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Urologic Oncology: Seminars and Original Investigations 37 (2019) 291.e1−291.e7

UROLOGIC ONCOLOGY

Original article

The clinical implication of gamma globulin levels in patients with nonmuscle-invasive bladder cancer

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Received 11 September 2018; received in revised form 5 December 2018; accepted 28 December 2018

Abstract

Objective: The production of antibody, also referred immunoglobulin, is the principal functions of B cells. Gamma globulin fraction determined by serum protein electrophoresis is composed almost entirely of immunoglobulin. This study aimed to investigate the association between gamma globulin level and oncological outcomes in patients with nonmuscle-invasive bladder cancer (NMIBC).

Patients and methods: A total of 274 patients with NMIBC who underwent transurethral surgery between 2000 and 2015 were identified. One hundred forty-four patients (52.6%) had received adjuvant intravesical bacillus Calmette-Guérin. Gamma globulin fraction (%) was determined by serum protein electrophoresis, and gamma globulin level (mg/dl) was calculated by multiplying the total protein level (mg/dl) by the gamma globulin fraction (%). The association between gamma globulin levels and oncological outcomes was statistically evaluated.

Results: During a median follow-up period of 39 months, 99 (36.1%) patients experienced at least 1 tumor recurrence and 16 (5.8%) patients had disease progression. The median (interquartile range) gamma globulin level was 1.2 (1.0−1.3) mg/dl. Recurrence-free survival rate of patients with gamma globulin levels of ≥1.4 mg/dl was significant lower than that of patients with gamma globulin levels of <1.4 mg/dl ($P < 0.01$). There was no significant difference in progression-free survival between the 2 groups ($P = 0.17$). Multivariate analysis revealed that gamma globulin level of ≥1.4 mg/dl is significantly associated with higher recurrence rate (hazard ratio = 1.83, $P < 0.01$).

Conclusion: Gamma globulin level is significantly associated with tumor recurrence. Our results suggest that B cell immunity may be involved in tumor recurrence in patients with NMIBC.

Keywords: Bladder cancer; B lymphocyte; Gamma globulin; Humoral immunity; Immunoglobulin; Immune-oncology

1. Introduction

Over the past 2 decades, there has been a significant advancement in understanding the role of the immune system in cancer development and/or progression [1]. In 2011, the United State Food and Drug Administration approved ipilimumab, the first anticancer drug targeting immune checkpoint pathways that are often activated to inhibit the nascent antitumor immune response in cancer, for unresectable and/or metastatic melanoma [2]. This age represents a new era, in which systematic immunotherapy has become a standard treatment for cancer.

Worldwide in 2012, bladder cancer was the ninth most common type of cancer [3]. The efficacy of immune checkpoint inhibitors has been demonstrated in patients with advanced bladder cancer [4]; furthermore, to date some immune checkpoint inhibitors have been approved for both second-line treatment in platinum-refractory patients [4,5] and first-line treatment in cisplatin-eligible patients [6]. In the management of bladder cancer, immunotherapy is not a new option. About 40 years ago, Morales et al. reported the use of intravesical instillation of bacillus Calmette-Guérin (BCG) in nonmuscle-invasive bladder cancer (NMIBC) [7]. Since then, it has been an established immunotherapy to prevent recurrence and/or progression of NMIBC [8].

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.urolonc.2018.12.026
1078-1439/

Current immunotherapeutic strategies, including both intravesical BCG and immune checkpoint inhibitors, have focused exclusively on T cell-mediated immunity [9], while B cell-mediated immunity in cancer requires further investigation. T cells are involved in cell-mediated immune responses, whereas B cells play an essential role in the humoral responses. B cells' principal function is the production of antibodies, or immunoglobulin (Ig). The gamma globulin fraction, which can be determined by serum protein electrophoresis (SPEP), is composed almost exclusively of Ig. To date, there are only a few studies on the association between serum gamma globulin and malignancy.

The present study aimed to investigate the clinical implication of gamma globulin levels on the oncological outcomes in patients with NMIBC.

