Incidence and Effect of Thromboembolic Events in Radical Cystectomy Patients Undergoing Preoperative Chemotherapy for Muscle-invasive Bladder Cancer

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Abstract

We hypothesized that the incidence of thromboembolic events (TEEs) in patients receiving preoperative chemotherapy (POC) before radical cystectomy and pelvic lymph node dissection might be severely under-appreciated given the association between cisplatin and TEEs. We conducted a retrospective review of 357 consecutive patients who had received POC at our institution and provide a detailed review of the incidence and timing of the TEEs. The overall TEE rate was 22%, with a 16% incidence in the preoperative setting. Forty patients (11.2%) required an inferior vena cava filter. The occurrence of TEEs did not significantly affect other perioperative outcomes, including the risk of recurrence and overall survival.

Background—We evaluated the incidence and effect of thromboembolic events (TEEs) in patients with muscle-invasive bladder cancer treated with preoperative chemotherapy (POC) and radical cystectomy (RC) with pelvic lymph node dissection (PLND).

Patients and Methods—We performed a retrospective review of all patients who had undergone POC followed by RC plus PLND for muscle-invasive bladder cancer from June 2000 to January 2013 (n = 357). The chemotherapy type (neoadjuvant vs. induction), incidence and timing

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Disclosure

The authors declare that they have no conflicts of interest.

Supplemental Data

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of TEE diagnosis (preoperatively vs. 90 days postoperatively), and effect of TEEs on clinical outcomes were recorded.

Results—Overall, 79 patients (22%; 95% confidence interval [CI], 18%–27%) experienced a TEE: 57 (16%) occurred during POC and 22 (6.2%) were diagnosed postoperatively. Forty patients (11%; 95% CI, 8.1%–15%) required an inferior vena cava filter. We found no significant differences in neoadjuvant versus induction chemotherapy and the risk of TEEs (difference, 3.3%; 95% CI, –5% to 12%; $P = .5$). No significant difference were found in the rates of POC completion according to the presence of a TEE (difference, 1.0%; 95% CI, –11% to 13%; $P = .9$). The occurrence of TEE did not significantly affect other perioperative outcomes. The risk of recurrence and overall survival were not associated with TEE on multivariable analysis.

Conclusion—We found a high incidence of TEEs (22%) in patients undergoing POC before RC plus PLND, with a 16% incidence in the preoperative period. TEEs in the POC setting leads to invasive procedures; however, we did not find a significant effect on POC completion or postoperative complication risk. Further research is required to determine whether preventative TEE measures during POC can improve clinical outcomes.

Keywords

Anticoagulation; Cisplatin; Deep venous thrombosis; Thromboembolism; Venous thromboembolism

Introduction

Patients with cancer have a fourfold increase risk of having a thromboembolic event (TEE) owing to the prothrombotic effects of malignancy.¹ The occurrence of TEEs has been associated with worse survival and carries a significant financial burden, approximately \$20,000 per patient and > \$1.5 billion annually in the United States.^{2–4} Patients undergoing major cancer surgery have a particularly high risk of developing a TEE.⁵ Our group previously reported an 8% incidence of TEEs after radical cystectomy (RC) plus pelvic lymph node dissection (PLND), with reported rates ranging from 3% to 24% when TEE was evaluated 90 days after discharge.^{6–9} These data almost certainly underestimate the incidence, because patients are not screened for TEEs, and asymptomatic TEEs can be missed.

Population-based studies have indicated that the risk of TEEs in patients with cancer receiving chemotherapy is 6.5-fold greater than that of the general population and significantly greater than the risk of those with cancer who are not receiving chemotherapy.¹ Cisplatin has been associated with especially high rates of TEEs (> 18%).¹⁰

In key randomized trials that established neoadjuvant chemotherapy (NAC) followed by RC plus PLND as the standard of care for patients with locally advanced bladder cancer, the data regarding the timing and incidence of TEEs have likely been underestimated or not reported.^{11–13} Specifically, it is unknown whether TEEs in the pre-operative setting affect patients' ability to complete chemotherapy, lead to delays in surgery or changes in surgical complication profiles, or affect time-to-event outcomes. In the present study, we have reported the incidence and timing of TEE and its effect on the clinical and oncologic

outcomes in a contemporary cohort of patients undergoing preoperative chemotherapy (POC) followed by RC plus PLND.

