A Carboplatin-Based Regimen for the Treatment of Patients with Advanced Transitional Cell Carcinoma of the Urothelium

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BACKGROUND. Many patients with advanced transitional cell carcinoma are unable to receive cisplatin-based therapy. The efficacy and toxicity of a carboplatin-based regimen in the treatment of patients with advanced transitional cell carcinoma was therefore evaluated.

METHODS. Twenty-three patients with advanced transitional cell carcinoma were treated. Metastatic disease was present in 19 of 23 patients (83%) whereas 4 patients with T4, and/or N1, disease were treated. Patients were treated every 28 days with methotrexate, 30 mg/m^2 intravenously (i.v.) on Days 1 and 15, along with leucovorin, 15 mg/m^2 orally every 6 hours, 3 times daily beginning 24 hours after each methotrexate dose; vinblastine, 3 mg/m^2 i.v. on Days 1 and 15; mitoxantrone, 15 mg/m^2 i.v. on Day 1; and carboplatin, 300 mg/m^2 i.v. on Day 1, adjusted for creatinine clearance (MVNCa). Dosage in subsequent cycles was adjusted according to hematologic toxicity.

RESULTS. Median age was 70 years (range, 52–83 years) and median pretreatment creatinine clearance was 50 mL/min (range, 30–106 mL/min). Of 23 patients, 8 (34.8%) obtained a complete response, and 5 (21.7%) obtained a partial response. The overall response proportion was 56.5% (95% confidence interval, 34.5–76.8%). Median survival was 10 months (range, 1–44+ months). Toxicity was moderate. Grade 4 neutropenia occurred in 10 of 107 (9.3%) administered treatment cycles; Grade 4 thrombocytopenia occurred in 11 of 107 (10.3%). There were 4 episodes of febrile neutropenia (3.7% of cycles). Renal, neurologic, or otic toxicity were not observed. Age older than 70 did not appear to impact on response proportion, survival, and toxicity.

CONCLUSIONS. The carboplatin-based MVNCa regimen is active in the treatment of patients with advanced transitional cell carcinoma and is well tolerated. Therapy with this regimen may be a less toxic alternative for patients for whom treatment with cisplatin is not an option. ***Cancer* 1996; 78:1775–80.**

KEYWORDS: bladder carcinoma, carboplatin, chemotherapy, renal insufficiency.

Significant advances in the treatment of advanced transitional cell carcinoma (TCC) of the uroepithelium have been made in the past decade. Although in the past, patients who were not surgically curable had little chance for long term survival, the advent of cisplatin-based combination chemotherapy regimens has afforded these patients the potential for prolonged survival. The regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), pioneered at Memorial Sloan-Kettering Cancer Center,[1] and another popular regimen comprised of cisplatin, methotrexate, and vinblastine (CMV), advanced by investigators from the Northern California Oncology Group,[2] have

been shown to be effective in the treatment of TCC. Complete responses to MVAC have been reported in 13–35% of patients with metastatic or unresectable disease, with an overall response proportion of 38–72%.[3] MVAC has been shown to be superior to cisplatin, cyclophosphamide, and doxorubicin (CISCA), and to single agent cisplatin.[4,5] Although a direct comparison has not been undertaken between the CMV and MVAC regimens, results obtained with the CMV regimen do not appear to be significantly different, with an overall response proportion of 56% reported.[6] Despite these encouraging data, the reported median survival of patients treated with MVAC or CMV has only been 8 to 13.4 months, and the percentage of patients surviving beyond 2 years is less than 25%.[2,3]

Unfortunately, many patients with advanced TCC are not eligible to receive cisplatin-containing regimens for a variety of reasons. The toxicity associated with either the MVAC or CMV regimen is not insignificant, and is comprised primarily of myelosuppression, mucositis, and renal insufficiency. Many patients with bladder carcinoma are older and/or may have a less than optimal performance status, making the use of these regimens potentially hazardous. Furthermore, careful consideration of quality of life issues is warranted when aggressive therapy is recommended in this age group. The nausea and vomiting previously experienced with cisplatin has largely been eradicated with the use of new antiemetic agents. Nonetheless, the constitutional symptoms as well as renal, neurologic, and auditory toxicity associated with the use of cisplatin make it a difficult drug to use in an elderly population. Finally, renal insufficiency, due to a variety of causes, including obstructive uropathy, is not infrequent in patients with advanced TCC, thereby precluding the use of cisplatin-based therapy.

