Future Implications of Phase 2 Chemotherapy Trials in Ninety-five Patients with Measurable Advanced Bladder Cancer

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Summary

The efficacy of five chemotherapeutic agents was evaluated at Memorial Sloan-Kettering Cancer Center in 95 patients with measurable, advanced bladder cancer. Patient selection for these Phase 2 disease-oriented trials was relatively strict and included only patients who had measurable parameters, namely, metastases to lung, liver, skin, s.c. areas, and lymph nodes. For Protocol 1 Adriamycin was used in two schedules, intermittent and bolus, and produced complete and partial remissions in 16% (5 of 37) of adequately treated patients. The combination of Adriamycin and cyclophosphamide, administered every 3 weeks, was not synergistic and yielded responses in only 17% (3 of 18). Diaminedichloroplatinum(Ill) (Protocol 3) at a dose of 1.6 mg/kg every 3 to 4 weeks was tried because of its activity in the N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide tumor model and produced an overall 35% (8 of 23) response rate and remissions in 50% of previously untreated patients. The most recent protocol (4) was a combination of diaminedichloroplatinum(Ill) and cyclophosphamide and gave complete and partial remissions in 61% (11 of 18) of patients. Preliminary trials with cyclophosphamide used alone, bleomycin infusion, and methotrexate have given 17% (1 of 6), 0% (0 of 5), and 40% (2 of 5) remissions, respectively.

A review of the literature combined with these studies at Memorial Sloan-Kettering Cancer Center revealed diaminedichloroplatinum(Ill) alone or in combination with cyclophosphamide to be the most active agent in the treatment of advanced bladder cancer. The difficulties in evaluating responses in this tumor and possible drug combinations for future trials are discussed.

Intraabdominal metastases, impedes accurate objective evaluation. Phase 2 studies, particularly disease-oriented trials, demand a clear end point of response. Investigators generally consider “indicator” lesions in lung, liver, lymph nodes, skin, and s.c. areas to be readily measurable objective parameters, which can be accurately and repeatedly followed. While metastases from bladder cancer to these sites are uncommon, they are not rare. Fetter et al. (4) in 1959 noted metastases in lung (16%), liver (15%), and skin and lymph nodes (28%) in a review of 1033 autopsies of patients with bladder cancer. Recent studies in patients with bladder cancer who relapse after therapy with preoperative irradiation and radical cystectomy show a decrease in local recurrence but an increase in distant metastases (18). As local treatment improves and survival lengthens, a higher incidence of measurable distant lesions can be expected.

During the past 2 years, 4 disease-oriented Phase 2 trials in bladder cancer were completed at MSKCC, specifically entering patients with measurable parameters. Patients were accepted for these protocols if metastatic lesions were present in lung, liver, lymph nodes, and skin or s.c. areas. The only other metastatic site accepted as an objective parameter was retroperitoneal lymph node involvement, which was biopsy proven at recent laparotomy and visible on lymphangiogram. Patients accepted for protocol studies with metastases in other sites had these relatively nonmeasurable lesions evaluated also. Patients without indicator lesions were placed on other chemotherapeutic regimens for nonmeasurable disease. Results of these latter trials are not included in this paper.

Materials and Methods

Each patient had an initial history and complete physical examination, and all accessible lesions were measured in 2 or more diameters. Pelvic and intraabdominal lesions were measured by 2 physicians at MSKCC: 1 from the Solid Tumor Service, Department of Medicine; and 1 from the Urology Service, Department of Surgery. All pathological material, which included urine and sputum cytologies and biopsies from bladder, liver, lungs, lymph nodes, and skin, was reviewed by our Department of Pathology. Laboratory tests included a complete blood and platelet count, blood urea nitrogen, serum creatinine, glucose, calcium, phosphorus.