Patients and Methods

After institutional review board approval, we performed a retrospective review of all patients with muscle-invasive bladder cancer who had undergone POC, followed by RC plus PLND with curative intent from June 2000 to January 2013 at Memorial Sloan Kettering Cancer Center. Two patients receiving salvage cystectomy were excluded, leaving 357 patients for the analyses. Patients were considered to have received NAC if no evidence of nodal or distant disease was found. Patients with radiographically suspicious or biopsy-proven positive pelvic lymph nodes who had undergone chemotherapy with a good response and plan for curative surgery received 6 cycles of chemotherapy and were considered to have received induction chemotherapy.

Patients underwent axial imaging before or just after completing POC and then every 3 to 4 months in the first postoperative year, every 6 months in the second, and then annually, or more often if necessary. Detailed information regarding the occurrence of TEEs, timing of TEEs, and placement of inferior vena cava (IVC) filter was recorded. TEEs were defined as radiographically confirmed pulmonary embolism, deep venous thrombosis (DVT), or arterial thrombosis. Multiple institutional databases were queried for the Current Procedural Terminology and International Classification of Diseases codes related to TEEs, IVC filter placement, DVT, pulmonary embolism, and myocardial infarction. All radiographic studies obtained during administration of chemotherapy, during admission for cystectomy, and 90-days postoperatively were reviewed to confirm the presence or absence of TEEs. The medical records were further reviewed to determine whether patients had been taking an anticoagulant or antiplatelet agent during POC, suggesting that a TEE had occurred. The decision for placement of an IVC filter was at the discretion of the surgeon and was usually recommended in the setting of a documented preoperative DVT.

For patients with a documented TEE, the treatment dose anticoagulation was generally withheld the day before and the day of surgery. Prophylactic dose anticoagulation was initiated on postoperative day 1 in accordance with our enhanced recovery pathway, barring any bleeding concerns. Full-dose anticoagulation was generally resumed on postoperative day 2 or when the hemoglobin had stabilized and hematuria had begun to resolve.

Statistical Analysis

Variability in the prespecified clinical parameters was examined using the Wilcoxon rank-sum and Fisher exact test. We used a χ^2 test to determine whether the occurrence of a TEE during POC led to a greater proportion of patients ending their regimens early. We used the t test to assess whether the occurrence of TEEs are associated with the interval between the end of POC and performance of RC plus PLND.

In patients with a follow-up period of 90 days ($n = 329$), univariable Cox models were used to estimate the risk of recurrence, distant metastases, and death between patients who experienced a TEE and those who did not. Patients who were no longer at risk of recurrence,

metastasis, or death at the 90-day postoperative landmark because they had already experienced the event or had been censored were excluded. This resulted in the further exclusion of 10 and 7 patients when modeling recurrence and distant metastasis, respectively. We generated multivariable models, which included the POC regimen (neoadjuvant vs. induction), soft tissue margin status, pathologic tumor stage, and smoking status for all 3 survival outcomes.

We used χ^2 tests to determine whether significant differences were present in the rates of TEEs preoperatively and within 90 days of RC plus PLND for NAC versus induction chemotherapy. We also hypothesized that the risk of adverse oncologic outcomes for patients who experienced a TEE in the induction regimen group would be increased compared with the NAC group. We performed multivariable interaction analyses that included the interaction term and the presence of surgical margins, pathologic tumor stage, and smoker status at RC to determine whether induction chemotherapy in conjunction with a TEE resulted in a greater risk of recurrence, distant metastasis, or overall death.

