Invasive bladder cancer is a chemotherapy-sensitive neoplasm. Historically, the development of cisplatin (Platinol)-based chemotherapy regimens has represented an important advance for patients with metastatic bladder cancer.

Introduction

An estimated 54,300 new cases of bladder carcinoma will be diagnosed in the United States in 2001, with 12,400 deaths attributable to this cancer. The majority of these tumors will be superficial, confined to the mucosa and lamina propria of the bladder. Although these superficial bladder cancers frequently recur and may be multifocal, survival is excellent. To decrease rates of recurrence and progression, these tumors are best approached with cystoscopic surgery and, in select cases, intravesical drug therapy with, for example, bacillus Calmette-Guérin or chemotherapeutic agents.

When a tumor invades the muscular wall of the bladder, the prognosis markedly worsens because of the increased risk of metastatic progression. For this reason, there is a clear need for effective systemic chemotherapy for bladder cancer. Systemic chemotherapy may be used for the palliation of metastatic disease, and in a select minority of these patients, to achieve long-term survival. In the earlier-disease, perioperative setting, chemotherapy may be considered to eradicate microscopic metastases and increase surgical cure rates. This article will discuss recent developments in chemotherapy for invasive bladder cancer.

Chemotherapy for Advanced Bladder Cancer

Transitional cell carcinoma of the urothelium is a chemotherapy-sensitive tumor. Significant response rates have been demonstrated with the single agents cisplatin (Platinol), methotrexate, cyclophosphamide (Cytoxan, Neosar), doxorubicin, and vinblastine, among others. Cisplatin-based combination regimens, such as M-VAC (methotrexate, vinblastine, doxorubicin [Adriamycin], cisplatin) and CMV (cisplatin, methotrexate, vinblastine), have been studied extensively.

M-VAC-Based Treatment

Investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) developed M-VAC in the 1980s, and a phase II investigation suggested response rates as high as 72%, with a 36% complete response rate. Randomized trials have demonstrated that M-VAC is superior to both single-agent cisplatin and CISCA (cisplatin, cyclophosphamide, Adriamycin).[3,4]

The Intergroup phase III trial in 246 evaluable, previously untreated patients with advanced urothelial carcinoma who had been randomized to single-agent cisplatin vs M-VAC revealed the combination to have a higher response rate (39% vs 12%; \( P = .0001 \)) and improved overall survival (12.5 vs 8.2 months; \( P = .0002 \)).[3] When investigators at the M. D. Anderson Cancer Center randomized patients with advanced disease to M-VAC vs CISCA, M-VAC was shown to be superior with respect to response rate (65% vs 46%; \( P < .05 \)) and overall survival (46 vs 36 weeks; \( P = .000315 \)).[4] Based on these randomized trials, M-VAC has emerged as the standard treatment for patients with metastatic urothelial carcinoma.

The most important limitation of M-VAC is toxicity and poor patient tolerance. In the Intergroup trial, the combination showed substantially more toxicity, including mucositis, myelosuppression, and treatment-related deaths, than single-agent cisplatin. Additionally, some patients with advanced urothelial carcinoma have age- and/or disease-related renal dysfunction that makes cisplatin-based...
Recent Developments in Chemotherapy for Bladder Cancer
Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

regimens problematic. Nevertheless, M-VAC remains an important milestone in the development of chemotherapy for bladder cancer.

In an effort to improve the therapeutic index of M-VAC, studies have been conducted to find ways to improve the tolerability or increase the efficacy of the regimen. The addition of granulocyte colony-stimulating factor (G-CSF [Neupogen]) to M-VAC has been shown to abrogate some of the toxicities, including mucositis and granulocytopenia.[5] Several studies have attempted dose intensification of M-VAC by using hematopoietic growth factors; however, the results have generally been disappointing.[6-8] At the 2000 meeting of the American Society of Clinical Oncology (ASCO), the European Organization for the Research and Treatment of Cancer (EORTC) reported the results of a phase III trial that failed to demonstrate a survival advantage for high-dose-intensity M-VAC and G-CSF, compared to standard M-VAC.[9]

Early phase II trials of M-VAC suggested that this regimen had the potential to cure patients with advanced urothelial cancer. But the effectiveness of M-VAC with respect to long-term survival, and which patients were most likely to derive a long-term benefit, was unknown. A recent study by Bajorin et al from MSKCC addressed these issues. In this series, in which 203 patients with advanced bladder cancer were treated with M-VAC, the presence of visceral (lung, liver, or bone) metastases and a baseline Karnofsky performance status less than 80% predicted independently for a poor outcome. Patients with both of these risk factors had a 5-year survival of 0% (median survival: 9.3 months). However, if patients had neither risk factor, the probability of achieving 5-year survival jumped to 33% (median survival: 33 months).[10]

