

High Incidence of Thromboembolic Events in Patients Treated With Cisplatin-Based Chemotherapy: A Large Retrospective Analysis

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ABSTRACT

Purpose

This study was designed to determine the incidence of venous and arterial thromboembolic events (TEEs) in patients treated with cisplatin-based chemotherapy and to analyze the prognostic value of patients' baseline and treatment characteristics in predicting TEE occurrence.

Patients and Methods

We performed a large retrospective analysis of all patients treated with cisplatin-based chemotherapy for any type of malignancy at Memorial Sloan-Kettering Cancer Center in 2008. A TEE was cisplatin-associated if it occurred between the time of the first dose of cisplatin and 4 weeks after the last dose.

Results

Among 932 patients, 169 (18.1%) experienced a TEE during treatment or within 4 weeks of the last dose. TEEs included deep vein thrombosis (DVT) alone in 49.7%, pulmonary embolus (PE) alone in 25.4%, DVT plus PE in 13.6%, arterial TEE alone in 8.3%, or DVT plus arterial TEE in 3.0%. TEEs occurred within 100 days of initiation of treatment in 88% of patients. By univariate analysis, sex, age, race, Karnofsky performance status (KPS), exposure to erythropoiesis-stimulating agents, presence of central venous catheter (CVC), site of cancer, stage of cancer, leukocyte and hemoglobin levels, and Khorana score were all identified as risk factors. However, by multivariate analysis, only age, KPS, presence of CVC, and Khorana score retained significance.

Conclusion

This large retrospective analysis confirms the unacceptable incidence of TEEs in patients receiving cisplatin-based chemotherapy. In view of the controversy associated with prophylactic anticoagulation in patients with cancer treated with chemotherapy, randomized studies are urgently needed in this specific cancer population treated with cisplatin-based regimens.

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INTRODUCTION

Cancer is associated with an increased risk in venous and arterial thromboembolic events (TEEs), including deep venous thrombosis (DVT), pulmonary embolus (PE), cerebrovascular accident, and unstable angina/myocardial infarction (MI). Although the average annual incidence rate of venous thromboembolism in the general population is approximately 117 per 100,000, the incidence in patients with cancer is approximately one in 200.^{1,2} On the basis of a large cohort study,³ cancer alone is associated with a 4.1-fold increased risk of TEE. As a leading cause of death, TEEs significantly reduce survival of patients with cancer.⁴⁻⁶ In addition, TEEs result in a substantial economic burden because of the need for hospitalization, with a mean estimated cost of more than \$20,000, which is probably an underesti-

mate because 25% of patients with cancer who have a TEE potentially need to be readmitted as a result of bleeding or a recurrent event.⁷

Several factors are known to influence the incidence of TEEs in patients with cancer, including but not limited to age, type/site/extent of cancer, hospitalization, indwelling catheters, and hereditary predisposition. Besides these factors, active treatment with several agents, including chemotherapy, imparts a significant risk. Several controlled clinical trials of systemic chemotherapy in women with breast cancer have shown a clear link between chemotherapy and increased incidence of TEEs.⁸⁻¹⁵ A large cohort study³ has shown that although cancer alone is associated with a 4.1-fold increase in the risk of thrombosis, the addition of chemotherapy enhances that risk to 6.5-fold.

Among chemotherapeutic agents, cisplatin-based regimens particularly have been associated with a wide range of thromboembolic complications.¹⁶⁻²⁵ In one retrospective study of patients with urothelial cancer, 35 (12.9%) of 271 patients receiving multiagent cisplatin-based chemotherapy experienced a TEE, with three events directly resulting in death.²⁶ Another retrospective study of patients with germ cell cancer receiving cisplatin-based chemotherapy found that 15 (8.4%) of 179 patients experienced a TEE, with one fatality.²⁷ In a prospective study of 108 patients with stage III to IV non-small-cell lung cancer treated with cisplatin and gemcitabine, 19 (17.6%) of 108 patients experienced a TEE. Four of those 19 patients died as a result of the event.²⁸ The direct role of cisplatin in thromboembolic toxicity is also suggested in a prospective, randomized, double-blind trial comparing cisplatin-based chemotherapy with oxaliplatin-based chemotherapy in 214 patients with locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. This study found a statistically significant difference in the incidence of TEEs between the two groups: 7.8% in the cisplatin group versus 0.9% in the oxaliplatin group.²⁹ Similar observations were reported in an analysis of the Randomised ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) study,³⁰ which showed a statistically significant difference in the incidence of TEEs in the cisplatin-containing regimens compared with the oxaliplatin-containing regimens in patients with advanced gastroesophageal cancer (15.1% v 7.6%, respectively; $P < .001$).

