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The High Incidence of Vascular Thromboembolic Events in Advanced Urothelial Cancer Treated with Platinum Chemotherapy Agents

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Abstract

Background—This study compared the incidence of vascular thromboembolic events (VTEs) in advanced urothelial carcinoma (UC) patients treated with either gemcitabine/carboplatin (GCb), gemcitabine/carboplatin/bevacizumab (GCbBev) or gemcitabine/cisplatin (GCis).

Patients and Methods—Patients with advanced UC treated with GCbBev on protocol were analyzed prospectively and two contemporary control cohorts receiving GCb or GCis were obtained retrospectively. VTE was defined as either venous or arterial (myocardial infarctions or cerebral vascular accidents) thrombosis. VTEs were treatment-related if they occurred between the start of treatment and 4 weeks after completion of chemotherapy. Associations with chemotherapy regimen were tested using either the Fisher's exact test or Kruskal-Wallis test. Clinical factors associated with VTEs were analyzed using conditional logistic regression stratified by treatment regimen.

Results—Among 198 patients, VTEs occurred in 13/51 (26%) GCbBev patients, 22/92 (24%) GCb patients and 8/55 (15%) GCis patients. Patient characteristics were significantly different between treatment cohorts in terms of age, prior cystectomy, tumor near pelvic vessels, Khorana risk group and anti-platelet therapy. The type of chemotherapy was not associated with any VTEs or type of VTEs (arterial vs. venous). Prior cystectomy was associated with increased risk of VTEs (OR 2.2, 95% CI 1.0–4.9, p=0.047).

Conclusions—This is the largest series reporting VTEs in UC patients treated with first–line combination platinum-based therapy. The incidence of VTE in cisplatin-treated patients is similar to prior reports. However, the VTE rate in carboplatin-treated patients had not been previously

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defined and thus represents a new baseline. The addition of bevacizumab does not appear to increase VTE risk. This high incidence of carboplatin-related VTEs warrants further study.

Keywords

bladder cancer; thrombotic events; thromboembolic; urothelial carcinoma; deep venous thrombosis; pulmonary embolism; bevacizumab; carboplatin chemotherapy; cisplatin chemotherapy

INTRODUCTION

Cancer and cancer therapy, including chemotherapy and vascular endothelial growth factor (VEGF) targeted therapies, have been associated with an increased incidence of VTEs: deep venous thrombosis (DVT), pulmonary embolus (PE), arterial thrombosis and embolus, cerebrovascular accident (CVA), and unstable angina (UA)/myocardial infarction (MI). A population-based case control study showed that VTE risk was increased sevenfold in patients with cancer.[1] Patients with metastatic disease and those undergoing chemotherapy are at highest risk of VTEs[1–5] and these events can be a leading cause of death in cancer patients.[4, 6, 7] The hypercoagulable and thrombotic state in cancer patients may be due to multiple mechanisms including activation of the coagulation cascade through the release of tissue factors and other procoagulants, changes in cellular blood components, increased platelet aggregation, and endothelial cell damage by tumor cells.[8] Chemotherapeutics may magnify this effect and promote VTEs by worsening endothelial damage, enhancing platelet aggregation, and increasing oxidative damage leading to vascular toxicity.[9]

The cancers thought to have highest risk of chemotherapy-related VTEs are gastric and pancreas adenocarcinomas, with thoracic, lymphoma, gynecologic, bladder, and testicular cancers considered to have a moderate risk.[10] Among platinum-based chemotherapy agents, cisplatin is reported to have a high incidence of treatment-related VTE.[9, 11–14] In a retrospective study of 932 patients with various tumor types treated with cisplatin-based chemotherapy, there was an 18% incidence of VTEs.[15] A separate meta-analysis revealed a significantly increased risk of VTEs associated with cisplatin-based regimens (RR, 1.67; 95% CI, 1.25 to 2.23; p=0.01).[16] Cisplatin-based chemotherapy combinations are standard, first-line treatment in advanced UC and are associated with a 13% incidence of venous thromboembolism.[17]

