Original Article

Vinflunine in Platinum-Pretreated Patients With Locally Advanced or Metastatic Urothelial Carcinoma

Results of a Large Phase 2 Study

David J. Vaughn, MD[1]; Sandy Srinivas, MD[2]; Walter M. Stadler, MD[3]; Roberto Pili, MD[4]; Daniel Petrylak, MD[5]; Cora N. Sternberg, MD[6]; David C. Smith, MD[7]; Sarah Ringuette, MD[8]; Edwin de Wit, MD[8]; Virginie Pautret, MD[9]; and Claude George, MD[10]

BACKGROUND: The activity and safety of vinflunine was evaluated in patients with locally advanced or metastatic urothelial carcinoma (UC) who developed disease progression within 12 months of platinum-containing chemotherapy. **METHODS:** Patients with UC were eligible if they received a prior platinum-based regimen in the neoadjuvant/adjuvant setting or as first-line treatment for advanced/metastatic disease and had developed disease progression within 12 months. Vinflunine was administered intravenously every 3 weeks. Patients with Karnofsky performance status of 80 or 90, impaired renal function, prior pelvic irradiation, or age $\geq$75 years received an initial dose of 280 mg/m^2, which was escalated to 320 mg/m^2 in Cycle 2 if well tolerated. All other patients received an initial dose of 320 mg/m^2. The primary endpoint was response rate defined by an independent response review committee (IRRC). **RESULTS:** Per the IRRC, 22 patients achieved a partial response, with a response rate of 15% (95% confidence interval, 9%-21%) with a median duration of response of 6.0 months. Sixty-four (42%) patients had stable disease. The median progression-free survival was 2.8 months, and the median overall survival was 8.2 months. Myelosuppression was the most frequent adverse event, with grade 3 of 4 (adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria [version 2.0] guidelines) neutropenia reported in 58% of the patients. Grade 3 of 4 febrile neutropenia occurred in 10 (7%) patients. Nonhematologic treatment-related events (grade 3 of 4) were generally manageable and included constipation (17%), asthenia/fatigue (13%), ileus (5%), and abdominal pain (5%). No cumulative toxicity was observed. **CONCLUSIONS:** Vinflunine demonstrates moderate activity in patients with platinum-pretreated UC. Toxicity is manageable and noncumulative. **Cancer 2009;115:4110–7. © 2009 American Cancer Society.**

KEY WORDS: platinum-containing chemotherapy, toxicity, urothelial carcinoma, vinflunine.

Corresponding author: David J. Vaughn, MD, Abramson Cancer Center of the University of Pennsylvania, 16 Penn Tower, 300 Spruce Street, Philadelphia, PA 19104; Fax: (215) 662-7804; david.vaughn@uphs.upenn.edu

[1]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Department of Medicine, Stanford University, Stanford, California; [3]Department of Medicine, University of Chicago, Chicago, Illinois; [4]Department of Medicine, Johns Hopkins University, Baltimore, Maryland; [5]Department of Medicine, Columbia University, New York, New York; [6]Department of Medicine, San Camillo Forlanini Hospital, Rome, Italy; [7]Department of Medicine, University of Michigan, Ann Arbor, Michigan; [8]Bristol-Myers Squibb, Wallingford, Connecticut; [9]Bristol-Myers Squibb, Braine L'Alleud, Belgium; [10]Bristol-Myers Squibb, Princeton, New Jersey

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The combination of methotrexate, vinblastine, doxorubicin, and cisplatin has been the comparative standard of care for metastatic urothelial cancer since it was demonstrated to increase survival over single-agent cisplatin in 1992.[1] The combination of gemcitabine and cisplatin was found to have similar efficacy in this population with a study designed to show superiority.[2,3] Nevertheless, because of a modest safety advantage, it has become 1 of the most frequently used regimens for the first-line treatment of urothelial carcinoma (UC) patients. Unfortunately, the vast majority of patients treated with combination cisplatin-based regimens develop progressive disease within 8 months of treatment, and the median survival is reported to be only 13 to 15 months.[2]

To our knowledge, there currently is no approved treatment option for the UC patients who develop disease recurrence or progression after a platinum-containing regimen. Multiple agents against both traditional and novel targets have been studied in small single-arm clinical trials in the second-line setting.[4-6] Despite initial enthusiasm for several, none had sufficient robust activity to generate a phase 3 trial.

