



Hammamet, Tunisia, 1999. Courtesy of J. Bryan Murphy, MD, Clearwater, Florida.

Several cytotoxic combinations have led to improved survival for patients with metastatic bladder cancer, and some have high response rates.

Progress in the Management of Metastatic Bladder Cancer

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Background: *Inadequate survival results from single agents in the management of advanced bladder cancer have prompted several trials involving multidrug combinations to increase response rates and survival.*

Methods: *Since the development of the MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin) and the CMV regimen (cisplatin, methotrexate, and vinblastine), other regimens have been tested. We evaluate results from regimens that include cisplatin combined with gemcitabine, paclitaxel, or docetaxel, and paclitaxel combined with gemcitabine or carboplatin.*

Results: *Objective results observed with various new combinations are promising. Objective response (OR) rates of 41%, 59%, and 71% are reported with a regimen of gemcitabine plus cisplatin. Paclitaxel plus cisplatin produced OR rates of 65% and 72%.*

Conclusions: *The use of combination cytotoxic chemotherapy regimens in treating patients with metastatic bladder cancer has nearly doubled median survival to 12 months, with a 3-year survival of approximately 20% to 25%. Caution must be exercised in using some of the newer regimens as survival may be inferior compared with the MVAC regimen.*

Introduction

Improved understanding of the molecular biology of urothelial malignancies is helping to define more clearly the role of new prognostic indices and multidisciplinary treatment for advanced disease. The development of new chemotherapeutic agents has expanded a relatively limited armamentarium against advanced urothelial cancer.

The median survival of patients with metastatic cancer of the urinary tract who receive only sup-

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portive care is less than 4 to 6 months. For patients treated with conventional single-agent chemotherapy, the median survival increases to approximately 7 to 8 months.^{1,4} With the introduction of combination cytotoxic regimens including cisplatin, methotrexate, and vinblastine (with or without doxorubicin) to the management of metastatic bladder cancer, median survival figures have nearly doubled to 12 months, with a 3-year survival of approximately 20% to 25%.^{3,5-7} Nevertheless, death from cancer ultimately occurs in more than 90% of such cases. Hence, the search for novel therapeutic strategies remains a priority.

Prognostic Factors for Metastatic Disease

The common sites of metastasis of bladder cancer and other urothelial malignancies include regional and distant lymph nodes, bone, lung, skin, and liver.² Metastases to abdominal viscera, brain, and meninges are seen less frequently. An increased likelihood of central nervous system relapses may be explained by the prolonged duration of remissions that are achieved in treating metastatic disease.⁸

Sites of metastatic involvement correlate with response rate and survival and are important predictors of treatment outcome. Patients with lymph node, lung, and soft-tissue metastases have better survival than those with metastases to bone and liver.^{3,9} Poor Karnofsky performance status (<80), weight loss, elevated serum alkaline phosphatase or LDH levels, and nontransitional cell histology adversely influence prognosis.^{2,9,10} Biopsies of distant metastatic sites are often consistent histologically with a transitional cell carcinoma (TCC) pattern. However, clinical and experimental studies have demonstrated a significant disparity within these metastatic areas with respect to growth parameters, ploidy, karyotype oncogene expression, tumor markers, grade, and histologic features.^{2,3,9,10} Metastatic sites may also contain adenocarcinoma and/or squamous carcinoma, reflecting either the stem cell function of TCC or the emergence of second primary tumors. These characteristics contribute to additional variation in the treatment outcomes.