While cisplatin is the treatment of choice in the neoadjuvant[18, 19], adjuvant[20], and advanced UC disease settings[21], patients are often ineligible for the drug due to co-morbid factors such as age, renal insufficiency, cardiac complications, and hearing loss.[22] Carboplatin, another platinum-based agent, is frequently substituted for cisplatin based on a more favorable side effect profile. Although there is a clinical impression that VTEs occur at a lower rate in patients receiving platinum analogs such as carboplatin and oxaliplatin, there are minimal published data on these agents and their associated risk of VTEs.[9, 13, 23] Gemcitabine is also frequently used in UC in combination with cisplatin or carboplatin.[21, 24–28] Gemcitabine in combination with a platinum-agent has been associated with increased thrombotic and vascular side effects[14, 29–31] in contrast to studies on its use as a single agent in the treatment of UC.[27, 32, 33]

In the treatment of advanced cancers, vascular endothelial growth factor (VEGF) inhibitors have been added to standard chemotherapy agents to improve overall survival, albeit at the expense of an apparent increased incidence of VTEs. A large meta-analysis (n=7,956) demonstrated higher rates of all-grade (11.9%) and high grade (6.3%) venous thromboembolic events in patients treated with VEGF inhibitor bevacizumab compared to non-VEGF controls.[34] Another pooled analysis of breast, colon and non-small cell lung cancer (NSCLC) patients showed an increased risk for arterial thromboembolic events.[35] Other VEGF targeted therapies (sunitinib, sorafenib) have also been associated with an increased incidence of arterial thromboembolism.[36]

The role of bevacizumab in VTE risk in advanced UC and other cancers is controversial. A phase II study in 43 chemotherapy-naive patients treated with GCisBev reported an overall response rate of 72% and a median overall survival of 19.1 months,[37] both improvements to historical data.[21] However, the rate of DVT/PE was 39% in the initial 18 patients, with an additional patient experiencing sudden cardiac death. After a protocol amendment reduced the gemcitabine dose from 1200mg/m^2 to 1000mg/m^2, the DVT/PE rate in the remaining patients decreased to 8% (2/25) resulting in a final 21% overall rate of DVT/PE. The largest published trial exploring GCbBev was a phase III randomized control trial in women with platinum-sensitive ovarian, primary peritoneal or fallopian tube cancers. In this trial of 484 women, the VTE rates of GCb with or without Bev were 6.9% and 3.4%, respectively.[38] In contrast, a prospective phase II study of GCbBev in patients with advanced UC unfit for cisplatin-based therapy reported a DVT/PE incidence of 20%.[39]

The concerning rate of VTEs in UC patients, specifically those treated with platinum analogs and VEGF targeted therapies, prompted us to conduct this study. The primary objective of this analysis was to determine the incidence of VTE in UC patients treated with platinum agents (cisplatin or carboplatin) alone or in combination with bevacizumab.

METHODS

Patients

Data from previously untreated patients with advanced UC who were prospectively registered to an IRB approved protocol of GCbBev from 6/2006 to 6/2010 were reviewed. The treatment schedule was one loading dose of bevacizumab 10 mg/kg followed 2 weeks later by 6 cycles of gemcitabine (1,000 mg/m2 on day [d]1 and d8) plus carboplatin (AUC 5 or 4.5 based on physician determination of patient ability to tolerate higher dose of drug) and bevacizumab 15 mg/kg on d1 every 21 days followed by maintenance bevacizumab at 21d intervals for one year. Two contemporary chemotherapy-naïve advanced UC control groups who received GCb or GCis for a planned 6 cycles were retrospectively identified. The contemporary control group's chemotherapy dosing (dose levels, modifications or discontinuation) was determined by treating physician. All patients were evaluated for incidence of VTEs (PE, DVT, CVA and UA/MI), baseline demographic data, and relevant clinical history including previous pelvic surgical, baseline anticoagulation use (anti-platelet, vitamin K antagonist or low molecular weight heparin), history of previous intravenous catheter (IVC) filter placement, central venous access device placement and MSKCC risk group status (performance status and sites of disease). Patients with simultaneous PE and

DVT were considered to have one VTE. Only treatment-related VTEs were evaluated as part of this study and an event was considered to be treatment-related if the event occurred in the interval between the first dose of chemotherapy and 4 weeks after the last dose of chemotherapy. Khorana risk score was calculated using derived and validated factors including: body mass index (BMI), history of exposure to erythropoiesis-stimulating agents within 3 months, and white blood cell (WBC), platelet and hemoglobin counts.

