CAN THE SYSTEMIC IMMUNE INFLAMMATION INDEX BE A PREDICTOR OF BCG RESPONSE IN PATIENTS WITH HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER?

INTRODUCTION

Bladder cancer (BC) is the fifth most common malignancy and the eighth most common cause of cancer-related deaths in the North America (1,2). Transitional cell carcinoma constitutes 90% of all BCs and 75% of newly diagnosed BCs are non-muscle invasive bladder cancer (NMIBC).

The gold standard treatment for NMIBC is transurethral resection of the bladder (TURB). Intravesical instillation chemotherapy or intravesical bacillus Calmette-Guérin (BCG) could be administered following the pathological examination (3). However, under optimal therapy, up to 80% of tumors might recur and up to 40% might progress to muscle-invasive disease depending on the risk factors (4). Treatment options in patients with recurrent progressive NMIBC despite the optimal BCG therapy are limited and these patients usually undergo a radical cystectomy (RC) procedure. In these patients, predicting the prognosis and BCG failure will prevent useless BCG treatment and its adverse effects as well as a delayed RC procedure in some individuals. European Association of Urology (EAU) recommends the use of EORTC (European Organization for Research and Treatment of Cancer) and CUETO (Club Urologico Espanol de Tratamiento Oncologico) scoring systems for this purpose (5). However, there is not any reliable biomarker for this prediction yet.

Accumulating evidence suggests important roles of both local and systemic inflammatory responses in the progression of numerous tumors (6). Recently, researchers found that immune response cells (neutrophils, monocytes, and lymphocytes), platelets, and their

associated signaling pathways are important elements of the tumor microenvironment and could affect tumor progression and metastasis (7). The systemic immune-inflammation index (SII), which depends on the peripheral lymphocyte, neutrophil, and platelet counts, came into use lately as an indicator of the preoperative balance of inflammatory factors and immune status, for more accurate predictions of prognosis. A systematic meta-analysis by Yang and colleagues revealed that a high SII might be a reliable prognostic factor for poor outcomes of various cancers (8). In recent years, the prognostic value of the SII in patients with renal cell carcinoma and muscle invasive bladder cancer (MIBC) was highlighted (9, 10). To the best of our knowledge, there is no study investigating the prognostic role of the SII in patients with NMIBC in English literature. In this study, we aimed to assess the predictive role and clinical importance of the SII in BCG therapy response in patients with high-risk NMIBC systematically.

MATERIALS AND METHODS

Patient selection and data collection

We examined the medical records of the patients with NMIBC, who were treated in two different centers in the same time period, between January 2015 and January 2020 retrospectively. Patients, who were in high-risk group for NMIBC according to EAU guideline criteria (5), had no history of malignancies, and completed at least 6-course BCG induction therapy, were enrolled in the study. Exclusion criteria were being older than 80 years, histological variants in resections during follow-up, intravesical chemotherapy administration due to the lack of BCG despite inclusion in the BCG protocol, follow-up shorter than 12 months, moving to a different center in the follow-up, and unavailable data.

We classified the patients into two groups according to their BCG treatment responses. The patients with complete response to BCG (no tumor recurrence in control cystoscopies)

constituted the group 1 (n=59) and the patients with a BCG failure constituted the group 2 (n=37). In the group 2, BCG-unresponsive patients fell into subgroup 2a (n=16) and BCG-relapsing patients fell into subgroup 2b (n=21). The patients, in whom the induction treatment was discontinued due to BCG intolerance, were excluded (Figure 1).

We carried out a re-TURB procedure before BCG induction in all patients. In the follow-up, we examined the patients with cytology and cystoscopy every 3 months in first 2 years, every 6 months up to 5 years, and annually after 5 years. We performed a computed tomography urography annually in first 2 years and every 2 years thereafter. Age, gender, diagnoses and initial complaints of the patients, preoperative complete blood count results, dimensions of the bladder tumor measured by the urinary ultrasonography, stages and degrees of the tumors, presence of carcinoma in-situ (CIS), number of the BCG-courses and control cystoscopies, stage and degrees of the recurrent tumors in the control cystoscopies, adjuvant therapies, and the duration of the follow-up were collected. Detection of MIBC in TURB at any time in the follow-up was considered as progression.

BCG failure was defined according to criteria specified in the EAU guideline (5):

1) BCG-unresponsive: BCG refractory [recurrence of high-grade pTa/T1 tumor at 3 months or of isolated CIS at both 3 and 6 months after TURB] or recurrence of high-grade pTa/T1 tumor at 6 months after last BCG administration or recurrence of CIS at 12 months after last BCG administration.
2) BCG-relapsing: Recurrence of high-grade tumor 6 months after TURB despite initial response to BCG (Recurrence of low-grade tumors was not accepted as failure).
3) BCG intolerant.

