RESEARCH ARTICLE

Predictive Effect of Preoperative Anemia on Long-Term Survival Outcomes with Non-Muscle Invasive Bladder Cancer

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Abstract

Background: Anemia is the most common hematologic abnormality in bladder cancer (BC) patients. We evaluated the impact of preoperative anemia on oncologic outcomes in BC undergoing transurethral resection of a bladder tumor (TURBT) for the first time diagnosis. Materials and Methods: We retrospectively evaluated the data collected from 639 patients who underwent TURBT between January 2006 and September 2014 in our department. Of these patients, 320 qualified for inclusion in the study. The primary efficacy endpoint was the effect of preoperative anemia status on cancer-specific and overall survival. Independent t-test and chi-square analyses were performed to assess the effects of anemia on oncologic outcomes. Survival was estimated by using the Kaplan-Meier test. Results: There were 118 (36.9%) and 202 (63.1%) patients in the anemia (Group-1) and non-anemia groups (Group-2), respectively. The median follow-up duration was 68 months. Anemia was associated with decreased overall survival (p<0.001). Comparison between cancer-specific survival of two groups did not show any statistically significant difference (p=0.17). Conclusions: Preoperative anemia status of BC patients according to World Health Organization classification is associated with decreased overall survival, but not with cancer-specific survival. We think that preoperative hemoglobin levels should be considered in patient counseling and decision-making for additional therapy.

Keywords: Urothelial carcinoma - hemoglobin - anemia - survival - bladder..

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Introduction

Bladder cancer (BC) is the fourth most common cancer type in the USA and 75% is non-muscle invasive bladder cancer (NMBIC) at the time of diagnosis; and half of these show recurrence and/or progression after transurethral resection of bladder tumor (TURBT) (Burger et al., 2013). Although the basis of the treatment consists of complete TURBT, the main aim of the treatment is to reduce the recurrence and prevent the progression (Basiri et al., 2014).

The ability to predict poor prognosis before initial treatment enables physicians to select early intervention and/or intensive systemic treatment for better outcome (Ikeda et al., 2014). Various predictive models have been widely studied to reduce BC-related death (Lammers et al., 2015). Previous studies have attempted to identify variables that have prognostic value in patients with T2 to T4 stage BC undergoing cystectomy, one of which was pretreatment hemoglobin (Hb) level (Thrasher et al., 1994; Gierth et al., 2015; Milojevic et al., 2015).

Anemia is the most common hematologic abnormality of BC patients and is caused by complex and multifactorial reasons, of which bone marrow suppression and preoperative macroscopic hematuria have an important role in these patients (Mercadante et al., 2000; Rink et al., 2014). It was postulated that this negative effect on survival was due to decreased immunity of the patient as well as late diagnosis and cancer treatment (Rink et al., 2014). Besides, anemia is also associated with the elevated level of cytokines due to the interaction between the tumor cells and the immune system. This situation was explained with decreased lifetime of erythrocytes due to aggressively increased levels of inflammatory cytokines, suppression of erythroid progenitor cells, restricted iron use, decreased level of erythropoietin and/or decreased response level of bone narrow to erythropoietin (Birgegard et al., 2005).

Although a previous study has emphasized the prognostic importance of anemia in patients with T2 to T4 stage BC, our first aim was to analyze preoperative anemia status of patients who were first treated with TURBT for NMBIC (Panneerselvam et al., 2012). Our second aim was to identify Hb level affecting distant cancer-specific survival (CCS) and overall survival (OS). We hypothesized that preoperative anemia would be associated with unfavorable outcomes comparable to those of other urological cancers (Van Belle and Cocquyt, 2003; Hutterer et al., 2015).

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Materials and Methods

The study was approved by our institutional review board with a waiver of informed consent, and therefore was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We retrospectively evaluated the data collected from 639 patients who underwent TURBT between January 2006 and September 2014 in our department. The exclusion criteria were patients with a histopathology other than transitional cell carcinoma (TCC), concomitant TCC in urethra or upper urinary tract, bleeding disorders, chronic renal disease, and patients requiring blood transfusions at the perioperative period. We evaluated demographic, operative and pathologic parameters of all patients including age, gender, Hb level, hematocrit (Htc), blood urea nitrogen (BUN), creatinine, tumor grade and stage, and follow-up time.

