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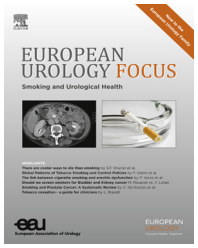

European Association of Urology

Bladder Cancer

The Impact of Perioperative Blood Transfusion on Survival of Bladder Cancer Patients Submitted to Radical Cystectomy: Role of Anemia Status

Marco Moschini[a,b,*], *Marco Bianchi*[a], *Giorgio Gandaglia*[a], *Vito Cucchiara*[a], *Stefano Luzzago*[a], *Federico Pellucchi*[c], *Rocco Damiano*[b], *Vincenzo Serretta*[d], *Alberto Briganti*[a], *Francesco Montorsi*[a], *Andrea Salonia*[a], *Renzo Colombo*[a]

[a] *Unit of Urology/Division of Oncology, IRCCS Ospedale San Raffaele, URI Milan, Italy;* [b] *Department of Urology, Magna Graecia University of Catanzaro, Catanzaro, Italy;* [c] *Department of Urology, AO Papa Giovanni XXIII, Bergamo, Italy;* [d] *UO di Urologia, Policlinico Universitario "Paolo Giaccone", Palermo, Italy*

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Abstract

Background: The prognostic role of perioperative blood transfusion (PBT) in patients who underwent radical cystectomy (RC) for bladder cancer (BCa), although supported by clinical evidence, still remains to be assessed definitively.
Objective: To investigate the impact of PBT on RC patients for overall survival and after stratifying according to preoperative anemia status and to define whether the oncologic impact may be assumed to be a primary effect of PBT or attributed to the reduced preoperative hemoglobin (Hb) level.
Design, setting, and participants: A total of 1490 consecutive patients with nonmetastatic BCa who underwent RC and pelvic lymph node dissection between January 1990 and August 2013 at a single referral center entered the study. PBT and preoperative Hb levels were statistically correlated with postoperative oncologic outcomes.
Outcome measurements and statistical analysis: Kaplan-Meier analyses were used to evaluate the impact of PBT on overall mortality (OM) and cancer-specific mortality (CSM). Multivariable Cox regression analyses tested the relationship between PBT and the risk of OM and CSM in the overall population and after stratifying patients according to the severity of their anemia.
Results and limitations: A total of 580 patients (38.9%) received PBT. Mean postoperative follow-up was 125.13 mo (median: 110 mo). Overall 5- and 10-yr CSM survival rates were 58.3% and 47.6%, respectively. At multivariable Cox regression analyses, PBT could not be associated with an increased risk of either CSM or OM (all $p > 0.3$). Conversely, preoperative Hb levels were significantly associated with OM (hazard ratio [HR]: 0.88; confidence interval [CI], 0.83–0.95) and CSM (HR: 0.84; 95% CI, 0.77–0.95) (all $p < 0.001$). A significant detrimental effect of PBT on OM (HR: 1.65; 95% CI, 1.08–2.52) and CSM (HR: 1.68; 95% CI, 1.04–2.70) (all $p < 0.03$) was found in patients without preoperative anemia status.
Conclusions: In nonanemic BCa patients proposed for RC, PBT is associated with a significant detrimental effect on CSM and OM. This effect seems to be attributable to the direct impact of PBT, regardless of the preoperative Hb value.
Patient summary: In nonanemic patients proposed for radical cystectomy, a negative prognostic impact of perioperative blood transfusion should be taken into account.

* Corresponding author. Department of Urology, University "Vita-Salute," San Raffaele Hospital, Via Olgettina, 60-20132 Milan, Italy. Tel. +39 02 06435664; Fax: +39 02 26435659.
E-mail address: marco.moschini87@gmail.com (M. Moschini).

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1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the treatment of choice for muscle-invasive and high-risk non–muscle-invasive bladder cancer (BCa) patients [1]. However, the 5-yr overall life expectancy after surgery is not optimal, ranging from 42% to 58% according to the stage of the disease and node status [2]. To improve this survival rate, the assessment of reliable prognostic factors could help configure tailored adjuvant treatments and follow-up schemes.

Several biochemical or hematologic factors have been described in this patient population [3–7]. Although the perioperative blood transfusion (PBT) was supported as a possible risk factor for cancer-specific mortality (CSM) and overall mortality (OM) by some studies [8–10], this role could not be confirmed at multivariable analyses by some other investigations [9,11]. Based on a recent study by Abel et al [12], only the intraoperative transfusion relates to a negative effect on survival in BCa patients submitted to RC. Moreover, the impact of PBT on postoperative survival may be assumed as a result of a direct effect or as an indirect effect mediated by low preoperative hemoglobin (Hb) values. This configures an intriguing point because there is evidence that anemia status was found as a conditioning factor for poor postoperative oncologic outcomes in BCa [13,14] as well as in many other different cancers [15–18].