It was with these considerations in mind that we designed a trial substituting carboplatin for cisplatin in the MVAC regimen. Carboplatin has minimal, if any, renal, neurologic, or auditory toxicity at conventional doses, and can be safely utilized in patients with renal insufficiency. Furthermore, because it does not require aggressive hydration before, during, and after its administration, carboplatin can be easily administered in the outpatient setting. Because of previously published experience with a regimen utilizing mitoxantrone in lieu of doxorubicin,[7] this substitution was made as well, in hopes of limiting mucositis and potential cardiac toxicity.

MATERIALS AND METHODS

Twenty-five patients were enrolled in the study. Two chose to receive other therapy after enrollment and were deemed inevaluable. Twenty-three patients (16 men and 7 women) between the ages of 52 and 83 (median age 70) with previously untreated advanced TCC were entered into treatment. Twelve of 23 of the patients (52%) were 70 years old or older. Entry criteria included metastatic or inoperable TCC that was measurable, a Karnofsky performance status ≥ 60%, a calculated creatinine clearance of at least 30 mL/min, a cardiac ejection fraction ≥ 40%, and signed informed consent. Three patients had a primary TCC of the renal pelvis, whereas all the remaining patients were felt to have had a bladder primary TCC. Nineteen patients (83%) had metastatic disease, whereas 4 had unresectable locally advanced disease, defined as T4 and/or N1 disease, (1 patient with N2 disease was included in this category). Karnofsky performance status ranged from 60% to 100%, with a median of 70%. The median pretreatment creatinine clearance was 50 mL/min (range 30–106 mL/min.) The median cardiac ejection fraction was 61.5% (range, 50–80%). Table 1 summarizes the pretreatment characteristics of the patients.

TABLE 1
Pretreatment Patient Characteristics

Sex	Male	16
	Female	7
Age (yrs)	Median (range)	70 (52–83)
	% ≥ 70	52%
Clinical stage	TxNxM+	19
	T4NoMo	3
	T4N2Mo	1
Metastatic sites	Distant lymph nodes	11
	Bone	7
	Pelvis (soft tissue)	4
	Lung	2
	Liver	2
No. of metastatic sites per patient	More than 1	13
	Single site:	
	Distant lymph nodes	6
	Bone	2
	Liver	1
	Lung	1
Primary tumor	Bladder	20
	Renal pelvis	3
Karnofsky performance status	Median (range)	70% (60–100%)
Creatinine clearance	Median (range)	50 mL/min (30–105)
Cardiac ejection fraction	Median (range)	61.5% (50–80%)

Patients were treated every 28 days with a regimen comprised of methotrexate, 30 mg/m^2 intravenously (i.v.) on Days 1 and 15; vinblastine, 3 mg/m^2 i.v. on Days 1 and 15; mitoxantrone, 15 mg/m^2 on Day 1; and carboplatin, 300 mg/m^2 i.v. on Day 1, with incremental dose reductions for a creatinine clearance (Cr Cl) < 90 mL/min (MVNCa). (Carboplatin dose for Cr Cl 70–89 mL/min was 275 mg/m^2, 250 mg/m^2 for Cr Cl 50–69 mL/min, and 225 mg/m^2 for Cr Cl 30–49 mL/min).

All patients received 3 doses of oral leucovorin, 15 mg/m^2, every 6 hours, beginning 24 hours after completion of methotrexate administration to obviate the possibility of methotrexate toxicity in patients with the potential for reabsorption of renally excreted methotrexate in ileal loops or urinary conduits. Granulocyte-colony stimulating factor was administered in a subcutaneous dose of 5 μg/kg/day on Days 4–11 and 17–25. All drugs but mitoxantrone were increased by 25% on the first day of the subsequent cycle if there was no febrile neutropenia, Grade 4 neutropenia, or Grade 4 thrombocytopenia during the previous cycle. Day 1 of therapy was delayed until neutropenia or thrombocytopenia was resolved. In the event of febrile neutropenia, or any Grade 4 toxicity, including hematologic toxicity other than anemia, dosage of all the chemotherapeutic drugs was decreased by 25% in all subsequent cycles.