Statistical Analysis

Associations between chemotherapy regimen cohort and categorical characteristics were analyzed using Fisher's exact test. The number of metastatic sites and Khorana risk score were treated as continuous variables, and associations with chemotherapy regimen cohort were analyzed using the Kruskal-Wallis test. Because there were differences in patient characteristics by chemotherapy regimen received, risk factors associated with VTEs were analyzed using conditional logistic regression, with chemotherapy regimen cohort as the stratification variable. Statistical significance was defined as a p-value <0.05. Analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Characteristics of 198 patients by treatment group are shown in Table 1. The majority of patients were treated with carboplatin-based treatment (N=143) in contrast to cisplatin-based therapy (N=55). As expected, most primary tumors were in the bladder for all cohorts (60.8 to 76.4%) and the majority of patients had pure transitional cell histology (61.8 to 80.4%). Differences in age distributions were observed among the three cohorts. The GCb cohort included the highest percentage of patients age ≤ 65 (81.5%), followed by GCbBev (60.8%), with substantially fewer among those treated with GCis (38.2%) (p<.001). These age distributions indicate that our center treats a population of patients who are cisplatin-ineligible due to co-morbidities rather than those who are ineligible solely due to age-related renal dysfunction.

Marked differences existed in the percentage of patients who had received prior definitive surgery to manage their disease. A prior cystectomy was less frequently performed prior to treatment in the GCis-treated cohort (5.5%), while over half of all patients on the prospective trial of GCbBev (64.7%) received prior surgery. Consequently, there were differences in patients with existing tumor near pelvic vessels prior to chemotherapy, highest in those treated with GCis at 69.1% and approximating 50% in the carboplatin-treated cohorts. The majority of patients had either 1 or 2 MSKCC poor risk features, with Karnofsky performance status < 80 ranging from 11.8% to 23.9% in the various cohorts.

The Khorana score is a validated prediction model designed to risk-stratify patients with cancers undergoing systemic chemotherapy for their treatment-related thrombosis risk. The score is derived using 5 predictive variables: site of cancer, platelet count ≥ 350,000, hemoglobin < 10g/dL and/or use of erythropoiesis-stimulating agents, white blood cell count >11,000, and body mass index ≥ 35 kg/m2. The majority of patients in each cohort were categorized as Khorana risk group 1 or group 2 with 80.4%, 72.7% and 69.6% in the GCbBev, GCis, and GCb categories, respectively. At least half of all patients had been

exposed to erythropoiesis-stimulating agents and/or had central venous access devices. Finally, the use of anti-platelet therapy was unevenly distributed across the three groups, with approximately 50% fewer patients in the GCis cohort receiving therapy compared to either other cohort.

When comparing baseline characteristics of patients treated with the three chemotherapy regimens, age (≤65 vs. >65; p<0.001), prior cystectomy (p<0.001), tumor near pelvic vessels (p=0.027), Khorana risk group (p=0.025), and anti-platelet therapy (p=0.036) were significantly associated with the chemotherapy regimen, reflecting cohort-specific differences. In contrast, other baseline characteristics including race, gender, performance status, bladder (vs non-bladder) primaries, and pure transitional cell carcinoma (TCC) vs TCC with foci of mixed histologies were within expected distributions for this population treated at our center. Analysis indicated that significant differences in these distributions did not exist across the cohorts.

The incidence of VTEs with each chemotherapy regimen is shown in Table 2. VTEs occurred in 13/51 (26%) GCbBev patients, 22/92 (24%) GCb patients, and 8/55 (15%) GCis patients. The combined VTE incidence in carboplatin-treated patients was 24%. The specific chemotherapy regimen was not significantly associated with any VTE (p=0.300) or with type of VTE (p=0.111) in univariate analysis (Table 2). We also evaluated associations between patient characteristics and VTEs (Table 3). The only factor significantly associated with an increased risk of VTEs was a history of prior cystectomy (p=0.047).