The results of these studies as well as our clinical experience prompted us to conduct a large retrospective analysis of all patients treated with cisplatin-based chemotherapy in 2008 for any type of malignancy at Memorial Sloan-Kettering Cancer Center (MSKCC). The primary objective of this study was to determine the overall incidence of TEEs in these patients.

PATIENTS AND METHODS

Patient Population

In this retrospective study, we have included all adult patients treated with cisplatin-based chemotherapy who received the first cisplatin dose between January 1, 2008, and December 31, 2008, and had at least 4 weeks of follow-up after their last cisplatin dose. Cisplatin treatment into 2009 was allowed as long as they had at least 4 weeks of follow-up after their last cisplatin dose as of July 31, 2009, when the data were censored for analysis. This study was approved by the institutional review board at MSKCC.

Retrospective Data Collection

Electronic medical records were reviewed to identify patients who experienced a venous or arterial TEE. As initial screening, all reports of imaging studies were reviewed. A TEE occurrence was recorded only if an imaging study documented such an event. Because events diagnosed in other institutions could be missed by this initial screening, the patients' electronic medication profiles were scrutinized searching for the addition of an anticoagulant or antiplatelet agent, which would suggest that a TEE had occurred. If such an addition was noted, further investigation was conducted to confirm the occurrence of a TEE. TEE occurrence was based only on results of angiography, magnetic resonance imaging, computed tomography, venous Doppler ultrasound, ventilation/perfusion scan, or clinical and laboratory documentation of MI by ECG or troponin. A TEE was considered cisplatin-associated if it was diagnosed between the time of the first dose of cisplatin and 4 weeks after the last dose and was determined to be a new event not seen on a previous recent imaging study or, for MI, a new event as determined by clinical presentation, ECG, or troponin.

Baseline characteristics were collected by using electronic medical records and included hemoglobin level, platelet and WBC counts, site of cancer, extent of disease, and thrombotic risk factors. The latter included surgery within 2 months of beginning cisplatin-based treatment, cardiac disease, obesity (body mass index [BMI] ≥ 30 kg/m²), diabetes, Karnofsky performance status (KPS), history of previous TEE, presence of central venous catheter (CVC), presence of an inferior vena cava filter, and administration of an erythropoiesis-stimulating agent (ESA) within 6 weeks before cisplatin initiation, during cisplatin treatment, or within 4 weeks after the last cisplatin dose. Concurrent anticoagulation/antiplatelet therapy during the cisplatin-based chemotherapy was also documented.

Treatment characteristics were collected, including chemotherapy regimens, number of cisplatin doses, mean cisplatin dose, and cumulative cisplatin dose. The mean cisplatin dose was calculated by dividing the cumulative cisplatin dose by the number of doses.

Statistical Analysis

The primary objective of this study was to determine the overall incidence, timing, and characteristics of TEEs (venous or arterial) in adult patients treated with cisplatin-based chemotherapy. Secondary objectives were to analyze the prognostic value of baseline and treatment characteristics in predicting the occurrence of a TEE in patients treated with cisplatin-based chemotherapy. The association between each baseline and treatment characteristic detailed in the previous section and the development of a TEE during the defined treatment period was evaluated by using the χ^2 test for categorical variables, the Mantel-Haenszel test for trend for ordinal variables, and the Wilcoxon rank sum test for continuous variables. Variables found to be significant ($P \leq .05$) by univariate analysis were subsequently entered into a multivariate logistic regression model.

