Streszczenie w języku angielskim – lek. Aleksander Ślusarczyk

Title

Identification of risk factors for BCG failure in patients with non-muscle invasive bladder cancer.

Abstract

Introduction

Bladder cancer (BC) is the tenth most common malignancy worldwide. Approximately 75% of BC patients present with non-muscle invasive bladder cancer (NMIBC). Complete transurethral resection of the bladder tumour (TURBT) constitutes a standard treatment for NMIBC. Intravesical Bacillus Calmette-Guerin (BCG) vaccine instillations are a gold standard adjuvant treatment for urothelial NMIBC stratified as high-risk of progression. Unfortunately up to 40% of patients fail to respond to BCG therapy and around 15% develop tumour progression to muscle-invasive bladder cancer (MIBC). Patients who experience progression to MIBC confer a worse prognosis compared to those with primary muscleinvasive malignancy. Therefore, correct qualification for BCG immunotherapy and suitable risk stratification at baseline are of utmost significance to achieve best long-term oncological outcomes.

Currently used risk tables released by EORTC were established on patients treated mostly with intravesical chemotherapy and TURBT. Another tool established by Club Urológico Español de Tratamiento Oncológico (CUETO) is based on data from patients treated with TURBT and adjuvant BCG. Not surprisingly, external validation of EORTC and CUETO models reveals inaccuracy of both risk tables, with a tendency of both tools to overestimate the risk of recurrence and progression in the group of high-risk patients. Moreover, wellestablished models predicting BCG failure are still lacking. In recent years, the prognostic role of blood-count derived inflammatory markers (calculated as a ratio between cell counts) has been extensively studied in urological cancers.

Age confers one of the strongest single risk factors for developing bladder cancer. The prevalence of bladder cancer is highest in elderlies, with 73 years being an average age of diagnosis. Advanced age is associated with impaired immune system function, which might compromise the efficacy of BCG immunotherapy. BCG efficacy was not extensively studied in elderlies (older than 80 years) in whom potential quality of life impairment and serious treatment complications might be of high significance.

Objective

The aim of the study was to identify factors predicting BCG failure in patients with high-risk NMIBC (study no. 1) and to evaluate the benefits from BCG therapy in elderly patients over 80 years of age (study no. 2).

Material and Methods

One hundred and eighty-three consecutive patients with high-risk NMIBC, who underwent transurethral resection of the bladder tumour (TURBT) and were further treated with BCG instillations were included in the study (No. 1). High-risk NMIBC was defined in accordance with the European Association of Urology clinical guideline (EAU) 2019 (the time when the study was conducted). High-risk NMIBC included urothelial cancer invading the submucosa (T1 stage), carcinoma in situ (CIS), high-grade (HG) cancer and large, multiple and recurrent low-grade bladder tumours (TaLG). The study was performed retrospectively. The study endpoint was BCG failure defined as tumour progression or high-grade tumour recurrence/ persistence during BCG and up to 6 months after last BCG exposure. Such endpoint was designed to denote a group of patients who do not obtain any benefit from BCG and for

whom only oncological treatment with evidenced long-term efficacy was cystectomy. To identify predictors of BCG failure Kaplan-Meier method and logistic regression were used. Based on univariable analyses, variables were selected for multivariable analysis, performed with logistic regression.

Sixty-seven patients with high-grade T1 bladder cancer who were over 80 years old at the time of TURBT were included in study no. 2. To analyse the efficacy of BCG and predict recurrence-free survival (RFS), progression-free survival (PFS), overall survival (OS) and cancer-specific survival (CSS) Kaplan-Meier curves and Cox proportional hazards were utilized.

Results

Among 183 patients 15 individuals (8,2%) developed tumour progression and 40 experienced high-grade tumour recurrence (21,9%). In 39 cases (21,3%) BCG failure was retrospectively diagnosed based on the definition established using the EAU 2019 clinical guideline. In

univariable analysis tumour multiplicity (OR=2,65; 95% CI, 1,28-5,49; P <0,05), CUETO recurrence risk score (OR=1,18; 95% CI, 1,03-1,35; P <0,05), CUETO progression risk score (OR=1,20; 95% CI 1,01-1,43; P <0,05) and several blood count-derived inflammatory markers were predictive for BCG failure. No residual tumour on re-TURBT was a favourable prognostic factor (OR=0,32; 95% CI, 0,12-0,87; P=0,01).

Patients with high preoperative neutrophil-to-lymphocyte ratio (NLR >2.3), platelet-tolymphocyte ratio (PLR >147), neutrophil-to-erythrocyte ratio (NER >0.93), higher systemic inflammatory marker (SIM) score and with low lymphocyte-to-monocyte ratio (LMR <2.55) had a shorter time to BCG failure (P <0,05). Systemic Inflammatory Marker (SIM) score was calculated based on categorized values of NLR, PLR and LMR, and constituted another factor stratifying patients into risk groups for time to BCG failure. In the multivariable model, blood count-derived inflammatory markers (NLR, PLR, LMR, NER and SIM score) and CUETO recurrence risk score were independent prognostic factors.

In the second analysis regarding patients over 80 years of age, oncological outcomes were compared between patients who received at least the induction course of BCG and non-BCG treated individuals matched to each other based on age and Charlson comorbidity index. Thirty case-control pairs (treated with TURBT + BCG vs TURBT alone) were included in the final analysis. Rates of disease recurrence (80% vs 53%) and cancer-specific mortality (40% vs 10%) were significantly higher in the group of patients who did not receive BCG. Already BCG induction constituted independent prognostic factor for cancer-specific survival (HR=0,23; 95% CI, 0,06-0,87; P <0,05).

Conclusions

Tools dedicated to evaluate the risk of BCG failure should base on clinicopathologic features and perhaps values of systemic inflammatory markers, which constitute independent predictors of response to BCG. Identification of patients with an especially high risk of failing BCG could prevent tumour progression and prompt early radical cystectomy, which is associated with serious complication risks but provides superior long-term oncological outcomes in the group of patients being at highest risk for BCG failure. Our study demonstrates the prognostic value of simple blood count-derived inflammatory markers (NLR, PLR, LMR, NER and SIM score), which could be adjunct to currently used CUETO risk scores. In this study, a novel inflammatory marker was derived- neutrophil-to-erythrocyte ratio (NER) and for the first time, the value of SIM score in predicting BCG failure was demonstrated.

Regardless of advanced age, BCG should be strongly recommended as adjuvant therapy for patients with high-risk NMIBC. Already induction course of BCG reduces the rate of recurrence and improves CSS in T1HG patients over 80 years of age.