Original Study

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 underappreciated 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 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.

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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 preoperative 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