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Original article

Preoperative anemia is associated with disease recurrence and progression in patients with non–muscle-invasive bladder cancer

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Abstract

Purpose: To evaluate the effect of preoperative anemia (PA) on oncological outcomes in a multicenter cohort of patients with non–muscle-invasive bladder cancer (NMIBC) treated with transurethral resection of the bladder (TURB) and adjuvant intravesical therapies. We hypothesize that PA represents a marker of disease aggressiveness and could be used to improve the discrimination of prognostic tools for the prediction of disease recurrence and progression.

Methods: This multicenter retrospective study included 1,117 patients from 4 different centers. The presence of PA was assessed according to the World Health Organization classification as a preoperative hemoglobin level of $\leq$13 g/dl in men and $\leq$12 g/dl in women. PA evaluation was done at each institution, generally 1 to 3 days before surgery. Multivariable Cox regression models were performed to evaluate the prognostic effect of PA on survival outcomes.

Results: Overall, 381 (34%) patients with NMIBC treated with TURB, had PA. Median follow-up for patients alive at last follow-up was 62.7 months (interquartile range: 25–110.7). On multivariable Cox regression analyses that accounted for the effect of standard clinicopathologic prognosticators, PA was independently associated with recurrence-free survival ($P = 0.045$) and progression-free survival ($P = 0.01$). Adding PA to a model for the prediction of disease recurrence and progression improved the discrimination of the prognostic models marginally from 69.8% to 70.3% and from 71.6% to 73.1%, respectively.

Conclusions: PA was found in more than one-third of patients with NMIBC treated with TURB. PA was associated with poor oncological outcomes and was an independent predictor of intravesical disease recurrence and progression. However, the additional prognostic information provided by PA remains limited.

Keywords: Preoperative anemia; Non–muscle-invasive bladder cancer; Survival; Recurrence; Progression

1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) confined to mucosa (Ta, Tis) or submucosa (T1) represents

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approximately 75% of newly diagnosed bladder cancers (BCa) in western countries [1]. Patients with NMIBC have a relatively favorable prognosis, with a 10-year cancer-specific survival (CSS) of 75% to 80% in high-grade and almost 100% in low-grade NMIBC [2]. Standard treatment for these patients is transurethral resection of the bladder (TURB) with or without intravesical therapies [3]. Intravesical instillation, consisting of chemotherapy or immunotherapy, reduces recurrence and progression rates compared to TURB alone [4,5]. Nevertheless, most patients with NMIBC experience intravesical disease recurrence, and a nonnegligible percentage of those develop muscle-invasive disease [6]. Those who experience progression to muscle-invasive BCa have a worse survival compared to those who present with primary invasive disease [7].

Predicting disease recurrence and progression is of fundamental importance to accurately risk stratify patients in order to select those who are likely to benefit from adjuvant therapies or even from early radical cystectomy (RC) and, in addition, to risk-adapted follow-up schemes. Many predictive tools have been developed for this purpose [8–10], mainly based on patient and tumor characteristics such as age, sex, tumor stage, grade, size, focality, and the presence of concomitant carcinoma in situ (CIS). Unfortunately, the accuracy of these tools remains low, especially for high-grade disease.

Preoperative anemia (PA) is commonly found in patients with cancer. Actually, the reported prevalence of PA in patients undergoing surgery for cancers ranges between 25% and 75% [11]. The pathogenesis of PA is multifactorial and can be a result of cancer invasion, chemoradiation treatments, renal insufficiency, or chemical factors induced by the tumor [12]. Interestingly, PA has been associated with worse oncological outcomes in patients undergoing surgery for various types of cancers such as breast and kidney [13,14].

This association has also been reported in patients with BCa treated with RC [15,16]. Conversely, the effect of PA on outcomes of patients with NMIBC remains poorly investigated. Actually, to our knowledge, there is only 1 single-center study reporting the effect of PA on overall survival (OS) and CSS in 320 patients with NMIBC treated with TURB [17]. However, the association between PA and disease recurrence and progression in this setting is still unknown.

Therefore, the aim of our study was to evaluate the effect of PA on oncological outcomes (recurrence, progression, OS, and CSS) in a large, multicenter cohort of patients with NMIBC treated with TURB and adjuvant intravesical therapies. We hypothesized that PA would be associated with worse prognosis.

2. Materials and methods

This was an institutional review board–approved study with all participating sites providing the necessary data-sharing agreements before the initiation of the study. Records of 1,117 patients with pathologically proven primary or recurrent NMIBC treated with TURB at 4 academic centers between 1996 and 2007 were included for the purpose of the study.

None of the patients had upper tract urothelial carcinoma, prostatic stroma invasion, or metastatic BCa at the time of surgery. After TURB, patients were treated according to international guidelines at the time with either immediate single-dose postoperative instillation chemotherapy (40 mg mitomycin C, 80 mg epirubicin, or 50 mg doxorubicin), adjuvant intravesical mitomycin C chemotherapy, or adjuvant bacillus Calmette-Guerin immunotherapy. Maintenance therapy was given at the physician's discretion. Usually, adjuvant treatment started after 7 to 21 days from TURB and repeated once weekly for 6 weeks. A re-TURB was not routinely performed. Follow-up was performed according to the international guidelines at that time and usually was based on the individual risk of recurrence or progression to muscle-invasive disease. Patients were usually followed with urine cytology, ultrasound of the abdomen/pelvis, flexible cystourethroscopy, and cold biopsy/TURB of suspected areas when nedeed. Imaging of the upper tract was usually carried out at diagnosis and yearly thereafter. If urine cytology was positive, mapping bladder biopsies, prostatic urethra resection, and upper urinary tract evaluation were performed.

The presence of PA was assessed according to the World Health Organization (WHO) classification as a preoperative hemoglobin level of $\leq$13 g/dl in men and $\leq$12 g/dl in women. PA evaluation was performed at each institution, generally 1 to 3 days before TURB. Histological examination was performed by experienced uro-pathologists at each center. Tumor stage was assigned according to 2002 American Joint Committee on Cancer TNM Staging system, whereas tumor grade was determined according to 1973 WHO system. Concomitant CIS was defined as the presence of CIS associated with another tumor that was not CIS.

Disease recurrence was defined as first pathologically proven tumor relapse in bladder or prostatic urethra, regardless of tumor stage. Disease progression was defined as pathologically proven tumor relapse in bladder or prostatic urethra of tumor stage T2 or higher. Cause of death was determined from the death certificate and chart review [18].

2.1. Statistical analysis

Chi-square and Mann-Whitney *U* tests were performed for categorical and continuous variables to compare the populations, respectively. Kaplan-Meier curves were built to evaluate differences in recurrence-free survival (RFS) and progression-free survival (PFS) according to the presence of PA. Log-rank test was used to provide differential