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2 The abbreviations used are: MSKCC, Memorial Sloan-Kettering Cancer Center; CR, complete remission; PR, partial remission; MR, minor remission; DDP, diaminedichloroplatinum(Ill).
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phorus, total protein, albumin, uric acid, prothrombin time, electrolytes, bilirubin, alkaline phosphatase, lactic dehydrogenase, glutamic-oxaloacetic transaminase, 5'-nucleotidase, and carcinoembryonic antigen. Roentgenographic studies included bone surveys; standard posteroanterior, lateral, and stereoscopic chest X-rays; i.v. pyelograms or loopograms; and lymphangiograms in nonresectable patients found at laparotomy to have biopsy-proven lymph node involvement. The majority of patients also had repeated urine and sputum cytologies and liver and bone scans. Depending on the protocol used, some patients were followed with 24-hr creatinine clearances, audiograms, electrocardiograms, and prejection period/left ventricular ejection time ratios. During the past 10 months, patients who have, in addition to indicator lesions, pelvic or intraabdominal masses had these nonmeasurable sites evaluated by computerized transaxial tomography. All roentgenographic studies were evaluated independently by 1 member of the Department of Diagnostic Radiology. Appropriate measurements and diagnostic tests were performed prior to the administration of each dose or at 3- to 6-week intervals.

Response Criteria

When comparing the efficacy of antineoplastic chemotherapeutic drugs, it is important to know what response criteria are employed. Major differences in remission rates between clinical studies may be related to definitions used for response. At MSKCC use of the term “complete remission” (CR) requires disappearance of all objective lesions and a mandatory systematic restaging by all evaluable diagnostic procedures for confirmation (Table 1). APR denotes 50% or greater reduction in the product of 2 diameters, except for pelvic or abdominal masses, which require a 75% decrease. Patients achieving PR status for less than 1 month or who show a mixed response, with some lesions either progressing or remaining stable while others are regressing, are listed as nonresponders (progression). MR denotes a 25 to 50% tumor decrease; stabilization is defined as either a 25% decrease or not greater than a 25% increase in lesions for at least 3 months. These latter categories, MR and stabilization, are recorded but never included in the overall objective response rates. The duration of response is measured from the time a CR, PR, or MR is achieved, while stabilization is measured from the start of chemotherapy. An adequate trial is defined as 2 doses with or without hematological depression or 1 dose with active progression of disease and 1-month survival.

Leukopenia is defined as a WBC of less than 4,500 cells/cu m and thrombocytopenia as a platelet count of less than 175,000 cells/cu m. Overall toxicity is described as 1+ (mild), 2+ (moderate), 3+ (severe, life-threatening), and 4+ (drug-related death). The Karnofsky performance scale is used to evaluate subjective changes (8). All other subjective or symptomatic toxicities are recorded.

Protocols

For Protocol 1, Adriamycin was used as a single agent (22). The drug was administered i.v. as a single bolus either every 3 weeks at doses of 45, 60, or 75 mg/sq m or intermitently at doses of 8 or 15 mg/sq m 5 to 6 times within 10 days. For Protocol 2, combination chemotherapy [Adriamycin and cyclophosphamide (21)] was used. The initial dose was Adriamycin (45 or 60 mg/sq m) and cyclophosphamide (450 or 600 mg/sq m) every 3 weeks. Depending upon the degree of myelosuppression, subsequent doses were readjusted upward to Adriamycin/cyclophosphamide, 60/450, 60/600, 75/700, or downward to 35/350 mg/sq m.

Protocol 3 was DDP administered i.v. every 3 to 4 weeks at doses of 1.25 or 1.6 mg/kg (20). The most recent protocol (Protocol 4) was a combination of DDP (1.6 mg/kg) and cyclophosphamide (250, 500, 750, or 1000 mg/sq m) administered i.v. every 3 to 4 weeks. Patients who had extensive prior irradiation started at 250 or 500 mg/sq m, while previously untreated patients received higher doses. All patients entering Protocols 3 and 4 needed a creatinine clearance of 60 to 65 ml/min, blood urea nitrogen of 25 mg/100 ml (normal, 1.0 mg/100 ml), serum creatinine of 1.5 mg/100 ml (normal, 1.0 mg/100 ml), and no significant hearing deficit. Before DDP administration 250 to 750 ml of 5% dextrose in water was given in 1 hr and continued for 1 to 2 hr thereafter.