Extent of disease was assessed by means of physical examination, computed tomography (CT) of the abdomen and pelvis, bone scan, and chest X-ray. If indicated, cystoscopy and chest CT were performed. Imaging studies were obtained every two cycles for response evaluation. If initial cystoscopy, bone scan, or chest CT revealed disease, these studies were repeated as well. Patients with metastatic disease were treated until complete response (followed by two additional cycles of therapy after obtaining a complete response), tumor progression, or if toxicity became limiting. Patients with unresectable locally advanced disease were evaluated every two cycles for potential surgical resectability. These patients continued on therapy until definitive local therapy was appropriate, or until evidence of progressive disease. Response criteria utilized were those developed by the First International Consensus Development Conference on Bladder Cancer.[8] Toxicity was graded according to World Health Organization criteria, and duration of response and survival was measured from the start of therapy.

Statistical Considerations

This phase II trial was designed to have 80% power to detect a response proportion of 45% (vs. the null hypothesis: response proportion = 20%), with an α = 0.05. Survival was measured from the onset of therapy, and response duration was measured from the time of best objective response to the time of progression.

RESULTS

Twenty-three patients were evaluable for response (1 patient died after 1 cycle of therapy, and has been scored as a nonresponder). Of these 23 patients, 8 (34.8%) had a complete response (CR), and 5 (21.7%) a partial response (PR) for an overall response proportion of 56.5% (95% confidence interval, 34.5–76.8%). Of the 19 patients with metastatic disease, 5 (27.8%) had a PR, and 5 (27.8%) had a CR, for a response proportion of 52.6%. The median duration of response in all 13 responding patients was 8 months, and was 5.5 months in the 10 responding patients with metastatic disease. Of four patients with locally advanced unresectable disease, three obtained a clinical CR (negative imaging studies and negative cystoscopy with biopsy.) Of these, one patient with a T4, N2 tumor underwent cystectomy, was found to have no residual carcinoma and was scored a pathologic CR. One patient with locally advanced disease failed to respond to chemotherapy. Table 2 summarizes clinical characteristics of responding patients.

The median overall survival for all 23 patients was 10 months (range, 1–44^+ months). Four patients are alive 7^+, 14^+, 16+, and 44^+ months after initiation of therapy. Median survival for the 19 patients with metastatic disease was 8 months. Of the patients with locally advanced TCC, one underwent cystectomy. He was found to have no residual cancer and was alive with no evidence of disease 44^+ months after treatment. Two patients with locally advanced disease who achieved a clinical CR refused subsequent cystectomy and remained free of disease at 14^+ and 16^+ months, whereas a 4th patient with unresectable disease died of an unrelated cause at 10 months.

Sixteen of 23 patients (69%) were 65 years old or older, and 12 of 23 (52%) were 70 years old or older. In the group of patients 70 years old or older, a response proportion of 58.3% and a median survival of 11 months was observed. The response proportion and survival of this older group was not appreciably different from that of patients younger than 70 (odds ratio for response in older group vs younger group = 1.16), despite the fact that 92% of patients 70 years or older had metastatic disease. Nonetheless, the small sample size prevents definitive conclusions from being drawn.

Overall, 107 cycles of chemotherapy were administered. The median number of cycles received per patient was 4 (range, 1–8 cycles). The median number of chemotherapy cycles received by responding patients was 6 (range, 4–8 cycles), compared with 4 (range, 1–4 cycles) in nonresponding patients.

Toxicity was moderate. Significant nausea, vomiting, or mucositis was not observed. Grade 4 neutropenia was infrequent, occurring a total of 10 times in 107 administered cycles of chemotherapy (9.3%). Four episodes of febrile neutropenia occurred (3.7% of cycles). One treatment-related death occurred in a 62-year-old patient who was treated with a single cycle of MVNCa, became febrile and neutropenic, failed to obtain prompt medical attention, and subsequently