RESULTS

Baseline Characteristics and Treatment Characteristics of the Study Population

Overall, 1,093 patients received at least one dose of cisplatin in 2008, of which 932 met the inclusion criteria. Patients' baseline and treatment characteristics are detailed in Table 1. Also included in Table 1 is the Khorana risk score.³¹ The following were reasons for exclusion: age was younger than 18 years ($n = 1$), an accurate cisplatin start date in 2008 could not be determined ($n = 1$), patient was lost to follow-up/insufficient follow-up after last cisplatin dose/still receiving cisplatin as of July 31, 2009 ($n = 11$), and the first cisplatin dose was received in 2007 ($n = 148$).

Incidence, Timing, and Characteristics of TEEs

Among 932 patients included in the study, 169 (18.1%; 95% CI, 15.7% to 20.8%) patients developed a TEE within 4 weeks of their last cisplatin dose (Table 2). Patients who experienced two or more TEEs either simultaneously or at different times were counted as one event. The majority of events were DVTs alone ($n = 84$), followed by PEs alone ($n = 43$), DVT plus PE ($n = 23$), arterial thromboses alone ($n = 14$), and DVT plus an arterial thrombosis ($n = 5$). Details of events in Table 2 show that 95 events were symptomatic, and 74 were found incidentally. We consider that most, if not all, events would warrant therapeutic intervention.

Figure 1 represents the time to TEE from cisplatin start among patients who developed a TEE. The majority of events (88%) occurred within the first 100 days of starting cisplatin. Overall, the median time until TEE occurrence was 48 days (interquartile range, 26 to 73 days).

Thirty-one patients (3.3%) died during cisplatin treatment or within 4 weeks of the last cisplatin dose. Among these 31 patients, 13

Table 1. Baseline and Treatment Characteristics of the Total Study Population (N = 932)		
Characteristic	No. of Patients	%
Age, years		
Median	60	
Range	19-87	
Sex		
Male	500	53.6
Female	432	46.4
Race/ethnicity		
White	791	84.9
Asian	62	6.7
African American	60	6.4
Other/unknown	19	2.0
Thrombosis risk factors		
Hypertension	295	31.7
Coronary artery disease	62	6.7
Atrial fibrillation/arrhythmias	26	2.8
Prior strokes	4	0.4
Central venous catheter	266	28.5
Surgery within 2 months	169	18.1
ESA 6 weeks before/4 weeks after	167	17.9
Karnofsky performance status, %		
Median	80	
IQR	80-90	
Obesity (BMI \geq 30 kg/m ²)	157	16.8
Diabetes	99	10.6
Previous TEE	90	9.7
IVC filter	11	1.2
Khorana variables		
Site of cancer		
Very high risk	193	21.7
High risk	319	34.2
Prechemotherapy platelet count \geq 350,000/ μ L	230	24.7
Prechemotherapy leukocyte count $>$ 11,000/ μ L	156	16.7
Prechemotherapy hemoglobin $<$ 10 g/dL or use of ESA	214	23.0
BMI \geq 35 kg/m ²	35	3.8
Khorana risk score		
0	224	24.0
1	293	31.4
2	245	26.3
3	129	13.8
4	35	3.8
5	6	0.6
Khorana risk group		
Low	224	24.0
Intermediate	538	57.7
High	170	18.2
Cancer diagnosis		
Lung	204	21.9
Gastric/GE junction	114	12.2
Head and neck	94	10.1
Pancreatic	79	8.5
Melanoma	69	7.4
Ovarian	57	6.1
Esophageal	46	4.9
Germ cell	39	4.2
Cervical/uterine/vulvar	39	4.2
Bladder	33	3.5
Endometrial	22	2.4
Cholangiocarcinoma	18	1.9
Mesothelioma	15	1.6
Colorectal/anal/small bowel	13	1.4
Other	90	9.7

(continued in next column)