Patients showing progression of disease on these protocols are started on other agents, such as methotrexate, cyclophosphamide, or bleomycin. Previous studies in other solid tumors indicate that most chemotherapeutic drugs used as secondary rather than initial therapy induce fewer remissions. However, when a drug produces a significant number of remissions in previously treated cases, it is subsequently incorporated into treatment protocols for previously untreated patients. The schedule for methotrexate is 250 mg/sq m i.v. infused over 4 hr, followed 24 hr later by citrovorum rescue, 15 mg p.o. every 6 hr for 12 doses. Hydration to produce an hourly urine output of at least 100 ml is started 12 hr before methotrexate and continued for 12 to 24 hr thereafter. For 24 hr before and after drug administration, p.o. and i.v. sodium bicarbonate is given to induce alkalization of the urine to pH 7.0. Any rise in serum creatinine above 1.8 mg/100 ml is treated vigorously with higher doses of citrovorum factor. Two weeks later, maintenance therapy is begun with i.v. methotrexate (0.5 to 1.5 mg/kg weekly).

The schedule for bleomycin is 0.25 to 0.5 mg/kg daily by constant infusion for 7 to 9 days or until mucositis occurs.

### Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>100% decrease of all lesions</td>
</tr>
<tr>
<td>PR</td>
<td>50% decrease in products of 2 diameters</td>
</tr>
<tr>
<td></td>
<td>75% decrease in products of pelvic or abdominal masses</td>
</tr>
<tr>
<td>MR</td>
<td>25% decrease in products of 2 diameters</td>
</tr>
<tr>
<td></td>
<td>50% decrease in products of 2 diameters, lasting only 1 month</td>
</tr>
<tr>
<td></td>
<td>50% decrease in products of pelvic or abdominal masses</td>
</tr>
<tr>
<td>Stabilization</td>
<td>25% decrease in products of 2 diameters (minimum, 4 months)</td>
</tr>
<tr>
<td>Progression</td>
<td>25% increase or mixed response</td>
</tr>
</tbody>
</table>
Chemotherapy Trials in Bladder Cancer

Cyclophosphamide used singly is administered at 25 to 40 mg/kg i.v. every 3 weeks or 3 mg/kg/day p.o.

Patient Characteristics

The characteristics of the patient population entered into Protocols 1 to 4 are outlined in Tables 2 and 3. Over three-fourths of the patients were males, and over one-half presented with poorly differentiated or anaplastic (Grades III and IV) epidermoid (transitional cell) carcinoma. The primary tumor originated from the ureter in 3 patients and from the urethra in 2 patients. Four patients had adenocarcinoma, and 2 of these were of urachal origin. Approximately 26% of the patients with epidermoid carcinoma showed papillary features: Almost all patients had a prior laparotomy, and the incidence of urinary diversion rose from 57% in Protocol 1 to 80% in Protocol 4. Almost all patients had received prior irradiation, generally 2000 rads to the true pelvis in 5 days preoperatively.

There are differences in patient characteristics in these 4 clinical trials, indicating a trend to enter patients earlier onto chemotherapeutic protocols. There has been: (a) a slight increase in performance status; (b) a decrease in the number of symptomatic patients; (c) a decrease in the extent of prior irradiation, with only 11% of the cases in Protocol 4 having radiation therapy administered to areas other than the pelvis; and, most importantly, (d) a lower incidence of prior chemotherapy. The latter 2 characteristics could result in significant variations in response rates found in the 4 protocols. Other parameters in this patient population were examined, such as the "natural" history of bladder cancer, but were not found useful in delineating responders. The types of lesions evaluated (Table 3) illustrate that many of the criteria for admission to these protocols were met.

Results

There have been 128 disease-oriented trials in 95 patients during the past 2 years at MSKCC. These include 45 cases entered into Protocol 1, 24 into Protocol 2, 20 into Protocol 3, 20 into Protocol 4, 5 treated with methotrexate, 13 treated with cyclophosphamide, and 5 treated with bleomycin.