More recently, the expression of P-glycoprotein, encoded by the multidrug resistance 1 gene, MDR1,^{11,12} and glutathione¹³ by bladder cancer cells have been implicated as predictors of resistance and toxicity to drug therapies (Table 1). Overexpression of metallothioneins in tumor specimens of metastatic urothelial disease has been linked to cisplatin resistance and is associated with a poorer outcome from chemotherapy.¹⁴

Table 1. — Potential Predictors of Response and Outcome to Chemotherapy in Urothelial Malignancies

P-glycoprotein (MDR-1) expression ^{11,12}
Glutathione expression ¹³
Metallothionein overexpression ¹⁴
Altered p53 expression ^{15,16}
MRP (multidrug resistance-associated protein) mRNA induction ¹⁷
Epidermal growth factor receptor overexpression ¹⁸

Induction of p53 gene expression has been shown in recent investigations to be facilitated by prior exposure to cytotoxic agents such as cisplatin and mitomycin C. This altered expression of p53 may correlate with increased resistance to combination chemotherapy protocols, eg, the MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin)¹⁵ and may be associated with previous intravesicular treatment. By contrast, response to paclitaxel-based chemotherapy regimens has been shown to be independent of p53 mutations in some studies.¹⁶ A concomitant induction of multidrug resistance-associated protein (MRP) mRNA, decreased levels of topoisomerase II mRNA, and decreased drug accumulation during development of multidrug resistance in human bladder cancer cells has also been demonstrated.¹⁷

The overexpression of epidermal growth factor receptor (EGFR) has been related to several malignant characteristics, including invasive growth, high-grade histology, DNA ploidy, high proliferation rate, and prognosis in superficial and invasive bladder cancer. The implications for the biology of metastatic disease, clinical behavior, therapeutic strategies, and survival outcomes remain to be fully explored.¹⁸

The potential value of a biochemical or secretory marker of urothelial malignancy has been the subject of ongoing investigations. One such marker — hepatocyte growth factor or scatter factor, produced by fibroblasts and other mesenchymal cells — has been shown in experimental models to be capable of amplification of malignant phenotype and invasion.¹⁹ However, since other factors, including epidermal growth factor integrins and E-cadherin, have also been shown to mediate tumor invasion, angiogenesis, progression, and metastasis, the unique role of this scatter factor remains unclear. Further study of such factors may help to define their role in the molecular pathways of invasion and metastasis, mechanisms of resistance to treatment, and improved comprehension of tumor cell heterogeneity in this malignancy.

Single-Agent Cytotoxic Chemotherapy

Cisplatin, methotrexate, vinblastine, mitomycin C, and doxorubicin are the standard single agents with known activity against urinary bladder TCC.^{2,4,20} Cisplatin and methotrexate are traditionally the most active agents and the most widely studied. Although a dose-response relationship has not been established in randomized comparisons, single-agent trials have suggested only a limited dose-rate and dose-response relationship for cisplatin or methotrexate.²¹

Several cisplatin analogues including carboplatin, cis-dichloro-trans-dihydroxy-bis-isopropylamine (CHIP), and oxaliplatin²²⁻²⁶ have been studied. The most widely tested is carboplatin, due to its milder toxicity profile, which is desirable for the characteristically older bladder cancer population. The response rates to carboplatin appear to be lower than for cisplatin. It is not clear if the drug is less active or if the differences are due to such factors as patient selection and dosing differences. Hence, as a routine, carboplatin should not be substituted for cisplatin.

Pilot trials of a fourth-generation platinum analog, oxaliplatin, against TCC have had encouraging preliminary results in Europe. Additional phase II studies are underway, including those in combination with other active agents. We are about to commence a phase II clinical trial of oxaliplatin plus gemcitabine against advanced bladder cancer in an effort to overcome some of the standard pathways of cytotoxic resistance.

Other cytotoxics, such as doxorubicin, vinblastine, cyclophosphamide, 5-fluorouracil (5-FU), and mitomycin C,²⁰ have had a lower level of activity when used as single agents in metastatic bladder cancer. Most agents yield objective responses in 10% to 20% of cases, including complete responses in only 5% to 10%. In addition, the duration of response has been short at less than 4 to 6 months.