At 6-year follow-up of the previously described Intergroup trial comparing M-VAC and single-agent cisplatin in patients with advanced urothelial cancer, the chance of long-term, cancer-free survival in patients treated with M-VAC was only 3.7%. Predictors for poor outcome in this study included nontransitional histology, poor performance status, and/or bone/visceral metastasis.[11] Thus, the probability of long-term survival for many patients treated with M-VAC is small. The identified poor prognostic factors are clinically useful in predicting the potential for a long-term benefit from combination chemotherapy regimens such as M-VAC. This information can also be used when evaluating reported trials of new chemotherapy regimens, since patient selection may significantly influence results.

In summary, M-VAC is an active—but toxic—regimen for advanced bladder cancer. Given the small chance for long-term survival for most patients treated with this regimen, efforts to identify new agents and combinations with improved efficacy or tolerability have been ongoing. Newer agents with significant activity include gemcitabine (Gemzar) and paclitaxel (Taxol).

Gemcitabine for Advanced Bladder Cancer

Gemcitabine (2’2’-difluorodeoxycytidine) is a cytosine analog with a structure that is similar to cytarabine. Gemcitabine is approved by the US Food and Drug Administration for the palliative treatment of patients with advanced pancreatic cancer, but it has broad antitumor activity, including activity in bladder cancer.

A review of gemcitabine in bladder cancer was recently published.[12] In phase I studies of gemcitabine, responses were reported in patients with bladder cancer.[13] Based on this activity, phase II studies were initiated in advanced urothelial cancer. Loruso et al treated 31 evaluable patients who had previously received cisplatin with gemcitabine, 1,200 mg/m² administered on days 1, 8, and 15 every 28 days. A response rate of 22.5% was demonstrated (95% confidence interval [CI] = 8%-37%).[14] Stadler et al[15] and Moore et al[16] performed phase II trials in patients with advanced bladder cancer who were previously untreated with chemotherapy. Patients received gemcitabine, 1,200 mg/m², on days 1, 8, and 15 every 28 days. Response rates in these trials were 28% (95% CI = 15%-45%) in the Stadler trial and 24% (95% CI = 12%-41%) in the Moore trial. Median survival was 12.5 and 8 months, respectively. In all these phase II trials, this therapy was well tolerated; toxicity was generally mild and reversible.

Gemcitabine/Cisplatin: Based on the significant single-agent activity and the acceptable toxicity profile of gemcitabine in patients with bladder cancer, combination trials with cisplatin were
performed subsequently. Three phase II trials of the combination of gemcitabine/cisplatin have been reported (Table 1).[17-20]

Von der Masse et al treated 44 patients with gemcitabine, 1,000 mg/m², and cisplatin, 35 mg/m², on days 1, 8, and 15 every 28 days.[17] A response rate of 41% (95% CI = 25%-58%) was reported. Toxicities included grade 3/4 granulocytopenia in 46% and thrombocytopenia in 71% of patients. Moore et al treated 31 patients with gemcitabine, 1,000 mg/m², on days 1, 8, and 15, and cisplatin, 70 mg/m², on day 2 every 28 days.[18] An overall response rate of 57% was demonstrated in this study (95% CI = 37%-76%). Toxicity was principally hematologic with grade 3/4 granulocytopenia reported in 39% and grade 3/4 thrombocytopenia in 55% of patients. Median survival for all patients was 13.2 months. Kaufman et al reported the results of a multi-institutional phase II trial of the combination of gemcitabine/cisplatin.[19] A total of 46 patients were treated in this study. Initial doses were gemcitabine, 1,000 mg/m² on days 1, 8, and 15 every 28 days, with cisplatin, 100 mg/m², on day 2. Due to excessive hematologic toxicity in the first cohort of 11 patients, the cisplatin dose was reduced to 75 mg/m² for the duration of the trial. The objective response rate was 41% with a median survival of 14.3 months. Toxicity included grade 3/4 granulocytopenia in 74% and grade 3/4 thrombocytopenia in 65% of patients.