Recurrence-free survival (RFS) was defined as the time from the date of initial TURB (before BCG induction) to the date of the first bladder tumor recurrence that fulfilled the

BCG failure criteria. Progression-free survival (PFS) was defined as the time from the date of initial TURB (before BCG induction) to the date of detection of MIBC.

Laboratory measurements

Preoperative laboratory results were extracted from our medical records. The tests for neutrophil, lymphocyte, and platelet counts were performed within 1 week before surgery. Neutrophile lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were calculated with these data. The SII was calculated as in the formula: SII = neutrophil × platelet/lymphocyte (8).

Pathological analysis

All the surgical specimens were processed according to the standardized procedures and examined by the same genitourinary pathologist. The tumor grade was determined according to the World Health Organization 1973 and 2004 classifications and 2017 TNM stage was determined according to the International Union for Cancer Control/American Joint Cancer Committee 2004 classification (11).

Statistical analysis

All analyses were performed with IBM SPSS Statistics 22 (IBM SPSS, Turkey) computer program. Normal distribution of the data was checked by Kolmogorov Smirnov and Shapiro Wilks tests. Besides the descriptive statistical methods (mean, standard deviation, frequency), normally distributed quantitative parameters of groups were compared by Student t test, whereas non-normally distributed quantitative data were analyzed with Mann Whitney U test. Chi-square and Fisher's Exact tests were used for comparing qualitative data. Optimal cut-off point was determined with ROC curve analysis. Spearman's rho correlation test was used for correlations between parameters and for multivariate analysis backward stepwise logistic

regression model was constructed. A p-value < 0.05 was considered as statistically significant.

Ethical approval and informed consent

The protocol of the present study was reviewed and approved by the Regional Ethic *Committee* (Hamidiye-KAEK 20/73), and was in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants included in the study.

RESULTS

A total of 96 patients between 33 and 82 years of age were enrolled in the study. Of those, 10 (10.4%) were female, 86 (89.6%) were male, the mean age was 62.80±9.6 years, and the mean follow-up duration was 34.635±14.7 months. None of the patients died during follow-up.

Demographical and clinical data of the groups are demonstrated in Table 1. In group 2, NLR, PLR, and SII were significantly higher than those of group 1 (p:0.007, p:0.005, and p:0.000, respectively). Inflammatory biomarkers of group 1, group 2a, and group 2b are shown in Table 2. In group 2a and 2b, SII was significantly higher than that in group 1 (p=0.000 and p=0.001, respectively).

Associations of inflammatory biomarkers with tumor size, grade, and CIS presence are represented in Table 3. In patients with a tumor greater than 30 mm in size, SII and NLR were significantly higher than those in patients with a tumor lower than 30 mm in size (p=0.002 and p=0.02, respectively). However, tumor grade and CIS presence were not associated with any inflammatory biomarker (p>0.05).

A ROC curve was plotted for SII value to predict BCG failure (Figure 2). Area under curve (AUC) was 0.761 with a standard error of 0.05, significantly higher than 0.5 (p=0.001). The

cut-off value of the SII for prediction of the BCG failure was 672.75 with a sensitivity of 67.6%, a specificity of 79.7%, and an accuracy of 75%.

Comparisons between 17 patients with progression to MIBC and the remaining 79 are demonstrated in Table 4. A backward stepwise logistic regression model was constructed with the NLR, PLR, and SII, which were found to be significant predictors for progression to MIBC (p:0.000, Negelkerke R square:0.270, explanatory coefficient of the model:83.3%). Effect of the SII to the model was statistically significant (p=0.003) and a higher SII increased the progression one-fold. Effect of the tumor size to the model was near to the statistical significance level (p=0.055). A tumor greater than 30 mm in size and a high SII together increased the progression 3.6 folds. Tumor grade (low-grade or high-grade) and CIS presence did not affect the progression to MIBC significantly (p>0.05).

A ROC curve was plotted for inflammatory biomarkers to predict progression to MIBC (Figure 3a). AUCs for NLR, PLR, and SII were 0.719, 0.765, and 0.818 respectively. In comparisons of AUCs, PLR and SII were not different significantly in terms of predicting the progression. However, the SII was significantly different from the NLR regarding the prediction of the progression (p=0.018). In the ROC curve (Figure 3b) for SII to predict progression to MIBC, AUC was 0.818 and the standard error was 0.05. AUC in the ROC curve was significantly higher than 0.5 (p=0.001). The cut-off value for SII predicting the progression to MIBC was 624.2 with a sensitivity, specificity, and accuracy of 94.1%, 64.6%, and 69.8%, respectively.