Vinflunine is a novel microtubule inhibitor of the vinca alkaloid class.[7,8] Preclinical studies demonstrated that it has more activity than vinblastine or vinorelbine.[9,10] For example, in an orthotopic model of bladder cancer in mice, vinflunine was found to be more effective than vinorelbine.[11] The clinical activity of vinflunine was recently assessed in 51 bladder cancer patients from Europe who had received prior platinum treatment.[12] The response rate (RR) was 18% (95% confidence interval [95% CI], 8%-31%), with a median progression-free survival (PFS) of 3.0 months and a median overall survival (OS) of 6.6 months. Given these promising results, and the unmet need for second-line treatment, 2 trials were initiated evaluating the efficacy of vinflunine in this setting. The first was a multicenter, open-label, single-agent, large phase 2 trial, evaluating the activity of vinflunine in patients with UC who developed disease progression within 12 months of receiving platinum-based chemotherapy. For registrational purposes, this trial was performed largely in the United States; it is the subject of this report. The second was a phase 3 trial comparing best supportive care versus vinflunine plus best supportive care for platinum-pretreated UC patients. Initial results of this trial have been reported recently by Bellmunt Molins et al.[13]

PATIENTS

Eligible patients had histologically proven advanced or metastatic UC (excluding pure nontransitional histologies) that was not amenable to definitive regional/local therapy, with documented disease recurrence or progression within 12 months of the last dose of platinum-containing chemotherapy. At least 2 cycles of cisplatin ($\geq$60 mg/m^2) or carboplatin (area under the curve, $\geq$4) in any previous setting were required. Platinum-based chemotherapy could have been used in the metastatic, adjuvant, or neoadjuvant settings. Eligible patients were aged $\geq$18 years with a Karnofsky performance status (KPS) $\geq$80 and adequate hematologic (absolute neutrophil count $\geq$1500 cells/mm^3 and platelet count $\geq$100,000 cells/mm^3) and hepatic function (based on total serum bilirubin level and transaminases). Patients with renal impairment were eligible if the calculated creatinine clearance using the Cockcroft-Gault formula was $>$20 mL/min. Patients who received $>$1 previous chemotherapy regimen in any setting or prior radiation to $>$30% of the bone marrow, or those who had pre-existing peripheral neuropathy (grade 2 or higher), were deemed ineligible. The study was reviewed and approved by institutional review boards or ethical committees at the participating institutions, and all patients provided written informed consent.

VINFLUNINE ADMINISTRATION AND EVALUATION OF ENDPOINTS

Vinflunine was administered every 3 weeks as a 15-minute to 20-minute intravenous infusion. Based on initial experience with the tolerability of vinflunine and its partly renal clearance, patients with a KPS of 80 or 90, renal impairment (calculated creatinine clearance between 20 mL/min and 60 mL/min), prior pelvic irradiation, or age $\geq$75 years received an initial dose of vinflunine of 280 mg/m^2, which was escalated to 320 mg/m^2 in Cycle 2 if well tolerated. Other patients received an initial vinflunine dose of 320 mg/m^2, which could be reduced to 280 mg/m^2 or 250 mg/m^2 in subsequent cycles because of grade 3 of 4 toxicity. Treatment was discontinued if serious toxicity was again observed at the lower dose. No

dose re-escalation was allowed after dose reduction. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0) guidelines. To prevent constipation, dietary measures and laxatives were administered to patients from Day 1 to Day 5 or 7 of each cycle. Tumor assessments using computed tomography or magnetic resonance imaging were obtained within 4 weeks of study entry and were repeated every 6 weeks, using the same methods used at baseline. An independent response review committee (IRRC) reviewed all tumor assessments and determined the best response, and the duration of response or stable disease (SD) was determined according to the bidimensional modified World Health Organization criteria.[14]

STATISTICAL ANALYSIS

The primary objective of this trial was to confirm the activity of vinflunine demonstrated in the smaller phase 2 trial,[12] and to define the objective RR with more precision. The primary hypothesis of the trial was that vinflunine would result in a RR of approximately 15%. If the RR was determined to be >15%, the agent would be considered worthy of further study. The sample size was predetermined to achieve a desired CI width around the estimated RR. Assuming an estimated RR of 15%, for 150 patients, the exact 2-sided 95% CI would extend to a maximum width of 12%, and the lower limit of the CI would be ≥10%.

The primary endpoint was RR as defined by the IRRC. The secondary endpoints were duration of response, time to response, disease control rate, PFS, OS, and the safety profile of vinflunine.