In addition, although the preoperative Hb level represents the main parameter taken into account by the physician for deciding whether a blood transfusion should be administered, only a few studies have investigated the relationship between PBT and Hb level [8,10,12], and probably no one has ever stratified the population to account for preoperative anemia status.

We carried out a retrospective study to assess the possible prognostic impact of PBT in terms of CSM and OM considering both the overall population and subgroups of patients stratified according to their preoperative anemia status.

2. Materials and methods

2.1. Study population

After institutional review board and European Commission approvals were obtained, pre-, intra-, and postoperative clinical data included in the institutional database concerning 1490 consecutive patients found with nonmetastatic BCa submitted to RC and bilateral PLND between January 1990 and August 2013 were retrospectively analyzed.

2.2. Prognostic factors and outcome variables

Clinical and pathologic characteristics of preoperative patients including year of surgery, age at surgery, gender, body mass index (BMI), preoperative Hb level, and Charlson Comorbidity Index (CCI) were evaluated at the time of hospital admission. Perioperative data including number of transfusions, pathologic T stage and grade of tumor, lymph node status, surgical margin status, and administration of adjuvant chemotherapy were available for all patients. Pathologic findings were assessed by a dedicated genitourinary pathologist team and attributed according to the 2009 TNM classification [19] for stage and according to the 1998 World Health Organization (WHO)/International Society of Urologic Pathology consensus classification [20] for grade. The detection of one or more involved nodes was defined as lymph node invasion (LNI). Positive soft tissue surgical margins were defined when transitional tumor could be detected at any inked areas of soft tissue at the time of RC. PBT was defined as a transfusion of allogenic red blood cells during the operative surgery or during the postoperative hospitalization period. According to the WHO definition [21], anemia status was stratified as mild, moderate, or severe when preoperative Hb values of <13 g/dl for men and <12 g/dl for women, <11 g/dl, and <8 g/dl were registered, respectively.

Clinical follow-up consisted of a baseline visit 3 mo after surgery and then every 6 mo for 5 yr. Radiologic follow-up included chest and abdomen contrast computed tomography completed every 6 mo in all patients. Cystoscopy, urine cytology, urethral washings, and bone scan were completed only in selected cases. The postoperative oncologic outcome based on CSM and OM was obtainable for all patients from the institutional database.

2.3. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges (IQRs) were reported for continuously coded variables. The Mann-Whitney test and chi-square test were used to compare the statistical significance of differences in medians and proportions, respectively. The statistical analyses had several aspects. First, Kaplan-Meier analyses were used to evaluate the impact of PBT on the OM and CSM. Second, multivariable Cox regression analyses tested the relationship between PBT and the risk of OM and CSM in the overall population and after stratifying patients according to the severity of their anemia. For the results analyses, moderate and severe anemia status were considered together due to the low number of patients found with severe anemia. Covariates consisted of age, gender, preoperative Hb levels, pathologic stage and tumor grade, surgical margin status, LNI, CCI, adjuvant chemotherapy, and concomitant carcinoma in situ (CIS).

Statistical significance was considered when $p < 0.05$. Statistical analyses were performed by using SPSS v.22.0 (IBM Corp, Armonk, NY, USA) and the R statistical package system (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Table 1 shows the clinical and pathologic characteristics of patients included in the study. A total of 580 (38.9%) received PBT. Female patients received PBT more frequently than male ($p = 0.005$), and PBT was more frequently administered during the last 5 yr ($p < 0.001$). During the same period of time, patients showed lower preoperative Hb levels ($p < 0.001$) and were more frequently found with severe ($p < 0.001$) anemia status. As expected, perioperative blood loss was higher for patients who received PBT compared with those who did not; median value: 1400 (IQR: 900–2000) and 800 (IQR: 600–1100) ml, respectively ($p < 0.001$). No difference could be observed for age, BMI, number of nodes removed, pathologic T stage, grade (WHO 1973), presence of CIS, surgical margin status, LNI, and adjuvant chemotherapy ($p > 0.07$).

3.2. Survival estimates

Mean follow-up after surgery was 125.13 mo (median: 110 mo). Overall, the 5- and 10-yr CSM survival rates were 58.3% and 47.6%, respectively (Fig. 1). After stratification of

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