TABLE 2
Clinical Features of Responding Patients

Patient no.	Age/sex	Extent of Dz	Sites of response	Best response	Response duration (mos)	Overall survival (mos)
1	68, M	Met	Distant nodes	CR	6	12
2	62, M	LA	Bladder (T4), lymph nodes (N2)	pCR	37+	44+
3	75, F	Met	Pelvic mass	PR	10	12
4	66, F	Met	Pelvic mass	CR	9	18
5	74, F	Met	Mediastinum, distant lymph nodes	PR	2	6
6	83, M	Met	Distant lymph nodes	CR	8	18
7	81 M	Met	Distant lymph nodes	CR	4	10
8	68, M	LA	Bladder (T4)	CR	13+	16+
9	59, M	LA	Bladder (T4)	CR	10+	14+
10	72, M	Met	Liver	PR	2	5
11	73, M	Met	Pelvic mass, distant lymph nodes	CR	10	12.5
12	57, M	Met	Distant lymph nodes	PR	3	9
13	73 M	Met	Distant lymph nodes	PR	5	10

M: male; F: female; Met: metastatic disease; LA: locally advanced; Dz: disease; CR: (clinical) complete response; pCR: pathologic complete response.

died from fulminant sepsis and fungemia. Although this patient could not be evaluated for response assessment, he was scored as a nonresponder, and was also included in survival calculations. In 107 cycles of administered chemotherapy, there were 11 episodes of Grade 4 thrombocytopenia (10% of cycles). Platelet transfusions were required on five occasions (four patients), and there were no hemorrhagic episodes. Approximately 56% of the patients required packed red blood cell (PRBC) transfusions. In those patients requiring transfusion, the average number of PRBC units transfused was 4.6. Nonhematologic toxicity was mild. There was no significant renal toxicity. Carboplatin dose modifications for changes in renal function were uncommon. In 107 cycles, only 2 cycles (1.9%) required carboplatin dose reductions because of declining renal function. No episodes of peripheral neuropathy or ototoxicity were observed. No other Grade 3 or 4 toxic events occured.

Toxicity observed in the group of patients older than 70 years of age was not appreciably different from that observed in younger patients. In the 55 cycles of therapy administered to patients 70 years or older, 7 episodes of neutropenia (12.7%), and 2 episodes of febrile neutropenia (3.6%) occurred. Thrombocytopenia, red cell transfusion requirements, or nonhematologic adverse events were not more apparent in the elderly group.

DISCUSSION

Cisplatin-based chemotherapy has become the standard of care for patients with unresectable or metastatic TCC. Unfortunately, there is a significant group of patients in whom the use of cisplatin is limited, either because of concomitant medical problems, age, subsequent toxicity, or patient acceptance. Antecedent renal insufficiency limits the use of cisplatin, and even in otherwise healthy elderly patients the large volumes of fluid required for the safe administration of cisplatin mandate careful monitoring to avoid fluid overload. Patients with compromised pulmonary or cardiac function are obviously at particular risk of developing complications from fluid overload. Elderly patients tend to be more frail, have age-related physiologic changes, and on occasion, a poorer performance status that appears to make them more vulnerable to the side effects of chemotherapy. Toxic side effects, particularly renal insufficiency, also occasionally limit the amount of cisplatin that can be used. The usual need for overnight hospitalization or prolonged outpatient intravenous hydration to ensure forced diuresis before the administration of cisplatin makes it slightly cumbersome and can impact on the patient's quality of life.

Carboplatin is an analog of cisplatin that appears to have a similar mechanism of action[9] and spectrum of antineoplastic activity as cisplatin, and that may also have a more favorable toxicity profile. Carboplatin has been tested in the treatment of TCC fairly extensively. As a single agent, responses in 0–28% of patients have been reported.[10] A 45% response proportion has been reported for carboplatin in combination with methotrexate. When standard doses of carboplatin have been used in combination with methotrexate and vinblastine, 42–53% of patients will exhibit a response.[11–13] Waxman et al. added mitoxantrone

to a carboplatin-based regimen, treating patients with methotrexate, 50 mg/m^2; vinblastine, 3 mg/m^2; mitoxantrone, 10 mg/m^2, and a considerably lower carboplatin dose than that used in this trial (200 mg/m^2) on Day 1, and methotrexate, 50 mg/m^2 on Day 15 of a 28-day cycle. Although 64 patients were evaluable for response, only 27 patients were being treated for metastatic disease. An overall response proportion of 45% was reported.[7,14]

