carcinogenic nitrosamines from their precursors in urine. Also HPV have been retrieved in about 46% of examined samples of Bilharzial bladder carcinoma by in situ hybridization [3].

Molecular biologic analysis of Bilharzial bladder tumors, showed point mutations at H-ras in about 16% of Bilharzial bladder cancers. P53 mutations were detected in 20-86% of studied cases, also deletions of P16/INK4A have been reported [3,4,5].

The most common numerical chromosomal abnormalities detected were loss of chromosome 9 in 48% of studied cases, numerical alterations in chromosome 17 in 19.4%, gain of chromosome 7 in 10% and characteristic loss of Y chromosome in 36% of studied cases [6,7].

Tumor expression of EGFR, Rb and P34 was positive in 63.5%, 57% and 48% of examined samples respectively. Multidrug Resistance Gene (MDR) was detected in about 40% of examined samples [8,9].

Histopathology:
Bilharzial bladder carcinoma is the most common cancer, particularly in Egyptian males, accounting for 14-30% of all malignant diseases presenting to, NCI, Cairo University [10,11].
Bilharzial bladder carcinoma has a distinct clinicopathologic pattern, that differs in some aspects from western type of bladder carcinoma. Peak age of diagnosis is usually 50±5 years, with a male: female ratio of 5:1.

The majority of patients (86-91%) presented with advanced stage disease (T3-T4), most tumors present as fungating nodular masses with deep infiltration, into the bladder wall, P3 (73%), P4 (16%), whereas papillary and superficial tumor types are rare [12].

Classically carcinoma in bilharzial bladder is most commonly of squamous cell type. Decline in prevalence of bilharziasis in Egypt during the past decade was associated with significant changes in the pathology of bladder carcinoma, with decrease in bilharzial infestation and decline in relative frequency of squamous carcinoma and increase in transitional carcinoma, studies consistently proved a decline in squamous carcinoma and increase in the frequency of transitional cell carcinoma from 21% to 40% as reported by Zaghloul et al., 1996, Khaled et al., 1996 and Ghoneim et al., 1997 [13,14]. Usual site of these cancers is the upper part of bladder, the trigone is rare site of bilharzial cancer development [15]. Tumor multicentricity is not uncommon; occurring in 6-22% of cases. The frequency of nodal metastasis is about 18% [13].

A prognostic model index formed of the 3 known independent 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. This simple and easy-to-apply prognostic index (Fig. 3) may guide for more rationale choice of patients into future clinical trials [11].
Treatment options:

Surgery:

Radical cystectomy with urinary diversion is the only curative modality so far identified, with long term survival rates in the range of 27-39%, post operative mortality about 4% and most patients had advanced stage tumors. Five years survival rate was 48%, 5 years disease free survival was 23% for node positive cases versus 53% for node negative cases [16].

Twenty five percent of patients presenting with bladder cancer, are inoperable. In addition, the reported overall rate of local recurrence following radical cystectomy ranges from 40%-50%. Most of them occur during the first year following surgery [13].

In contrast to reports claiming rare incidence of distant metastasis from Bilharzial bladder carcinoma, due to extensive fibrosis blocking lymphatic channels, compared to non-bilharzial carcinoma, yet its incidence was estimated to be as high as 23%, in Bilharzial bladder cancer patients. The risk factors for developing distant metastasis are positive nodal involvement (54%), stage P4a disease (33%) and high grade tumors (38%) [17].

Radiation therapy:

Beside its essential role as a palliative treatment for advanced cases of Bilharzial bladder cancer presenting either with brain, spine, or bone metastasis, or even as haemostatic for bleeding advanced tumors, radiation therapy has been deployed in adjuvant setting for advanced cases of bladder cancer after radical cystectomy, where it markedly reduced the incidence of local recurrence and improved the 5 years disease free survival to 47 ±6% compared to 25±5% for patients treated with surgery alone [17].

Neoadjuvant radiotherapy have also been used either alone or in combination with chemotherapy and proved successful to improve the 5 years survival rates for cases with PT3 and PT4 to 43% compared to 19% for those treated with surgery alone [18].

Systemic chemotherapy:

Although the western type of bladder transitional carcinoma is a chemosensitive malignancy however only a small proportion (=10%) of patients with advanced disease succeed to have long term survival following chemotherapy.

A number of single chemotherapeutic agents with different mechanisms of action are active against bladder tumors, producing as overall response rate of 12%-31%, with a duration of response on the order of 3-4 months. Complete responses are rare usually less than 10%. The most active single agents include: Paclitaxel, methotrexate doxorubicin, cisplatin, cyclophosphamide, ifosfamide, pemetrexed and gemcitabine [19].

A series of phase II study was conducted at Cairo NCI, starting in 1976, in which various chemotherapeutic agents were screened in groups of 20-25 patients, with inoperable metastatic or recurrent bilharzial bladder cancer, who had not previously received chemotherapy. Drugs known to be the most active in transitional cell carcinoma of the bladder e.g. methotrexate, cisplatin derivatives and doxorubicin were found to be relatively ineffective for bilharzial bladder cancer. The drug epidoxorubicin, showed the highest objective response rate of 60% in 18 patients [20]. These results led to conduction of a randomized study evaluating neoadjuvant epidoxorubicin. Seventy-one patients with T2-T3 lesions were randomized to receive either 2 courses of epidoxorubicin preoperatively and 4 additional courses after radical cystectomy or radical cystectomy alone. The estimated disease-free survival rates for chemotherapy-treated patients Vs. cystectomy alone were 74% and 38% respectively (p=0.05) [21].

Table (2): Activity of single agent chemotherapy in BBC [20].