Adriamycin (22) used singly (Protocol 1) yielded clinically useful remissions (CR, PR) in only 16%, but in patients who had no prior chemotherapy a response rate of 27% was found. Objective regression of disease, mostly in skin, lung, liver, and lymph nodes, was rapid, occurring within 3 to 4 weeks and lasting 1 to 5 months. No responses were found after 3 weeks. Four patients achieved MR status, generally lasting 6 weeks, and 4 additional patients showed stabilization, lasting 4 to 9 months. Initial clinical drug-oriented trials with Adriamycin used multiple schedules and doses (2, 22). The intermittent schedule was eventually abandoned when pharmacological data suggested increased efficacy when Adriamycin was administered as a single bolus every 3 weeks. Only 1 of 15 (7%) patients treated with the intermittent schedule responded, compared to 4 of 20 (20%) treated with bolus administration. Previous studies with
Adriamycin suggested that more responses occurred with higher doses, 75 mg/sq m (22). While there was 1 patient in Protocol 1 who progressed on 45 mg/sq m and subsequently responded to 75 mg/sq m, the only patient achieving a CR received 45 mg/sq m. This patient expired 8 months later from acute congestive heart failure after reaching a total dose of 430 mg/sq m. Postmortem examination found no evidence of residual disease but raised the question of possible drug-related cardiomyopathy.

The intermittent schedules of Adriamycin produced mucositis and diarrhea but less nausea and vomiting than bolus administration. Alopecia, anorexia, and nausea were dose dependent and almost universal at higher doses. Severe toxicity, 3+ or 4+, occurred in one-third of the patients (22). Most patients were over 65 years of age and had advanced disease, extensive prior therapy with poor hematopoietic reserve, and generally a history of recurrent urinary tract infection with compromised renal function. These factors, coupled with moderate leukopenia, rapidly led to sepsis. Electrocardiographic changes were noted in 12%, but the majority of patients did not receive a total dose above 300 mg/sq m. One patient who achieved prolonged stabilization of her disease received a total dose of 950 mg/sq m. Adriamycin was stopped because of minor ST- and T-wave changes, which eventually reverted to normal. Other side effects included increased skin pigmentation and a reddish discoloration of the urine in 9%, occurring 12 to 24 hr after Adriamycin administration. This was more evident in patients with an ileal conduit and frequently was thought by them to be hematuria. In this 1st study 16% of the patients did not receive an adequate trial. Since the number of patients with urothelial cancer with measurable parameters is few, any patient with indicator lesions is admitted for protocol study, regardless of performance status. Six of 7 patients who did not achieve an adequate trial had a median performance status of 30 and died within 12 days after the 1st dose.

The combination of cyclophosphamide and Adriamycin (Protocol 2) was disappointing (21). Only 3 of 18 (17%) patients achieved PR status. Toxicity was similar to that with Protocol 1 but more severe. In 41 evaluable cases life-threatening toxicity required hospitalization in 39% because of severe myelosuppression with leukopenia of 1800 cells/cu m (median). In addition to Adriamycin toxicity, cyclophosphamide produced hemorrhagic cystitis. Nine patients never had cystectomy, and 2 of these had no prior bladder irradiation. Two of the remaining 7 patients (22%) experienced hematuria, which, after cystoscopic examination, was attributed to cyclophosphamide toxicity.

Protocol 3 used DDP singly (20) because of the findings by Soloway et al. (15) of antitumor activity in the N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide-induced bladder cancer model in mice. Clinically, DDP produced significant remissions (PR) in 35% of patients with advanced urinary tract cancer (20). In patients who had had no previous chemotherapy, a response rate of 50% was achieved (Table 4). The median duration was short (3 months). Responses were rapid, generally occurring within 7 to 21 days, and were found in irradiated and nonirradiated areas. Maximal responses were usually noted within 4 weeks, and the degree of response was not increased with subsequent doses. The dose-limiting toxicity of DDP has been decreased auditory acuity and impairment of renal function (7). Although no major deterioration of renal function occurred in the DDP study, some clinical abnormalities persisted for 4 months. Three of 4 patients showed pathological renal lesions at autopsy (20). Mild leukopenia (range, 1.9 to 4.2 × 10^3 cells/cu m) was found in 17% and thrombocytopenia (100 to 173 × 10^3 cells/cu m) was found in 23% 2 to 4 weeks after each dose. Six patients (26%) showed a greater than 2-g/100 ml decrease in hemoglobin. Six patients noted minor hearing deficits, and 3 patients had audiograms showing 10- to 25-db decreases at 8000 and 6000 Hz. However, the limiting toxicity was anorexia, nausea, and vomiting, which were not dose dependent. After the 2nd or 3rd dose, patients frequently vomited prior to DDP administration, and standard antiemetic therapy was not effective. Four patients (16%) needed hospitalization for persistent vomiting and resultant dehydration. The majority of patients who responded to DDP refused additional doses because of the severity of vomiting and persistent nausea. Most responses were therefore unmaintained.

