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Carboplatin and Vinblastine for the Treatment of Metastatic Transitional Cell Carcinoma of the Urothelial Tract

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Many patients with metastatic transitional-cell carcinoma (TCC) are not appropriate candidates for standard cisplatin-based combination, because of inadequate renal function, poor performance status (PS), and other comorbid medical conditions. We have evaluated the efficacy and toxicity of a combination of carboplatin and vinblastine (CV) as a palliative regimen in these patients. The medical records of patients with metastatic TCC, who had been treated with CV at the British Columbia Cancer Agency from 1995 until 1999, were retrospectively reviewed. Treatment consisted of carboplatin (area under the curve = 5) on day 1, and vinblastine (4 mg/m^2) on days 1 and 8, repeated every 4 weeks. A total of 42 patients were included in this study, of whom 39 had measurable disease. Median age was 73 years. Fifty-two percent of patients had a PS (Eastern Cooperative Oncology Group) of 2 or 3. Node-only disease was present in 26% of patients, bone metastasis in 26%, and liver metastasis in 24%. A total of 119 cycles were administered. Grade IV granulocytopenia occurred in 26% of patients, grade III anemia in 12%, and there were 3 episodes of febrile neutropenia occurring in two patients. The major nonhematologic toxicity was grade III fatigue in 17% of patients. There were no grade IV nonhematologic toxicity or treatment-related deaths. The overall response rate was 33% (13 of 39). Five patients (13%) achieved a complete response and 8 patients (20%) a partial response. The median duration of response was 32 weeks and median overall survival for all patients was 26 weeks. The combination of carboplatin and vinblastine given in this schedule is a feasible, well-tolerated, and active alternative for patients with metastatic TCC unfit for standard chemotherapy.

Key Words: Carboplatin—Vinblastine—Chemotherapy—Metastatic transitional cell carcinoma.

Metastatic transitional-cell carcinoma (TCC) of the urothelial tract carries a poor prognosis, even with aggressive systemic therapy.[1,2] A cooperative group study comparing methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) with single-agent cisplatin therapy demonstrated the superiority of the combination with a response rate of 39% and a median survival time of 12.5 months,[3] setting MVAC as a standard regimen for the treatment of TCC. This benefit, however, is at the expense of significant toxicity, including neutropenic fever reported developing in 10% of patients, 10% experiencing grade III or IV mucositis and nausea and vomiting, and a 4% treatment-related death rate.[2,3]

Many patients with advanced TCC are not appropriate candidates for such cisplatin-based combination chemotherapy either because of inadequate renal function, poor performance status, and/or other comorbid medical conditions. Effective but less toxic alternative regimens are required for this group of patients.

Carboplatin is a second-generation platinum compound designed to have broad therapeutic activity and less toxicity than cisplatin. Carboplatin has been shown to be active in TCC when used in combination regimens.[4] Vinblastine has also shown activity as a single agent and in combination in patients with metastatic TCC.[3] Combination carboplatin and vinblastine (CV) has been evaluated in several tumor sites including the gastrointestinal tract, head and neck, and non–small-cell lung cancer and has been shown to have a well-tolerated toxicity profile,[5–8] with mild to moderate leukopenia and gastrointestinal toxicity. CV for advanced TCC has not been previously described. Because of the potential for a reasonable response rate, ease of delivery, and low toxicity profile, we have used CV in patients deemed unfit for standard chemotherapy regimens and report our experience here.

MATERIALS AND METHODS

Patient Eligibility

All patients were treated at one of four cancer centers of the British Columbia Cancer Agency, a provincial institution that coordinates cancer care delivery for the province of British

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TABLE 1. *Patient characteristics*

Characteristic	No. (n = 42)
Median age (range)	73 (51–82)
Sex (M:F)	29:13
PS (ECOG)	
0–1	20 (48%)
2–3	22 (52%)
Primary site	
Bladder	29 (69%)
Renal–Pelvis	6 (14%)
Ureter	5 (12%)
Prostate	2 (5%)
Sites of metastasis	
Lymph node	30 (71%)
Bone	11 (26%)
Lung	10 (24%)
Liver	10 (24%)
Other	5 (12%)
Number of metastatic sites	
1	22 (52%)
2	17 (40%)
3	2 (5%)
4	1 (2%)
Median GFR (range)	53 ml/min (0–104)
Reasons for CV	
Low GFR	26 (62%)
Heart disease	7 (16%)
Poor PS	5 (12%)
Other	4 (10%)

CV, carboplatin and vinblastine; ECOG, Eastern Cooperative Oncology Group; GFR, Glomerular filtration rate; PS, performance status.