Table 1. Baseline and Treatment Characteristics of the Total Study Population (N = 932) (continued)		
Characteristic	No. of Patients	%
Stage of disease		
Early	66	7.1
Locally advanced	415	44.5
Metastatic	426	45.7
Undocumented	19	2
Other	6	0.6
Chemotherapy regimens		
Cisplatin + gemcitabine	134	14.4
Cisplatin + radiation	94	10.1
Cisplatin + irinotecan	89	9.6
Cisplatin + etoposide	80	8.6
Cisplatin + vinblastine + temozolomide	57	6.1
Cisplatin + pemetrexed	43	4.6
Cisplatin IP + paclitaxel IV/IP	33	3.5
Cisplatin + pemetrexed + bevacizumab	33	3.5
Other cisplatin-based regimens	369	39.6
Mean cisplatin dose, mg/m ²		
Median	40	
IQR	25-65	
Cumulative cisplatin dose, mg/m ²		
Median	200	
IQR	120-300	
No. of cisplatin doses		
Median	5	
IQR	3-7	
Entire time on cisplatin, days		
Median	61	
IQR	28-91	

Abbreviations: BMI, body mass index; ESA, erythropoiesis-stimulating agent; GE, gastroesophageal; IP, intraperitoneal; IQR, interquartile range; IV, intravenous; IVC, inferior vena cava; TEE, thromboembolic event.

had a known major TEE that occurred within days of death during the hospitalization that culminated in death, two had events highly suggestive of catastrophic TEE although unproven, and the remaining patients had advanced disease during their last hospitalization but immediate cause of death was not investigated.

Univariate and Multivariate Analysis of Baseline and Treatment Characteristics

To examine the association of each baseline and treatment variable with the development of TEE, a univariate analysis was conducted. Sex, age, race, KPS, ESA use, presence of CVC, site and stage of cancer, leukocyte and hemoglobin level, and Khorana score were all associated with a significant increase in risk of TEE (Table 3). Since more than 20 cancers were represented (Table 4), we examined the subset of cancer types with at least 50 patients (pancreatic, gastric/gastroesophageal (GE) junction, ovarian, melanoma, head and neck, and lung). The incidence of thromboses was significantly different by cancer type ($P < .001$), with cancers of the pancreas and gastric/GE junction having the highest incidence of TEEs: 36.7% and 27.2%, respectively (Table 3). Regarding disease stage, the incidence of TEEs was higher in patients with metastatic disease (21.6%) compared with patients who had early-stage disease (16.7%) or locally advanced disease (15.2%), with $P = .05$ on univariate analysis (Table 3).

Table 2. Overall Incidence of Thromboembolic Events (N = 932)

Thromboembolic Event	No. of Patients	%
Thrombosis	169	18.1
Types of thromboses (n = 169)		
DVT alone	84	49.7
PE alone	43	25.4
DVT + PE	23	13.6
Arterial thrombosis alone	14	8.3
DVT + arterial thrombosis	5	3.0
Subtypes of DVTs (n = 112)		
Proximal lower extremity	22	19.6
Proximal lower and distal lower extremity	18	16.1
Proximal lower extremity and central*	5	4.4
Proximal lower extremity and central* and distal lower extremity	1	0.9
Proximal upper extremity	2	1.8
Proximal upper and distal upper extremity	3	2.7
Proximal upper and internal jugular vein and distal upper extremity	4	3.6
Internal jugular vein	5	4.4
Internal jugular vein and distal upper extremity	1	0.9
Central*	27	24.1
Distal lower extremity	20	17.9
Distal lower and distal upper extremity	1	0.9
Distal upper extremity	3	2.7
Subtypes of arterial events (n = 19)		
Central†	6	31.6
Myocardial infarction	2	10.5
Cerebrovascular accident	10	52.6
Transient ischemic attack	1	5.3
Symptomatic or incidental event (n = 169)		
Symptomatic	95	56.2
Incidental	74	43.8

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolus.
 *Central venous thromboses sites include brachiocephalic vein (n = 1), gonadal vein (n = 7), hepatic vein (n = 1), inferior vena cava (n = 5), pelvic vein (n = 4), portal vein (n = 6), renal vein (n = 4), splenic vein (n = 3), superior mesenteric vein (n = 6), and superior vena cava (n = 3).
 †Central arterial thromboses sites include aortic arch (n = 1), infrarenal aorta (n = 3), internal carotid (n = 1), splenic artery (n = 1), and superior mesenteric artery (n = 1).

Of the five predictive variables included in the previously validated Khorana risk model, only three were significantly associated with TEE occurrence in our study: site of cancer ($P < .001$), prechemotherapy leukocyte count more than $11,000/\mu\text{L}$ ($P = .03$), and prechemotherapy hemoglobin level less than 10 g/dL or use of an ESA ($P = .03$). Despite the lack of association between the remaining two variables, the overall Khorana risk score was significantly associated with TEE occurrence ($P < .001$).