The chemotherapy regimens were categorized as gemcitabine plus cisplatin, gemcitabine plus carboplatin, cisplatin containing, or other. Regimens that were not exclusive to 1 group were included in the “other” category. Significant differences in the TEE rates between the chemotherapy groups were evaluated using a χ^2 test. All analyses were conducted using Stata, version 12.0 (StataCorp, College Station, TX).

Results

The patient characteristics are reported in Table 1. Induction chemotherapy was administered to 139 patients (39%) and 218 (69%) received NAC. Overall, 79 patients (22%; 95% confidence interval [CI] 18%–27%) experienced a TEE at any point from the start of chemotherapy to 90 days after RC plus PLND (Table 1). A preoperative TEE occurred in 57 patients (16%). A TEE was diagnosed in an additional 22 patients (6.2%) 90 days postoperatively. Of all the patients who developed a TEE, 51 had received a standard NAC regimen and 28, an induction chemotherapy regimen. We found no significant increase in the risk of TEEs for patients who had received induction POC compared with patients who had received NAC (difference, 3.3%; 95% CI, –5% to 12%; $P = .5$). Similarly, we found no significantly increased risk of TEEs preoperatively (difference, –1.0%; 95% CI, –9% to 7%; $P = .8$) and postoperatively (difference, 4.2%; 95% CI, –0.5% to 9%; $P = .11$) between the induction regimen and standard NAC. We did not find any significant differences in the perioperative outcomes when stratified by the occurrence of TEEs (Table 2). The incidence of TEEs was associated with a greater proportion of patients with high-stage tumors ($P = .016$). Most of the patient population, ($n = 239$; 67%) received POC with gemcitabine and cisplatin, and 58 (24%) developed a TEE. Among the remaining chemotherapy groups, 24 patients developed a TEE. These differences were not statistically significant ($P = .4$).

Of the patients who experienced a TEE during POC, 79% completed their planned chemotherapy cycles compared with a 78% completion rate for patients who did not experience a TEE during POC (difference, 1.0%; 95% CI, –11% to 13%; $P = .9$). Our interaction analysis for TEE and inductive chemotherapy similarly demonstrated no

significant difference in the completion rates for patients who experienced both events ($P = .3$). Regression modeling of the months to RC plus PLND from POC demonstrated no statistically significant differences in the interval to RC plus PLND for patients who experienced a preoperative TEE compared with those who did not (difference, 2.3; 95% CI, 0.3–3.5; $P = .095$). The interval from the end of chemotherapy to surgery was approximately 2 months for patients who did not experience a preoperative TEE compared with 1 month for those who did.

Distant metastases were diagnosed in 111 patients. The recurrence of cancer developed in 132 patients. A total of 168 patients died of any cause. The median follow-up period for survivors was 5.2 years. The risk of recurrence or metastasis was not significantly greater for patients who experienced a TEE at any point compared with those who did not experience a TEE in our univariable or multivariable Cox models ($2P > .4$; Table 3; Figures 1–3; Supplemental Table 1; in the online version). Our interaction analyses for TEE and inductive chemotherapy did not identify a significant increase in the risk of recurrence ($2P = .9$), distant metastasis ($2P = .4$), or overall death ($2P = .7$).

Discussion

In the present large study focusing on the incidence of TEE in the preoperative period in patients undergoing POC, we found the incidence of TEE during POC to be greater than the previously reported 16%. The occurrence of preoperative TEEs was not significantly associated with the ability to complete POC, the interval from POC completion to RC, or the perioperative and oncologic outcomes after RC plus PLND. Importantly, 33 of 57 patients (58%) who experienced a preoperative TEE had an IVC filter inserted.

