Vinblastine, Ifosfamide, and Gallium Nitrate—An Active New Regimen in Patients with Advanced Carcinoma of the Urothelium

A Phase II Trial of the Eastern Cooperative Oncology Group (E5892)

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BACKGROUND. This study was conducted to assess the efficacy and toxicity of vinblastine, ifosfamide, and gallium nitrate (VIG) as first-line chemotherapy in patients with locally advanced or metastatic carcinoma of the urothelium.

METHODS. Forty-five eligible patients were enrolled and stratified into good and poor risk groups. Poor risk was defined as age $\geq$ 70 years, 1 functioning kidney, and prior adjuvant or neoadjuvant chemotherapy. Good risk patients were treated with vinblastine, 0.11 mg/kg, on Days 1 and 2; ifosfamide, 1.2 g/m^2, on Days 1–5 with mesna uroprotection; and gallium nitrate, 300 mg/m^2, as a continuous infusion on Days 1–5. Poor risk patients received similar therapy with doses decreased by 20% and administered over 4 days. All patients received recombinant human granulocyte-colony stimulating factor. Cycles were repeated at 21-day intervals until disease progression or to a maximum of 6 cycles.

RESULTS. Twenty of 45 patients (44%; 95% confidence interval, 30–60%) demonstrated an objective response, with 6 patients (13%) achieving a complete clinical response. The median duration of response was 47 weeks and the median survival duration for all patients was 10 months. Hematologic toxicity was significant, with 28 patients and 31 patients experiencing Grade 3 or 4 leukopenia and anemia, respectively. Six patients had clinically significant cardiac events (primarily atrial arrhythmias). There were two early deaths that were possibly treatment related.

CONCLUSIONS. VIG is an active regimen in patients with advanced urothelial carcinoma. Toxicity is significant but acceptable. Patients with significant cardiac disease (especially arrhythmias) should be treated with extra care. The 4-day regimen appears to have similar therapeutic efficacy with less toxicity. ***Cancer* 1997; 79:110–4.** © *1997 American Cancer Society.*

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The methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) and cisplatin, methotrexate, vinblastine (CMV) regimens that provided the first glimmer of hope for patients with advanced bladder carcinoma are now a decade old and remain the nonprotocol therapy of choice for patients with advanced bladder carcinoma.[1,2] In prospective randomized trials, M-VAC has proven superior over single agent cisplatin[3] and combinations such as the cisplatin, doxorubicin, and cyclophosphamide regimen (CISCA).[4] Attempts to improve response rate and survival by dose escalation of M-VAC have not been successful.[5,6] In addition, based on prospective randomized trials, cisplatin

is now believed to have less single agent activity (< 20%) than reported in earlier studies.[3]

Over the last several years, several agents, both new and old, have demonstrated activity in urothelial carcinoma including ifosfamide,[7] gallium nitrate,[8] gemcitabine,[9] and paclitaxel.[10] Gallium nitrate and ifosfamide both have single agent activity of >20% in previously treated patients.[7,11] Einhorn et al. performed a Phase II trial of vinblastine, ifosfamide, and gallium nitrate (VIG) in 27 patients with advanced urothelial carcinoma.[12] Eighteen patients (67%) achieved an objective response with 11 (41%) achieving disease free status 5 from chemotherapy alone and 6 with adjuvant surgery). The toxicity was primarily hematologic, and more pronounced in those patients older than age 70, those with a prior nephrectomy, and in patients treated with prior pelvic radiotherapy or adjuvant cisplatin-based therapy. To confirm these findings in a multiinstitutional setting, the Eastern Cooperative Oncology Group (ECOG) performed a Phase II trial of VIG in previously untreated (for metastatic disease) patients with advanced urothelial carcinoma.

METHODS

Study Design

Eligible patients had histologically confirmed carcinoma of the urothelium and evidence of progressive, bidimensionally measurable regional or metastatic disease. Patients must have been disease free from prior malignancies for at least 5 years, with an ECOG performance status of 0 to 2 at entry. Patients must not have received prior biologic response modifiers or radiation therapy, and at least 4 weeks must have elapsed since major surgery and the patient must have recovered fully. Prior chemotherapy for metastatic disease was excluded; however, patients may have had 1 prior chemotherapy regimen in the neoadjuvant or adjuvant setting when administered at least 6 months prior to planned study entry. Adequate renal and hepatic function was required as manifested by a serum creatinine $\leq$ 1.5 mg/dL, aspartate aminotransferase (AST) $\leq$ 2 times the upper limit of normal, and a bilirubin $\leq$ 1.5 times the upper limit of normal. Adequate bone marrow reserve was mandated, with an absolute neutrophil count $\geq$ 1800/μL and a platelet count $\geq$ 100,000/μL at entry. Informed written consent was obtained from all patients.