When analyzing the data by treatment variables, some cisplatin-based chemotherapy regimens were associated with a higher incidence of TEEs; however, reliable statistical analysis was not possible because of the multiplicity of the regimens and small sample sizes (Table 4). Univariate analysis revealed that mean cisplatin dose did not correlate with the incidence of TEE (Table 3).

Variables with a P value of $\leq .05$ on univariate analysis were subsequently entered into the multivariate logistic regression model. On multivariate analysis, variables significantly associated with TEE occurrence included age (odds ratio [OR], 1.19 per 10-year increase;

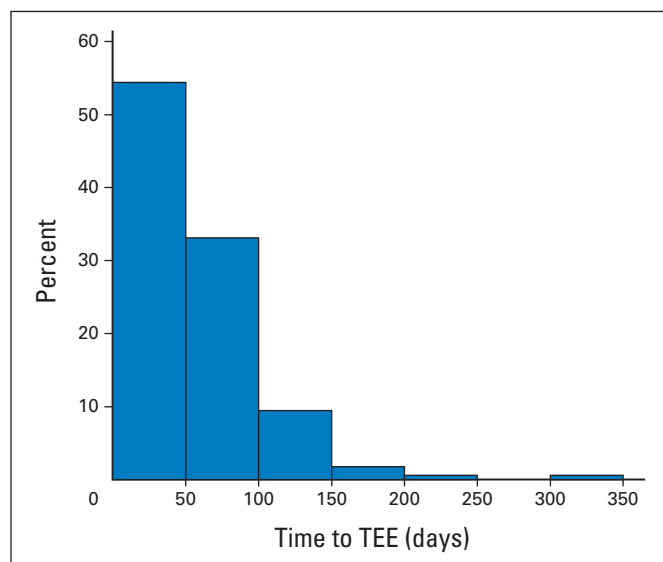


Fig 1. Time to thrombosis in patients who developed a thromboembolic event (TEE).

95% CI, 1.02 to 1.39; $P = .03$), KPS (odds ratio, 0.92 per 10-unit increase; 95% CI, 0.86 to 0.98; $P = .02$), presence of a CVC (OR, 1.61; 95% CI, 1.10 to 2.36; $P = .01$), and the Khorana risk group ($P = .04$; Table 5).

DISCUSSION

In this large retrospective analysis of 932 patients treated with cisplatin-based chemotherapy for a variety of cancers, we have observed an unacceptably high incidence of TEEs (18.1%) during the period of administration or within 4 weeks of completion of treatment. We believe that the true incidence may even be higher, since we may have failed to capture every patient with a TEE because of the retrospective nature of this analysis. We also note a death rate of 3.3% during the same observation period with a strong probability of a TEE contributing to or causing death in the majority of these patients. This large retrospective study confirms the high incidence of TEEs in patients treated with cisplatin-based chemotherapy.

Few small retrospective studies^{26,27} have reported a lower incidence of TEEs in cisplatin-treated patients, ranging from 8.4% to 12.9%. Such a discrepancy may be ascribed to several factors. The systematic strategy used in this study, which included a thorough review of patients' medications that triggered further investigations, may have allowed capturing additional patients with a TEE who would otherwise have been missed. In contrast, previous retrospective studies^{26,27} often did not clearly define their strategy for capturing events. In addition, some studies included only symptomatic events, whereas we included all events regardless of presentation.²⁶ It is also worth noting that some retrospective (and even prospective) studies fail to include cerebrovascular events and MIs, possibly because they are viewed as cardiovascular rather than TEEs and are derived from different physiopathologic mechanisms.^{32,33} The inadequate reporting of arterial events related to cisplatin chemotherapy has indeed been previously highlighted.³⁴ In contrast, arterial events represent a significant percentage of TEEs in this article and probably contribute to the higher incidence observed.