Columbia, Canada. Patients were identified through a pharmacy database, which tracks all patients being treated with chemotherapy throughout the British Columbia Cancer Agency. Patients eligible for analysis were those who had histologically proven metastatic TCC of the urothelial tract and had received CV from January 1, 1995 to December 31, 1999. CV was a prospectively designed protocol and criteria for its use was for patients with TCC who required palliative chemotherapy but were judged ineligible by the treating physician for standard cisplatin-base regimens because of impaired creatinine clearance (<60 ml/min), performance status (Eastern Cooperative Oncology Group) 2 to 4, or other comorbid medical illness. Those patients who had previously received localized radiotherapy treatment for pain or bleeding control were included for this analysis, but those who had had prior systemic chemotherapy or concurrent radiotherapy with CV were excluded. All other patients who received CV were considered eligible for toxicity and survival analysis, but only those with measurable disease were included for assessment of efficacy. All patient medical records were retrospectively reviewed and data were collected through a predesigned questionnaire and entered in a computer database.

Seventy-one patients were identified from the database. Twenty-six patients had received prior chemotherapy, two did not have metastatic disease (received CV as adjuvant therapy), and one received CV concurrently with radiotherapy. Thus, 42 patients were considered eligible and all patients' charts were available for review and included for analysis. Baseline patient characteristics are outlined in Table 1. The median age was 73. The male-to-female ratio was approximately 2:1. Performance status (Eastern Cooperative Oncology Group) of 2 or 3 was present in 22 patients (52%), creatinine clearance of less than 60 ml/min in 26 patients (62%), and significant heart disease was seen in 7 patients (16%). The primary site of disease was bladder in 29 patients (69%), followed by renal pelvis in 6 (14%). Thirty-one patients (74%) had visceral disease and 11 (26%) had node-only disease. Nine of the 42 patients had received palliative radiotherapy before chemotherapy to painful bony metastatic sites (7 patients) or to the pelvis to control local symptoms (2 patients). CV was initiated a median of 13.1 weeks (range: 1.4–31 weeks) after radiotherapy to bony sites, and 2.6 weeks (range: 0.1–5 weeks) after radiotherapy to the pelvis.

All responding patients had their diagnostic imaging reviewed. Patients for whom response data were not documented clearly were considered to have progressive disease. A complete response was defined as the complete disappearance of all measurable disease for a minimum of 30 days. A partial response was defined as a decrease of greater than or equal to 50% of the sum of the products of the bidimensional measurements of measurable lesions or greater than or equal to 30% by unidimensional measurements for at least 30 days. Stable disease was defined as a reduction of less than 50% for at least 12 weeks, and progressive disease was defined as an objective increase of more than 25% in the size of all the measurable lesions or the appearance of any new lesions. Patients in whom new symptoms developed requiring a change in treatment management were also deemed as having progressive disease.