DISCUSSION

Although VTEs may lead to increased rates of morbidity and mortality in patients with solid tumors undergoing systemic chemotherapy, advanced UC is associated with only a moderate risk of VTE. Based on the incidence of VTE in patients treated on an IRB-approved protocol of GCbBev, which was found to be higher than the incidence historically observed in patients treated with standard-of-care GCis chemotherapy [39, 40], we sought to further characterize the incidence of VTEs in UC patients receiving platinum-based chemotherapy. This study observed a continued high incidence of VTEs regardless of platinum analogue, with a particularly high incidence among those who received carboplatin-based treatment (24%). Although the VTE incidence seen with carboplatin-based therapy was not statistically different from patients treated with cisplatin-based regimens (15%), it does raise clinical concerns because patients with previous/recent thromboembolic or cardiac events are frequently offered carboplatin rather than cisplatin based on the drug's perceived decreased thrombogenic potential.

The frequency of VTEs associated with bevacizumab therapy is controversial. The above-mentioned phase III trial in ovarian cancer is the largest experience with GCbBev; that study reported a 6.9% VTE rate in patients treated with all three drugs.[38] Two small phase II trials also tested gemcitabine, carboplatin and bevacizumab in advanced NSCLC. One trial using a similar chemotherapy dosing regimen to our center's GCbBev trial reported a VTE rate of 2.1%[41], and the other, using a more aggressive dosing regimen of biweekly gemcitabine, reported a 17.1% incidence.[42] The initial high rate of VTEs in the phase II trial of GCisBev

for UC patients also raised concerns regarding bevacizumab-associated VTEs. That high rate of DVT/PE prompted the investigators to reduce the dose of gemcitabine, which substantially decreased the incidence of VTEs in subsequent patients. These reports lend credibility to the concept that the observed VTEs may have been a consequence of gemcitabine dose/exposure and not the use of bevacizumab. The definitive impact of bevacizumab on the risk of VTEs in UC patients awaits the results of a phase III trial comparing GCis with and without bevacizumab. [37]

Although urothelial, thoracic and gynecologic malignancies treated with systemic chemotherapy are thought to have a similar VTE risk[10], this generalization may be inaccurate. Our reported VTE incidence in UC patients treated with carboplatin is the highest reported incidence of VTE among patients treated this therapy, and is in fact higher than that seen in NSCLC and ovarian cancer. It could be hypothesized that the higher incidence of VTE in UC patients in contrast to NSCLC is due to higher rates of pelvic surgery. Ovarian cancer patients also receive pelvic surgery prior to chemotherapy, however, suggesting that surgery alone does not explain these findings. Thus, it is conceivable that UC may have a higher intrinsic VTE rate than other solid tumors when treated with chemotherapy.

Previous radical cystectomy was significantly associated with an increased risk of VTEs (OR 2.2, 95% CI 1.01–4.86) in an analysis stratified by chemotherapy regimen; this observation raises questions regarding the thrombogenic nature of cystectomy. Radical cystectomy may increase local pro-thrombogenic factors and increase the propensity for VTEs. While we would not use this finding to recommend empiric VTE prophylaxis in patients who have undergone a radical cystectomy and are receiving platinum-based treatments, future research into whether the post-surgical state enhances VTE risk in platinum-treated patients is warranted.

The Khorana score, a predictive model for chemotherapy-associated thrombosis, was assessed for correlation in this analysis and did not achieve significance.[10] This lack of impact may have been the result of different patient populations in the two studies. The Khorana study included only patients who received a maximum of 4 cycles of chemotherapy (in contrast to 6 cycles in this study), included only venous thromboembolic events (vs. both venous and arterial events), and had differences in baseline risk classifications. While approximately 27% of patients were considered low-risk (score=0) in the Khorana study, there were no low-risk patients in our population due to the fact that all patients had urothelial primary tumors (which are scored as high-risk sites of disease in the predictive model). This lack of low-risk patients in the MSKCC study resulted in a higher incidence of high-risk patients (26.8% vs 11%) and intermediate-risk patients (73.2% vs. 60%) , respectively, compared to the patient population in the Khorana study.

A clear limitation of any analysis across chemotherapy regimens is the baseline differences between cohorts. As was demonstrated in Table 1, age, prior cystectomy, tumor near pelvic vessels, Khorana risk group, and baseline anti-platelet therapy were all significantly associated with treatment cohort (all $p<0.05$). Each of these factors could potentially

contribute to an increased or decreased risk of VTEs and therefore confound any subsequent analysis.

