The Chemotherapy of Advanced Bladder Carcinoma

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Summary

This paper is a summary of the clinical chemotherapy of metastatic or recurrent bladder carcinoma. Mitomycin C, doxorubicin, methotrexate, and 5-fluorouracil appear to have cytotoxic activity against bladder carcinoma when used as single agents, although the reported objective responses to each agent vary greatly. Cyclophosphamide in intermittent high i.v. doses produced an objective response in 4 of 10 patients treated by the author, and other reports suggest that this drug also may have activity against bladder cancer. cis-Dichlorodiammineplatinum is a new drug that also deserves further study.

Introduction

The 5-year survival of patients with invasive bladder cancer, treated by the most expert radiation therapy and surgery, is between 25 and 50% (26). Most patients with bladder cancer will therefore require systemic therapy for recurrent or metastatic tumor. The role of chemotherapy in the treatment of bladder cancer has not been defined, but the response to cytotoxic agents has thus far been discouraging. Anecdotal reports of several patients treated with various agents outnumber the carefully conceived clinical trials. Furthermore, the studies do not include control populations or patients randomized to receive other therapy. Patient populations are often heterogeneous, and drug dosages and routes of administration are inconsistent. The criteria of response vary from author to author and frequently are not defined.

The published data must therefore be interpreted cautiously but still must provide the background for current and future clinical trials. The purpose of this paper is to review the published data on the chemotherapy of invasive bladder cancer, emphasizing the single agents that have potential for inclusion into future randomized studies. Details of drug mechanisms of action, dosage and administration, and toxicity are beyond the scope of this review; such information is readily accessible in standard texts.

5-FU

5-FU is a pyrimidine antagonist that has been used widely in the treatment of solid tumors and was one of the earliest agents used to treat metastatic bladder cancer. The standard method of therapy with 5-FU, i.e., a loading dose over 3 to 5 days followed by lower doses every 2 to 3 days until toxicity developed, was the method used in the reported series of patients with bladder cancer. The response rate ranges from 0 to 75% (Table 1). The most optimistic report was that of Wilson (32), who noted objective regression in 9 of 12 treated patients, although the extent of the objective response and the criteria for response were not detailed. Moore et al. (21) reported objective response in 6 of 9 patients with presumably metastatic bladder cancer, 1 of whom had complete regression of tumor. The 57% response (4 of 7) achieved by Glenn et al. (13) included responses only in patients with superficial tumors, and no patients with invasive cancers responded to the drug. Ansfield et al. (3) documented 1 response in 7 evaluable patients but more recently have noted prolonged survival in several patients, 1 of whom survived for 8 years (2).

Other authors, however, have had little success with 5-FU in the treatment of bladder cancer. Weiss et al. (31) noted no response in 6 patients. Field (11) varied the maintenance dosage somewhat and produced a response in only 1 of 9 patients, although this patient's response lasted for more than 1 year. Prout et al. (27) randomized patients with nonresectable bladder cancer to receive either placebo or 5-FU. They concluded that 5-FU produced no clinical response greater than that seen in the placebo group. However, most of the patients did not have measurable metastases, and many had extensive disease that would not be expected to respond to cytotoxic agents. This study diminished the enthusiasm for the use of this drug for bladder cancer, and further trials have not been reported. Nevertheless, many oncologists who have witnessed significant prolonged objective response are unwilling to abandon its use.

Jacobs et al. (17) advocated intermittent weekly i.v. 5-FU therapy in order to decrease toxicity. We have treated 6 patients with weekly i.v. injection of 500 mg of 5-FU, alone or in combination with cyclophosphamide. Toxicity was minimal, but no responses were observed.

5-FU has also been used as an adjuvant to radiation therapy. Kaufman et al. (19) reported improved long-term survival by a combination of i.v. 5-FU and pelvic irradiation prior to surgery. Edland et al. (9) conducted a prospective randomized study of 36 patients with advanced bladder cancer. Eighteen received external supervoltage radiation therapy alone, and 18 received radiation therapy combined with i.v. 5-FU. Combined therapy had no advantage over radiation therapy alone. The drug has also been administered i.a. (see below) and currently is undergoing evaluation as a topical intravesical agent.

The true efficacy of 5-FU in the treatment of bladder cancer is readily accessible in standard texts.

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3 The abbreviations used are: 5-FU, 5-fluorouracil; i.a., intraarterially.
cancer has not been completely defined. Most oncologists feel that the agent has some demonstrated cytotoxic effect in spite of the above-mentioned negative reports, but the published experience does not appear to justify its extensive use as a single agent for the treatment of bladder cancer. It may have a role in combination with other chemotherapeutic agents.