In a contemporary trial assessing NAC and RC plus PLND versus RC plus PLND alone, the incidence of preoperative TEEs was not reported, and only 1 patient (in the RC plus PLND-alone arm) experienced a postoperative TEE.¹³ In a cohort of 202 patients, of whom only 42 had received NAC, the overall TEE rate was 8.4%; however, it was threefold greater in the NAC arm (19%).⁷ NAC was an independent risk factor for TEEs, and 6 of 8 patients who had received NAC experienced a TEE before cystectomy. However, no distinction between patients receiving true neoadjuvant versus induction chemotherapy was made. A recent multi-institutional study reported a TEE rate during and after neoadjuvant chemotherapy similar to ours at 13.8%.¹⁴ Our data augment the published data by demonstrating that TEEs do not preclude chemotherapy completion, increase the interval from chemotherapy completion to RC plus PLND, or affect the time-to-event outcomes.

Cisplatin-based chemotherapy has been associated with high TEE rates^{10,15} and with 67% greater TEE rates than non-cisplatin-based regimens.¹⁶ The high TEE rate during POC supports our hypothesis that the incidence of TEEs in patients receiving POC before RC plus PLND might be underappreciated.¹⁷ Patients who experienced TEEs had greater rates of T3–T4 disease (61% vs. 42%); however, the development of TEEs was not significantly associated with worse perioperative or clinicopathologic outcomes. Advanced stage is a well-described risk factor for TEEs among patients with cancer. This might be attributable to the biologic aggressiveness of the cancer or the poorer performance status of patients with

advanced-stage disease, which might predispose them to developing a TEE.¹⁸ We did not find any preoperative factors that might be associated with TEEs.

Our findings raise the question of whether a role for prophylactic anticoagulation exists before the initiation of systemic chemotherapy. First, a reproducible risk exist of TEE-associated death in the 0.6% to 3.7% range seen across cancer types.^{19,20} Furthermore, patients who experience TEEs have a greater risk of mortality compared with those who do not when controlling for other factors.²¹ Although the difference did not reach conventional levels of significance ($2P = .06$), our 95% CIs revealed poorer overall survival among patients with a TEE (hazard ratio, 1.44; 95% CI, 0.98–2.10), which warrants further study in larger data sets. Because we only evaluated patients who had ultimately undergone RC plus PLND, it is possible that we did not capture mortality events during POC. Second, 33 of 57 patients (9% of the cohort; 58% of patients who experienced a TEE) underwent insertion of an IVC filter. This would be the equivalent of a grade III complication using the Clavien-Dindo scale or adverse event reporting scale and would certainly merit consideration of prevention.^{22,23} Additionally, the morbidity associated with a postoperative hemorrhage after anticoagulation therapy for TEE must be considered. Ideally, the IVC filter would be removed eventually, with additional potential morbidity and costs. Third, in a retrospective review, the hospital length of stay attributable to TEE was 11 days, with the associated costs > \$20,000 per hospitalization and > \$1.5 billion annually in the United States.^{2–4} It is possible that chemoprophylaxis during POC for RC plus PLND would decrease the health care costs.

The American Society of Clinical Oncology guidelines have not recommended primary prophylaxis against TEEs for ambulatory cancer patients, with a few exceptions.²⁴ In 1 double-blind randomized trial of patients with metastatic breast cancer in which patients received 1 mg of warfarin or placebo, the rate of TEE was 0.65% in the treatment group versus 4.4% in the placebo arm. In contrast, these findings were not confirmed in patients with stage III or IV non-small-cell lung cancer or metastatic breast cancer using prophylactic low-molecular-weight heparin.²⁵ In a recent Cochrane study of ambulatory cancer patients with no therapeutic or prophylactic indication for anticoagulation, parenteral, but not oral, anticoagulation was associated with a significantly decreased risk of TEEs and slightly increased risk of minor bleeding complications.^{26,27} The investigators recommended a shared patient–physician decision regarding the initiation of parenteral anticoagulation. In accordance with the American Society for Clinical Oncology guidelines, hospitalized patients with cancer should receive thromboprophylaxis, with TEE rates reported at 0.6% to 18%.²⁴ These guidelines also recommended chemoprophylaxis for patients undergoing major cancer surgery, for whom the risk of TEE is similar to the rate we have reported.²⁴ The guideline recommendation against primary TEE prophylaxis might have been driven by the low absolute rate of TEEs in the studies of ambulatory cancer patients the guidelines considered.²⁴ More recent studies of patients with metastatic pancreatic cancer, with TEE rates comparable to those we found, reported TEE rates of 31% versus 12% in the placebo and treatment arms, respectively.²⁸ It is important to acknowledge that potential cisplatin-induced anemia and thrombocytopenia and unique hematuria-related management considerations in bladder cancer patients raise legitimate concerns regarding prophylactic anticoagulation in this patient population.