In correlation analyses of SII between RFS and PFS, RFS and SII were inversely correlated with a level of 29.9% significantly (p=0.003) (Figure 4). However, SII and PFS were not correlated (p>0.05).

DISCUSSION

Inflammatory and immunological biomarkers became prominent as potential predictors for prognosis in several cancers in the recent years (12). Among these biomarkers NLR, PLR, and lymphocyte-to-monocyte ratio are tested mostly (13, 14). However, it is reported that SII revealed the immunological status better and it had a higher predictive safety for prognosis as a more objective index (15-17).

Previous studies showed the association of inflammatory biomarkers with the prognosis of BC. Guo and colleagues demonstrated that the preoperative C-reactive protein / albumin ratio (CAR) was an important predictor of the survival in patients with BC who underwent an RC procedure (18). In another study, the authors demonstrated that the high expression of CD14 in BC cells increased the release of the inflammatory mediators to alter the immunosuppressive characteristics and stimulate the proliferation of the tumor cells by polarizing the monocytes and the macrophages (19). Zhang and colleagues compared the SII with NLR, PLR, and CAR to predict the prognosis after BC in a cohort including individuals after RC. They reported that the SII was superior to other parameters and was an independent predictor for overall survival (10). In this study, out of 209 patients with BC, 59 had NMIBC and the association of the inflammatory biomarkers with the response to the BCG therapy was not assessed. Our study is the first study evaluating the association of the SII with the BCG response in patients with NMIBC.

We investigated the potential predictor biomarkers for BCG therapy response systematically in patients with high-risk NMIBC. In the BCG failure group, NLR, PLR, and SII were significantly higher. Predictive ability of SII was better than those of the other biomarkers. In subgroup analyses, differentiation of the BCG-complete-responsive group (group 1) and the

BCG relapse group (groups 2b) was relatively difficult and only SII was able to distinguish these two groups.

Zhang and colleagues calculated the cut-off value of the SII for poor prognosis in all BCs as 507 (10). Gorgel and colleagues reported a substantial correlation between preoperative high SII level and low cancer-specific survival (CSS) in patients who underwent an RC for MIBC and they calculated the SII cut-off level as 843 (20). In this study, we also sought to find an optimal cut-off value for SII in patients with high-risk NMIBC for predicting the BCG failure. The best numerical value for SII cut-off was 672 for predicting the BCG failure. Several studies propose variable cut-off values in the literature and increasing number of new results from well-designed researches will possibly provide new insights.

The International Bladder Cancer Group (IBCG) proposes the following definition for NMIBC progression: an increase in T stage from CIS or Ta to T1 (lamina propria invasion); development of ≥T2 or lymph node (N+) disease or distant metastasis (M1); or an increase in grade from low to high (21). However, in our study progression to MIBC was considered as progression consistent with the classical literature (22). In the separate analyses of these patients, NLR, PLR, SII values and the sizes of the primary tumors predicted the progression to MIBC. In the logistic regression model for NLR, PLR, SII, and primary tumor size, SII had a significant predictive power and a high SII increased the progression one-fold. A tumor greater than 30 mm in size and a high SII together increased the progression 3.6-fold. However, presence of CIS and tumor grade (low grade or high grade) were not associated with inflammatory biomarkers NLR, PLR, and SII.

The aforementioned studies reported a poor CSS in patients with MIBC who had a high SII (10, 20). We could not calculate a CSS because the duration of the follow-up was relatively short and no patients died in the follow-up. We found a significant correlation between the high SII level and low RFS in our study. In group 2, in which the SII was significantly high

and a high level of CIS, progression and distant metastases were present, the SII might be useful in the early diagnosis of a more aggressive disease. The SII was not associated with PFS in our study. This might be due to the small patient group which were from two centers and the short duration of the follow-up.

There are some limitations of this study. First, small number of patients from two centers might weaken the statistical analyses. Second, retrospective design of this study might result in a bias. Third, we calculated the cut-off value for SII individually as the other authors because there is no standard cut-off value. Therefore, our results should be validated by external cohorts from other centers.

CONCLUSION

The SII might be promising for prediction of BCG failure in patients with high-risk NMIBC because it is a successful, non-invasive and low-cost parameter. The cut-off value for SII is 672.75 and in patients with a high SII, BCG failure and progression to MIBC might be anticipated. However, these results should be validated in prospective randomized controlled studies with large patient groups.

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Figure Legends

Figure 1: Flowchart of patients who met inclusion/exclusion criteria for the study

Figure 2: ROC curve of SII for predicting BCG failure

Figure 3a: ROC curve of NLR, PLR, and SII for predicting rogression; **3b:** ROC curve of SII for predicting progression

Figure 4: Correlation between SII and RFS