Gemcitabine/Cisplatin vs M-VAC: Given the promising results noted in the phase II trials of gemcitabine/cisplatin, an industry-sponsored phase III trial comparing combination gemcitabine/cisplatin with the standard M-VAC regimen in patients with previously untreated, advanced bladder cancer has been performed in Europe and the United States.[20] This trial was initiated in 1996 and reached its accrual goal of 405 patients in 1998. Patients with previously untreated, locally advanced disease (T4b, N2, N3) or metastatic transitional cell carcinoma of the urothelium were randomized to received gemcitabine, 1,000 mg/m², on days 1, 8, and 15, and cisplatin 70 mg/m², on day 2 every 28 days vs M-VAC. The primary end point was overall survival, and the study was sufficiently powered to detect a 4-month improvement in survival. Secondary end points included response rate, time to tumor progression, toxicity, quality of life, and resource utilization. The median age of the study population was 63 years, and the arms were well balanced with respect to prognostic risk factors, performance status, and presence of visceral metastases.

The overall survival for the group treated with gemcitabine/cisplatin was 13.8 months vs 14.8 months for those treated with M-VAC (not a statistically significant difference). The response rate (49% for gemcitabine/cisplatin vs 46% for M-VAC) and complete response rates (12% for gemcitabine/cisplatin vs 12% for M-VAC) were also not significantly different. The M-VAC regimen was associated with significantly more grade 3/4 mucositis and granulocytopenic fever and sepsis. Gemcitabine/cisplatin was associated with significantly more grade 3/4 anemia and thrombocytopenia. Quality-of-life measures demonstrated that more patients in the gemcitabine/cisplatin arm fared well with respect to weight, performance status, and fatigue. Use of supportive measures (eg, G-CSF, antibiotics, antifungals, and number of days of hospitalization) was greater with M-VAC. Thus, this trial demonstrates that gemcitabine/cisplatin is associated with similar survival to M-VAC. (The study was not sufficiently powered to demonstrate equivalent survival between the two arms.) In addition, gemcitabine/cisplatin showed a more favorable toxicity profile than M-VAC. This trial establishes gemcitabine/cisplatin as an alternative to M-VAC for the treatment of patients with advanced urothelial carcinoma.

Paclitaxel for Advanced Bladder Cancer

Paclitaxel is a novel antimicrotubule agent that has demonstrated significant activity against human bladder cancer cell lines in preclinical studies.[21] Roth et al reported an initial phase II Eastern Cooperative Oncology Group (ECOG) trial of paclitaxel, 250 mg/m² administered over 24 hours every 3 weeks, with prophylactic G-CSF in patients with previously untreated, advanced transitional cell carcinoma of the urothelium.[22] Of the 26 patients, 11 (42%) achieved an objective response (95% CI = 23%-63%) with 7 patients achieving complete responses. Median survival was 8.4 months. Toxicities included granulocytopenia, anemia, mucositis, and neuropathy. This study demonstrated that paclitaxel is one of the most active single agents in urothelial cancer.

Based on the results of this initial trial, paclitaxel-based combination regimens have been developed, including both doublet and triplet combinations. Most of these regimens employ a 3-hour infusion of
paclitaxel. Paclitaxel has been combined with carboplatin (Paraplatin), cisplatin, gemcitabine, ifosfamide (Ifex), methotrexate, and other agents. Key studies of paclitaxel plus a platinum analog will be reviewed.

**Paclitaxel/Cisplatin:** Paclitaxel/cisplatin-based regimens have demonstrated significant activity in advanced urothelial carcinoma. Dreicer et al reported the results of a phase II ECOG trial of paclitaxel administered at 175 mg/m² over 3 hours, plus cisplatin at 75 mg/m² every 3 weeks, in patients with previously untreated, advanced urothelial cancer. Of the 52 patients, 26 (50%) achieved an objective response (95% CI = 36-64%). Toxicities were principally myelosuppression and neurotoxicity. Median survival was 10.6 months.[23] At the 1999 meeting of ASCO, Burch et al from the Mayo Clinic reported the results of a phase II trial of paclitaxel, 135 mg/m², administered over 3 hours, plus cisplatin, 70 mg/m², administered every 3 weeks. A total of 29 patients were treated in this trial and a response rate of 72% (95% CI = 56%-90%) was reported. Median survival was 13 months.[24]

**Paclitaxel/Ifosfamide/Cisplatin:** Bajorin and colleagues from MSKCC have reported the results of a triplet combination, ITP (ifosfamide, Taxol, Platinol), in patients with advanced urothelial carcinoma. Ifosfamide, 1.5 g/m²/d for 3 days, with paclitaxel, 200 mg/m² over 3 hours on day 1, and cisplatin, 70 mg/m² on day 1, were administered every 28 days (30 patients) or every 21 days (15 patients) with prophylactic G-CSF. Of the 44 patients, 30 achieved objective responses for a response rate of 68% (95% CI = 52%-81%) At a median follow-up of 28 months, the median survival was 20 months. Major toxicities were hematologic, renal, and neuropathic; there were no significant differences in toxicities between the every-28-day and every-21-day regimens.[25]