Treatment Plan

Carboplatin was administered intravenously for 15 to 30 minutes on day 1, dosed to an area under the curve of 5. The area under the curve (AUC) was calculated using the Calvert formula[9] [carboplatin dose = AUC × (GFR + 25)]. Glomerular filtration rate (GFR) was calculated by the Cockcroft formula. Vinblastine was given as an intravenous bolus days 1 and 8 at a dose of 4 mg/m^2. Cycles were repeated every 28 days for a total of 4 to 6 cycles at the discretion of the treating physician but were discontinued after two cycles if there was no evidence of response. Carboplatin dose was reduced to an AUC of 4 if the platelet count was 90 to 120 × 10^9/l, and delayed by 1-week intervals if the platelet count was < 90 × 10^9/l. The vinblastine dose was reduced by 25% if the absolute neutrophil (ANC) count was between 1.0 to 1.4 × 10^9 cells/l and delayed by 1-week intervals if the ANC was less than 1.0 × 10^9 cells/l. A total of 119 courses of CV were administered (median, 2.5 cycles, and range, 1–6 cycles). Ten and 13 patients required a dose reduction of the carboplatin and vinblastine, respectively. Details of treatment delivery are listed in Table 2.

Statistical Analysis

Analysis of response included 39 patients (3 patients were excluded because of a lack of measurable disease). For response rate, exact binomial 95% CI was calculated. All patients were included for survival analyses. The Kaplan-Meier method was used to determine duration of response, progression free survival (PFS), and overall survival (OS). Duration of response was calculated from the first day of chemotherapy to the date of documented progression. PFS was calculated from the first day of chemotherapy to the date on which progression was documented. OS was calculated from the first day of chemotherapy to the date of death. SPSS-9.0 for Windows was used for statistical analysis.

TABLE 2. *Treatment delivered*

Treatment data	No. of patients (%)
Cycles delivered	
1	8 (19%)
2	13 (31%)
3	5 (12%)
4	9 (21%)
5	3 (7%)
6	4 (10%)
Dose reductions	
Carboplatin	10
Vinblastine	13
Cycles changes	
Cycle delay	4
No day 8 vinblastine	9
Reasons for treatment termination	
Progressive disease	29 (69%)
Protocol End	10 (24%)
Toxicity or patient request	3 (7%)

RESULTS

Toxicity

Toxicity data are listed in Table 3 for the 42 patients. Grade IV granulocytopenia occurred in 11 patients (26%). Three episodes of neutropenic fever were encountered in two patients, with an average hospital stay of 6 days without the use of colony-stimulating factors. Grade III anemia occurred in 5 patients (12%). Four patients required one blood transfusion, and one patient required two transfusions. Significant thrombocytopenia was not encountered. There were no treatment-related deaths. Nonhematologic toxicity consisted primarily of grade III fatigue in 7 patients (17%), although this could not be differentiated from fatigue secondary to disease progression. Grade III nausea and vomiting occurred in two patients (5%) and grade III neuropathy in one patient (2%). There were no grade IV nonhematologic toxicities.

TABLE 3. *Toxicity according to NCIC common toxicity criteria*

Toxicity	No. of patients affected (%)			
	Grade I	Grade II	Grade III	Grade IV
Hematologic				
Granulocytopenia	6 (14)	3 (7)	7 (17)	11 (26)
Thrombocytopenia	9 (22)	2 (5)	1 (2)	1 (2)
Anemia	15 (36)	14 (33)	5 (12)	0
Nonhematologic				
Fatigue	1 (2)	15 (36)	7 (17)	0
Nausea	12 (29)	8 (19)	1 (2)	0
Vomiting	3 (7)	7 (17)	1 (2)	0
Neuropathy	0	2 (5)	1 (2)	0
Fever	2 (5)	1 (2)	0	0
Constipation	2 (5)	6 (14)	0	0
Hearing loss	1 (2)	2 (5)	0	0
Diarrhea	2 (5)	1 (2)	0	0
Alopecia	3 (7)	0	0	0
Stomatitis	1 (2)	0	0	0

NCIC, National Cancer Institute of Canada.

TABLE 4. *Response data*

Responses	Number of patients (n = 39)	Percentage
Overall response	13	33
CR	5	13
PR	8	20

CR, complete response; PR, partial response.

Response and Survival

Of the 39 patients with measurable disease, 13 patients (33%) achieved confirmed objective clinical response (95% CI, 18–48%), including five (13%) complete responses and 8 (20%) partial responses (Table 4). The median time to progression for all 42 patients was 11 weeks (95% CI of 7.9–14.1 weeks) (Fig. 1). The median response duration for patients with objective clinical response was 32 weeks (95% CI of 21.8–42.2 weeks) (Fig. 2). The median overall survival for all patients was 26 weeks (95% CI of 19.7–32.3 weeks) (Fig. 3).