2. Patients and methods

2.1. Patients selection

A total of 274 patients with primary NMIBC in who a SPEP was performed before surgery between 2000 and 2015 at Tokyo Saiseikai Central Hospital were included in this study. All patients underwent complete transurethral resection (TUR) for visible tumors with biopsies of any suspicious area. All surgical specimens were histologically confirmed to be urothelial carcinoma, which was graded according to the 1973 World Health Organization grading system [10] and staged according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification [11].

2.2. Treatment and follow-up

A SPEP was performed within 1 month of TUR. Gamma globulin fraction (%) was determined by SPEP, and the concentration of protein in gamma globulin fraction [gamma globulin level (mg/dl)], was calculated by multiplying the total protein level (mg/dl) by the gamma globulin fraction (%).

Our institutional policy on the treatment and follow-up of patients with NMIBC has been previously described [12,13]. Patients were followed-up every 3 months during the initial year, every 3 to 6 months for the next 4 years, and then every 6 to 12 months thereafter. Routine follow-up is comprised of patient history, physical examination, urinary cytology, and flexible cystoscopy. In patients who had low-risk NMIBC or who refused to undergo cystoscopy, transabdominal ultrasonography was used as a substitute for flexible cystoscopy [12]. To evaluate the upper urinary tract and/or extravesical lesions, intravenous urography, transabdominal ultrasonography, magnetic resonance imaging, and/or computed tomography were performed as appropriate. In our institute, all patients from 2004 onwards received a single immediate instillation of 50 mg epirubicin following TUR [14]. The decision of administering adjuvant intravesical immunotherapy with BCG depended on the discretion of the attending physician. Adjuvant BCG therapy was initiated at approximately 1 month after TUR and was continued weekly for 6 to 8 weeks. None of the patients received a purified protein derivative skin test [15] or maintenance BCG therapy [16].

2.3. Statistical analysis

Tumor recurrence was defined as the occurrence of new tumors in the urinary bladder, which were pathologically confirmed to be urothelial carcinoma. Disease progression was defined as the development of histologically confirmed muscle invasion (pathological stage $\geq$ pT2) or lymph node or distant metastasis detected by computed tomography.

The following data were collected for each patient: age ($\leq$70 vs. >70 years), sex (male vs. female), tumor grade (G1/2 vs. G3), T category (Ta/is vs. T1), number of tumors (single vs. multiple), tumor size ($\leq$30 vs. >30 mm), concomitant carcinoma in situ (CIS, negative vs. positive), use of a single immediate instillation of chemotherapy (no vs. yes), use of adjuvant BCG therapy (no vs. yes), and gamma globulin level. The categorical and continuous variables of the different groups were compared using the chi-squared test and Mann-Whitney *U* test, respectively. The correlation between 2 continuous variables was assessed using Spearman's rank correlation coefficient. The tumor recurrence rate was estimated using the Kaplan-Meier method and compared using the log-rank test. Associations between clinicopathological parameters and tumor recurrence were assessed by univariate and multivariable analyses using Cox hazards regression models with forward variable selection. All reported *P* values are 2-sided, and statistical significance was set at <0.05. Statistical analyses were performed with SPSS version 24.0 statistical software package (IBM Corporation, Armonk, NY). This study was approved by the Institutional Review Board of Tokyo Saiseikai Central Hospital.

3. Results

3.1. Clinicopathological characteristics of the entire cohort

The median age of all patients was 70 years (interquartile range [IQR]: 63−76 years), and 53% of patients (145) were >70 years old. Male patients accounted for 81% (222) of the cohort. In total, 37% (100) and 32% (88) of patients had grade 3 and T1 tumors, respectively. A total of 47% (130) of patients had multiple tumors, 17% of patients (47) had a maximum tumor diameter of >30 mm, and 19% (52) of patients had a concomitant CIS lesion. A total of 84% (231) and 53% (144) patients received single immediate instillation of chemotherapy and adjuvant BCG therapy, respectively. During a median follow-up period of 39 months (IQR: 14−79 months), 99 (36.1%) patients had at least 1 tumor recurrence and 16 (5.8%) patients had disease progression.