A follow-up phase I trial by the same investigators evaluated sequential therapy with the doublet AG (Adriamycin, gemcitabine) followed by ITP in patients with urothelial cancer. This study demonstrated the feasibility of administering doxorubicin, 50 mg/m² on day 1, and gemcitabine, 2,000 mg/m² on day 1, with G-CSF support every 2 weeks for six cycles followed by the 21-day ITP regimen for four cycles. Of the 14 patients, 8 achieved an objective response to AG; 9 of the 14 patients demonstrated a major response to the AG-ITP sequence. A phase II investigation of this approach is ongoing.[26]

**Paclitaxel/Cisplatin:** Cisplatin has traditionally been considered the preferred platinum analog in urothelial cancer. However, pooled results of phase II studies, in which 274 patients with advanced urothelial carcinoma were treated with single-agent carboplatin, demonstrated a response rate of 14%.[27] Neither direct randomized combination trials nor a prospective, randomized comparison of single-agent cisplatin vs carboplatin in this disease site have been performed. Given the lack of direct comparative data, one cannot assume that the efficacy of carboplatin is equivalent to cisplatin. Alternatively, no conclusive data exist on the superiority of cisplatin.

The lack of nephrotoxicity and the ability to dose carboplatin based on the glomerular filtration rate utilizing the Calvert formula[28] are potentially important advantages of this agent. This is especially so in the subgroup of patients who may have age- and disease-related alterations in renal function. Preliminary studies have demonstrated that paclitaxel may be used in the setting of renal insufficiency.[29] In an effort to develop an active and tolerable outpatient chemotherapy regimen that can be administered to patients of advanced age with abnormal renal function, paclitaxel/carboplatin trials have been performed in advanced urothelial cancer. Several trials of the paclitaxel/carboplatin regimen have been completed, and are summarized in Table 2.[30-33] These trials have demonstrated response rates ranging from 20.7% to 72%. This broad range of response proportion may relate, in part, to the specific patient characteristics treated within each trial.

At the University of Pennsylvania Cancer Center, we performed the initial phase I/II trial of paclitaxel/carboplatin in patients with advanced urothelial carcinoma.[30] During phase I testing, paclitaxel dose levels included 150 mg/m², 175 mg/m², 200 mg/m², or 225 mg/m² over 3 hours, followed by carboplatin dosed to an area under the concentration-time curve (AUC) of 6 every 3 weeks. A total of 16 patients were treated, and the maximum-tolerated dose of the regimen was not defined. Subsequently, 17 additional patients were enrolled at the phase II dose level of paclitaxel, 225 mg/m², over 3 hours, followed by carboplatin dosed to an AUC of 6. The median age of treated patients was 70 years; the median estimated creatinine clearance was 52 mL/min (range: 24-110). Objective responses were demonstrated at all dose levels. The phase II response rate was 50% (95%
CI = 28%-72%). The median survival for all treated patients was 8.5 months. Significant granulocytopenia was common, but significant thrombocytopenia was not. Sensorimotor neuropathy was the principal nonhematologic toxicity; grade 3 neuropathy developed in 5 patients.

Redman and colleagues at Wayne State University School of Medicine and the University of Michigan subsequently reported a phase II trial of paclitaxel, 200 mg/m² over 3 hours, plus carboplatin dosed to an AUC of 5 every 3 weeks.[31] A total of 36 patients with previously untreated, advanced urothelial carcinoma were treated. The median age of patients was 66 years. A total of 184 cycles of therapy were administered with a median number of six cycles per patient. Of the 35 evaluable patients, 18 demonstrated an objective response, for a response rate of 51.5% (95% CI = 35%-68%). Complete responses were demonstrated in 7 patients. The median survival was 9.5 months with an estimated 1-year survival of 38%. Toxicities included granulocytopenia, myalgias/arthralgias, and neuropathy.