Randomized clinical trials with single agents have produced lower objective response rates than many of the nonrandomized phase III studies have produced, perhaps due to patient selection or to greater stringency of assessment of outcome.²⁷ For example, three randomized trials have studied cisplatin as the sole agent to one randomized treatment group. Soloway et al²⁸ treated 50 patients with 70 mg/m² for 3 weeks, with 20% of patients responding and 3% achieving a complete response. Hillcoat et al¹ administered 80 mg/m² every 3 weeks to 55 patients, with 31% responding and 9% achieving a complete response. Loehrer et al³ treated 100 patients with 70 mg/m² every 4 weeks, with only 9% of patients responding and 3% achieving a

complete response. Whether there is a survival benefit of single-agent cisplatin over best palliative care has not been tested in a formal randomized trial, although reported survival figures are generally shorter for patients who do not receive chemotherapy. This could represent case selection bias.

The phenomenon of improved survival in association with chemotherapy has been increasingly reported in more recent times. This may be explained by the influence of stage migration.¹⁵ Stage migration occurs when meticulous staging has identified hitherto occult metastases so that smaller-volume disease is included within the metastatic category and thus potentially improving outcome. Also, oncologists have recently been offering chemotherapy at an earlier stage, based on the reasoning that there could be greater scope for benefiting patients.

Multidrug Regimens and Newer Agents

Based on inadequate survival results from single agents in advanced bladder cancer, several trials involving multidrug combinations were conducted with the goal of increasing response rates and survival.^{2,20,28-30} Response and survival were generally short in the early clinical trials, and no clear benefit for combination chemotherapy could be demonstrated. However, with the landmark development of the MVAC regimen at the Memorial Sloan-Kettering Cancer Center⁶ and the cisplatin, methotrexate, and vinblastine (CMV) regimen at Stanford University,⁵ significant improvements in remission rates were reported in single-institution studies. Long-term survival was recorded in 20% of patients treated with the MVAC combination.⁶ In a phase III trial, Logothetis et al³¹ compared MVAC with the CISCA regimen (cisplatin, cyclophosphamide, and doxorubicin). The MVAC regimen showed improved survival, which further validates the role of this regimen as a new standard.

Loehrer et al³² conducted a randomized trial comparing single-agent cisplatin with MVAC. Although significant improvement in median survival time was achieved with MVAC regimen compared with single-agent cisplatin, long-term survival was achieved in less than 5% of patients treated with MVAC.^{3,7} While MVAC increased median survival time from 8 months to 12 months, a 5-year progression-free survival of only 4% was reported.³³ Attempts to escalate and/or dose intensify these combinations have not been productive; in addition, the enhanced toxicities associated with escalated doses of MVAC have been substantial. TCC occurs in a relatively elderly population in whom coexisting medical illnesses are common. This is compounded by

myelosuppressive and renal toxicity of cytotoxics, characteristically poor performance status of these patients, and impaired renal function (often caused by obstructive uropathy). Neutropenic fever in 25% of patients, grade 2 to 3 mucositis in 49%, and a death rate of up to 3% have been attributed to MVAC.^{6,34,35}

Clinical researchers are now focusing their attention on the development of new agents that are at least as active in TCC as MVAC but with lesser toxicity. Against the background of proven clinical efficacy and benefit with established cytotoxic combinations to date, the testing approach for these newer agents is being designed to avoid the inadvertent reduction of survival. For example, some investigators prefer to test new single agents in patients with liver and bone metastases with early evaluation of response, or in patients with previously treated lymph node and soft-tissue disease.

The Eastern Cooperative Oncology Group (ECOG)³⁶ reported a trial of paclitaxel in 26 previously untreated patients who received a dose of 250 mg/m² by 24-hour continuous infusion every 3 weeks, supported by recombinant human granulocyte colony-stimulating factor (rhG-CSF) for at least 10 days during each cycle, until progression or intolerance. An objective response was achieved in 11 patients (42%), with 7 (27%) complete clinical responses. The median duration of response in the complete and partial responders was 7+ months. Overall, paclitaxel was well tolerated by patients. Given its relatively low renal excretion, paclitaxel may be desirable as a single agent in select patients with significant comorbidities, especially renal dysfunction, since it provides a more favorable risk:benefit ratio than regimens containing standard cisplatin and methotrexate combinations. Of note is the observation that the sites of metastases correlated with the pattern of response rates. This correlates with that seen with other conventional single agents or combination regimens; no responses were observed in hepatic metastases compared with a 62% response rate in nodal and soft-tissue disease and a 38% response rate in non-hepatic visceral metastasis. Docetaxel, another taxane, has a demonstrable response rate of 13% in previously treated patients with urothelial cancer, with an estimated median duration of survival of 9 months.³⁷