DISCUSSION

This combination of carboplatin and vinblastine resulted in a 33% overall objective response rate, indicating a moderate activity as a first-line treatment in this population with advanced TCC. Our results with CV were obtained at the expense of only mild toxicity for the majority of patients, and all had been negatively selected as being ineligible for standard chemotherapy regimens. Consistently, poor performance status (Karnofsky <80, Eastern Cooperative Oncology Group ≥ 2) and presence of visceral metastases have been defined as negative

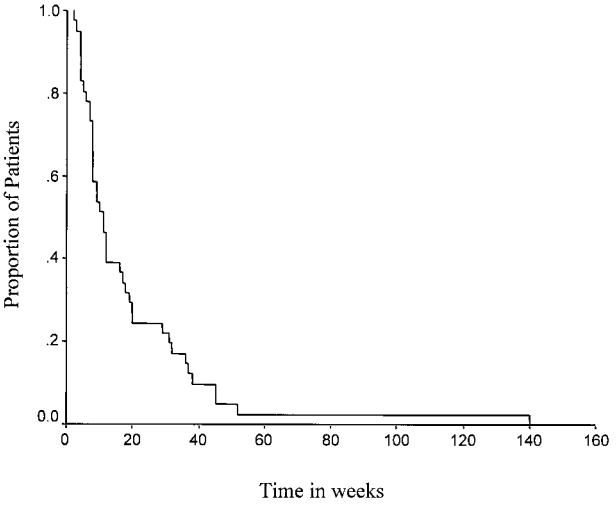

FIG. 1. Actuarial progression-free survival curve by the Kaplan-Meier method.

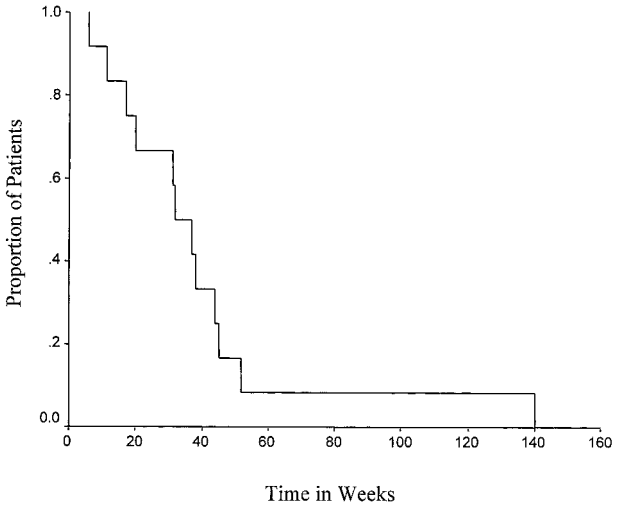

FIG. 2. Kaplan-Meier survival curve depicting duration of response.

prognostic factors for patients with metastatic TCC.[3,10] In our patient group, most had these features, with 52% having a poor performance status and 74% having visceral metastases.

Our analysis was conducted retrospectively, which has several limitations. The choice of treatment may not always be applied consistently and be clear from medical records; however, eligibility criteria for the use of CV in the province of British Columbia were set in advance. Another limitation of retrospective review is the lack of accuracy and completeness in data documentation. The British Columbia Cancer Agency pharmacy databases capture all patients receiving chemotherapy in the province of British Columbia at the four cancer centers, and all patients were included in this analysis. There were three patients for whom response data were not documented clearly, and therefore these patients were considered to have progressive disease in the analysis to avoid the potential for bias. In addition, all responders had their radiologic investigations retrospectively reviewed to confirm responses. Toxicities would have likely been underreported in the medical files, and therefore we may have underestimated the toxicity, especially nonhematologic. However, it would be expected that grade III and IV toxicities would be consistently documented by treating physicians. Furthermore, other studies prospectively evaluating combinations of carboplatin and vinblastine in other tumor sites have consistently reported a reasonable toxicity profile.

