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PRETREATMENT PLATELET-TO-LYMPHOCYTE RATIO AS BIOMARKER FOR NEOADJUVANT CHEMOTHERAPY PRIOR TO RADICAL CYSTECTOMY IN MUSCLE-INVASIVE BLADDER CANCER

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Abstract

Objectives : To evaluate the clinical benefit of neoadjuvant chemotherapy with gemcitabine and cisplatin (GC) in patients with muscle-invasive bladder cancer treated with radical cystectomy and to identify patients who may benefit from neoadjuvant chemotherapy and predictors of therapeutic response to it.

Methods : In this prospective study, we enrolled 37 patients with muscle-invasive bladder cancer (cT2-4aNanyM0). The primary endpoint was the pathological response rate at cystectomy after receiving neoadjuvant GC chemotherapy. Univariable and multivariable analyses were used to determine predictive factors of pT0N0 and ≤pT1N0. The secondary endpoints were adverse events during chemotherapy, surgical complications, as well as overall, disease-specific, and recurrence-free survival.

Results : A mean of 2.7 cycles of neoadjuvant GC was administered. Pathological complete response (pT0N0), partial response (pTisN0/pT1N0), and pathological response (≤pT1N0) rates were 24.3%, 27.0%, and 51.3%, respectively. Grade 3 or 4 non-hematologic adverse events were rare. Three-year overall, disease-specific, and recurrence-free survival rates were 70.7%, 81.3%, and 63.9%, respectively. Patients with pathological response (≤pT1N0) demonstrated a significantly improved 3-year overall survival rate (94.7% vs. 42.8%), disease-specific survival rate (94.7% vs. 62.9%), and recurrence-free survival rate (80.6% vs. 45.5%), compared with pathological non-responders (≥pT2Nany). Clinical stage cT2 and low pre-chemotherapy platelet-to-lymphocyte ratios were significant indicators of favorable pathological response to neoadjuvant GC.

Conclusions : Neoadjuvant chemotherapy using GC is safe and effective in patients with muscle-invasive bladder cancer. Pretreatment clinical T2 stage and low platelet-to-lymphocyte ratios were predictive markers for successful neoadjuvant treatment of muscle-invasive bladder cancer with GC.

Key words : bladder cancer, chemotherapy, cisplatin, cystectomy, gemcitabine

Introduction

Definitive treatment for muscle-invasive bladder cancer (MIBC) has traditionally involved curative-intent radical cystectomy with bilateral pelvic lymph node dissection. Tumor and nodal stage are strongly correlated with 5-year survival rates [1]. In patients who undergo radical cystectomy, the pathologic stage classification is higher than the predicted clinical stage classification in 42% of patients. Occult lymph node disease is identified in 20–45% of patients at the time of cystectomy with clinical T2-T4 disease [2-4]. These results suggest that micrometastasis is common in patients with clinically localized disease. Therefore, neoadjuvant chemotherapy is thought to provide additional benefit for clinically localized disease by treating micrometastases.

In 2003, in a phase III intergroup study of MIBC patients, a significant improvement in overall survival (OS) was demonstrated with the addition of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy prior to radical cystectomy [5]. The MVAC regimen was very effective, but severe toxicity was shown in several reports. For example, neutropenic sepsis occurred in more than 10% of patients, while the toxic death rate was 3–4% [6, 7]. Therefore, it can be assumed that the MVAC regimen was too strong for patients preparing to undergo cystectomy.

A gemcitabine and cisplatin (GC) regimen was associated with markedly less toxicity than the MVAC regimen for advanced or metastatic bladder cancer [8]. Moreover, GC had a good antitumorigenic treatment effect comparable to MVAC in metastatic or locally advanced bladder cancer cases [8]. Currently, the use of GC in the neoadjuvant setting is based on data extrapolated from the metastatic setting, as few retrospective series have reported on neoadjuvant chemotherapy with GC.