Ifosfamide was studied in a phase II trial³⁸ of 56 patients who had previously received chemotherapy. Of these, 26 received a 2-day schedule consisting of ifosfamide 3,750 mg/m² plus mesna 2,250 mg/m² given intravenously (IV), and 30 patients were treated on a 5-day regimen consisting of ifosfamide 1,500 mg/m² IV with mesna 750 mg/m² IV. Eleven patients (20%) had objective responses to treatment. Complete remission

was noted in 4 patients with soft-tissue/lymph node only disease and in 1 patient with skeletal and pulmonary metastasis. Renal and central nervous system toxicities were severe (grade 3 and 4) on the 2-day schedule, which necessitated a change to a more tolerable 5-day regimen. The response rate to ifosfamide of 20% in this series of previously treated patients implies significant activity for this drug. Combination regimens with this agent are undergoing exploration.

Based on the activity of cisplatin, other metallic compounds have been evaluated, including gallium and second- to fourth-generation platinum complexes. Gallium nitrate tends to concentrate in malignant tumors, and early studies demonstrated activity in TCC. It inhibits DNA polymerase and also causes inhibition of intracellular calcium and magnesium-dependant processes and the inhibition of transferrin-mediated iron uptake. In a small study by Seligman and Crawford,³⁹ gallium nitrate was administered by continuous infusion to patients with bladder cancer previously treated by MVAC or single-agent cisplatin. Although objective tumor responses were achieved in soft-tissue disease, toxicities included electrolyte abnormalities (hypocalcemia, hypomagnesemia, anemia, nephrotoxicity, and neurotoxicity [optic neuritis]).^{39,40} An evaluation by the Southwest Oncology Group (SWOG) has confirmed the relative lack of activity of this agent.⁴¹

As mentioned above, carboplatin has been occasionally substituted in combination regimens for patients who are ineligible to receive cisplatin treatment. Overall response rates ranging from 37% to 84% have been reported for bladder carcinoma in trials involving multidrug combinations including carboplatin.^{22,24,42} Bellmunt et al⁴² conducted an underpowered, randomized study to evaluate whether M-CAVI (methotrexate, carboplatin, and vinblastine) offers a therapeutic advantage over the cisplatin-based MVAC regimen in the treatment of surgically incurable bladder carcinoma. A total of 47 patients, of whom 17 had lymph node disease and 30 had distant metastases, were randomized to each group with similar patient characteristics in each. Overall response rates were 39% for M-CAVI and 52% for MVAC, with 3 complete responses among patients with MVAC and none in the M-CAVI group. It is unknown whether the absence of doxorubicin in the carboplatin-based regimen may have reduced the therapeutic efficacy or whether the applied carboplatin dose (area under the concentration-time curve [AUC] of 5) might have been inadequate in polychemotherapy. However, this study reiterates that carboplatin cannot be routinely substituted for cisplatin without the risk of compromising response. Nevertheless, carboplatin-based regimens could be beneficial to patients whose medical condi-

tions contraindicate the use of cisplatin. It is well known that there is summation toxicity from methotrexate-cisplatin regimens, depending on the schedule of delivery,^{1,26} and carboplatin may overcome this problem in selected cases.

Lobaplatin, a third-generation platinum complex, has been assessed recently by the European Organization for Research and Treatment of Cancer (EORTC), with 10% objective response rates in a series of cases, many of whom had previously received a platinum compound.⁴³ Oxaliplatin and JM216 are other platinum complexes not yet fully assessed in this context.

Because methotrexate has activity in advanced bladder cancer, trials with other antifolates and antimetabolites have been initiated. For example, Witte et al⁴⁴ reported a response rate of 18% from trimetrexate in patients who had received prior methotrexate, suggesting a lack of complete cross-resistance.