We found an incidence of TEE during POC of 16%, which was much greater than the 7% rate for the “highest risk” patients receiving chemotherapy using the validated Khorana score risk stratification.²⁹ It is possible that we actually underestimated the risk of TEE, given the retrospective nature of our review, the partial reliance on medical records obtained from referring medical oncologists, and the absence of routine screening of the lower extremities for DVT. This precluded us from reliably assessing the effects of symptomatic versus asymptomatic TEE on the parameters studied. It is also possible that identification of asymptomatic TEE during routine staging led to overdiagnosis and over-treatment. However, asymptomatic TEEs are often associated with subclinical symptoms, could become symptomatic in the future, and have been associated with an increased risk of mortality.^{21,30} We intentionally did not assess a comparator group that had not undergone POC because of the fundamental selection biases that would have resulted.

Conclusion

Our data suggest that the incidence of TEE during POC is high but do not provide evidence that TEE affects either chemotherapy completion or the perioperative and oncologic outcomes, despite the early reinitiation of anticoagulation. Nevertheless, primary prevention of TEEs during POC before RC plus PLND would provide an opportunity to decrease iatrogenic morbidity and costs and, with corroborated results, would be worthy of investigation in the context of a clinical trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- A retrospective review of 357 consecutive patients who had received POC at our institution before RC showed that the overall rate of TEE was 22% in our cohort, with a 16% incidence in the preoperative setting.
- TEEs in the POC setting led to invasive procedures (IVC filter placement) in 40 patients but did not independently affect patients' ability to complete POC.
- The risk of recurrence or metastasis was not significantly greater for patients who experienced a TEE at any point compared with those who did not experience a TEE in our univariable or multivariable Cox models.
- Further research is required to determine whether preventative TEE measures during POC might improve the clinical outcomes.

Figure 1. Kaplan-Meier Recurrence-free Survival (RFS) Estimates for Patients Without (Black) and With (Gray) a Thromboembolic Event at Any Time (n = 319)

Figure 2. Kaplan-Meier Metastatic-free Survival (MFS) Estimates for Patients Without (Black) and With (Gray) a Thromboembolic Event at Any Time (n = 322)

Figure 3.
Kaplan-Meier Overall Survival Estimates for Patients Without (Black) and With (Gray) a Thromboembolic Event at Any Time (n = 329)
Abbreviations: RC = radical cystectomy; VTE = venous thromboembolism.

Table 1

Patient Characteristics (n = 357)

Characteristic	n (%)
Age at cystectomy	
Median	65.6
IQR	57.9–71.2
Male gender	253 (71)
Karnofsky performance status	
70	4 (1.1)
80	99 (28)
90	254 (71)
Hemoglobin (g/dL)	
Median	12.7
IQR	11.5–14.0
Smoked tobacco	
Never	75 (21)
Former	212 (59)
Current	70 (20)
EBL (mL) (n = 352)	
Median	800
IQR	500–1200
Blood transfusion	262 (73)
Blood transfused (U)	
Median	2
IQR	0–3
Length of stay (d)	
Median	7
IQR	6–10
Perioperative complications	147 (41)
Positive surgical margins	16 (4.4)
Pathologic T stage	
pT0	70 (20)
pTa	4 (1.1)
pTis	55 (15)
pT1	26 (7.3)
pT2	43 (12)
pT3	120 (34)
pT4	39 (11)
Pathologic N stage	
pN0	258 (72)

Characteristic	n (%)
pN1	36 (10)
pN2	49 (14)
pN3	14 (4)
Induction POC	139 (39)
TEE	
None	278 (78)
Preoperative	57 (16)
Postoperative	22 (6.2)
Preoperative IVC filter	40 (11.2)

Abbreviations: EBL = estimated blood loss; IVC = inferior vena cava; IQR = interquartile range; POC = preoperative chemotherapy; TEE = thromboembolism event.