Although DDP appears to function in part as an alkylating agent, synergism has been found when it is used together with another alkylating agent, cyclophosphamide, in experimental tumor models (16). In the current protocol, 4, 18 of

### Table 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Symptomatic (%)</th>
<th>Performance status (median)</th>
<th>Lung</th>
<th>Nodes and skin</th>
<th>Liver</th>
<th>Lymphangiogram</th>
<th>By physical examination alone</th>
<th>With computed transaxial tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>76</td>
<td>60</td>
<td>58</td>
<td>53</td>
<td>30</td>
<td>11</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Cyclophosphamide and Adriamycin</td>
<td>45</td>
<td>75</td>
<td>70</td>
<td>30</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>cis-Platinum</td>
<td>70</td>
<td>70</td>
<td>46</td>
<td>38</td>
<td>33</td>
<td>54</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide and cis-platinum</td>
<td>50</td>
<td>70</td>
<td>40</td>
<td>39</td>
<td>22</td>
<td>30</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>
chemotherapy trials in bladder cancer

Table 4: Objective responses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. entered</th>
<th>No. adequate</th>
<th>CR</th>
<th>PR</th>
<th>CR + PR (%)</th>
<th>Prior chemotherapy</th>
<th>No chemotherapy</th>
<th>Median duration of response (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>45</td>
<td>37</td>
<td>1</td>
<td>5</td>
<td>16</td>
<td>9</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>3</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>cis-Platinum</td>
<td>24</td>
<td>23</td>
<td>0</td>
<td>8</td>
<td>35</td>
<td>0</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Cyclophosphamide and cis-platinum</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>11</td>
<td>61</td>
<td>0</td>
<td>65</td>
<td>2+</td>
</tr>
</tbody>
</table>

20 patients thus far admitted have received an adequate trial. PR status was achieved in 61% with responses generally occurring within 4 to 14 days (Table 4). All responses have been PR’s, and continued administration of cyclophosphamide and DDP has not induced CR status. The majority of patients responding to DDP, as in Protocol 3, have ultimately refused additional doses and therefore have had unmaintained remissions. Protocol 4 produced toxicity similar to that described in Protocol 3, but the combination of cyclophosphamide and DDP appears to produce more intense vomiting and an increased incidence of patient withdrawal from study. Leukopenia and thrombocytopenia were more frequent because of cyclophosphamide.

There have been 2 excellent responses (PR) in 5 patients treated with methotrexate. These responses have lasted 4+ and 6+ months and could almost be termed complete, with clearing of all adenopathy and skin nodules. Nine patients received cyclophosphamide, and 6 had an adequate trial. One patient had a PR for 7 months, and another patient achieved MR status. Five patients received bleomycin, and no responses were found in 3 adequately treated cases.

Discussion

Adriamycin has been one of the most thoroughly studied drugs against this tumor. Although earlier trials found remissions in 40 (2) to 55% (5), the overall response rate is 24% in 175 patients (21, 22). In the present study 27% of previously untreated patients obtained PR. The overall lower remission rate, 16%, found in the MSKCC study may be explained by initial lower performance status, extensive prior irradiation, and lower chemotherapy dose schedules. As previously mentioned, the only CR occurred at a dose of 45 mg/sq m. Although the duration of remissions has been short, averaging 3 months, some patients showed responses for 28 (22) to 52+ weeks (10).

A major toxicity of Adriamycin is cardiomyopathy, noted more often at cumulative doses above 550 mg/sq m although lower doses can also produce this effect (5). Since the average age of patients with bladder cancer is 69, the risk of cardiac abnormalities occurring in this patient population is probably high. Hopefully, other Adriamycin derivatives or ancillary agents (14) may be found to ameliorate this hazard.