We have observed a CR in 34.8% of patients and an overall response proportion of 55.6% with the carboplatin-containing regimen MVNCa. Other investigators have observed that the likelihood of accruing a benefit from treatment with either MVAC or CMV is dependent on patient selection, with improved likelihood of response and prolonged remissions being associated with site of metastatic disease (N+ Mo disease is generally more favorable than Nx M+ disease), good performance status, and absence of weight loss.[3,4,15] Although our study design did not specifically exclude good prognosis patients, the percent of patients with metastatic disease (83%) and the median performance status (70%) in our study indicates that in general, a group of patients with a worse prognosis have been successfully treated. Moreover, we have demonstrated that age need not necessarily prevent patients from receiving effective therapy for TCC. The median age of patients in this trial was 70 years (compared with median ages of 59–66 years in prior MVAC and CMV trials), and 52% of patients were 70 years old or older. These patients did not experience more toxicity, and in this series, their response and survival rates appear comparable to those of younger patients.

Our trial design does not allow definitive conclusions to be drawn about the relative efficacy of this regimen compared with other regimens in which carboplatin has been used. The response proportion we have observed overlaps the response proportions reported with other carboplatin-based regimens. Nonetheless, we believe our results compare favorably to other reports because a considerably larger proportion of our patient population was comprised of patients with metastatic (Nx,M$^+$) disease (83% in our series, compared with 42% in Waxman et al.[14] and 41% in Bellmunt et al.[13]).

Similarly, this study was not designed as a formal comparison of carboplatin-versus cisplatin-based regimens. However, the overlap of the 95% confidence limits for the response proportion observed in this study with those observed with MVAC and CMV trials suggests that these response proportions are not markedly different. Furthermore, the durability of these responses does not appear to be significantly different from the duration of responses to cisplatin-based regimens. The median survival in this trial was 10 months, compared with a reported median survival of 8 months for patients treated with CMV[2] and 8 to 13.4 months in patients treated with MVAC.[3] Sustained survival rates of up to 20% have been noted with both MVAC[3] and CMV.[16] A direct comparison of the MVNCa regimen with MVAC or CMV cannot be made in the absence of a randomized trial, and our results must be interpreted cautiously because the substitution of carboplatin for cisplatin in the treatment of other malignancies does not always yield equivalent response and survival rates. For example, although the response proportion and survival rates appear to be similar in some tumor sites such as ovarian carcinoma[17] and possibly head and neck cancer,[18] the substitution of carboplatin for cisplatin in the treatment of good risk advanced germ cell tumors has been associated with a higher relapse rate.[19] Furthermore, because mitoxantrone has limited single agent efficacy in TCC, it is difficult to judge its contribution to the efficacy of either the Waxman regimen[14] or the MVNCa regimen.

In our experience, the use of carboplatin instead of cisplatin in the MVNCa regimen not only may result in a similar response proportion, but also makes it preferable in some circumstances due to its ease of administration and applicability to a wide group of patients. The MVNCa regimen is a convenient outpatient regimen requiring only brief Day 1 and Day 15 office visits. Extensive prehydration was not required, and even patients with very poor renal function (with a creatinine clearance as low as 30 mL/min), who could not have safely received cisplatin, were able to receive treatment. The most frequent toxicity observed with these regimens was primarily hematologic, although febrile neutropenia occured in only 3.7% of treatment cycles. Constitutional symptoms, fatigue, mucositis, and the neurologic and renal toxicities observed with cisplatin were not apparent to any significant extent with this regimen. One toxic death (4%) occurred in a patient with widely metastatic disease who failed to obtain prompt medical attention after developing fever and neutropenia after his first cycle of chemotherapy.

In summary, the response and toxicity data that we have observed with the MVNCa regimen are encouraging, and indicate that carboplatin-based therapy is an alternative for patients with advanced TCC of the uroepithelium for whom treatment with conventional cisplatin-based therapy is not an option. MVNCa appears to be well tolerated by elderly patients, and may be useful in this group of patients. However, the routine substitution of carboplatin for cisplatin in patients with advanced TCC with normal renal function cannot be recommended until our re-

sults are validated by other investigators, and a trial designed to compare carboplatin-based therapy with cisplatin-based therapy is undertaken.

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