Therapy

Patients were stratified into good and poor risk groups. Poor risk was defined as age > 70, only 1 functioning kidney, or prior adjuvant/neoadjuvant cisplatin-based chemotherapy. Good risk patients were treated with vinblastine, 0.11 mg/kg, by slow intravenous push on Days 1 and 2 of each cycle; ifosfamide, 1.2 g/m^2, as a 4-hour intravenous infusion on Days 1–5 of each cycle with mesna, 240 mg/m^2, given intravenously 15 minutes prior to and 4 and 8 hours after ifosfamide initiation on Days 1–5 of each cycle; and gallium nitrate, 300 mg/m^2/day as a continuous intravenous infusion on Days 1–5 of each cycle. Calcitriol at 0.25 μg/day with dose escalation was administered as needed to manage hypocalcemia. Granulocyte-colony stimulating factor (G-CSF) was administered subcutaneously at 5 μg/kg/day beginning on Day 7 of each cycle and continuing until Day 13 with therapy beyond this point only if the total leukocyte count on Day 13 was <10,000/μL. Poor risk patients received the same drugs with a 20% dose decrease by administering vinblastine at 0.09 mg/kg on Days 1–2 of each cycle and by dropping Day 5 of ifosfamide, mesna, and gallium nitrate. G-CSF was initiated on Day 6 and continued until Day 12 using the same criteria as for good risk patients. Courses of VIG were scheduled to be repeated every 21 days, but were not started until the absolute neutrophil count was $\geq$ 1800/μL and platelet count was $\geq$100,000/μL. The doses of all 3 chemotherapy agents and mesna were reduced by 25% if patients experienced febrile neutropenia, a bleeding episode with a platelet count $\leq$ 40,000/μL, any platelet nadir < 20,000/μL, or any Grade 3 or 4 (common toxicity criteria) nonhematologic toxicity. Courses were to be repeated until either disease progression was documented or six cycles of therapy.

Baseline Data

Prior to study entry, all patients underwent physical examination and had their ECOG performance status and weight documented. There was also pretherapy determination of hemoglobin level, leukocyte count with differential, platelet count, serum levels of electrolytes, creatinine, calcium, magnesium, AST, and bilirubin as well as a urinalysis. A chest radiograph was required as was computed tomography of the chest and abdomen if these sites were used to evaluate measurable disease. A serum creatinine was done on Day 3 of each treatment cycle and serum calcium was done Days 2 and 4 of each cycle. Serum calcium, electrolytes, and creatinine were obtained weekly and at the start of each treatment cycle. Tumor measurements were performed with each cycle of therapy if determined by physical examination or every other cycle if evaluation required chest radiographs or computed tomographic scans. A complete response (CR) was defined as the complete disappearance of all clinically detectable disease measured by physical examination and/or radiographic studies for a period of at least 4 weeks. Categorization as a partial response (PR) re-

quired a ≥50% decrease in the sum of the products of the 2 longest perpendicular dimensions of all measurable lesions for a period of at least 4 weeks without an increase (≥25%) in the size of any area known to contain malignant disease and without the appearance of any new areas of malignancy. Progressive disease (PD) was defined as an increase of at least 25% in the size of measurable lesions or the development of any new lesions. Time to progression was measured from the time of initiation of therapy to the time PD was documented, and survival was measured from the initiation of therapy to the last clinic visit or death.

RESULTS

From November 1993 through February 1995, 48 patients were entered in this trial and were evaluable for toxicity. Two patients were ineligible for study entry due to protocol entry violations: one patient was entered with an elevated serum creatinine and the second patient had a large bladder tumor but no evidence of regional adenopathy or distant metastases. Of 45 eligible patients, 4 patients were not evaluable for response: 1 patient had a fatal myocardial infarction immediately after Cycle 1 of therapy, 1 patient developed a bowel obstruction believed to be unrelated to his bladder carcinoma and chemotherapy on Day 3 of Cycle 1 of therapy and underwent a laparotomy and was taken off study, a 3rd patient died suddenly of an unknown cause at home prior to being evaluated for response prior to Cycle 3, and a 4th patient received 1 cycle of therapy and then refused additional therapy or evaluation.