A significant concern with the use of neoadjuvant chemotherapy is that although only a small proportion of patients may have disease progression, tumor upstaging may result in decreased survival rates, compared with immediate radical cystectomy. To our knowledge, there are currently no predictive biomarkers for response to neoadjuvant chemotherapy in patients with MIBC. Discovering pretreatment factors that predict the response to neoadjuvant chemotherapy may play an even more important role in the management of patients with MIBC. Systemic inflammatory response (SIR) is associated with the outcomes of several types of cancer [9]. Neutrophils, lymphocytes, and platelets are important representative factors in tumor-induced SIR [10]. Of these markers, the neutrophil to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been identified as promising predictors. Investigations have demonstrated that NLR and PLR are highly repeatable, cost-effective, and widely available tests [11]. However, there are limited data on the use of SIR-related hematological biomarkers as predictors of clinical outcomes in patients with MIBC treated with neoadjuvant chemotherapy.

Based on this information, we conducted a prospective study to evaluate the toxicity and efficacy of neoadjuvant GC in Japanese patients with MIBC and to determine pretreatment variables that predict patients' responses to neoadjuvant GC.

Patients and Methods

Patient Eligibility

All patients met the following criteria: Eastern Cooperative Oncology Group performance status of 0–1; adequate baseline bone marrow function (white blood cell count ≥4000 cells/mm3, hemoglobin ≥9.5 g/dL, and platelet count ≥100000 cells/mm3); adequate hepatic function, total bilirubin level ≤2.0 mg/dL and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <2.5 times the upper limit of normal; and adequate renal function, serum creatinine level ≤1.2 mg/dL).

The study inclusion criteria were: T2-4aNanyM0; transurethral resection of the bladder tumor (TURBT) was performed within 8 weeks before first cycle of neoadjuvant chemotherapy; histologically proven urothelial carcinoma (UC), non-pure UC cases were included if UC histology was dominant; no prior or concomitant upper urinary tract UC history; and no prior chemotherapy or radiation therapy.

The protocol was approved by the Ethics Committee of Nara Medical University (#09-KEN025) and by the institutional review boards of the participating institutions. All patients provided written informed consent.

Study Design and Treatment Protocol

This study was designed as a study to evaluate the safety and efficacy of 3 cycles of neoadjuvant GC for MIBC. Treatment consisted of gemcitabine 1,000 mg/m2 intravenously on days 1, 8, and 15 and cisplatin 70 mg/m2 intravenously on day 2 of each 28-day treatment cycle. Treatment cycles were repeated every 28 days. Radical cystectomy with bilateral pelvic lymphadenectomy was performed within 4-8 weeks after the last cycle of chemotherapy in patients receiving neoadjuvant chemotherapy. Urinary reconstruction was determined by the surgeons and patients. During neoadjuvant chemotherapy, the therapeutic effect was evaluated with computed tomography after every cycle, according to RESIST criteria [12], and patients with disease progression underwent immediate cystectomy.

Follow-up and Evaluation

Follow-up Schedule

To assess for the toxicity of neoadjuvant GC, blood count and blood chemistry tests were carried out twice every week, and one chest X-ray was taken during the chemotherapy. Adverse events (AEs) were reported using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE ver4.0) [9]. Postoperative complications were documented using the Clavien-Dindo classification [13]. Post-treatment follow-up consisted of clinical and laboratory assessments every 3 months as well as cross-sectional imaging of the chest, abdomen, and pelvis every 3 months.

Endpoints

The primary endpoint of this trial was the pathological response rate at cystectomy. Pathological response rate was evaluated according to postsurgical stage. Complete pathologic

response (pCR) was defined as pT0N0, and partial pathologic response (pPR) was defined as pTis/Ta/T1. In addition, pCR and pPR were defined as pathological response (pR: ≤T1N0M0). Cases with a response other than pCR or pPR were defined as non-response (non-pR). Secondary endpoints were overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS), AEs during chemotherapy, and surgery-related complications.