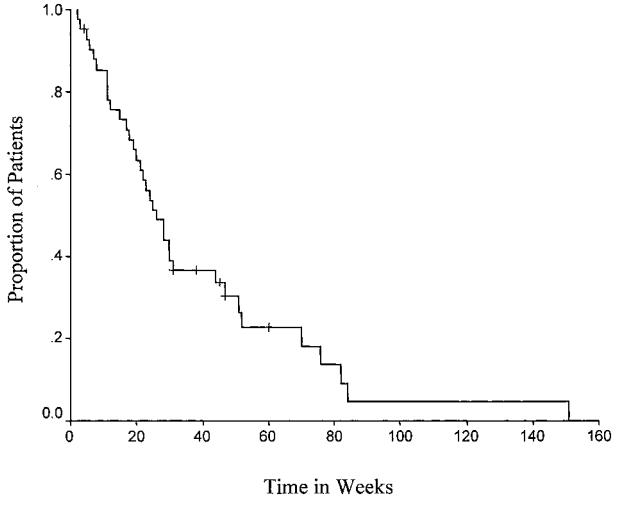

FIG. 3. Actuarial overall survival curve by the Kaplan-Meier method.

Other studies have reported on several chemotherapy combinations for urothelial cancer looking for efficacious yet tolerable regimens, some of which have included patients that were similar to the population studied here. Harland and Fenwick[11] reported in abstract form an evaluation of carboplatin and methotrexate combination in 34 patients, some of whom had glomerular filtration rate of less than 50 ml/min (11 patients) or a poor performance status (8 patients). This combination resulted in a 45% response rate for all patients with a mean duration of remission of 10 months. However, there were three early deaths reported in the poor performance status group. Arena et al.[12] evaluated carboplatin and 5-fluorouracil (5-FU) in 23 patients: 43% had an Eastern Cooperative Oncology Group performance status of 2 to 3, 22% had preexisting cardiac disease, and in 13% creatinine was significantly elevated. The overall response rate was 24% with a median duration of response of 8 months. Klocker et al.[13] evaluated the combination of carboplatin, methotrexate, and vinblastine. Seven patients were reported as having obstructive uropathy. Eight of 15 (53%) patients had a response, but there were no complete responses, and most patients had locally advanced disease, with only 4 patients having documented metastatic disease. Others[14,15] have also evaluated a similar combination of carboplatin, methotrexate, and vinblastine and found overall response rates of approximately 39%, with the majority of patients in these trials having good performance status. Early studies of paclitaxel and carboplatin had promising results with response rates in the 50% to 70% range; however, a recent phase II study performed by the Southwest Oncology Group[16] found only a 20.7% response rate, emphasizing the impact of patient selection on study outcomes. Thus, the activity of CV in our study is not out of keeping with what has been observed with other palliative combinations when considering patient population differences and sample size.

A phase III randomized study comparing gemcitabine and cisplatin with standard MVAC has been recently reported.[17] There were no differences in response rate, time to progression and overall survival between the two arms, but significant differences in the toxicity favoring the gemcitabine and cisplatin arm, especially in terms of neutropenic fever, sepsis and mucositis. Gemcitabine and cisplatin is thus a safer therapeutic alternative from

MVAC; however, there will still be patients not candidates for gemcitabine and cisplatin because of poor renal function. Furthermore, the majority of patients on the trial were Karnofsky performance status 80 or more, and caution should be taken in extrapolating the results to a poorer prognostic group.

Incorporation of new cytotoxic agents in combination chemotherapy regimens has thus far failed to definitively improve efficacy for TCC. While awaiting improved drug therapy for TCC, it is still worthwhile to report results of regimens using traditional agents that are economical and have a favorable therapeutic index for frail patients. This combination of carboplatin with vinblastine is a feasible, well-tolerated, and active alternative for patients with poor prognosis who are not candidates for more aggressive chemotherapy or clinical trial regimens.

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