Pycha et al from Vienna reported a phase II trial of paclitaxel, 175 mg/m² over 3 hours, plus carboplatin dosed to an AUC of 5 every 3 weeks. In this trial of 32 patients, a response rate of 72% (including 10 complete responders) was reported. Median survival for all treated patients was greater than 13 months. Principal toxicities were neuropathy and leukopenia.[32]

The cooperative groups have also studied the combination of paclitaxel/carboplatin. The Southwest Oncology Group (SWOG) initiated a phase II trial that included two cohorts: previously untreated patients and patients who received prior cisplatin treatment. Results of the first cohort (ie, previously untreated patients with advanced urothelial cancer) were reported recently.[33] In this trial, 29 patients were treated with paclitaxel, 200 mg/m² over 3 hours, plus carboplatin dosed to an AUC of 5 every 3 weeks. A response rate of 20.7% (95% CI = 8%-40%) was reported. Median progression-free survival was 4 months and the median overall survival was 9 months. Significant toxicities of the regimen included grade 4 granulocytopenia (38%) and grade 3/4 neurologic toxicity (24%).

It is important to learn why the response rate in this SWOG trial was significantly lower than the response rates demonstrated in prior studies. The authors have offered a potential explanation, which is that as opposed to the prior studies, the population of this cooperative group study included over three-quarters of patients with extranodal metastases. As previously discussed, patients with visceral metastatic disease derive less benefit from chemotherapy than patients with nodal or soft-tissue sites of disease. In addition, the authors point out that survival in this cooperative group trial was similar to that demonstrated in other phase II trials; the authors also suggest that survival—rather than response rate—be used to assess the efficacy of chemotherapy regimens for bladder cancer. Finally, although the authors point out the problems of comparing survival across phase II trials, they clarify that the median survival in many of the paclitaxel/carboplatin trials (approximately 9 months) is less than that demonstrated for M-VAC in the cooperative group setting.

Paclitaxel/Carboplatin vs M-VAC: To determine the effectiveness of paclitaxel/carboplatin compared to M-VAC in a prospective fashion, ECOG has initiated a phase III trial that is randomizing previously untreated patients with advanced urothelial cancer to paclitaxel/carboplatin or M-VAC. The primary end point of this trial is survival; the secondary end points include response rate, response duration, toxicity, and quality of life. This trial has an accrual goal of 330 patients.

A potentially important application of the paclitaxel/carboplatin regimen exists in patients with advanced bladder cancer and renal insufficiency. At the 2000 meeting of ASCO, ECOG reported the results of a phase II trial of paclitaxel, 225 mg/m² over 3 hours, followed by carboplatin dosed to an AUC of 6 in patients with advanced urothelial cancer and renal insufficiency (serum creatinine concentration of 1.6-4.0 g/dL).[34] A total of 42 patients were entered into the trial and 40 were treated. The median age of patients was 70; the median serum creatinine was 1.7 g/dL. Results showed three complete and six partial responses for a response rate of 22.5% (95% CI = 10.8%-38.5%). Significant toxicities included grade 4 granulocytopenia in 18 patients and grade 3 neurotoxicity in 14 patients. There were two early deaths that were possibly/probably related to treatment. Median overall survival was 7.1 months. This was the first cooperative group trial of chemotherapy in this specific patient population. It will serve as a reference trial for future trials in this patient population.
Gemcitabine/Taxane Combinations in Advanced Bladder Cancer

Given the activity of the single agents gemcitabine and paclitaxel in the advanced-disease setting, a logical approach would be to develop combination regimens that include these two agents (Table 3).[35-39] A phase II trial of paclitaxel, 200 mg/m² over 1 hour on day 1, and gemcitabine, 1,000 mg/m² on days 1, 8, and 15 every 28 days, was presented at the 2000 ASCO meeting. A total of 50 patients with advanced urothelial cancer were treated. The overall response rate was 57%. No significant difference in response rate was shown between chemotherapy-naïve and previously treated patients, thus suggesting activity of the regimen in patients with prior cisplatin exposure. The major toxicity was myelosuppression with grade 3/4 granulocytopenia in 31% and grade 3/4 thrombocytopenia in 8% of patients. Median survival was 15 months.[35]

Another phase II trial reported at ASCO involved the administration of paclitaxel, 150 mg/m² over 3 hours, followed by gemcitabine, 3,000 mg/m² over 30 minutes, on days 1 and 15 every 28 days. The initial report showed a response rate of 39%. Many patients required dose modification due to hematologic toxicity.[36]

Two trials examining the efficacy of gemcitabine/taxane combinations have been activated by ECOG. Based on the activity of docetaxel (Taxotere) in this disease site,[37] a phase II trial of docetaxel, 40 mg/m², plus gemcitabine, 1,000 mg/m², on days 1 and 8 every 21 days, specifically as salvage therapy for patients with previously treated, advanced transitional cell carcinoma, has been initiated. In addition, E5899, a phase II trial of paclitaxel, 100 mg/m², plus gemcitabine, 600 to 800 mg/m², on days 1, 8, and 15 every 28 days in patients with advanced urothelial carcinoma with renal insufficiency is underway.