Statistical Analysis

Overall survival (OS) was defined as the time from the start of chemotherapy to death from any cause. Disease-specific survival (DSS) was defined as surviving the protocol treatment and having no evidence of distant metastases, nodal recurrence, or local recurrence. Recurrence-free survival (RFS) was defined as the time from the start of chemotherapy to relapse (radiological or clinical) or death. Surviving patients lost to follow -up were censored at the last assessment date. OS, DSS, and PFS were estimated using the Kaplan–Meier method. For patients with pR, prognostic factors were analyzed by a univariate or multivariate logistic regression model. The chi-squared test and Fisher's exact test were performed to evaluate the effect of covariates on achieving a response to neoadjuvant chemotherapy. A P-value ≤0.05 was considered statistically significant. All analyses were carried out using SPSS v.22 (IBM, Chicago, IL, USA).

Results

Patient

Between March 2010 and March 2015, 37 patients were enrolled. All patient characteristics are shown in Table 1. Twenty-six (63.2%) patients completed 3 courses of GC neoadjuvant chemotherapy; 11 patients received 2 courses. The reasons for cessation of a third cycle were progression of disease during neoadjuvant chemotherapy in 3 patients and 7 patients requested immediate cystectomy before the third neoadjuvant chemotherapy cycle. One patient experienced a drug rash caused by GC in the second cycle. All 37 patients underwent cystectomy after GC neoadjuvant chemotherapy and were evaluated for response, toxicity, postsurgical complications, and survival.

The GC toxicity profile is presented in Table 2. With GC chemotherapy, common AEs were hematological toxicities. The most commonly reported grade 3-4 event was neutropenia. Fourteen (37.8%) patients experienced grade 3-4 neutropenia. Grade 4 febrile neutropenia occurred in 1 (2.7%) patient. Five (13.5%) patients developed grade 3-4 anemia. One patient needed erythrocyte transfusion. Four patients experienced grade 3-4 thrombocytopenia. No bleeding-related thrombocytopenia occurred in these patients. Non-hematological AEs were not common in GC neoadjuvant chemotherapy. Drug rash occurred in one patient (2.7%). Grade3 nausea was observed in one patient (2.7%). There was no treatment-related death during the chemotherapy. There were no cases of grade 3-4 biochemical toxicity in AST, ALT, or bilirubin levels. In renal function, no patients had grade 3-4 elevation of serum creatinine or blood urea nitrogen levels. In terms of postoperative complications, common early postoperative complications were gastrointestinal tract related complications and surgical site infections (Table 3).

Table 1. Baseline clinical characteristics in 37 patients

Patient characteristics (total n=37)	
Age (years old)	median 70.0 (44 - 80)
Sex	
Male	29
Female	8
PS (ECOG)	
0	36
1	1
Smoking status	
Current / previous	31
None	6
Charlson comorbidity index	
0	25
1 or 2	10
3 or 4	1
≧5	1
Clinical T stage	
T2	22
T3a/b	9
T4a	6
Clinical N stage	
N0	33
N1	2
N2	2
Histology	
Pure UC	28
Mixed adenocarcinoma differentiation	1
Mixed squamous variant differentiation	3
Mixed neuroendocrine differentiation	1
Nested variant	4
Neutrophil counts (/?L)	median 5450 (2865 - 9100)
Platelet counts(10^4/?L)	median 21.4 (10.4 -45.8)
CRP (mg/dL)	median 0.19 (0.1 - 0.5)
Albumin (g/dL)	median 4.3 (3.6 - 4.7)
NLR	median 2.17 (0.54 - 11.4)
PLR	median 150.9 (48.8 - 328.3)

PS: perfomance status, ECOG: Eastern Cooperative Oncology Group, UC: Urothelial carcinoma, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio

Table 2. Toxicity profile of neoadjuvant GC

Toxicity	Grade3 or Grade4 (n)
Neutropenia	14 (37.8%)
Anemia	2 (5.4%)
Thrombocytopenia	4 (10.8%)
Nausea	1(2.7%)
Drug rash	1(2.7%)
Febrile neutropenia	1(2.7%)

Table 3. Postoperative complication

Complication	Grade3	Grade4
Paralytic ileus	1 (2.7%)	0 (0%)
Occulusive ileus	2 (5.7%)	1 (0%)
Intestinal anastomotic leak	1 (2.7%)	2 (0%)
Postoperative wound infection	3 (8.1%)	3 (0%)
Abscess	2 (5.7%)	1 (2.7%)

Pathological Response

All 37 patients received at least 2 courses of GC. The pathologic outcomes at cystectomy are contrasted with the pre-chemotherapy clinical stage in Table 4. Each patient's baseline clinical stage was compared with the final pathologic stage, demonstrating that 62.1% of evaluated patients were down-staged to a lower pathologic stage at cystectomy. In addition, the proportions of pCR, pPR, and pR were 24.3%, 27.0%, and 51.3%, respectively. Nine (27.0%) patients were upstaged at cystectomy.

Table 4. Correlation of pretreatment clinical stage and final pathologic stage at radical cystectomy

Clinical stage	Pathological stage at radical cystectomy									Total (n)
	pR			non-pR						
	pCR	pPR								
	pT0N0	pTisN0	pT1N0	pT2N0	pT3N0	pT3N1	pT3N2	pT4N0	pT4N1	
cT2N0	6	5	4	3	1	1	0	0	0	20
cT2N1	0	0	0	1	0	0	0	0	0	1
cT2N2	0	0	0	0	0	0	1	0	0	1
cT3N0	2	1	0	2	1	0	1	0	0	7
cT3N1	1	0	0	0	0	0	0	0	0	1
cT3N2	0	0	0	0	1	0	0	0	0	1
cT4N0	0	0	0	0	1	0	0	3	2	6

pCR: pathological complete response (pT0N0), pPR: pathological partial response (pTis/Ta/T1N0), pR: pathological response (≤T1N0). The proportions of pCR, pPR, and pR were 24.3%, 27.0%, and 51.3%.

Recurrence, Progression, and Survival Outcomes

After a median follow-up period of 28 months (range, 6-61), 24 (64.8%) patients remained alive and disease free, and 10 (27.0%) patients died. Eleven (29.7%) patients had recurrence: 4 patients had pelvic recurrence, 1 patient had peritoneal metastasis, and 6 patients had distant metastases. Six (16.2%) of these patients' recurrences resulted in cancer-related death as of the time of data cutoff.

In all cases, the 3-year OS, DSS, and PFS rates were 70.1% (95% CI, 55.2-86.1), 81% (95% CI, 67.6-94.9), and 63.8% (95% CI, 45.8-81.9), respectively. Kaplan-Meier curves of estimated OS, DSS, and PFS are shown in Fig.1.

After neoadjuvant chemotherapy, 84.2% of patients with pR showed no disease recurrence, compared with 55.5% of non-pR patients. Patients with pR demonstrated a significantly improved 3-year OS rate (94.7% vs. 42.8%), DSS rate (94.7% vs. 62.9%), and RFS rate (80.6% vs. 45.5%), compared with pR patients (Fig.1). Patients with pCR did not show superiority, compared to those with only pPR (Fig.2).