Complete blood count, including Hb measurement, was performed at our institution 1 to 3 days prior to TURBT. Hb was also measured at least once within 10 days postoperatively. However, since post-TUR Hb levels are influenced by several factors, e.g. intraoperative blood loss, perioperative blood transfusion, diluting effects of intravenous fluid substitution, and variable hematopoiesis duration, we performed descriptive rather than outcome analysis with postoperative values. Preoperatively measured Hb values were stratified into either normal or anemia based on the cut-off value of 13 g/dL in male and 12 g/dL in female patients that determined by World Health Organization (Beutler and Waalen, 2006).

Additional intravesical immunotherapy was given to the patients after TURBT if needed according to their pathology result (Babjuk et al., 2013). Cystoscopy and urine cytology were repeated every 3 months during the first 2 years, every 6 months between the third and fifth year, and annually in the subsequent years. All visible recurrent lesions were resected with a histological confirmation thereafter. Intravenous urography and/or computed tomography urography were performed annually to evaluate upper urinary tract.

Table 1. Patient and Tumor Characteristics of Anemic and Non-anemic Groups

	Anemic (Group-1) (n=118)	Non-Anemic (Group-2) (n=202)	p value
Age (years)	61.9±4.1	62.3±5.6	0.793
Gender			0.712
Male	100 (84.7%)	168 (83.2%)	
Female	18 (15.3%)	34 (16.8%)	
Stage			0.233
Ta	36 (30.6%)	68 (33.7%)	
T1	80 (67.8%)	133 (65.9%)	
CIS	2 (1.6%)	1 (0.4%)	
Grade			0.827
Low	60 (50.8%)	105 (51.9%)	
High	58 (49.2%)	97 (48.0%)	
Hb (g/dL)	10.8±2.1	14.5±1.2	<0.001
Hct (%)	32.8±6.3	42.5±3.7	<0.001
BUN (mg/dL)	40.3±17.0	39.1±12.7	0.271
Cre (mg/dL)	1.2±0.7	1.3±3.4	0.599

Data are given as mean mean±SD or n (%).; CIS: Carcinoma in situ, Hb: Hemoglobin, Hct: Hematocrit, BUN: Blood urea nitrogen, Crea: Creatinine, SD: Standard deviation.

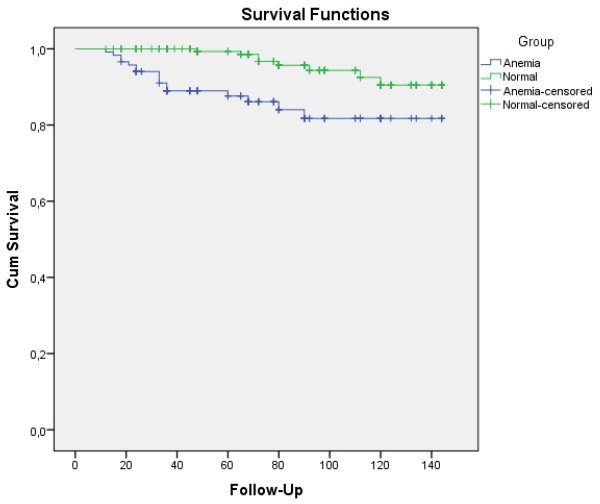

Figure 1. Kaplan-Meier Curves Showing Cancer Specific Survival of Anemic (Group-1) and Non-Anemic (Group-2) Patients

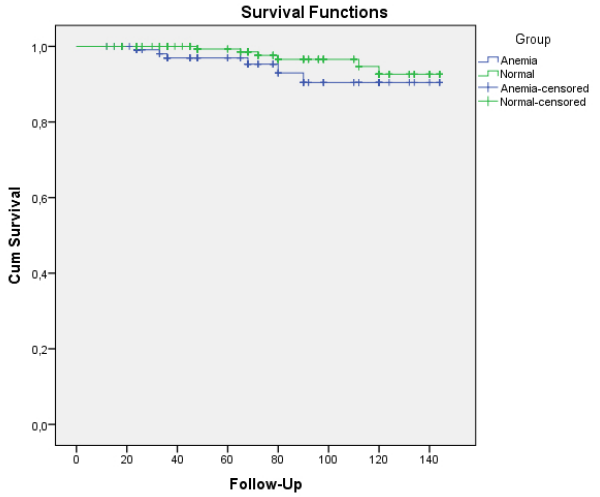

Figure 2. Kaplan-Meier Curves Showing Overall Survival of Anemic (Group-1) and Non-Anemic (Group-2) Patients

Statistical analysis:

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows version 19.0 (SPSS Inc., Chicago, Illinois, USA). Results were presented as mean ± standard deviation. The significance level (α) was accepted as 0.05, and a p value <0.05 was considered to be statistically significant. Parametric variables were compared by using independent t-test, and chi-square test was used for categorical variables.