Gemcitabine, an antimetabolite analogue of cytosine arabinoside, has a favorable activity and toxicity profile in bladder cancer. This prodrug, which undergoes intracellular phosphorylation to form its active metabolites, shows prolonged intracellular retention compared with the parent compound.

During a phase I trial, Pollera et al⁴⁵ observed impressive regression of hepatic metastases in a patient with bladder cancer. This prompted a phase II study of 15 patients with bladder cancer, of whom 14 were previously treated with MVAC and 1 was chemotherapy-naive.⁴⁵ Dose-limiting hematologic toxicity was identified at 1,370 mg/m² gemcitabine per week. A response rate of 28% was achieved, with 1 complete remission and 3 partial remissions. Dramatic responses to gemcitabine were seen in hepatic lesions, in contrast to some of the other newer regimens. This is in contrast to the results with some of the other newer agents. These encouraging results led to the initiation of several phase II studies in patients with TCC in Europe, the United States, and Canada.⁴⁶⁻⁴⁸

In a trial of gemcitabine in 34 patients previously treated with cisplatin, Lorusso et al⁴⁶ demonstrated an overall response rate of 22%, with 3 complete responses and 4 partial responses. They reported a median survival of 5 months and a decrease in cancer-related symptoms, as assessed by use of analgesics and improved performance status. Their data also suggest that cisplatin resistance in TCC does not necessarily imply resistance to gemcitabine.

In a collaborative study,⁴⁷ we treated 40 chemotherapy-naive patients with metastatic TCC with

1,200 mg/m² gemcitabine weekly for 3 of every 4 weeks. This trial showed 4 complete and 7 partial responses, with an overall response rate of 28%. The median survival in this group was 11 months, and toxicity was mild and reversible. Of particular significance was the response of hepatic metastases in three of four treated cases. In a Canadian trial⁴⁸ that included 40 chemotherapy-naive patients, a response rate of 24% was achieved with 2 complete and 6 partial responses. The median survival was 8 months, with 17% of patients alive at 24 months. Again, gemcitabine was well tolerated in this elderly population.

Phase I and II gemcitabine monotherapy trials have shown promising outcomes with regard to convenience in administration, acceptable toxicity, and activity in elderly patients. These results led to a series of phase II trials of gemcitabine in combination with cisplatin in chemotherapy-naive patients (Table 2). Three major phase II trial reports of gemcitabine and cisplatin have now been reported. Using a combination of 3 weekly doses of 1,000 mg/m² gemcitabine and 35 mg/m² cisplatin repeated every 28 days, von der Maase et al⁴⁹ treated 44 patients in which an overall response rate of 41% was achieved, including 4 complete and 11 partial remissions. However, it appeared that the level of toxicity significantly increased in comparison to single-agent therapy, with severe myelosuppression and nausea in the treated population.

We reported a phase II trial of cisplatin plus gemcitabine in which 47 patients with metastatic TCC were enrolled, 2 of whom had received prior neoadjuvant therapy.^{47,50} The regimen consisted of cisplatin 100 mg/m² on day 1 and gemcitabine 1,000 mg/m² on days 1, 8, and 15 repeated every 28 days. Since significant myelosuppression was identified in the first 11 patients, we reduced the dose of cisplatin by 25%. An objective response rate of 59% was reported with 11 complete and 12 partial responses. Moore et al⁵¹ reported similar results in a trial of gemcitabine plus cisplatin. A 57% response rate was demonstrated in 28 evaluable patients using cisplatin at 70 mg/m², with gemcitabine at 1,000 mg/m² given on days 1, 8 and 15 of a 28-day cycle.

Other drug combinations that have been tested previously include 5-FU and recombinant human interferon alpha-2a. Logothetis et al⁵² reported treating 30 patients who had failed to respond to primary methotrexate/cisplatin-based chemotherapy with continuous infusion 5-FU and interferon alpha-2a. The mean duration of response was 6 months. Nine patients achieved a partial response, of which 2 patients remain disease free after control by surgery or radiotherapy of the residual disease at 5 and 7 months.