Phase I/II trials of paclitaxel/gemcitabine/platinum combinations have also been reported. Bellmunt et al reported a phase I/II trial of paclitaxel/gemcitabine/cisplatin in patients with advanced transitional cell carcinoma of the urothelium. A phase II dose of paclitaxel, 80 mg/m² over 1 hour; gemcitabine, 1,000 mg/m² on days 1 and 8, plus cisplatin, 70 mg/m² on day 1 every 21 days, was recommended.[38] Among 58 evaluable patients, the response rate was 78% (95% CI = 60%-98%) with 28% achieving a complete response. Median survival for patients in the phase I study was 24 months; median survival for the whole group had not been reached at the time this trial was reported.

Investigators from Wayne State University and the University of Michigan have built upon their previous study of paclitaxel/carboplatin with a triplet combination of paclitaxel, 200 mg/m² over 3 hours, and carboplatin dosed to an AUC of 5 on day 1, with gemcitabine, 800 mg/m² on days 1 and 8 every 21 days.[39] Among 43 evaluable patients, a response rate of 63% was demonstrated, including a complete response rate of 30%. Given the activity of these regimens, including the relatively high complete response proportion, further development of gemcitabine/taxane/platinum combinations appears warranted.

As a follow-up to the recently reported industry-sponsored trial that demonstrated that gemcitabine/cisplatin has similar efficacy but better toxicity than M-VAC, the EORTC has proposed a phase III trial comparing gemcitabine/cisplatin with gemcitabine/cisplatin/paclitaxel in patients with advanced urothelial cancer.[38]

Adjuvant/Neoadjuvant Chemotherapy for Bladder Cancer

In the United States, radical cystectomy with bilateral pelvic lymph node dissection is the standard treatment for localized muscle-invasive bladder cancer. The prognosis of the patient depends primarily upon the tumor stage. The risk of recurrence for patients with extravesical extension or lymph node metastases is relatively high. Because transitional cell carcinoma is a chemotherapy-sensitive neoplasm, eradication of micrometastases with adjuvant or neoadjuvant systemic chemotherapy could potentially improve cure rates. An extensive discussion of adjuvant and neoadjuvant chemotherapy for bladder cancer is beyond the scope of this article; however, recent reviews have been published.[40,41] The ultimate benefit of recent advances in the development of new, active regimens for patients with advanced bladder cancer may be their
application in the earlier perioperative setting.

**Adjuvant Chemotherapy**

Adjuvant therapy is based on knowledge of the pathologic stage of the patient’s tumor. To determine the benefit of this approach, there is a need for sufficiently powered randomized trials with a surgery-only control arm. Although there is no trial that definitively proves the benefit of adjuvant chemotherapy in bladder cancer, two trials suggest potential.

Skinner et al reported a randomized trial of surgery alone or surgery followed by adjuvant chemotherapy with the cyclophosphamide/doxorubicin/cisplatin regimen in 91 patients with pT3/pT4 and/or node-positive disease.[42] This trial demonstrated a delay in the time to progression in favor of the chemotherapy arm (70% vs 46% disease-free survival at 3 years; \( P = .001 \)).

Stockle et al randomized patients with pT3b-pT4a or node-positive disease to M-VAC/MVEC (methotrexate, vinblastine, epirubicin [Ellence], cisplatin) or observation.[43] With only 49 patients treated, an interim analysis showed that the risk of recurrence was significantly decreased by adjuvant chemotherapy. Follow-up on these patients has been updated, and the patients who had been randomized to the chemotherapy arm continue to show an advantage with respect to event-free survival (40 vs 18 months; \( P = .004 \)).[40,43] Other small trials have not demonstrated a benefit with adjuvant chemotherapy. Outside of the context of a clinical trial, some clinicians recommend treatment with a standard regimen, such as M-VAC, for patients with high-risk, resected disease (eg, patients with extravesical extension or micrometastases to regional nodes), if the patient can tolerate chemotherapy.[41]

Clinical trials examining the role of adjuvant chemotherapy in bladder cancer continue ([Table 4]).[41] A randomized trial has been initiated by the ECOG consisting of four cycles of paclitaxel/carboplatin vs four cycles of M-VAC for postcystectomy patients with pT3b-pT4 and/or node-positive disease. This trial was activated in March 1999, and the investigators plan to accrue 490 patients. At MSKCC, the use of sequential drug therapy in the adjuvant setting is under investigation. High-risk patients are receiving sequential gemcitabine and doxorubicin followed by paclitaxel plus cisplatin or carboplatin.[41]