The addition of cyclophosphamide to Adriamycin did not appear clinically to be synergistic. Two other studies (9, 13) using this combination included 4 patients with urothelial tumors and found no responses. In contrast, Merrin et al. (12) reported responses to this combination in 50% of patients with Stage A to D (Jewett-Marshall) bladder cancer. In a similar patient population, they obtained 52% responses in 21 patients treated with cyclophosphamide alone and concluded that the addition of Adriamycin to cyclophosphamide was not useful in increasing remission rates (12). Previously published Phase 1 and 2 and disease-oriented trials with systemically administered cyclophosphamide were evaluated, and only 2 PR’s were found in 27 adequately treated patients with bladder cancer (21). Twelve patients did achieve MR status, but the criteria of evaluability, categories of response, and duration of remissions were not stated. Combined cyclophosphamide data from the literature (21), Merrin et al. (12), and MSKCC (21) indicate an overall response of 26% in 50 patients with bladder cancer.

At present DDP is one of the more active agents in the treatment of bladder cancer (20). Although synergism is found with DDP and cyclophosphamide in the N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide-induced bladder cancer model in mice (16) and is suggested by Protocol 4, only a prospective randomized trial with a larger number of cases could determine the relative usefulness of DDP alone compared to DDP and cyclophosphamide. The duration of response with DDP alone (Protocol 3) or in combination with cyclophosphamide (Protocol 4) is short (3 months), although some remissions persist for 6 to 12+ months without maintenance therapy (17, 20). Soloway (16) found a better response in mice with higher doses of DDP. Recent studies at MSKCC with a variety of solid tumors indicate a much higher remission rate with DDP (3 mg/kg or 120 mg/sq m) with mannitol infusion (7). A 6-hr infusion of DDP used by Merrin (11) in a small series of patients with bladder cancer obtained 60% responses. Obviously, other DDP dosages and schedules need to be investigated. The major toxicities of DDP are nausea, vomiting, anorexia, and renal and auditory abnormalities. Since the majority of patients are over 60 years old, many already show compromised renal function and evidence of presbycusis. These 2 factors, coupled with patients’ reluctance to continue therapy in spite of objective responses, suggest a practical limitation to DDP maintenance. In addition, clinical studies at MSKCC with DDP in patients with testicular, head and neck, and bladder
cancers indicate that the maximal effect is rapid and almost always obtained with the 1st dose, suggesting that DDP may be an agent especially useful for an induction phase of therapy.

Two responses to methotrexate were in patients who had received prior radiotherapy and chemotherapy. Both responses were dramatic and appeared to be clinically CR’s. Altman et al. (1) describe 4 patients with pelvis and rectus muscle involvement who responded to methotrexate. Hall et al. (6) found 3 CR’s and 2 PR’s in a series of 11 patients treated with methotrexate. Previous studies with cyclophosphamide, methotrexate, 5-fluorouracil, and mitomycin C (3) should be expanded, with standard doses and schedules, to determine their precise efficacy. Future clinical trials should probably include DDP, cyclophosphamide, Adriamycin, and methotrexate in combination or sequential regimens. Most studies, including Protocols 1 to 4, show only PR’s, and the aim of newer schedules should be the attainment of CR status.

The poor prognosis in patients with high-grade Stage B1, B2, or C bladder cancer and with resected Stage D1 lesions suggests the need for adjunct treatment with chemotherapy or immunotherapy. With the 25 to 50% remission rate presently attainable with Adriamycin or DDP alone or in combination with cyclophosphamide, it is not unreasonable to initiate, in a controlled prospective randomized fashion, adjunct chemotherapy trials in high-risk patients with bladder cancer. Another area for a chemotherapeutic approach would be the use of such agents preoperatively or during operative procedures. DDP, Adriamycin, or methotrexate systemically or intravesically may be useful in preventing intravesical “dissemination.”

There is progress in the chemotherapeutic approach to the treatment of urothelial tumors, but present data suggest the continuing need to define the efficacy of single-agent chemotherapy in advanced measurable bladder cancer.

References

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