All analyses were conducted on patients who received at least 1 dose of vinflunine (N = 151; 100%), except for duration of response and time to response, which were based on the response-evaluable population (N = 132; 87%). Duration of response, PFS, and OS were estimated using the Kaplan-Meier method.

RESULTS

Patient Characteristics

A total of 175 patients were enrolled, and 151 received at least 1 dose of vinflunine. Patient baseline characteristics are summarized in Table 1. As anticipated, the majority of the patients were male and elderly, with 17% of the patients aged ≥75 years. A high proportion of patients (40%) had renal impairment, defined with a calculated creatinine clearance between 20 mL/minute and 60 mL/minute. In accordance with the protocol, most patients with a decreased KPS, renal impairment, and/or age ≥75

Table 1. Summary of Patient Characteristics at Baseline (All Patients Treated)

Characteristic	Total, N = 151 (%)
Age, y	
Median	66
Range	31-83
<65	70 (46.4)
≥65 y	81 (53.6)
≥75 y	26 (17.2)
Sex	
Men	121 (80.1)
Women	30 (19.9)
Race	
White	130 (86.1)
Black	5 (3.3)
Asian	16 (10.6)
Karnofsky PS	
100	47 (31.1)
90	56 (37.1)
80	48 (31.8)
Renal impairment	
CrCl between 20 and 60 mL/min	61 (40.4)
Disease localization	
Urinary bladder	106 (70.2)
Other urinary localizations	45 (29.8)
Patients with at least 1 target lesion (IRRC)	140 (92.7)
No. of target lesions (IRRC)	
1	44 (29.1)
2	44 (29.1)
3	26 (17.2)
4	14 (9.3)
≥5	12 (7.9)
Patients with target lesions (IRRC)*	140 (92.7%)
Liver	76 (50.3%)
Lung	39 (25.8%)
Bladder	7 (4.6%)
Adrenal	3 (2.0%)
Kidney	1 (0.7%)
Spleen	1 (0.7%)
Lymph nodes and other target lesions†	90 (59.6%)
Patients without target lesions	11 (7.3%)

PS indicates performance status; CrCl, creatinine clearance; IRCC, independent response review committee.
* Patients may have disease in >1 site.
† Other target lesions may include visceral disease.

Table 2. Overall Response Rates According to the IRRC* and Investigators (N = 151)

Response	IRRC, No. (%)	Investigators, No. (%)
Best response		
Complete response	0 (0.0)	2 (1.3)
Partial response	22 (14.6)	13 (8.6)
Stable disease	64 (42.4)	68 (45.0)
Progressive disease	49 (32.5)	49 (32.5)
Not evaluable	16 (10.6)	19 (2.6)
Overall tumor response rate (%) (95% CI)	14.6% (9.4-21.2)	9.9% (5.7-15.9)

IRCC indicates independent response review committee; 95% CI, 95% confidence interval.
* Investigator and IRRC response assessments were concordant in 71% of patients.

years received an initial dose of 280 mg/m^2. Although the majority of the patients had UC of the urinary bladder, 30% had an upper tract or urethral UC. The IRRC review of the tumor assessments revealed that 11 (7%) patients did not have measurable disease at baseline. The majority of the patients (71%) had >1 measurable lesion, a large proportion of the lesions were metastatic to the lung or to the liver, and approximately half of the patients had visceral disease (49%). All patients had received prior platinum-containing chemotherapy, combined with gemcitabine in 91% of the patients, in either the neoadjuvant (4%), adjuvant (32%), or metastatic (61%) settings. Several patients had received both cisplatin and carboplatin. The time between prior chemotherapy and disease progression was <6 months in 77% of patients and <3 months in 54%. The interval was ≥12 months in 3 (2%) patients. Nearly all patients (93%) underwent primary definitive surgery for their UC, and 12% had received pelvic radiotherapy.

Efficacy Evaluation

The median duration of treatment was 9.3 weeks (range, 1.1 weeks-64.1 weeks), and the median duration of follow-up was 11.9 months. Per IRRC review, the RR was 15% (95% CI, 9%-21%, based on 151 subjects and 22 responses), and the median duration of response was 6.0 months (95% CI, 5.4 months-9.5 months). The IRRC response rate was higher than the investigators' assessed RR (Table 2). SD was observed in 64 patients (42%), with a median duration of disease stabilization of 4.0 months (95% CI, 3.5 months-4.7 months). The median time to response was 1.4 months (95% CI, 1.2 months-3.0 months), the median PFS was 2.8 months (95% CI, 2.6 months-3.8 months), and the median overall survival was 8.2 months (95% CI, 6.8 months-9.6 months) (Fig. 1), with 31% of the patients receiving subsequent chemotherapy. In the 132 evaluable patients as per IRRC, the overall RR was 16% (95% CI, 10%-23%), and 45% achieved SD. In a predefined subset analysis, responses were observed in patients with visceral disease (RR, 9%; 95% CI, 4%-19%), an estimated creatinine clearance between 20 mL/minute to 60 mL/minute (RR, 13%; 95% CI, 6%-24%), Karnofsky performance status of 80 (RR, 10%; 95% CI, 4%-23%), and age ≥65 years (RR, 21%; 95% CI, 13%-32%).