**Neoadjuvant Chemotherapy**

With respect to neoadjuvant chemotherapy for bladder cancer, published randomized trials to date have generally failed to demonstrate an effect on survival. The largest of these trials was the Medical Research Council/EORTC trial that randomized patients to three cycles of cisplatin/methotrexate/vinblastine followed by definitive local therapy vs definitive local therapy alone. This large prospective trial in 975 patients failed to demonstrate an improvement in overall survival with the use of neoadjuvant chemotherapy.[44] The Intergroup trial of neoadjuvant M-VAC for three cycles followed by cystectomy vs cystectomy alone for patients with muscle-invasive disease has been completed. This trial accrued over 300 patients between 1989 and 1998. Results are forthcoming.

**Prognostic Biomarkers in Invasive Bladder Cancer**

In an effort to better characterize the biology of bladder cancer, specific components of biochemical pathways, or structural molecules that are critical to cell architecture, have emerged as candidate tumor biomarkers. Comprehensive discussions of multiple potential biomarkers in bladder cancer have recently been published.[45,46] Although the clinical value of many of these markers will be minor, fairly large retrospective studies of archival material have demonstrated the potential clinical utility of some of these putative biomarkers. Several cell-cycle regulatory molecules, such as p53, p21\(^{WAF1/CIP1}\), and retinoblastoma (Rb), have emerged as biomarkers that can predict for disease progression and survival in patients with muscle-invasive disease treated by cystectomy. A prospective validation of these biomarkers has not yet been demonstrated.

**p53 and p21**
p53 has multiple functions, with a central role in tumor suppression by initiating either apoptosis or inducing cell-cycle arrest at G1/S following the detection of cellular DNA damage through the induction of p21WAF1/CIP1. Mutated p53 is dysfunctional and has a prolonged half-life, resulting in a nuclear accumulation of the abnormal protein.[47] This can be detected by immunohistochemical (IHC) techniques.

A strong concordance exists between p53 IHC overexpression and documented p53 mutations in bladder cancer, thereby providing an accessible biomarker for analysis of bladder cancer lesions.[48,49] In a retrospective review of 243 patients undergoing radical cystectomy, patients with organ-confined disease and altered p53 nuclear staining had a higher risk for disease progression (60%-80% vs 7%-11%) and disease-related mortality compared to patients with wild-type staining.[50] Furthermore, altered p53 expression was an independent predictor of these outcomes in organ-confined (P1 and P2) invasive lesions.

These findings have been confirmed in some but not all investigations.[51,52] Discrepancy in these analyses may in large part be due to the use of different antibodies for IHC among the studies and the use of different criteria for positivity among investigators. Such findings suggest the importance of standardizing criteria for biomarker positivity before employing such data in clinical decision making.

The effect of cell-cycle dysregulation on outcomes in advanced bladder cancer has been further demonstrated by the clinical analysis of p53 and p21WAF1/CIP1 expression. Cell-cycle arrest that is mediated by p53 is effected by the induction of p21WAF1/CIP1—a cyclin-dependent kinase inhibitor.[53] Besides induction through p53, p21WAF1/CIP1 may be constitutively expressed through several p53 independent pathways.[54]

In an analysis of 242 patients undergoing radical cystectomy with a median follow-up of 8.5 years, it was noted that outcomes (progression and death) could be predicted by the pattern of p53 and p21 expression.[55] Patients positive for p21WAF1/CIP1 had a significant decrease in tumor recurrence (30% vs 76%) and an increase in overall survival (63% vs 25%). In a multivariate analysis, p21WAF1/CIP1 was an independent predictor of recurrence and survival among several pathologic features, including p53 status. Furthermore, patients with altered p53 and absent p21WAF1/CIP1 expression had a poor prognosis with regard to disease progression (85%) and survival (15%), while patients with preserved p21WAF1/CIP1 expression demonstrated outcomes similar to those seen in patients with p53 wild-type tumors (50%-70% overall survival).

Role of pRb

Alterations in the Rb gene are common in bladder cancer, and the expression of Rb protein (pRb) has been studied in cystectomy patients.[56,57] In a series of 185 cases, Rb nuclear reactivity was measured (and scored as absent, 1+, or 2+). Absent or elevated pRb reflected worse progression (60% vs 30%) and worse 5-year survival (33% vs 66%) than normal (1+) heterogeneous nuclear reactivity (< 50% nuclei stained). When p53 status was also considered, a pattern of outcomes at 5 years was noted for wild type in both biomarkers (22% recurrence, 71% survival), alteration in either biomarker (42% recurrence, 51% survival), or altered Rb and p53 (79% recurrence, 16% survival). The data support the value of pRb as a biomarker and provide evidence that alterations in p53 and pRb may be synergistic in promoting tumor progression.