Adriamycin

Doxorubicin (Adriamycin; Adria Laboratories, Wilmington, Del.) is a new antitumor antibiotic similar in its mechanism of action to actinomycin. The drug has shown cytotoxic activity over a wide range of solid tumors. Dose-related cardiotoxicity has limited its long-term use. More experience with this drug in the treatment of metastatic bladder cancer has been accumulated than with any other. The range of reported objective responses in a collected series of 235 patients varied from 0 to 37% with an average of 23% (Table 1). Unlike earlier chemotherapeutic agents such as 5-FU, the criteria for response to doxorubicin have been more carefully stated and the results are therefore more meaningful.

The early studies by Bonadonna et al. (4) and by Middleman et al. (20), each reporting approximately a 35% objective response, stimulated extensive use of this drug in the treatment of bladder cancer. More recent reports, however, have been less optimistic (14). Slavik* summarized the results in 77 patients treated in cooperative studies and reported objective response in 21% of patients with metastatic bladder cancer. Weinstein and Schmidt (30) noted 1 objective response in 19 patients treated. Yagoda et al. (34) treated 42 patients with doxorubicin and found a complete or partial response in only 14%. Merrin et al. (19) observed 1 objective response in 10 patients. The same authors showed increased efficacy when cyclophosphamide was combined with doxorubicin, although the response was similar to that achieved with cyclophosphamide alone. However, Yagoda was unable to increase the response to doxorubicin by addition of i.v. cyclophosphamide (A. Yagoda, personal communication, November 1976).

Prospective randomized studies are currently comparing doxorubicin to other agents. At UCLA, patients are randomly assigned to receive either doxorubicin or intermittent high-dose cyclophosphamide (1.1 g/sq m every 3 weeks). Thus far 3 of 5 evaluable patients have had transient objective response to doxorubicin. The true role of doxorubicin in the treatment of bladder cancer awaits further clarification in these and other randomized studies.

Cyclophosphamide

The alkylating agent cyclophosphamide is one of the most effective cytotoxic drugs in the treatment of solid tumors, but few studies of this agent in the treatment of bladder cancer have been recorded. Fox (12) reported objective response in 2 of 8 patients. Anecdotals reports of 1 or 2 patients treated in other series have failed to show a response to cyclophosphamide or other alkylating agents. However, the dosage and route of administration of the drug vary greatly and may influence response of solid tumors. Jacobs (16) suggested that intermittent high-dose i.v. cyclophosphamide was better tolerated and more effective against solid tumors than was the standard constant infusion or p.o. administration. Experimental data in a murine bladder tumor support this view (7), and we instituted a nonrandomized study in patients with metastatic transitional cell carcinoma of the bladder. Patients received cyclophosphamide, 1.2 g/sq m every 3 weeks. Objective response was defined as a 50% or greater decrease in size of metastases with appearance of no new lesions. Ten patients were evaluable, 4 of whom had an objective response. Similar results were reported by Merrin et al. (19) who found a 53% objective response rate in patients treated with 1 g/sq m every 3 weeks. As noted above, several studies are now in progress that compare intermittent high-dose cyclophosphamide with other agents for the treatment of bladder cancer. The initial results suggest a role for cyclophosphamide. The treatment is well tolerated and can be administered in the outpatient setting. Patients appear to develop an intolerance to the drug, and toxicity often precludes treatment after 6 or 8 months. Combination of cyclophosphamide with other agents may offer a more tolerable treatment program of longer duration.

Methotrexate

Methotrexate is the most important drug of the folic acid antagonists and has been an effective agent either alone or in combination for the treatment of solid tumors, including choriocarcinoma. The drug has usually been administered by intermittent i.v. infusion, although the dosages have varied. The overall objective response rate of the collected series of 88 patients was 24% (Table 1). Objective response in the 3 series noted in Table 1 was usually interpreted as being either complete regression of tumor or unequivocal decrease in size of measurable tumor, although the degree of response was usually not specified. Hall et al. (14), in 1974, treated 42 patients with various stages of untreated tumor, local recurrence following radiation and surgery, or distant metastases. Seventeen patients with distant metastases were treated; 2 of these had complete disappearance of tumor and 4 had partial response. Altman et al. (1) noted complete regression of tumor in 1 of 11 cases and de-

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### Table 1

**Response of advanced bladder cancer to systemic chemotherapy**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients*</th>
<th>Av. (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>88</td>
<td>24</td>
<td>17-36</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>235</td>
<td>23</td>
<td>0-37</td>
</tr>
<tr>
<td>5-FU</td>
<td>56</td>
<td>39</td>
<td>0-75</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>41</td>
<td>41</td>
<td>0-53</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>50</td>
<td>20</td>
<td>16-33</td>
</tr>
<tr>
<td>cis-Dichlorodiammine-platinum(II)</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

* See text for references.
Chemotherapy i.a.