3.2. Determination of the optimal cutoff of gamma globulin level

The median gamma globulin level was 1.2 mg/dl (IQR: 1.0−1.3 mg/dl). A total of 150 (54.7%), 110 (40.1%), and 67 (24.5%) patients had gamma globulin levels greater than 1.2, 1.3, and 1.4 mg/dl, respectively. Of the 150, 110, and 67 patients, 62 (41.3%), 48 (43.6%), and 32 (47.8%) patients had at least 1 tumor recurrence. The overall 5-year recurrence-free survival (RFS) rate was 63.1% ± 2.9%. Significant differences were observed in the RFS between patients who had a gamma globulin level of ≥1.4 and <1.4 mg/dl (P < 0.01) and those who had a gamma globulin level of ≥1.3 and <1/3 mg/dl (P = 0.036) but not between patients who had a gamma globulin level of ≥1.2 and <1.2 mg/dl (P = 0.078, Fig. 1). In the subsequent analyses, patients who had a gamma globulin level of ≥1.4 and <1.4 mg/dl were identified as the high and low gamma globulin group, respectively. The distribution of clinicopathological characteristics according to this gamma globulin status is shown in Table 1. The patients with high gamma globulin levels were more likely to be >70 years old (P < 0.01), likely to receive single immediate instillation of chemotherapy (P < 0.01), and unlikely to receive adjuvant BCG therapy (P = 0.02).

3.3. Association between gamma globulin levels and oncological outcomes

As mentioned above, a significant difference was observed in the RFS between the high and low gamma globulin groups (P < 0.01). Univariate analysis revealed that tumor size (P < 0.01) and the gamma globulin level (P = 0.028) are associated with tumor recurrence. Multivariate analysis also revealed that a tumor size of >30 mm (hazard ratio = 2.02; 95% confidence interval: 1.27−3.21; P < 0.01) and a high gamma globulin level of ≥1.4 mg/dL (hazard ratio = 1.83; 95% confidence interval: 1.20−2.81; P < 0.01) were independently associated with higher tumor recurrence rate (Table 2). The overall 5-year progression-free survival (PFS) rate was 94.1% ± 1.5%. The Kaplan-Meier analysis revealed that the PFS rate of the high and low gamma globulin groups was 91.2% ± 3.8% and 95.1% ± 1.6%, respectively, without significant difference (P = 0.17; Fig. 2).

3.4. Association between gamma globulin levels and albumin-to-globulin ratio

We previously reported that low preoperative albumin-to-globulin ratio (AGR) is an independent risk factor for tumor recurrence and is a risk factor for disease progression in patients with NMIBC [13]. Patients with a high gamma globulin level (≥1.4 mg/dl) had a significantly lower AGR than that of patients with a low gamma globulin level (<1.4 mg/dl), and the gamma globulin level was negatively correlated with the AGR (Supplementary Fig. 1). As reported previously, there is a significant difference in the RFS between patients with low (<1.4 mg/dl) and high (≥1.4 mg/dl) AGRs (P < 0.01). Multivariate analysis using forward variable selection incorporating the AGR status also revealed that a tumor size of >30 mm and a high gamma globulin level of ≥1.4 mg/dl significantly associated with higher tumor recurrence.

4. Discussion

In the present study, we demonstrated that high gamma globulin levels are significantly associated with higher tumor recurrence in patients with NMIBC. The multivariate analysis suggested that patients with high gamma globulin level are likely to experience disease progression, although without statistical significance. To the best of our knowledge, this is the first study reporting on the association between gamma globulin level and oncological outcomes in patients with NMIBC.