Clinical Characteristics and Treatment

Patient characteristics are listed in Table 1. The median age was 65 years (range, 37–78 years) with the majority of patients being male and having pure transitional cell histology. Forty-three patients had bladder primaries with 2 having the renal pelvis as the primary site. Twenty-five patients (55.5%) were stratified as poor risk with 12 patients having a solitary functioning kidney, 7 patients not meeting age criteria, 5 patients with prior therapy, and 1 patient with both age criteria ineligibility and previous therapy. Twenty-one patients (47%) had multiple sites of metastatic disease. The median number of VIG cycles administered for the entire group was four (range, one to six). Eleven patients (24%) required dose modifications of therapy because of myelosuppresion (6), neurologic changes including neuropathy and confusion (2), fatigue and decrease in performance status (2), and renal insufficiency (1). Seven of these 11 patients were stratified in the poor risk group.

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)
Age (yrs)	
Median (range)	65 (37–78)
Female	6 (13)
Poor risk	25 (56)
Performance status	
Median (range)	1 (0–2)
Histology	
Transitional cell	40 (89)
Adenocarcinoma	4 (9)
Mixed	1 (2)
Sites of Metastases	
Liver	3
Lung	14
Bone	11
Soft tissue/lymph nodes	32
Multiple sites	21

Toxicity

There were two treatment-related deaths among eligible patients. One patient was a 73-year-old male with hypertension without a cardiac history who had a myocardial infarction and died while hospitalized receiving Cycle 1 of therapy. The second patient was a 66-year-old male with a history of hypertension who died at home unexpectedly 20 days after his 3rd cycle of therapy. No autopsies were performed.

Clinically significant hematologic toxicity manifested primarily as leukopenia and anemia. Twenty-eight patients experienced ≥ Grade 3 leukopenia (15 Grade 3 and 13 Grade 4), although only 7 experienced febrile neutropenia. Thirty-one patients developed ≥ Grade 3 anemia (29 Grade 3 and 2 Grade 4).

Clinically significant nonhematologic toxicity was primarily cardiac with 5 patients with Grade 3 and 1 Grade 5 events including myocardial infarction (1 patient), atrial fibrillation, atrial flutter, supraventricular tachycardia, and congestive heart failure. Other toxicities included 3 patients each with Grade 3 or 4 emesis, pulmonary toxicity, and diarrhea, 6 with Grade 3 nausea, 13 with metabolic toxicity (12 Grade 3 and 1 Grade 4, primarily hypocalcemia), and 6 with Grade 3 neurologic events.

Response

Six CR and 14 PR were observed for an overall response rate of 44% (95% confidence interval, 30%, 60%) (4 patients who were inevaluable for response were considered to have PD). An additional patient met initial criteria for a PR; however, confirmatory tumor measurements were not repeated per protocol require-

TABLE 2
Poor versus Good Risk Response and Toxicity

	Good risk	Poor risk
No. of patients	20	25
No. of complete responders	2	4
No. of partial responders	6	8
Response rate (95% CI)	40% (19%, 64%)	48% (28%, 69%)
Grade 3–4 granulocytopenia	13	10
Grade 3–4 cardiac toxicity	2	3

CI: confidence interval.

ments and this patient was coded as having stable disease. Response and toxicity by risk stratification is detailed in Table 2. Response was correlated with the dominant site of metastatic disease. Objective responses were obtained in 1 of 3 patients (1 PR) with liver metastases, 5 of 13 patients (1 CR, 4 PR) with lung metastases, and 16 of 29 patients (6 CR, 10 PR) with soft tissue or lymph node metastases. There were no responses in the four patients with pure adenocarcinoma. One patient with mixed histology (transitional cell and squamous cell carcinoma) achieved a CR.