Direct infusion of cytotoxic agents through the arterial blood supply of involved organs has been attempted for many solid tumors. Nevin et al. (22) treated advanced bladder cancer by continuous long-term infusion of 5-FU through the hypogastric arteries. This was followed by megavoltage radiation and subsequently by outpatient arterial infusion. Six of 10 patients experienced marked reduction in tumor size with complete destruction of tumor in 4 patients. Reduction in tumor size by continuous i.a. infusion of methotrexate was also observed by Sullivan (28) and Burn (6), reporting 3 of 3 and 2 of 6 responses, respectively. Mitomycin C was infused through the hypogastric artery by Ogata et al. (23). Their patients did not all have advanced disease, but 3 of 5 patients with advanced pelvic tumor had marked decrease in tumor size.

Mitomycin C

Mitomycin C is an antitumor antibiotic with a mode of action somewhat similar to that of alkylating agents. The drug has shown some effectiveness in the treatment of bladder cancer. Early et al. (8) reported objective response in 6 of 19 evaluable patients, but severe myelosuppression was reported in some instances. Pavone-Macaluso (25) reported 4 significant objective responses in 23 patients. He also emphasized, as have other authors, that a significant number of patients with no demonstrable decrease in tumor burden had a subjective response to the drug. Omura et al. (24) reported partial regression of 2 of 6 patients with metastatic transitional cell carcinoma. Numerous other authors have reported an occasional response of bladder cancer to mitomycin C, but the response rate in the 3 large series mentioned before was 16 to 33%. The average overall objective response rate of 20%, along with the potential severe toxicity, argues against widespread use of this drug as a single agent for the treatment of disseminated transitional cell carcinoma.

Other Single Agents

Surprisingly little is known about the response of transitional cell carcinoma to most chemotherapeutic agents now in use. Vincristine, at various dosage levels, produced objective response in 6 of 20 patients with metastatic bladder cancer (15). Epipodophyllotoxin (VM-26), in the report by the European Organization for Research (10), was found to increase in size of metastases in 3 others. Burfield (5) reported temporary objective response in 6 of 35 patients with advanced bladder cancer treated by i.v. methotrexate. Methotrexate i.a. has occasionally produced regression of tumor, but method of treatment, dosage, and duration of treatment vary considerably.

In view of the promising results in the few reported series, it is surprising that methotrexate has not been more widely used in the treatment of bladder cancer. Recently, the drug has been given in intermittent high doses i.v. followed by detoxification with citrovorum factor, with encouraging results, although this approach has not been explored in the treatment of bladder cancer.

Future Research

The ideal application of cytotoxic drugs is in the adjuvant treatment of cancer following potentially curative surgery or irradiation, when tumor burden is minimal. Use of adjuvant therapy imposes considerable cost and toxicity to patients, a significant but unrecognized number of whom would be cured without the adjuvant therapy. It is imperative, therefore, that the requisites for adjuvant drug therapy be carefully considered. Patients must have a high risk of recurrence or metastasis in order to justify subjecting the entire population to the potential toxicity of drug treatment. Invasive bladder cancer fulfills this criterion, since survival of patients with invasive bladder cancer following surgery and radiation is approximately 30% at 5 years. The agent must have been demonstrated to have cytotoxic effect against the tumor. As noted above, the information regarding single-agent therapy for bladder cancer is sparse, except for several agents (Table 1). The average objective response rate to several of these drugs might warrant their present use as adjuvants, but the broad range of reported objective response makes the results difficult to interpret. Furthermore, these studies do not represent randomized trials, and the agents produce considerable toxicity. Further careful definition of proven objective response rates must be forthcoming before selection of adjuvant drugs can be considered.

Combination chemotherapy has proven to be an effective method to treat solid tumors. For combination therapy to be acceptable, drugs with varying toxicities must be used in order not to compound toxic effects. Furthermore, each agent must have been proven to be effective when used alone. Drugs with varying modes of action should be selected. Few studies using combined chemotherapy for bladder cancer have been reported, and until effective single agents are identified the combined toxicity of multiple agents is difficult to justify.

The immediate future investigation of the chemotherapy of bladder cancer must therefore be directed toward identification of effective single agents through randomized trials with both established and new drugs.

References

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