Serum proteins are predominantly composed of albumin, followed by globulin and fibrinogen. Gamma globulin is 1 of the 3 main globulin fractions, the other 2 being alpha and beta globulin, and composed almost exclusively of Ig (antibody). A few clinical studies have investigated the association between gamma globulin level determined by SPEP and oncological outcomes. Particularly, Rasouli et al. compared the serum protein levels determined by SPEP among 85 patients with malignancy and 85 matched healthy individuals, and reported that the percentage of the gamma globulin fraction was significantly higher in patients with malignancy [17]. In the present study, the percentage of gamma globulin fraction was also significantly higher in 99 patients who experienced at least 1 tumor recurrence compared to 175 patients who did not (17.2% ± 0.4% vs. 16.2% ± 0.2%, P = 0.01). However, the percentage of gamma globulin fraction is affected by albumin or other globulin's levels. Therefore, we used absolute gamma globulin value in our analyses instead of the percentage of gamma globulin faction. In a different study, Gross et al. compared the serum gamma globulin level, determined by paper electrophoresis, among 22 female patients with malignancy and 20 healthy females, and reported no significant difference in serum gamma globulin level between the 2 groups [18]. In the present study, we found that the gamma globulin level was also significantly higher in 99 patients who experienced tumor recurrence compared to 175 patients who did not (1.27% ± 0.03% vs. 1.18% ± 0.02%, P < 0.01). The method of analyzing the serum protein in the previous study was paper electrophoresis; however, gel electrophoresis is the widely used method, including our study. Moreover, these previous studies included patients with different types of malignancies;