Predictors of Response to Neoadjuvant Gemcitabine and Cisplatin

Divided by response to neoadjuvant chemotherapy, the proportion of clinical T2 was 84.2% in pR cases. On the other hand, the proportion was 33.3% in non-pR cases. When comparing the two groups, the pre-chemotherapy cT stage, pN stage showed a significant association with response to neoadjuvant chemotherapy. In SIR related variates, PLR was significantly lower in the pR group (Table 5). In the logistic regression model for achieving pR, pretreatment clinical

T stage (OR, 9.34; 95% CI, 1.67-52.19) and pre-chemotherapy PLR (OR, 1.01; 95% CI, 1.00-1.03) were significant predictive factors (Table 6)

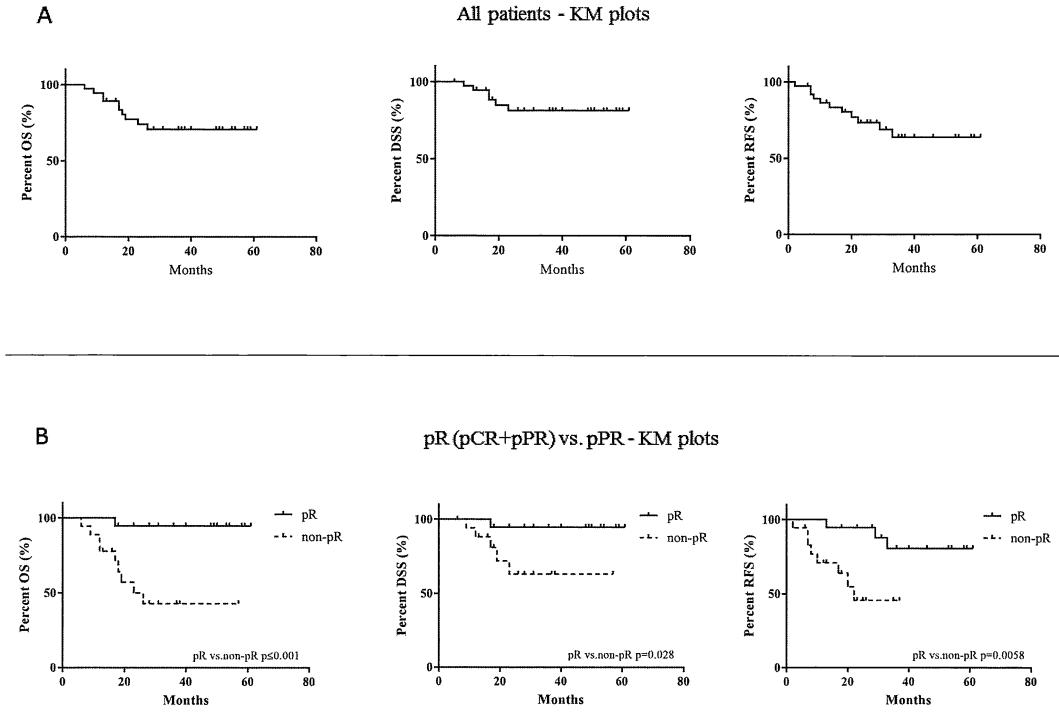

Fig.1.
A. Overall survival, disease specific survival and recurrence free survival with gemcitabine and cisplatin (GC) neoadjuvant therapy for all patients.
B. Overall survival, disease specific survival and recurrence free survival with GC neoadjuvant therapy according to degree of pathological response.

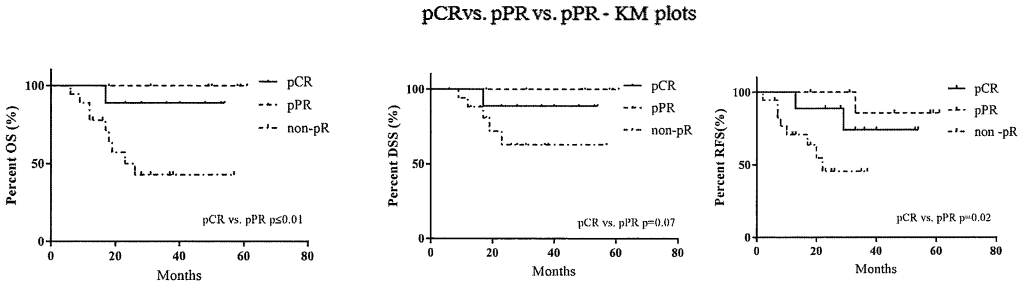

Fig.2. Overall survival, disease-specific survival, and recurrence-free survival after GC neoadjuvant therapy according to the degree of pathological response. The 3-year overall survival, disease-specific survival, and recurrence-free survival of patients with pathological complete response (pCR) is equivalent to that of patients with pathological partial response (pPR).

