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Bladder Cancer

Perioperative Blood Transfusion and Radical Cystectomy: Does Timing of Transfusion Affect Bladder Cancer Mortality?

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Abstract

Background: While perioperative blood transfusion (BT) has been associated with adverse outcomes in multiple malignancies, the importance of BT timing has not been established.
Objective: The objective of this study was to evaluate whether intraoperative BT is associated with worse cancer outcomes in bladder cancer patients treated with radical cystectomy (RC).
Design, setting, and participants: Outcomes from two independent cohorts of consecutive patients with bladder cancer treated with RC were analyzed.
Outcome measurements and statistical analysis: Recurrence-free survival, cancer-specific survival (CSS), and overall survival were estimated and multivariate analyses were performed to evaluate the association of BT timing with cancer outcomes.
Results and limitations: In the primary cohort of 360 patients, 241 (67%) received perioperative BT, including 162 intraoperatively and 79 postoperatively. Five-year CSS was 44% among patients who received an intraoperative BT versus 64% for patients who received postoperative BT ($p = 0.0005$). After multivariate analysis, intraoperative BT was associated with an increased risk of cancer mortality (hazard ratio [HR]: 1.93; $p = 0.02$), while receipt of postoperative BT was not ($p = 0.60$). In the validation cohort of 1770 patients, 1100 (62%) received perioperative BT with a median postoperative follow-up of 11 yr (interquartile range: 8.0–15.7). Five-year RFS ($p < 0.001$) and CSS ($p < 0.001$) were significantly worse among patients who received an intraoperative BT. Intraoperative BT was independently associated with recurrence (HR: 1.45; $p = 0.001$), cancer-specific mortality (HR: 1.55; $p = 0.0001$), and all-cause mortality (HR: 1.40; $p < 0.0001$). Postoperative BT was not associated with risk of disease recurrence or cancer death.
Conclusions: Intraoperative BT is associated with increased risk of bladder cancer recurrence and mortality.
Patient summary: In this study, the effects of blood transfusion on bladder cancer surgery outcomes were evaluated. Intraoperative blood transfusion, but not postoperative transfusion, was associated with higher rates of recurrence and cancer-specific mortality.

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1. Introduction

Perioperative blood transfusion (BT) has been associated with adverse cancer-specific mortality in many malignancies [1–4], including bladder cancer [5–7]. An immunosuppressive effect from BT has been well described in many studies [8]. However, additional mechanisms to explain the association of perioperative BT with poor cancer outcomes include decreased host immunity caused by anesthetics and opioids [9] and release of increased numbers of circulating tumor cells caused by surgical manipulation [10]. These proposed mechanisms would likely have a maximum effect during surgery and potentially cause worse outcomes for patients who were transfused intraoperatively. However, if intraoperative BT is associated with worse outcomes, further studies could investigate alternative transfusion strategies, including delaying BT, as a potential mechanism to improve outcomes.

Radical cystectomy (RC) for bladder cancer is an excellent model to test whether the timing of BT is independently associated with disease recurrence and mortality. Perioperative BT is administered to approximately 60% of patients undergoing this surgery [6] and three recent studies have demonstrated an association of perioperative BT with bladder cancer-specific survival in patients undergoing RC [5–7]. However, there is a paucity of data that specifically examine the importance of the timing of BT and it is unknown whether outcomes differ for patients who receive blood during surgery compared with those who receive blood after surgery, during their postoperative hospitalization. Given the proposed mechanisms by which BT may affect cancer biology, patients who receive BT intraoperatively might be expected to have worse outcomes compared with patients who receive BT after surgery has concluded. The objective of this study is to evaluate the association of the timing of perioperative BT with recurrence and survival in bladder cancer patients treated with RC, using a multi-institutional dataset to allow for a testing cohort and a validation population.

2. Patients and methods

After obtaining institutional review board approval, an institutional database identified 360 consecutive patients with bladder cancer treated with RC without perioperative chemotherapy between January 1, 2003, and December 31, 2012, at the University of Wisconsin (UW) hospital. Patients who received neoadjuvant or adjuvant chemotherapy were excluded because of the potential confounding impact of chemotherapy-induced anemia and the association of perioperative chemotherapy with cancer outcomes. Findings from the UW dataset were subsequently evaluated in an external cohort consisting of 1770 patients who underwent RC without perioperative chemotherapy for bladder cancer at the Mayo Clinic between 1980 and 2005, as previously described [6].

Clinical and pathologic variables reviewed included age, sex, body mass index, preoperative hemoglobin level (Mayo cohort only), diabetes, smoking, pathologic T and N stages [11], and Eastern Cooperative Oncology Group (ECOG) performance status (Mayo cohort only). Tumor grade and histologic subtype was not separately reported or analyzed here, as the majority of patients undergoing cystectomy had high-grade urothelial carcinoma.

Perioperative BT was defined as receipt of packed red blood cells either during surgery (intraoperative BT) or during the postsurgical hospitalization (postoperative BT). Indication for transfusion was based on the discretion of the surgical and anesthesia teams for each patient, without standardized criteria. Transfusion with other blood products was not recorded. Standard surveillance after RC consisted of quarterly evaluation for the first 2 yr after surgery, semiannual evaluation for 3 yr, and annual follow-up thereafter [6].

Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were estimated using the Kaplan-Meier method and compared between cohorts with the log-rank test. Fisher exact or chi-square tests were used to evaluate differences among groups. Univariate and multivariate Cox proportional hazards analyses were performed to evaluate the associations of clinical and pathologic variables with the risks for RFS, CSS, and OS. A p value <0.05 was considered statistically significant and the SAS software package (SAS Institute, Cary, NC, USA) was used for all analyses.

3. Results

3.1. Primary cohort

Of the 360 patients who underwent RC at UW, 241 (65%) received a perioperative BT (Table 1). Of these, 66 patients (18%) received an intraoperative BT only, 79 patients (22%) received a postoperative BT, and 96 patients (27%) received both intraoperative and postoperative BT. Median follow-up after surgery in this cohort was 18.7 mo (interquartile range [IQR]: 8.1–50.4), during which time 113 patients had disease recurrence, including 92 who had nonurinary tract recurrence; 157 patients died, including 106 who died of bladder cancer.

Consistent with prior reports [6,7], patients in the initial cohort who received a perioperative BT had a worse 5-yr CSS (50%) than patients who did not receive perioperative BT (62%; $p = 0.02$) (Supplementary Fig. 1). The timing of BT was associated with disease recurrence, and the 5-yr RFS was significantly worse among patients who received an intraoperative BT (46%) or intraoperative and postoperative BT (62%) compared with patients who received only postoperative BT (71%) or patients who did not receive any perioperative BT (69%; $p = 0.01$) (Fig. 1A). Receipt of an intraoperative BT was also associated with adverse CSS. The 5-yr CSS for patients who received an intraoperative BT was 38% (50% for those who received both an intraoperative BT and a postoperative BT) compared with 64% for patients who received only postoperative transfusion and 62% for patients who did not receive perioperative BT ($p = 0.004$). Of note, no significant difference in CSS was found between patients who received an intraoperative BT and those who received both intraoperative and postoperative BT ($p = 0.71$), despite patients in the intraoperative and postoperative BT group having received more units of blood (median: 4.5 vs 2.0 units; $p < 0.0001$) compared with patients who received intraoperative BT only. In addition, patients who received an intraoperative transfusion (with or without postoperative transfusion) were found to have a significantly lower 5-yr CSS (44%) when directly compared with only patients who received a postoperative BT (64%; $p = 0.004$) (Fig. 1B).