Angiogenesis-Related Predictors

In addition to cell-cycle regulators, the direct measurement of tumor angiogenesis (microvessel density) or biomarkers associated with angiogenesis may have potential as prognostic predictors for chemotherapy response. Tumors with low microvessel counts are associated with greater progression and decreased survival in patients with and without p53 alterations.[58] Additionally, patients with low thrombospondin-1 (TSP-1) expression in tumor specimens demonstrate increased recurrence rates and decreased overall survival.[59] However, the predictive power of this angiogenesis inhibitor is not independent of p53 expression, thereby suggesting that p53 may affect tumor angiogenesis by regulating the level of TSP expression.
Rationale for Retrospective Analysis

The findings in these series provided the rationale for applying this approach of retrospective molecular biomarker analysis to patients who received chemotherapy for bladder cancer. In one investigation of patients receiving neoadjuvant chemotherapy for muscle-invasive disease, altered p53 expression was associated with a significantly higher degree of disease progression and death, while those patients with wild-type p53 and other favorable features experienced a 77% 5-year survival.[60]

In another review, patients who participated in an adjuvant chemotherapy trial were evaluated with regard to the p53 status of their lesions. In patients receiving adjuvant chemotherapy who displayed wild-type p53 expression, a 3-fold lower risk of tumor recurrence and a 2.6-fold improved survival was noted compared to the control group with altered p53 expression.[61] In other smaller series of patients who received adjuvant chemotherapy, altered p53 expression was not informative with regard to response or outcome.[62,63] Results of these retrospective evaluations provide the basis for two recently initiated prospective chemotherapy trials in patients with localized bladder cancer.

Prospective Clinical Trials

At MSKCC, a trial has been initiated to demonstrate the use of neoadjuvant chemotherapy in patients with muscle-invasive lesions who have favorable clinical and molecular features.[41] Patients with organ-confined, muscle-invasive disease, without hydronephrosis and wild-type p53 nuclear staining on IHC, will undergo complete transurethral resection of the tumor and then neoadjuvant M-VAC followed by conservative management of the primary bladder tumor when possible. The goals of this study are (1) to determine the feasibility of this treatment plan in these patients, and (2) to determine the proportion of patients (treated with this regimen) in whom bladder preservation, rather than radical cystectomy, is possible.

A multi-institutional study sponsored by the National Institutes of Health and based at the University of Southern California is investigating the effect of altered p53 expression on the adjuvant treatment of patients with organ-confined bladder cancer (Table 4). Approximately 540 patients will be studied among the different treatment arms. In this trial, patients who demonstrate organ-confined disease after cystectomy shall undergo IHC analysis of their tumor. Those patients with wild-type p53 tumors shall undergo routine follow-up, while patients with altered p53 expression tumors shall be randomized 1:1 to surgery alone or surgery followed by three cycles of adjuvant M-VAC. The study is designed to detect a 20% difference in survival between the groups.

As these investigations mature, other biomarkers may emerge as potential candidates for further prospective clinical trials. Nonetheless, at this time, it is apparent that a candidate biomarker must be measurable by IHC, since a certain level of technical ease and reproducibility must be available if the marker is to gain acceptance in broad clinical application. However, the rapid pace of biotechnology suggests that detailed and reproducible molecular phenotyping of tumors, with innovations such as microchip arrays, will allow us to accurately analyze candidate biomarkers in an effort to predict which patients with invasive bladder cancer will most likely derive benefit from chemotherapy.[64]

Conclusions

In sum, the development of new agents, such as gemcitabine and paclitaxel, have resulted in new options for patients with advanced urothelial carcinoma. Randomized trials comparing gemcitabine/cisplatin and paclitaxel/carboplatin to M-VAC are important to further define the role of these regimens in the treatment of patients with advanced disease. The application of new regimens in early-disease, perioperative settings is currently under investigation.

Future advances in chemotherapy for patients with invasive bladder cancer may result from further investigations into the biology of the disease that aim to identify subsets of patient who may or may not benefit from chemotherapy. Clinicians are encouraged to offer patients the opportunity to
participate in well-designed clinical trials that focus on the ongoing development of chemotherapy in bladder cancer.

References:


Source URL: http://www.diagnosticimaging.com/review-article/recent-developments-chemotherapy-bladder-cancer

Links:
[1] http://www.diagnosticimaging.com/review-article