Safety Evaluation

A total of 577 cycles of vinflunine were administered, with a median of 3 cycles per patient (range, 1 cycle-21 cycles). Forty (26%) patients received an initial dose of 320 mg/m^2; this was reduced to ≤280 mg/m^2 in Cycle 2 in 13 patients with a relative dose intensity over the median 2 administered cycles of 99% (range, 67%-116%). For the 111 (74%) patients who received an initial dose of 280 mg/m^2, 41 (37%) had a dose escalation to 320 mg/m^2, and 22 (20%) had a dose reduction, giving a relative dose intensity of 93% (range, 42%-101%) over the median 3 administered cycles. Thirty-nine (26%) of 151 patients had a delay in at least 1 cycle of treatment.

The main toxicity of vinflunine was hematologic (Table 3), with grade 3 of 4 neutropenia reported in 58% of the patients, leukopenia in 49%, and anemia in 16%. However, severe thrombocytopenia was rare (3% of the patients). Ten (7%) patients experienced febrile neutropenia; in none of the patients did this lead to study discontinuation. Grade 3 of 4 nonhematologic treatment–related adverse events (Table 4) included constipation (17% of the patients), asthenia/fatigue (13%), abdominal pain (5%), and ileus (5%). Constipation was most prevalent during the first cycle. Despite the prior treatment with platinum, peripheral neuropathy was rare, and only 1 patient (1%) experienced grade 3 atypical peripheral sensory neuropathy. This safety profile was similar in patients with renal impairment, in whom vinflunine did not induce a deterioration of renal function.