Table 3. Univariate Analysis of Patient and Treatment Variables			
Variable	Rate of TEE		P
	No.*	%	
Sex			.05
Male	79/500	15.8	
Female	90/432	20.8	
Age, years (patients with TEE v patients with no TEE)			.02
Median	62 v 59		
Range	23-83 v 19-87		
Race/ethnicity			.05
Asian	10/62	16.1	
African American	14/60	23.3	
White	141/791	17.8	
Obese (BMI \geq 30 kg/m ²)			.43
No	144/775	18.6	
Yes	25/157	15.9	
Surgery within 2 months			.76
No	137/763	18.0	
Yes	32/169	18.9	
Previous TEE			.63
No	151/842	17.9	
Yes	18/90	20.0	
Anticoagulation/antiplatelet			.50
No	144/776	18.6	
Yes	25/156	16.0	
IVC filter			.43
No	166/921	18.0	
Yes	3/11	27.3	
Karnofsky performance status (patients with TEE v patients with no TEE)			.01
Mean	71 v 79		
SD	30 v 21		
Diabetes			.99
No	151/833	18.1	
Yes	18/99	18.2	
ESA 6 weeks before/4 weeks after			.002
No	125/765	16.3	
Yes	44/167	26.3	
Central venous catheter/pacemaker			.002
No	104/666	15.6	
Yes	65/266	24.4	
Hypertension			.65
No	113/637	17.7	
Yes	56/295	19.0	
Coronary artery disease			.67
No	159/870	18.3	
Yes	10/62	16.1	
Atrial fibrillation/cardiac arrhythmias			.38
No	166/906	18.3	
Yes	3/26	11.5	
Prior strokes			.72
No	168/928	18.1	
Yes	1/4	25.0	
Stage			.05
Early	11/66	16.7	
Locally advanced	63/415	15.2	
Metastatic	92/426	21.6	

(continued in next column)

Table 3. Univariate Analysis of Patient and Treatment Variables (continued)			
Variable	Rate of TEE		P
	No.	%	
Disease (restricted to groups with > 50 patients)			< .001
Lung	24/204	11.8	
Gastric and GE junction	31/114	27.2	
Head and neck	12/94	12.8	
Pancreatic	29/79	36.7	
Melanoma	9/69	13.0	
Ovarian	12/57	21.1	
Mean cisplatin dose, mg/m ² (patients with TEE v patients with no TEE)			.07
Median	45 v 40		
IQR	25-68 v 25-60		
Khorana variables			
Site of cancer			< .001
Very high risk	60/193	31.1	
High risk	41/319	12.8	
Other	68/420	16.2	
Platelet count \geq 350,000/ μ L†			.17
No	120/702	17.1	
Yes	49/230	21.3	
Leukocyte count > 11,000/ μ L†			.03
No	131/776	16.9	
Yes	38/156	24.4	
Hemoglobin < 10 g/dL or use of ESA†			.03
No	119/718	16.6	
Yes	50/214	23.4	
Body mass index \geq 35 kg/m ²			.82
No	162/897	18.1	
Yes	7/35	20	
Khorana risk group			< .001
Low	29/224	13.0	
Intermediate	91/537	17.1	
High	48/170	28.2	

Abbreviations: BMI, body mass index; ESA, erythropoiesis-stimulating agent; GE, gastroesophageal; IQR, interquartile range; IVC, inferior vena cava; SD, standard deviation; TEE, thromboembolic event.
*Ratios represent No. of patients with TEE over the total No. of patients in respective categories.
†Prechemotherapy hematologic parameters.

Conversely, and in accordance with our results, few small prospective trials^{28,30} indicate an incidence of TEEs in cisplatin-treated patients ranging up to 17.6%. Importantly, in these studies, arterial events including cerebrovascular accidents and MIs account for a substantial percentage of TEEs. The pathogenesis of cisplatin-associated vascular toxicity, which may include hypomagnesemia, increased von Willebrand factor, and damage to endothelial cells via increased formation of procoagulant endothelial microparticles,^{17,23} is likely to involve a pathway affecting both venous and arterial systems. This is in contrast with most other thrombosis risk factors that often involve mostly the venous compartment.