The response rate for the combination of these drugs is higher than anticipated for each when used alone.

In 1997, SWOG⁵³ also reported a phase II trial of continuous infusion 5-FU and cisplatin for advanced/recurrent TCC of the bladder in previously untreated patients. This trial was stimulated by the pilot data at Wayne State University, where 12 patients with advanced bladder cancer demonstrated a 58% response rate (33% complete and 25% partial) with tolerable myelosuppression and transient nephrotoxicity.⁵⁴ The SWOG trial, which reported a response rate of 28% (with upper 95% confidence interval [CI] limit for a response rate of 45%), was terminated early for lack of strict adherence to evaluation guidelines. The actual efficacy of this combination needs further study. The combination of cisplatin and interferon alpha-2b was adapted by Parnis et al⁵⁵ to take advantage of the potential *in vivo* modulation of cisplatin by interferon alpha used in patients with advanced melanoma. However, they did not demonstrate any advantage over using cisplatin alone and thus inferior results to standard combination regimens of CMV and MVAC.

Piritrexim, a dihydrofolate reductase (DHFR), has a bioavailability of 75% after oral dosing. In a report by de Wit et al⁵⁶ on 33 patients treated with 25 mg piritrexim 3 times daily for 5 days, repeated weekly, a complete response of 19+ weeks was demonstrated in 1 patient and a partial response of 22 weeks in 10 patients. A phase II study of oral piritrexim in advanced and previously treated patients with TCC of the bladder was also

reported by Khorsand et al.⁵⁷ Of 17 patients entered into the trial, 13 were evaluable. No complete responses were seen, 3 patients (23%) had partial responses, and 5 patients had stable disease at 8 to 14 months. Myelosuppression was the dose-limiting toxicity. Exploration of piritrexim is warranted in combination with other active drugs and as palliative treatment for patients who are not candidates for more aggressive therapy.

Topotecan, a topoisomerase I inhibitor, was tested by ECOG⁵⁸ as a single agent against previously treated advanced bladder cancer. In a trial with 46 patients, 32 of whom had been treated previously with cisplatin-based chemotherapy, an objective response rate of 10% was reported in lymph nodes, soft tissues, lung, and liver, but with significant toxicity. This early experience is not encouraging for further development, especially as so many other novel compounds have characteristics more appropriate for these elderly patients.

Combination Regimens of Newer Agents

The resurgence of agents with activity in TCC has expanded the opportunity to combine them into synergistic and possibly more effective combinations. Recent clinical trials have placed an emphasis on defining the nature of response and toxicity to all possible combinations while recognizing that quality of life is an important endpoint in the treatment of patients with metastatic cancer (Table 2).

Table 2. — Combination Regimens of New Agents in Metastatic TCC

Regimen	Number of Patients	Objective Response Rate (%)	Complete Response Rate (%)	Reference
Gemcitabine + cisplatin	44	41	4	von der Maase et al ⁴⁹
	47	59	11	Stadler et al ⁵⁰
	17	71	23	Moore et al ⁵¹
Paclitaxel + cisplatin	20	65	20	Murphy et al ⁶¹
	29	72	34	Burch et al ⁶²
Paclitaxel + carboplatin	33	50	12	Vaughn et al ⁶⁴
	32	71	31	Pycha et al ⁶⁵
Docetaxel + cisplatin	25	60	28	Sengelov et al ⁶⁶
	19	53	21	Garcia del Muro et al ⁶⁷
Paclitaxel + cisplatin + methotrexate	25	40	0	Tu et al ⁶⁸
Cisplatin + 5-fluorouracil + methotrexate	24	67	7	Oh et al ⁶⁹
Cisplatin + paclitaxel + ifosfamide	44	68	23	Bajorin et al ⁷⁰ and McCaffrey et al ⁷¹
Gemcitabine + paclitaxel	26	60	8	Meluch et al ⁷³