In summary, patients with advanced UC treated with either cisplatin- or carboplatin-based chemotherapy are at high risk for VTE. The incidence of VTE observed with carboplatin therapy was higher than expected given the limited information from existing carboplatin literature and a contemporary prospective study in ovarian cancer. Bevacizumab, when added to carboplatin, did not increase VTE risk in this study. These observations add to our understanding of adverse effects associated with platinum-based therapy for advanced UC, though the causes and impact of chemotherapy-associated VTEs warrant further investigation.

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Table 1

Patient characteristics by chemotherapy regimen.

	GCbBev (n=51; 26%)	GCis (n=55; 28%)	GCb (n=92; 46%)	p-value[1]
Age				<.001
≤ 65	31 (60.8)	21 (38.2)	75 (81.5)	
> 65	20 (39.2)	34 (61.8)	17 (18.5)	
Sex				0.264
Male	37 (72.5)	44 (80.0)	62 (67.4)	
Female	14 (27.5)	11 (20.0)	30 (32.6)	
Race				0.494
White	48 (94.1)	50 (90.9)	82 (89.1)	
Black	0 (0.0)	2 (3.6)	6 (6.5)	
Asian	2 (3.9)	1 (1.8)	3 (3.3)	
Other	1 (2.0)	2 (3.6)	1 (1.1)	
Primary site				0.267
bladder	31 (60.8)	42 (76.4)	67 (72.8)	
renal pelvis	18 (35.3)	10 (18.2)	16 (17.4)	
ureter	2 (3.9)	0 (0.0)	3 (3.3)	
bladder/renal pelvis	0 (0.0)	1 (1.8)	3 (3.3)	
renal pelvis/ureter	0 (0.0)	1 (1.8)	1 (1.1)	
urethra	0 (0.0)	1 (1.8)	1 (1.1)	
bladder/ureter/renal pelvis	0 (0.0)	0 (0.0)	1 (1.1)	
Histology				0.103
TCC	41 (80.4)	34 (61.8)	64 (69.6)	
TCC mixed	10 (19.6)	21 (38.2)	28 (30.4)	
Prior pelvic surgery < 3mo	4 (7.8)	9 (16.4)	8 (8.7)	0.275
Prior Cystectomy	33 (64.7)	3 (5.5)	26 (28.3)	<.001
Tumor near pelvic vessels	23 (45.1)	38 (69.1)	46 (50.0)	0.027
Number of metastatic sites				0.525
0	0 (0.0)	0 (0.0)	3 (3.3)	
1	24 (47.1)	32 (58.2)	41 (44.6)	
2	12 (23.5)	11 (20.0)	28 (30.4)	
3	11 (21.6)	9 (16.4)	13 (14.1)	
4	4 (7.8)	1 (1.8)	6 (6.5)	
5	0 (0.0)	2 (3.6)	1 (1.1)	
Karnofsky performance status, N (%)				0.124
≤ 70	6 (11.8)	7 (12.7)	22 (23.9)	
> 70	45 (88.2)	48 (87.3)	70 (76.1)	
MSKCC risk group				0.225