In the 20 responding patients, the median time to best objective response was 6 weeks (range, 5–15 weeks). The median duration of response in the 6 patients achieving CR was 47 weeks; 3 of these patients remained alive, 2 free of disease at 19 and 28 months, respectively. Four of 14 patients who achieved PR remained alive and disease free at 15, 15, 20, and 21 months, respectively. The median survival for all patients was 10 months.

DISCUSSION

The introduction in the mid 1980s of the two major cisplatin-based regimens M-VAC and CMV represented a significant development in the management of patients with advanced bladder carcinoma. Although a small subset of patients with metastatic urothelial carcinoma will achieve long term disease free survival,[13] these cisplatin-based regimens are frequently difficult to administer in a dose-intensive manner given the well known toxicities of the therapy, including myelosuppresion, mucositis, and significant fatigue. Despite efforts at dose intensification of the M-VAC regimen, it is increasingly clear that new directions will be necessary to improve the durability of responses, and the potential to impact on survival.[14] Over the last few years, several chemotherapeutic agents, including ifosfamide and gallium nitrate, have demonstrated single agent activity in patients with advanced urothelial carcinoma. Witte et al.,[7] treated 56 patients with ifosfamide who had failed 1 prior regimen and demonstrated a 21% response rate; several groups have reported response rates for gallium nitrate ranging from 17–27%.[11,15] Using basic oncologic principles of multiagent therapy, the authors felt it was logical to design the VIG regimen. The VIG regimen was piloted by Einhorn et al.[12] in 27 patients with advanced urothelial carcinoma who had not received prior chemotherapy for metastatic disease. The major toxicity observed was granulocytopenia, with eight patients developing febrile neutropenic events, and there was one treatment-related fatality. Toxicity was more severe in patients older than age 70, those with a solitary functioning kidney, prior neoadjuvant or adjuvant cisplatin-based therapy, or pelvic irradiation. Eighteen patients (67%) achieved an objective response, including 11 (41%) who attained a disease free status (5 with VIG alone and 6 with adjuvant surgery). Based upon these early results, the ECOG initiated this confirmatory Phase II trial.

As a result of the toxicity observed in the pilot Phase II trial, patients in this trial were stratified into good and poor risk groups. Poor risk was defined as patient age older than 70 years, those with a single functioning kidney, and those patients who had received prior cisplatin-based therapy in the adjuvant or neoadjuvant setting. Poor risk patients were treated with VIG at doses 20% less than good risk patients. Not surprisingly, the multiinstitutional experience demonstrated a lower response rate than reported in the pilot experience; however, VIG remained an active regimen with a 44% response rate, with 6 CR. Six of the responding patients remained alive and free of PD with follow-up ranging from 15–28 months. The toxicity associated with this regimen was considerable, but several features are noteworthy. Subsequent work with gallium-based therapies has convinced the authors that more aggressive efforts to maintain normocalcemia (higher doses of calcitriol or calcium carbonate) will obviate some of the toxicity observed in this trial. In addition, the high response rate and lower toxicity observed using the poor risk dose regimen suggests that this should become the preferred dosage and schedule for the VIG regimen.

The appropriate use of the VIG regimen in patients with advanced urothelial carcinoma remains undefined. Of the five patients who had received cisplatin-based combination therapy in either the adjuvant or neoadjuvant setting, three demonstrated responses (one CR, two PR). Anecdotally, other responses to VIG have been observed when it was used as salvage therapy (typically partial and of relatively brief duration) after M-VAC (Dreicer R, personal communication). The use of VIG as initial therapy for patients with ad-

vanced urothelial carcinoma is complicated by the lack of comparative data to the M-VAC standard and because it is a relatively intensive regimen that requires a relatively lengthy hospital stay with the potential for significant morbidity. In this era of increasing scrutiny of costs, changes in the standard of care must be justified by a significant impact on response, survival, or in some cases, a reduction in toxicity associated with similar response rates. Given the significant costs associated with the 96-hour hospitalization required to administer VIG, and the overlapping confidence intervals of the response rates of VIG and those reported for M-VAC, the authors do not believe that the results of this study warrant the resources required to conduct a Phase III trial comparing these regimens. In summary, VIG represents a novel, noncisplatin-containing regimen with moderate activity in patients with advanced urothelial carcinoma. The poor risk dose regimen should become the standard VIG regimen because of its activity and improved side effect profile. The ultimate utility of this regimen remains unclear.

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