<table>
<thead>
<tr>
<th>Evaluable</th>
<th>CR</th>
<th>PR</th>
<th>OR</th>
<th>Imp SD PD</th>
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<tbody>
<tr>
<td>Bleomycin</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>(0%) 6 13</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>(0%) 2 21</td>
</tr>
<tr>
<td>Tenoposide</td>
<td>26</td>
<td>0</td>
<td>1</td>
<td>(4%) 2 17</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>32</td>
<td>2</td>
<td>0</td>
<td>(6%) 3 10</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>14</td>
<td>0</td>
<td>1</td>
<td>(7%) 2 11</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>18</td>
<td>1</td>
<td>2</td>
<td>(16%) 0 12</td>
</tr>
<tr>
<td>Dibromodulcitol</td>
<td>22</td>
<td>1</td>
<td>3</td>
<td>(18%) 0 12</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>21</td>
<td>1</td>
<td>3</td>
<td>(19%) 2 9 6</td>
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<tr>
<td>Pentamethylenemelamine</td>
<td>25</td>
<td>1</td>
<td>7</td>
<td>(32%) 2 9 6</td>
</tr>
<tr>
<td>Etoposide</td>
<td>19</td>
<td>0</td>
<td>7</td>
<td>(36%) 3 5 4</td>
</tr>
<tr>
<td>Hexamethyamine</td>
<td>26</td>
<td>0</td>
<td>10</td>
<td>(38%) 12 0 4</td>
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<tr>
<td>Ifosfamide</td>
<td>20</td>
<td>0</td>
<td>8</td>
<td>(40%) 2 8 2</td>
</tr>
<tr>
<td>Vincristine</td>
<td>25</td>
<td>2</td>
<td>9</td>
<td>(44%) 0 8 6</td>
</tr>
<tr>
<td>Vindeze</td>
<td>32</td>
<td>3</td>
<td>10</td>
<td>(41%) 0 9 10</td>
</tr>
<tr>
<td>Epidoxorubicin</td>
<td>18</td>
<td>0</td>
<td>9</td>
<td>(50%) 0 7 2</td>
</tr>
<tr>
<td>(Phase I)</td>
<td>18</td>
<td>0</td>
<td>11</td>
<td>(60%) 0 7 0</td>
</tr>
<tr>
<td>(Phase III)</td>
<td>26</td>
<td>2</td>
<td>2</td>
<td>(15.38%) 0 8 14</td>
</tr>
</tbody>
</table>

Other active drugs included vincristine, ifosfamide and etoposide, with a response rate of 41%, 40% and 36%, respectively [20]. 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 [22].

Unfortunately, in spite of quite good response rates, very few durable remissions were observed, this outcome has improved, however, with the development of 3 and 4 drug combination regimens, which resulted in durable complete responses.

Khaled et al., (1996) used a combination of epidoxorubicin plus vincristine alternating with ifosfamide and etoposide in patients with locally advanced and metastatic disease, giving a response rate of 41 % with a median duration of response of 5 months. Such variability in response rate, called for conduction of a randomized phase III trial to compare between the most active single agent and combination treatment [23].

We conducted a phase III study, upon 55 patients, over the period from April 1999 to Dec. 2002. Presenting with either metastatic, inoperable, or recurrent disease. The 55 patient’s evaluable for response, 26 patients were randomized to receive single agent epidoxorubicin and the remaining 29 patients received the combination of epidoxorubicin with vincristine alternating with etoposide and ifosfamide. The clinicopathologic characteristics of the two groups were comparable, except for the higher frequency of grade 3 tumors in the combination chemotherapy group.

Those who received single agent chemotherapy, had a response in only 4 cases (response rate (15.38%) with only 2 cases achieving complete remission, those receiving combination chemotherapy had a response in 11 patients (response rate of 37.9%) with only 2 patients achieving complete responses. Combination treatment group had a higher 2 years PFS of 36.2%, in contrast to 15% in the group receiving epidoxorubicin treatment, a difference that proved to be statistically significant (p=0.04) [14].

At the same time and as a result of the reported encouraging data of the combination gemcitabine and cisplatin in bladder cancer of the western type, a phase II study was performed in 37 patients with previously untreated advanced bilharzial bladder cancer. Although the overall response rate in this study (54%), yet; this is the first study to report on the achievement of a CR rate of 24% (8/33 patients) in advanced Bilharzial bladder cancer [24].

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 survival rates. In this randomized phase III trial that accrued patients with (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 pre-operatively, or arm II (56): Radical cystectomy only. 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 chemotherapy group at 69% compared to 54% for patients undergoing cystectomy alone (p=0.9). Severe toxicity was observed infrequently [25].

In adjuvant setting, gemcitabine-cisplatin given with hyperfractionated postoperative radiotherapy (4500 cGy/3 weeks/ 30 fractions), proved to be tolerable and preliminary results showed improvement of the one-year DFS in the Gem-Cis group though not reaching the level of significance [26].

Another 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, of 54 evaluable patients, 5 (9%) achieved Complete Remission and 27 (50%) Partial Remission, for an overall response rate of
59%. The median survival time was 11.5 months. While the one-year overall survival rate was 28%. Both hematological and non-hematological toxicities were minimal and tolerable [27]. Protracted six hours infusion proved more cost-effective regimen over the conventional one hour infusion regimen, without any significant difference in overall response, or toxicity profile [28].

Table (3): Combination chemotherapy in BBC.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Evaluable CR</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>Epidx-VCR // VP16-Ifos</td>
<td>29</td>
<td>2 (11/29) 37.9%</td>
</tr>
<tr>
<td>Cis/Gem (Standard dose)</td>
<td>33</td>
<td>8 (18/33) 54%</td>
</tr>
<tr>
<td>Cis/Gem (Low dose-prolonged infusion)</td>
<td>54</td>
<td>5 (32/54) 59%</td>
</tr>
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</table>

References