Results

Between January 2006 and September 2014, 639 patients with NMIBC underwent TURBT in our department, of which 320 qualified for inclusion in the study. The excluded 319 patients were adenocarcinoma

in 22 (6%), squamous cell carcinoma in 14 (4%), concomitant TCC in ureters in 10 (3%), chronic diseases or bleeding disorders in 44 (13%), need for transfusion in 3 (0.1%), and lack of follow-up in 226 (73%). The anemia group (Group-1) included 118 (36.9%) patients, versus 202 (63.1%) patients in the non-anemia group (Group-2). There were not any significant differences in age, gender, tumor stage and grade, and preoperative BUN and creatinine levels between the two groups ($p>0.05$ for all). The Hb and Htc levels were significantly different among two groups ($p<0.001$). Descriptive statistics are given in Table 1.

At a median follow-up of 68 months, 24 patients (7.5%) died of which 12 (50%) were due to BC. On the Kaplan-Meier analysis, preoperative anemia according to the WHO classification was found to be associated with decreased OS, but not associated with CCS ($p<0.001$ and $p=0.17$, respectively, Figures 1 and 2).

Discussion

We evaluated the effect of preoperative anemia profile on OS and CCS of NMIBC patients in this retrospective cohort study. We already know that the Hb level is a universal predictive biomarker due to its easy measurement, well-defined standards and low cost, and has already been established in daily clinical practice.

Although we found that preoperative anemia is a strong predictor of overall mortality in patients with NMIBC who have undergone TURBT with curative intent, our findings did not confirm those in previous studies in which pretreatment anemia was associated with unfavorable oncologic outcomes of different malignancies, including MIBC treated with radical cystectomy (Van Belle and Cocquyt, 2003; Rink et al., 2012a). Van Belle and Cocquyt showed that patients with preoperative anemia who underwent radical nephroureterectomy due to upper tract urothelial carcinoma had decreased CCS and recurrence-free survival (Van Belle and Cocquyt, 2003). We suspect that the difference between our results and other studies might be explained by different histopathological features and aggressiveness of tumors. It seems that the patient with more aggressive tumors are more affected by changes in Hb levels.

Tumor grade and stage are the most important current prognostic variables of BC. The OS in NMIBC is related to different prognostic factors. The preoperative anemia was not reported as a prognostic factor in the literature before, however, it was found to affect the OS, but not CCS in patients with NIMBC in our study. Although low-grade lesions have good prognosis, survival decreases with increasing stage and grade. Pagano et al. demonstrated that the 5-year OS of patients with T3 stage disease was 31%, where it was only 21% in T4 stage disease (Pagano et al., 1991). These ratios were significantly lower than the patients with low stage tumors. In addition, they also showed that patient OS with high-grade tumors was lower than the patients with low-grade tumors (Pagano et al., 1991). We suspect that the more aggressive biologic features of high-grade tumors created this survival difference versus the low-grade tumors.

In our study pretreatment anemia was associated with tumor aggressiveness. In addition, anemic patients showed a trend towards more advanced tumor stages, although this was not statistically significant. All of these factors are predictors of disease recurrence and inferior survival, and aggressive NMIBC tumor features may be exacerbated by anemia (Kikuchi et al., 2009; Rink et al., 2012b).

Our study has certainly some limitations. First, it was a retrospective cohort study with an inherent potential for bias. Second, a relatively small number of patients were enrolled in this study. We know that macroscopic hematuria, one of the most important features of NMIBC, might be a cause of aggressive blood loss (Mercadante et al., 2000). A third limitation is that we do not have any data about gross hematuria that may affect the results.

On the other hand, the present study had a strength, like the median follow-up time of nearly 6 years which is a considerable period in the management of BCs. Although our results need to be validated with prospective randomized trials, to the best of our knowledge, it is the first study in the literature that compares the effect of preoperative anemia on OS and CCS between anemic and non-anemic NMIBC patients.

As a conclusion, Hb is a promising blood biomarker that is available and easy to use in clinical practice, and may improve the prediction of NMIBC outcomes. Preoperative anemia according to the WHO classification is associated with decreased OS, but not with CCS. We think that preoperative Hb levels would be considered in patient counseling and decision-making for additional therapy. However, further prospective, controlled, multi-centered studies are warranted to validate our findings.

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Orcun Celik and Murat Akand contributed equally to this work, and are first co-authors of the article.

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