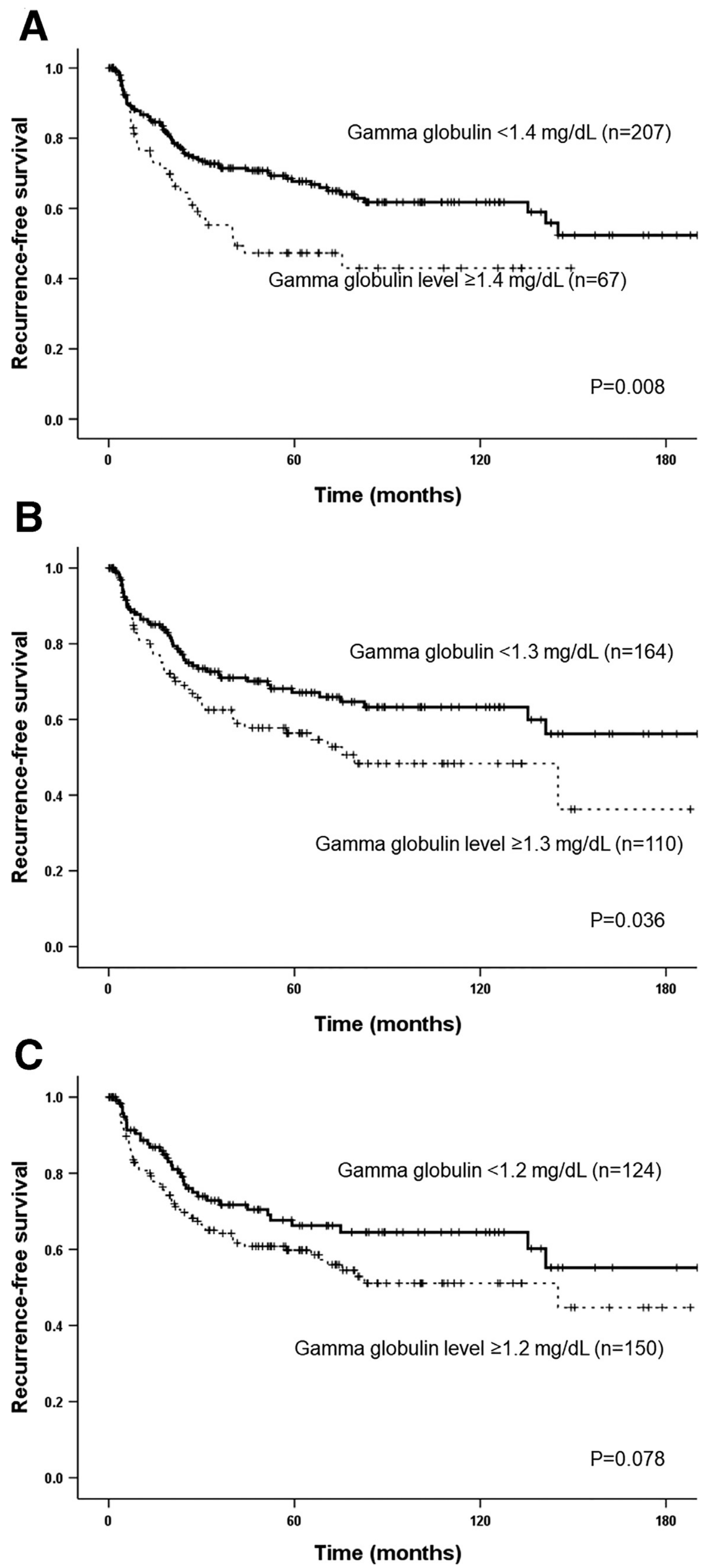

Fig. 1. Recurrence-free survival rates after transurethral resection for gamma globulin levels of (A) ≥1.4 vs. <1.4 mg/dl, (B) ≥1.3 vs. <1.3 mg/dl, or (C) ≥1.2 vs. <1.2 mg/dl.

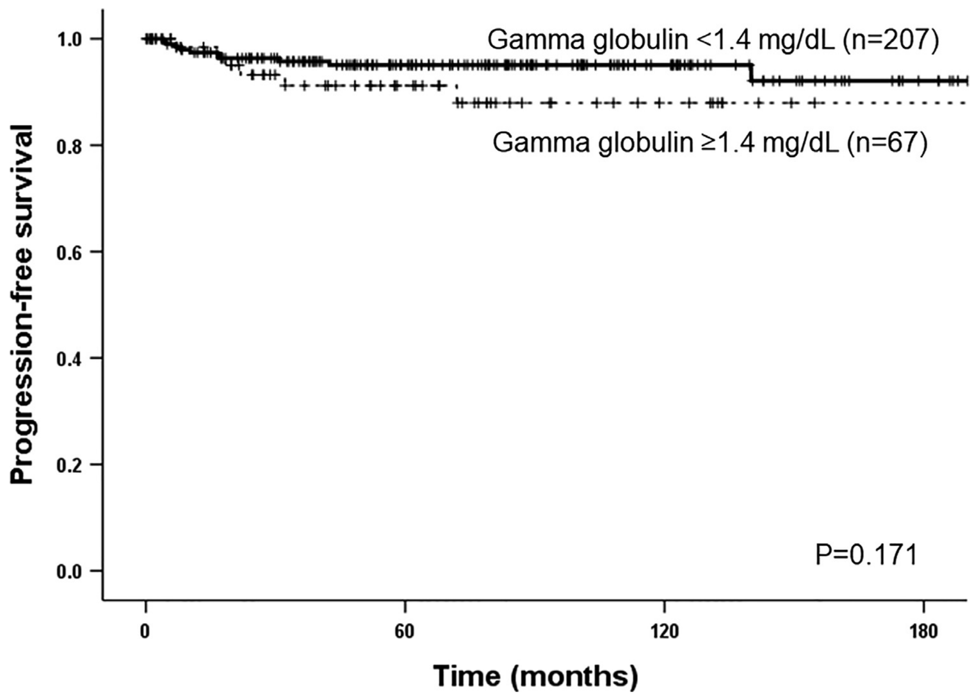

Fig. 2. Progression-free survival rates after transurethral resection for gamma globulin levels of ≥1.4 vs. <1.4 mg/dl.

Table 1
Clinicopathological characteristics of 274 patients with nonmuscle-invasive bladder cancer.