Table 2

Perioperative Outcomes Stratified by Development a TEE (n = 357)

Variable	Preoperative TEE				P Value ^a
	No (n = 300)	Yes (n = 57)	Diff	95% CI	
Age during chemotherapy (y)	64.11 (10)	65.33 (10)	-1.22	-4.08 to 1.64	.4
Male gender	212 (71)	41 (72)	-1.3%	-14 to 11	.8
Karnofsky performance status	86.90 (5)	87.54 (4)	-0.64	-2.0 to 0.7	.4
Inductive chemotherapy with suspicion of nodal metastasis	116 (39)	23 (40)	-1.7%	-16 to 12	.8
Smoked tobacco			NA	NA	.7
Never	61 (20)	14 (25)			
Former	179 (60)	33 (58)			
Current	60 (20)	10 (18)			
Race			NA	NA	.3
Asian	8 (2.7)	2 (3.5)			
Black	8 (2.7)	4 (7.0)			
White	276 (92)	49 (86)			
Unknown	8 (2.7)	2 (3.5)			
T stage at diagnosis (n = 356)			NA	NA	.5
Ta	18 (6.0)	3 (5.3)			
Tis	9 (3.0)	0 (0)			
T1	74 (25)	13 (23)			
T2	194 (65)	39 (68)			
T3	1 (0.3)	0 (0)			
T4	1 (0.3)	0 (0)			
Tx	2 (0.7)	2 (3.5)			
EBL (mL) (n = 355)	900 (500–1300)	700 (500–1000)	158	-32 to 349	.030
Blood transfusion	221 (74)	41 (72)	1.7%	-11 to 14	.9
Blood transfused (U)	2 (0–3)	2 (0–3)	0.0	-0.5 to 0.6	.9
Length of stay (days)	7 (6, 9)	8 (6, 10)	-0.7	-2.3 to 0.9	.11
Perioperative complications	121 (40)	26 (46)	-5	-19 to 9	.5

Variable	Preoperative TEE				P Value ^d
	No (n = 300)	Yes (n = 57)	Diff	95% CI	
Positive surgical margins	22 (7.3)	5 (8.8)	-1.4%	-9 to 6	.8
Pathologic stage			NA	NA	.016
pT0	67 (22)	3 (5.3)			
pTa	4 (1.3)	0 (0)			
pTis	44 (15)	11 (19)			
pT1	23 (7.7)	3 (5.2)			
pT2	38 (13)	5 (8.8)			
pT3	92 (31)	28 (49)			
pT4	32 (11)	7 (12)			

Data presented as median (interquartile range) or n (%).

Abbreviations: Diff = difference; EBL = estimated blood loss; NA = not applicable; TEE = thromboembolism event.

^aWilcoxon rank-sum or Fisher's exact test.

Table 3

Comparison of Survival Outcomes Stratified by TEE Incidence

Outcome	Univariable			Multivariable ^a		
	HR	95% CI	P Value	HR	95% CI	P Value
Recurrence (n = 319)						
No TEE	Ref			Ref		
TEE at any time	0.99	0.61–1.59	.1	0.84	0.52–1.38	.5
Metastasis (n = 322)						
No TEE	Ref			Ref		
TEE at any time	0.98	0.58–1.63	.9	0.78	0.46–1.33	.4
Overall death (n = 329)						
No TEE	Ref			Ref		
TEE at any time	1.44	0.98–2.10	.061	1.31	0.89–1.93	.2

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference; TEE = thromboembolism event.

^aModel adjusted for chemotherapy regimen (neoadjuvant vs. induction), surgical margin status, pathologic tumor stage, and smoker status.