The timing of the TEEs in relation to initiation of therapy further suggests a relation between cisplatin administration and TEE occurrence. In this study, 88% of TEEs occurred within the first 100 days of starting cisplatin. A similar finding was noted by Numico et al,²⁸ in which 45% of the vascular events occurred during the first two courses of cisplatin and gemcitabine. Likewise, in the study by Weijl et al,²⁷ the

Table 4. Thromboembolic Rate According to Underlying Cancer and Treatment Regimen

Cancer Type and Treatment Regimen	No. of Patients*	%
Cancer diagnosis		
Colorectal/anal/small bowel	5/13	38.5
Pancreatic	29/79	36.7
Gallbladder/ampullary	3/10	30.0
Gastric/GE junction	31/114	27.2
Cholangiocarcinoma	5/18	27.8
Ovarian	12/57	21.0
Bladder	6/33	18.2
Sarcoma	2/11	18.2
Germ cell/seminoma	7/39	18.0
Esophageal	8/46	17.4
Endometrial	3/22	13.6
Melanoma	9/69	13.0
Head and neck	12/94	12.8
Lung	24/204	11.8
Cervical/uterine/vulvar	4/39	10.3
Hematologic malignancies	1/11	9.1
Neuroendocrine/carcinoid	0/11	0
Other	8/62	12.9
Chemotherapy regimens		
Cisplatin + docetaxel + fluorouracil/leucovorin + bevacizumab	11/16	68.8
Cisplatin + docetaxel + fluorouracil/leucovorin	7/11	63.6
Cisplatin IP + paclitaxel IV/IP + bevacizumab	6/13	46.2
Cisplatin + docetaxel + fluorouracil	5/17	29.4
Cisplatin + gemcitabine	38/134	28.4
Cisplatin + paclitaxel + ifosfamide	2/11	18.2
Cisplatin + irinotecan	15/89	16.9
Cisplatin + pemetrexed	6/43	14
Cisplatin + etoposide	10/80	12.5
Cisplatin + fluorouracil + epirubicin	2/16	12.5
Cisplatin + vinblastine + temozolomide	7/57	12.3
Cisplatin + pemetrexed + bevacizumab	4/33	12.1
Cisplatin + radiation	9/94	9.6
Cisplatin IP + paclitaxel IV/IP	3/33	9.1
Other cisplatin-based regimens	44/285	15.4

Abbreviations: GE, gastroesophageal; IP, intraperitoneal; IV, intravenous.
*Ratios represent No. of patients with TEE over the total No. of patients in respective categories.

Table 5. Multivariate Analysis of Baseline and Treatment Variables

Variable	Odds Ratio	95% CI	Adjusted P
Sex			
Male	1		.15
Female	1.31	0.91 to 1.88	
Age (per 10-year increase)	1.19	1.02 to 1.39	.03
Race/ethnicity			
White	1		.51
Asian	0.87	0.41 to 1.85	
African American	1.43	0.74 to 2.76	
KPS (per 10-unit increase)	0.92	0.86 to 0.98	.02
Central venous catheter/pacemaker	1.61	1.10 to 2.36	.01
Stage			
Early	1		.57
Locally advanced	0.84	0.41 to 1.72	
Metastatic	1.03	0.50 to 2.13	
Khorana risk group			
Low	1		.04
Intermediate	1.33	0.81 to 2.16	
High	2.06	1.16 to 3.65	

Abbreviation: KPS, Karnofsky performance status.

highlight that when we used the five Khorana variables that segregate outpatients undergoing chemotherapy into low-, intermediate-, and high-risk groups, the incidence of TEE was much higher in this study for each specified risk group in comparison to Khorana's original study: 13% versus 0.3% among patients with a score of 0, 17.1% versus 2% among those with a score of 1 or 2, and 28.2% versus 6.7% among those with a score of 3 or higher.³¹ It is therefore likely that exposure to cisplatin may dwarf the added risk associated with BMI and platelet count, which would explain the lack of prognostic significance for these variables by univariate analysis. The same rationale may underlie the lack of statistical significance of a history of previous TEEs and recent surgery, both strong risk factors for thrombosis in previous studies. Interestingly, by multivariate analysis, only age, KPS, presence of CVC, and Khorana score retained statistical significance.