	GCbBev (n=51; 26%)	GCis (n=55; 28%)	GCb (n=92; 46%)	p-value[1]
0	14 (27.5)	24 (43.6)	32 (34.8)	
1/2	37 (72.5)	31 (56.4)	60 (65.2)	
BMI				0.773
≥ 35	3 (5.9)	3 (5.5)	8 (8.7)	
< 35	48 (94.1)	52 (94.5)	84 (91.3)	
WBC				0.868
> 11	6 (11.8)	8 (14.5)	14 (15.2)	
≤ 11	45 (88.2)	47 (85.5)	78 (84.8)	
PLT				0.181
≥ 350	12 (23.5)	13 (23.6)	33 (35.9)	
< 350	39 (76.5)	42 (76.4)	59 (64.1)	
HGB				0.272
< 10	3 (5.9)	4 (7.3)	13 (14.1)	
≥ 10	48 (94.1)	51 (92.7)	79 (85.9)	
Exposure to erythropoiesis-stimulating agents and/or central venous line/ catheter				0.185
Any	27 (52.9)	38 (69.1)	61 (66.3)	
None	24 (47.1)	17 (30.9)	31 (33.7)	
Khorana risk group				0.021
1	25 (49.0)	17 (30.9)	22 (23.9)	
2	16 (31.4)	23 (41.8)	42 (45.7)	
3	9 (17.6)	11 (20.0)	22 (23.9)	
4	1 (2.0)	4 (7.3)	5 (5.4)	
5	0 (0.0)	0 (0.0)	1 (1.1)	
IVC filter	1 (2.0)	4 (7.3)	2 (2.2)	0.290
Anticoagulation	3 (5.9)	8 (14.5)	14 (15.2)	0.231
ASA/Plavix	9 (17.6)	5 (9.1)	24 (26.1)	0.036
Bleeding issues	6 (11.8)	1 (1.8)	6 (6.5)	0.110
Pretreatment history of VTE	2 (3.9)	8 (14.5)	8 (8.7)	0.155

[1] p-value from Fisher's exact test when categorical or Kruskal-Wallis test when continuous.

Table 2

Vascular thromboembolic events (VTE) by treatment group.

	GCbBev (n=51; 26%)	GCis (n=55; 28%)	GCb (n=92; 46%)	p-value[1]
Any VTE	13 (25.5)	8 (14.5)	22 (23.9)	0.300
Type of VTE[2]				0.111
Arterial	1 (7.7)	0 (0.0)	7 (31.8)	
Venous	12 (92.3)	8 (100.0)	15 (68.2)	

[1] p-value from Fisher's exact test.

[2] Among those who had a VTE (n=43).

Table 3

Conditional logistic regression analysis of associations between patient characteristics and vascular thromboembolic events (VTE), stratified by chemotherapy regimen.

	OR (95% CI)	p-value
Age		0.411
≤ 65	1.00	
> 65	0.72 (0.33 – 1.58)	
Sex		0.371
Male	1.00	
Female	0.70 (0.32 – 1.54)	
Race		0.504
White	1.00	
Other	1.45 (0.49 – 4.34)	
Primary site		0.997
bladder	1.00	
renal pelvis	1.02 (0.45 – 2.33)	
other	0.96 (0.25 – 3.67)	
Histology		0.209
TCC	1.00	
TCC mixed	0.59 (0.26 – 1.34)	
Prior pelvic surgery < 3mo		0.212
No	1.00	
Yes	0.39 (0.09 – 1.72)	
Prior cystectomy		0.047
No	1.00	
Yes	2.22 (1.01 – 4.86)	
Tumor near pelvic vessels		0.109
No	1.00	
Yes	1.78 (0.88 – 3.61)	
Number of metastatic sites	1.06 (0.76 – 1.47)	0.734
Karnofsky performance status		0.931
≤ 70	1.00	
> 70	0.96 (0.40 – 2.32)	
MSKCC risk group		0.795
0	1.00	
1 or 2	1.10 (0.54 – 2.26)	
BMI		0.939
≥ 35	1.00	
< 35	1.05 (0.28 – 3.95)	
WBC		0.607

	OR (95% CI)	p-value
> 11	1.00	
≤ 11	1.31 (0.47 – 3.68)	
PLT		0.148
≥ 350	1.00	
< 350	1.82 (0.81 – 4.12)	
HGB		0.795
< 10	1.00	
≥ 10	1.17 (0.37 – 3.71)	
Exposure to erythropoiesis-stimulating agents and/or central venous line/catheter		0.473
Any	1.00	
None	1.29 (0.64 – 2.58)	
Khorana risk group	0.86 (0.57 – 1.28)	0.447
IVC filter		0.115
No	1.00	
Yes	3.54 (0.73 – 17.05)	
Anticoagulation		0.703
No	1.00	
Yes	1.21 (0.45 – 3.28)	
ASA/Plavix		0.445
No	1.00	
Yes	0.70 (0.28 – 1.74)	
Bleeding issues		0.458
No	1.00	
Yes	0.56 (0.12 – 2.62)	
Pretreatment history of VTE		0.383
No	1.00	
Yes	1.64 (0.54, 4.96)	