The combination of vinblastine, ifosfamide, and gallium was studied in a series of 25 chemotherapy-naïve patients with TCC by ECOG.⁵⁹ Complete responses were achieved in 5 patients (20%), but relapses occurred early. Significant myelosuppression, renal dysfunction, and neurological toxicity, including the potential for transient blindness (from gallium), limited the feasibility of this regimen. The combination of gallium nitrate and 5-FU was compared with the MVAC regimen by McCaffrey et al⁶⁰ in a phase II randomized trial. Only 12% of patients in the gallium/5-FU arm achieved objective responses compared with 94% in the MVAC arm, a higher response rate than those previously reported for MVAC trials. The survival in both arms (with cross-over having been allowed) was approximately 18 months. This may be explained by the phenomenon of stage migration as described above. This phenomenon is of particular importance when trying to set the use of new regimens into a realistic context.

Several investigators have developed combination regimens based on the activity of paclitaxel and cisplatin against bladder cancer. Murphy et al⁶¹ studied a series of 20 cases combining paclitaxel (170 mg/m² via 24-hour infusion) followed by cisplatin (75 mg/m²). Objective responses were achieved in 65% of cases, with complete remissions in 20%. This regimen was myelosuppressive, with 1 death reported from neutropenic sepsis. Burch et al⁶² reported a phase II trial of combined paclitaxel 135 mg/m² over 3 hours and cisplatin 70 mg/m² over 2 hours given every 3 weeks. This regimen was assessed in 29 patients with previously untreated metastatic urothelial cancer, yielding a complete response rate of 34%, a total response rate 72%, and a median survival of 13 months. This combination was adequately tolerated and administered with convenience in an outpatient setting.

The substitution of carboplatin for cisplatin in combination with paclitaxel has been studied.⁶³⁻⁶⁵ A phase I-II trial with paclitaxel (170 to 225 mg/m²) over 3 hours followed by carboplatin at AUC 6 involving 33 patients was conducted by Vaughn and colleagues.⁶⁴ They reported an overall response rate of 50%. Others investigating the paclitaxel/cisplatin combination confirmed this activity as first-line therapy for metastatic TCC. Pycha et al⁶⁵ recently reported their completed phase II study using paclitaxel 175 mg/m² as a 3-hour infusion and carboplatin dosed to AUC 5. Of 32 patients, 23 (71%) responded to treatment. Complete remission was seen in 10 (31%) of the 32 patients and partial remission in 13 (41%). These response rates compare well with those of MVAC, although reported survival times may be somewhat reduced. Time to progression after complete remission was at a median of 7 months,⁴⁻¹³ and no nephrotoxicity was observed. Red-

man et al⁶³ reported 7 complete remissions and 11 partial remissions among 36 evaluable cases with a median survival of only 9.5 months. To date, there is no randomized trial information comparing cisplatin with carboplatin in taxane-based regimens. However, ECOG is currently assessing MVAC vs paclitaxel/carboplatin in an Intergroup trial (E-4897).

The combination of docetaxel and cisplatin has also been shown to be effective with a manageable safety profile. Based on studies of patients with ovarian, non-small cell lung, breast, and gastric cancer, docetaxel has documented activity in cisplatin-resistant patients, and the combination has also been shown to be active. In a study by Sengelov et al⁶⁶ that included 25 previously untreated patients, docetaxel 75 mg/m² was combined with cisplatin 75 mg/m² every 3 weeks. Of the 25 patients, 20 had metastatic disease and 5 had locoregional disease. An objective response was achieved in 15 patients (60%), including 7 (26%) with a complete response, and the median survival time of 13.6 months. The main toxicities were nausea and vomiting, whereas myelosuppression, mucositis, and peripheral neuropathy were tolerable. An ongoing Spanish trial of this combination was reported by Garcia del Muro and colleagues⁶⁷ in a series of 19 chemotherapy-naïve patients — 14 with metastatic cancer and 5 with locally advanced urothelial cancer. Of the 19 patients, 4 (21%) have had a complete response, 6 (21%) have had a partial response, and 2 have had no changes. The overall response rate has been 53%, with the main toxicities being manageable hematological events. Larger randomized studies of docetaxel and cisplatin against standard MVAC are needed to test the validity of these significant preliminary results.