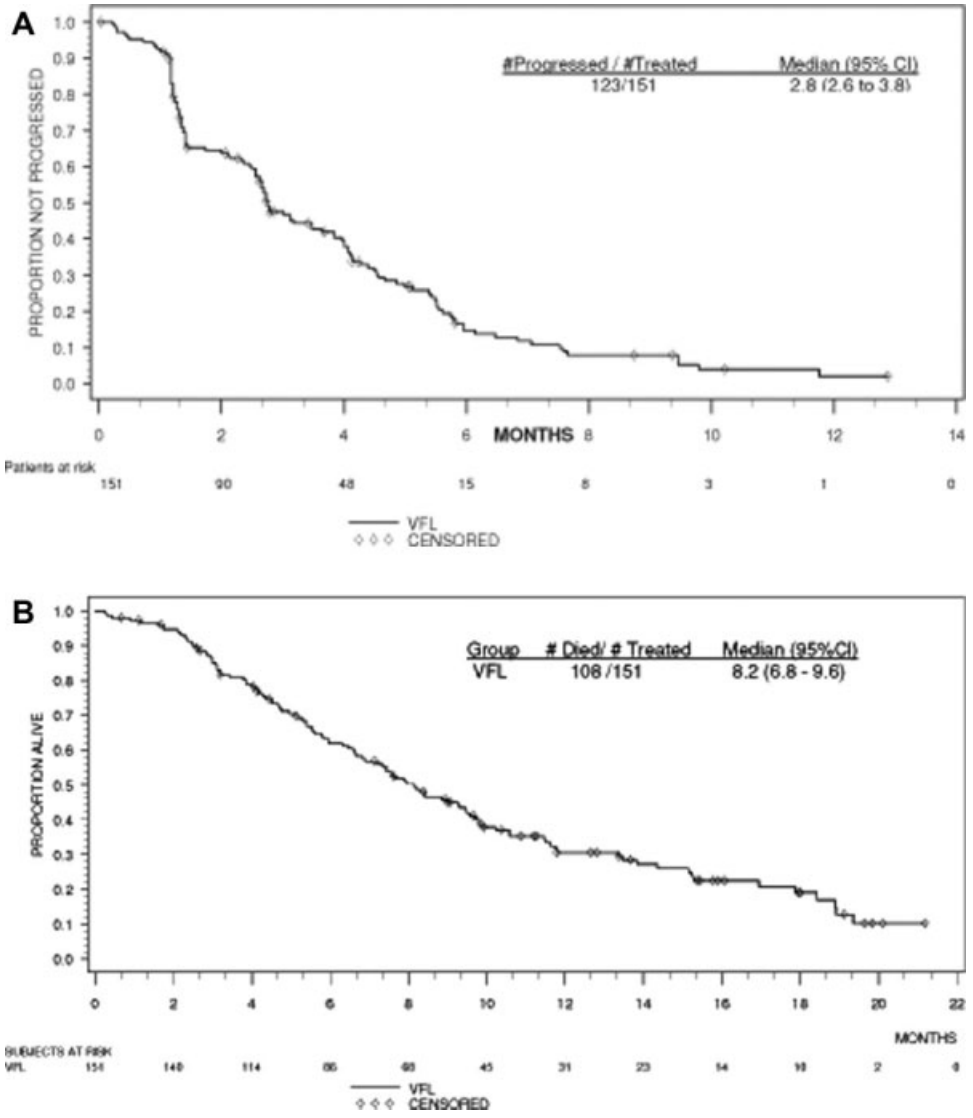

FIGURE 1. (A) Kaplan-Meier estimates by an independent response review committee of progression-free survival and (B) Kaplan-Meier estimates of overall survival are shown. 95% CI indicates 95% confidence interval; VFL, vinflunine.

Twenty-two (15%) patients discontinued treatment because of vinflunine-related adverse events. Two (1%) treatment-related deaths were reported, 1 because of myocardial infarction in an 83-year-old patient during the 4th cycle, and the other because of neutropenic sepsis during the first cycle in a patient with several risk factors.

DISCUSSION

The results of the current study indicate that vinflunine has moderate activity in platinum-pretreated patients with advanced UC. The RR defined by the IRRC was similar to the estimate identified at study design, and confirmed the RR previously obtained with single-agent vinflunine in this patient population.[12] Responses were observed in all subsets of patients, including those with poor prognostic factors (visceral disease and decreased KPS) or with unfavorable characteristics (renal impairment, advanced age, and refractory disease defined as disease recurring <3 months after last prior therapy).

To our knowledge the current phase 2 study is the largest ever performed in this setting; a review of the

Table 3. Hematologic Laboratory Abnormalities

Abnormality	Total, N = 148, No. (%)		Initial Dose of 280 mg/m^2, N = 109, No. (%)		Initial Dose of 320 mg/m^2, N = 39, No. (%)	
	Overall	Grade* 3/4	Overall	Grade 3/4	Overall	Grade 3/4
Leukopenia	129 (87.2)	73 (49.3)	92 (84.4)	51 (46.8)	37 (94.9)	22 (56.4)
Neutropenia	122 (82.4)	86 (58.1)	89 (81.7)	58 (53.2)	33 (84.6)	28 (71.8)
Anemia	144 (97.3)	23 (15.5)	107 (98.2)	18 (16.5)	37 (94.9)	5 (12.8)
Thrombocytopenia	90 (60.8)	5 (3.4)	66 (60.6)	4 (3.7)	24 (61.5)	1 (2.6)

*Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0) guidelines.

