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Original article

Thromboembolic events in patients with urothelial carcinoma undergoing neoadjuvant chemotherapy and radical cystectomy

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Abstract

Objectives: Patients receiving cisplatin are at high risk of thromboembolic events (TEEs). The objective of this study was to assess the effect of cisplatin-based neoadjuvant chemotherapy (NCT) on the incidence of perioperative TEEs in patients undergoing radical cystectomy.

Methods and materials: We analyzed a consecutive sample of 202 patients with urothelial carcinoma treated with radical cystectomy between 2005 and 2013. Data were collected retrospectively by reviewing medical records. Median follow-up was 16.9 months. Events of interest were defined as venous or arterial TEEs occurring from the date of diagnosis to 30 days after surgery. TEE incidence among patients treated with NCT and cystectomy was compared with that among patients treated with cystectomy alone using Fisher exact test and Cox proportional hazards regression. Proportional hazards regression was also used to assess whether TEE is a predictor of cancer progression and survival.

Results: Of 202 patients, 17 (8.4%) developed a TEE, including 8 of 42 (19.1%) treated with NCT and cystectomy and 9 of 160 (5.6%) treated with cystectomy alone (risk ratio = 3.39, 95% CI: 1.39–8.24). After adjustment for observation time, there remained an association between treatment with NCT and risk of TEE (hazard ratio = 2.40; 95% CI: 0.92–6.27; $P = 0.07$). Overall, 7 events occurred before cystectomy and 10 occurred postoperatively. Among patients treated with NCT, 6 of 8 events occurred before cystectomy. Detection of TEE was clinically significant as preoperative TEE was found to be an independent predictor of progression and cancer-specific mortality (adjusted hazard ratio = 3.91, 95% CI: 1.34–11.45). The main limitations of our study are its retrospective data collection and small absolute number of events.

Conclusions: TEE occurs commonly in patients with urothelial carcinoma undergoing NCT. Preoperative TEE is an independent predictor of progression and cancer-specific mortality.

Keywords: Thromboembolism; Urothelial carcinoma; Neoadjuvant chemotherapy

1. Introduction

Venous and arterial thromboembolic events are significant causes of morbidity and mortality in patients with cancer [1,2]. Although malignancy itself induces a hypercoagulable

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state and thus increases the risk of thromboembolism, recent evidence suggests that many chemotherapy agents further compound this risk [3].

In patients with muscle-invasive bladder cancer, neoadjuvant chemotherapy (NCT) has been shown to provide a small but tangible survival benefit compared with radical cystectomy alone [4]. The mainstay chemotherapy drug for treatment of urothelial carcinoma is cisplatin, a DNA cross-linking agent that has classically been combined with methotrexate, vinblastine, and adriamycin (MVAC) and, more recently, with gemcitabine (GC). A recent systematic review showed cisplatin-based chemotherapy to be associated with an increased risk of venous thromboembolism (VTE) compared with non–cisplatin-based regimens in patients with solid organ malignancies [5], suggesting that patients with urothelial carcinoma may be at high risk of thromboembolic events (TEEs) while undergoing NCT.

In spite of this, the incidence and clinical implications of TEEs in patients with urothelial carcinoma treated with cisplatin-based chemotherapy with neoadjuvant intent have yet to be described in the literature. This is of utmost importance, as per definition NCT is followed by radical cystectomy and its feasibility, risk, and timing may be affected by the development of TEEs.

The main objective of our study was therefore to determine whether cisplatin-based NCT is associated with an increased incidence of both preoperative and postoperative TEEs compared with cystectomy alone. A secondary objective was to determine whether the development of TEEs is associated with cancer progression and patient survival.

2. Materials and methods

Between 2005 and 2013, 266 patients with urothelial carcinoma of the bladder, prostate, or urethra underwent radical cystectomy with curative intent at 2 tertiary-care hospitals in Hamilton, Ontario, Canada. Of these patients, 38 underwent cystectomy for high-risk, non–muscle-invasive bladder cancer and were thus excluded from the analysis. An additional 26 patients were excluded because of preoperative anticoagulation (10 patients), past history of VTE (6), insufficient outcome data (5), recent chemotherapy for another primary malignancy (2), salvage cystectomy (2), and neoadjuvant radiation therapy (1). All patients with clinical category T2 to T4 muscle-invasive urothelial carcinoma of the bladder without contraindications to cisplatin-based chemotherapy were offered NCT following consultation in our multidisciplinary bladder cancer clinic.

Clinical data were abstracted by retrospective review of hospital records and electronic medical records. TEEs were ascertained by reviewing the reports of all imaging studies, including staging computed tomography scans, leg Doppler ultrasounds, and angiograms. Vital status was ascertained by periodic review of hospital records and electronic medical records.

Among patients treated with NCT, baseline TEE risk was assessed using the Khorana criteria, a validated risk stratification model for VTE in patients with cancer receiving chemotherapy [6]. The Khorana score is calculated using 5 clinical variables: cancer site, body mass index ≥ 35 kg/m^2, prechemotherapy platelet count $> 350 \times 10^9$/l, hemoglobin concentration < 100 g/l (or use of erythropoietin), and leukocyte count $\geq 11 \times 10^9$/l. Low (score of 0), intermediate (1–2), and high-risk (≥ 3) categories correspond to VTE risks of approximately 0.5%, 2%, and 7%, respectively [6].

TEEs were defined as radiographically confirmed deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial thrombosis. Doppler ultrasound was performed only for clinical suspicion of DVT or PE but not routinely for detection of subclinical DVT. Events of interest were defined a priori as those that occurred from the time of diagnosis to 30 days after surgery. Among patients receiving NCT, events occurring before the start of NCT were excluded. Cancer progression was defined as development of lymph node or visceral metastases after surgery.

Crude associations between patient characteristics and TEEs were tested using the Wilcoxon rank sum test for continuous variables (age and Charlson comorbidity index [CCI]) and Fisher exact test for categorical variables (sex, pathologic stage, and NCT). To account for longer observation times in patients treated with NCT, we performed Cox proportional hazards regression, with the time at risk defined as the time from diagnosis or start of NCT to either the development of TEE or 30 days after surgery. Overall, cancer-specific, and progression-free survival among those patients who developed a TEE and those who did not were compared using the Kaplan-Meier method and the log-rank test. Proportional hazards regression was used to determine whether TEE predicted disease progression and survival independent of age, sex, CCI, pathologic stage, and NCT. Statistical analyses were performed with Statistical Analysis Software, version 9 (SAS Institute, Cary, NC).

The study was approved by the Hamilton Integrated Research Ethics Board.

3. Results

Overall, 202 patients with a median (interquartile range [IQR]) age of 69.3 (62.1–78.0) years were included in the analysis. Of them, 150 patients (74.3%) were male. A total of 42 patients (20.8%) received NCT, with GC and MVAC being the most commonly used regimens (59% and 37% of patients receiving NCT, respectively). Patients who received NCT were, on average, younger and more likely to be female than those who did not receive NCT (Table 2). However, there was no association between treatment with NCT and either CCI or pathologic stage at cystectomy. Time from diagnosis to cystectomy was