Tu et al⁶⁸ attempted a broader range of anticancer agents in their investigations against TCC. Paclitaxel 200 mg/m² over 3 hours was combined with methotrexate 30 mg/m² and cisplatin 70 mg/m². A total of 25 patients who had been previously treated with the MVAC regimen or other platinum-based protocols were included, and 10 objective partial responses were reported.

Oh et al⁶⁹ enrolled 24 patients with muscle-invasive and metastatic urothelial cancer into a phase II study testing an IV regimen of methotrexate 60 mg/m² on day 1, cisplatin 25 mg/m² per day on days 2 to 6, 5-FU 800 mg/m² per day on days 3 to 6, and leucovorin 500 mg/m² per day on days 3 to 6. This study achieved an overall response rate of 67%. Median survival was 64 months in the muscle-invasive group and 17 months in the metastatic group, with a median duration of response at 6 months in the latter group. However, significant hematologic toxicity was seen, with 80% of patients developing grade 3 to 4 myelosuppression.

Broadening the spectrum of cytotoxic agents improved the response duration and survival figures, albeit at the cost of significant bone marrow toxicity. It is probable that previous chemotherapeutic exposure may also have contributed to such significant myelosuppression.

A phase II trial including 29 patients with locally advanced and metastatic disease assessed the ITP regimen: a combination of ifosfamide 1.5 g/m² per day for 3 days, cisplatin 70 mg/m² on day 1, and paclitaxel 200 mg/m² on day 1.^{70,71} An overall response rate of 82% was reported in both the primary site and metastatic sites including liver, lung, bone, and nodes. This regimen caused significant myelosuppression but negligible non-myeloid toxicity. The duration of response was relatively short (1.5 to 11.7 months) but not substantially different from several other reported regimens. A subsequent cohort of 15 patients was added to this group; ITP was administered to the latter at 3-week intervals, given the acceptable toxicity in the former cohort. The median survival for 44 patients was 18 months. The ITP regimen is presently undergoing further investigation as a part of a sequential phase I regimen at Memorial Sloan-Kettering Cancer Center⁷² in which doxorubicin and gemcitabine every 2 weeks for 6 cycles are followed by ITP every three weeks for 4 cycles. Preliminary data show results that are comparable to those achieved with ITP alone, although the duration of response may be longer. These encouraging results will need to be substantiated in randomized trials.

Meluch et al⁷³ conducted a phase II trial including 26 patients that combined paclitaxel 200 mg/m² IV over 1 hour administered on day 1 and gemcitabine 1,000 mg/m² IV on days 1, 8, and 15, every 21 days. Of 15 previously untreated patients, 12 (80%) responded. Of 10 patients previously treated with platinum-based regimens, 3 (30%) responded. As expected, grade 3 and 4 myelosuppression was the principle toxicity in half the number of patients. Further follow-up of response rates and duration are awaited.

At the Annual Scientific Meeting of the American Society of Clinical Oncology in May 2000, von der Maase et al⁷⁴ reported the first results of a randomized trial that compared the MVAC regimen to gemcitabine plus cisplatin. Although the case numbers were too small for an equivalence trial, there was no substantial survival difference, and the toxicity was significantly less with the 2-day combination.

Conclusions

The last 2 decades have seen a gradual improvement in the management of metastatic bladder cancer,

with the median survival doubling to 12 months and the 3-year survival rate increasing from less than 5% to 15% to 20%. This progress has been possible because of efficiently designed and rationalized trials targeting therapeutic approaches to the molecular and histological characteristics of urothelial cancers. Unfortunately, the accrual of cases to many of the best national trials is inadequate due to exclusion of patients under managed care, government restrictions, and case accrual competition from the pharmaceutical industry. The academic and clinical community must continue to strive to improve outcomes through the development of wider patient access to high-quality clinical trials.

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