It is important to note that in this study, several treatment characteristics were difficult to analyze because of the retrospective nature of the study and the inclusion of many different cancers and chemotherapeutic regimens resulting in small sample sizes within these groups. Likewise, the strong association of specific regimens with specific diseases, such as cisplatin plus docetaxel plus fluorouracil/leucovorin with bevacizumab and gastric/GE junction cancer, hindered the statistical analysis. A comparison between various regimens was therefore difficult to perform.

Considering the high incidence of TEE seen in this study and acknowledging its impact on hospital cost, morbidity, and mortality, the question of thromboprophylaxis needs to be addressed. Established guidelines recommend prophylactic anticoagulation for all oncology patients in high-risk settings, such as hospitalization, major surgery, or postoperatively.³⁵ However, in the ambulatory setting, prophylactic anticoagulation is not currently recommended except for patients with multiple myeloma receiving thalidomide-lenalidomide-based combinations, in whom the incidence of TEE is similar to that observed in this study.³⁵ Data on primary prevention of

median time interval between initiation of cisplatin-based treatment and first TEE was 52 days.

In this study, we have attempted to identify risk factors associated with the development of TEEs in patients receiving cisplatin. Several patient baseline and treatment characteristics previously associated with thrombosis were analyzed by univariate and multivariate analysis. Sex, age, race, KPS, exposure to ESA, presence of CVC, type and stage of cancer, prechemotherapy hemoglobin level and leukocyte count, and the Khorana score were all associated with significantly increased risk of TEE by univariate analysis. It is interesting to note that among the five Khorana variables, platelet number and BMI were not identified as independent risk factors, although the overall Khorana score including these two variables was. This discrepancy is probably due to the fact that the patient population under consideration in this study (exclusively cisplatin-exposed patients) carries a much higher risk of thrombosis than the general cancer population analyzed in the Khorana study. In this regard, it is interesting to

thrombosis in ambulatory patients with cancer receiving chemotherapy are limited with mixed results.³⁶⁻⁴⁰ Levine et al³⁸ showed a significant reduction in the rate of thrombosis in women with metastatic breast cancer receiving low-dose warfarin; however, the TOPIC I and II trials³⁷ showed no benefit with low-molecular-weight heparin prophylaxis in metastatic breast cancer and advanced stages of non-small-cell lung cancer, respectively. More recently, the CONKO 004 trial^{41,42} (A Prospective, Randomized Trial of Simultaneous Pancreatic Cancer Treatment With Enoxaparin and Chemotherapy) showed a significant decrease in symptomatic TEEs that used enoxaparin in advanced pancreatic cancer after 3 months (1.3% v 9.9%) and after 12 months (5.0% v 15.1%). Similarly, the United Kingdom FRAGEM (Gemcitabine With or Without Prophylactic Weight-Adjusted Dalteparin in Patients With Advanced or Metastatic Pancreatic Cancer) study⁴³ reported benefit from using dalteparin in advanced pancreatic cancer (12% v 31%; $P = .02$), and the randomized PROTECT (Prophylaxis of Thromboembolism during Chemotherapy) Trial⁴⁴ showed benefit from using nadroparin in metastatic or locally advanced cancers (2.0% v 3.9%; $P = .02$) compared with placebo. Overall, although acknowledging that the question of prophylactic anticoagulation remains controversial in patients with cancer, we believe that prospective randomized studies evaluating the benefit of prophylactic anticoagulation are warranted in patients with cancer who are receiving cisplatin on the basis of their high risk. We also speculate, since the risk of TEE was 13%, even in the low-risk category as specified by the Khorana predictive model, that all patients receiving cisplatin-based chemotherapy should be considered for thromboprophylaxis, unless there is a contraindication, at least until a more applicable predictive model is available for this group of patients.

In summary, this large retrospective analysis confirms the high incidence of TEEs in patients treated with cisplatin-based chemotherapy, which in our opinion, is unacceptable. The vast majority of events occur early in the treatment course. As expected, the incidence of TEEs varied according to the type of underlying primary malignancy and stage of disease, with age, KPS, presence of CVC, and Khorana score being significant predictors by multivariate analysis. On the basis of the results of this and previous studies, TEE prophylaxis may be advisable for patients receiving cisplatin-based chemotherapy. Prospective studies are urgently needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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