	All patients ($n = 274$)	Low gamma globulin (<1.4 mg/dl) ($n = 207$)	High gamma globulin (≥1.4 mg/dl) ($n = 67$)	*P* value
Age, *n* (%)				<0.01
≤70 y	129 (47.1)	108 (52.2)	21 (31.3)	
>70 y	145 (52.9)	99 (47.8)	46 (68.7)	
Sex, *n* (%)				0.13
Male	222 (81.0)	172 (83.1)	50 (74.6)	
Female	52 (19.0)	35 (16.9)	17 (25.3)	
Tumor grade, *n* (%)				0.31
G1/2	174 (63.5)	128 (61.8)	46 (68.7)	
G3	100 (36.5)	79 (38.2)	21 (31.3)	
T category, *n* (%)				0.88
pTa/is	186 (67.9)	140 (67.6)	46 (68.7)	
pT1	88 (32.1)	67 (32.4)	21 (31.3)	
Tumor multiplicity, *n* (%)				0.60
Single	144 (52.6)	107 (51.7)	37 (55.2)	
Multiple	130 (47.4)	100 (48.3)	30 (44.8)	
Tumor size, *n* (%)				0.58
≤30 mm	227 (82.8)	170 (82.1)	57 (85.1)	
>30 mm	47 (17.2)	37 (17.9)	10 (14.9)	
Concomitant CIS, *n* (%)				0.65
Negative	222 (81.0)	169 (81.6)	53 (79.1)	
Positive	52 (19.0)	38 (18.4)	14 (20.9)	
Single immediate instillation of chemotherapy, *n* (%)				<0.01
No	43 (15.7)	40 (19.3)	3 (4.5)	
Yes	231 (84.3)	167 (80.7)	64 (95.5)	
Adjuvant BCG therapy, *n* (%)				0.02
No	130 (47.4)	90 (43.4)	40 (59.7)	
Yes	144 (52.6)	117 (56.6)	27 (40.3)	

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ.
All statistical differences between 2 groups were evaluated by the chi-squared test.

Table 2
Univariate and multivariate Cox regression analysis for predicting tumor recurrence.

	Tumor recurrence Univariate P value	Multivariate HR (95% CI)	P value
Age			
≤70 y			
>70 y	0.22		
Sex			
Female			
Male	0.84		
Tumor grade			
G1/2			
G3	0.67		
T category			
pTa/is			
pT1	0.12		
Tumor multiplicity			
Single			
Multiple	0.60		
Tumor size			
≤30 mm		1 (Reference)	
>30 mm	<0.01	2.02 (1.27−3.21)	<0.01
Concomitant CIS			
Negative			
Positive	0.70		
Single immediate instillation of chemotherapy			
No			
Yes	0.20		
Adjuvant BCG therapy			
No			
Yes	0.19		
Gamma globulin level			
<1.4 mg/dl		1 (Reference)	
≥1.4 mg/dl	0.028	1.83 (1.20−2.81)	<0.01

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio.

therefore, the clinical impact of globulin level on oncological outcomes was not evaluated.

Patients with malignancies exhibit humoral immune responses against tumor-associated antigens. Subsequently, cancer-specific antibodies are produced and detected in blood serum [19−21]. However, whether an increase or decrease in the level of antibodies is beneficial for the oncological outcomes remains unknown. Coussens et al. demonstrated that peripheral B cell activation is an essential step for early cancer development, and B cell and B cell-derived IgG are necessary for establishing a chronic inflammatory state, promoting de novo carcinogenesis [22]. Qiu et al. demonstrated that human carcinomas produce and secret IgG, and blockage of the tumor-derived IgG increases tumor cell apoptosis and inhibits tumor growth [23]. Furthermore, Sheng et al. suggested that a higher IgG expression in bladder cancer tissues is correlated with a higher histological grade and recurrence [24]. Although each antibody isotype was not measured in this study, IgG is the most common isotype found in serum. Therefore, our results support the role of serum Ig in promoting bladder cancer recurrence. Conversely, it has been proposed that B cells inhibit tumor development by producing antibodies against tumor-associated antigens that induce tumor cell lysis [25] or promote antitumor T cell responses [26].

The present study has several limitations, such as first, it is a retrospective study performed at a single institution with a small patient population and second, we were unable to show the presence of a significant difference in the PFS between low and high gamma globulin groups. This is partly due to the small patient population enrolled in this study. However, based on our results we suggest that B cell immunity may be involved in tumor recurrence and/or development. Further, basic and clinical studies are required to clarify the role of B cell immunity in patients with NMIBC.

5. Conclusions

The results of the present study suggested that a high gamma globulin level is significantly associated with tumor recurrence in patients with NMIBC. Our results indicated that B cell immunity may be involved in the biological behavior of NMIBC and can be a potential therapeutic target of NMIBC.

Acknowledgment

The authors would like to thank Enago (www.enago.jp) for the English language review.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.12.026.

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