Table 4. Non–Hematologic Treatment-Related Adverse Events*

Adverse Event	All Treated Patients, N = 151, No. (%)		Initial Dose of 280 mg/m^2, N = 111, No. (%)		Initial Dose of 320 mg/m^2, N = 40, No. (%)	
	Overall	Grade 3/4	Overall	Grade 3/4	Overall	Grade 3/4
Constipation	96 (63.6)	25 (16.6)	70 (63.1)	17 (15.3)	26 (65.0)	8 (20.0)
Asthenia/fatigue	91 (60.3)	19 (12.6)	68 (61.3)	15 (13.5)	23 (57.5)	4 (10.0)
Nausea	68 (45.0)	5 (3.3)	55 (49.5)	5 (4.5)	13 (32.5)	—
Local injection/infusion site reactions†	54 (35.8)	1 (0.7)	43 (38.7)	—	11 (27.5)	1 (2.5)
Vomiting	38 (25.2)	3 (2.0)	33 (29.7)	2 (1.8)	5 (12.5)	1 (2.5)
Abdominal pain‡	36 (23.8)	7 (4.6)	27 (24.3)	7 (6.3)	9 (22.5)	—
Stomatitis/mucositis	34 (22.5)	5 (3.3)	21 (18.9)	2 (1.8)	13 (32.5)	3 (7.5)
Diarrhea	28 (18.5)	3 (2.0)	21 (18.9)	2 (1.8)	7 (17.5)	1 (2.5)
Myalgia	27 (17.9)	4 (2.6)	16 (14.4)	2 (1.8)	11 (27.5)	2 (5.0)
Peripheral sensory neuropathy§	17 (11.3)	1 (0.7)	10 (9.0)	—	7 (17.5)	1 (2.5)
Febrile neutropenia	10 (6.6)	10 (6.6)	4 (3.6)	4 (3.6)	6 (15.0)	6 (15.0)
Ileus	8 (5.3)	7 (4.6)	6 (5.4)	6 (5.4)	2 (5.0)	1 (2.5)
Cardiac arrhythmia	4 (2.6)	2 (1.3)	1 (0.9)	—	3 (7.5)	2 (5.0)
Infections with severe neutropenia	3 (2.0)	3 (2.0)	3 (2.7)	3 (2.7)	—	—
Extravasation	2 (1.3)	—	2 (1.8)	—	—	—
Immediate hypersensitivity‖	2 (1.3)	—	2 (1.8)	—	—	—
Intestinal obstruction	1 (0.7)	1 (0.7)	1 (0.9)	1 (0.9)	—	—
Myocardial infarction/ischemia	1 (0.7)	1 (0.7)	1 (0.9)	1 (0.9)	—	—

*Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0) guidelines.
†Includes injection site reaction, pain, irritation, rash, erythema, and hypersensitivity, as well as infusion site pain, reaction, erythema, and phlebitis.
‡Includes abdominal pain, lower abdominal pain, and upper abdominal pain.
§Includes paresthesia, hypoesthesia, neuropathy, neuropathy peripheral, and peripheral sensory neuropathy.
‖Includes hypersensitivity and generalized pruritus.

literature indicates that, to date, all trials performed with single agents in the second-line setting included <60 patients.[4-6] Because patient populations are different between studies, one cannot compare efficacy endpoints among studies.

The high frequency of renal impairment in this patient population is an important point. The causes of renal impairment are multiple, including disease-related (ureteral obstruction), treatment-related (prior nephrectomy, nephrotoxicity of cisplatin), and patient-related (age, comorbidities) factors. Vinflunine has a mixed metabolism through the liver (approximately two-thirds) and the kidney, a characteristic that makes it potentially advantageous for the treatment of UC.[14] Vinflunine did

not demonstrate any evidence of nephrotoxicity, even in the patient population with impaired renal function.

The safety profile of vinflunine in this study is similar to a previous pooled analysis of several clinical trials.[15] The main toxicity of vinflunine is hematologic. Although the incidence of grade 3 of 4 neutropenia was found to be high with vinflunine (58%), the frequency of febrile neutropenia was low (7%), and this adverse event was not a cause for study discontinuation. Of note, a patient with poor risk factors died in the first cycle from severe sepsis; therefore, prophylactic measures such as growth factors and/or antibiotics should be implemented in such patients.

The main nonhematologic adverse events were fatigue and constipation, which were both noncumulative and reversible. Constipation was most frequently observed during the first cycle, indicating that it was most likely not because of neurotoxicity. Prophylactic measures against constipation must be used, especially in patients with an increased risk for constipation, such as the use of opioid analgesics. Despite prior treatment with platinum compounds, the incidence of peripheral neuropathy was low after vinflunine, something that was predicted based on the characteristics of the microtubule binding of vinflunine.[15] However, the relative low incidence of neurotoxicity could in part be related to the finding that the median number of cycles received was only 3, thus limiting the potential for cumulative toxicity. In this study, 2 initial dose levels of vinflunine were used based on the baseline characteristics of the patients. It does not appear that the safety profile of vinflunine is different according to the initial dose, a satisfactory result because patients receiving the lower dose had an unfavorable profile (decreased KPS, renal impairment, and/or pelvic irradiation).

New agents with improved efficacy and adequate tolerability are needed for patients with advanced UC who have received previous platinum-based regimens, a patient population for which to our knowledge no standard of care exists. Therapy for these patients is further complicated by poor performance status, comorbidities, and inadequate renal function. In this respect, vinflunine is moderately active and has a manageable and noncumulative toxicity profile without nephrotoxicity.

Conflict of Interest Disclosures

Sponsored by Bristol-Myers Squibb.

Drs. de Wit, George, Pautret, and Ringuette are employees of Bristol-Myers Squibb and own stock in the company.

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