Table 5. Comparison of clinicopathological factors acoording to pathological response

Factors	pR (<pT2) (n=19)	non-pR(≥pT2) (n=18)	p value
Sex			
Male	16	13	0.31[a]
Female	3	5	
Age (years)	median 70 (48-79)	median 71 (44-80)	0.89[b]
Smoking history			
Yes	16	15	0.51[a]
No	3	4	
Clinical T stage			
≤T2	16	6	0.0025[a]
≥T3	3	12	
Clinical N stage			
N0	18	15	0.28[a]
N1-N2	1	3	
Post surgical N stage			
N0	19	13	0.019[a]
N1,N2	0	5	
Histology			
Pure UC	15	13	0.46[a]
Mixed	4	5	
Surgical margin			
Yes	0	3	0.11[a]
No	19	15	
Neutrophil counts (/μL)	median 3100 (1300 - 7300)	median 4000 (1600 - 9100)	0.67[b]
Platelet counts(10^4/μL)	median 20.4 (13.0 - 25.4)	median 23.3 (10.4 - 45.8)	0.096[b]
CRP (mg/dL)	median 0.2 (0-0.5)	median 0.1 (0-0.6)	0.49[b]
Albumin (g/dL)	median 4.2 (3.6-4.7)	median 4.3 (3.6-1.7)	0.22[b]
NLR	median 1.94 (0.54 - 7.3)	median 2.74 (0.73 - 11.38)	0.29[b]
PLR	median 118.2(70.42 - 214)	median 184.9 (48.85 – 328.3)	0.036[b]

UC: urothelial carcinoma, NLR: neutrophil-to-lymphocyte ratio,
PLR: platelet-to-lymphocyte ratio, a: Fisher's exact test b: Mann-Whitney U test

Table 6. Multivariate analysis of predictive factors for pathologic response (≤pT1N0)

Variables	Univariate		Multivariate	
	OR (95% CI)	p value	HR (95% CI)	p value
Age (<64 vs ≥65 years old)	0.56 (0.14-2.26)	0.42	-	-
Gender (Male vs Female)	2.05 (0.41-10.23)	0.38	-	-
Tumor multiplicity (Solitary vs Multiple)	0.36 (0.095-1.38)	0.14	-	-
Concomitant CIS (No vs Yes)	0.32 (0.076-1.33)	0.31	-	-
Histology (Pure UC vs Mixed)	0.80 (0.18-3.62)	0.77	-	-
Clinical T stage (T2 vs ≥T3)	8.38 (1.77-39.69)	<0.01	9.34 (1.67-52.19)	0.011
Clinical N stage (N0 vs N1/N2)	3.60 (0.34-38.3)	0.29	-	-
Prechemotherapy NLR (continuous)	1.23 (0.94-1.71)	0.23	-	-
Prechemotherapy PLR (continuous)	1.02 (1.00-1.02)	0.03	1.01 (1.00-1.03)	0.048

OR: Odds ratio, CIS: carcinoma in situ, UC: urothelial carcinoma,
NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio

Discussion

We performed an open-label, single-arm prospective study of 37 patients with MIBC treated with neoadjuvant gemcitabine and cisplatin before radical cystectomy to evaluate the safety and clinical benefit of preoperative chemotherapy in this population. Level 1 evidence indicates that neoadjuvant chemotherapy prior to radical cystectomy improves the survival benefit of patients with MIBC compared with radical cystectomy alone [5,14-16]. In patients with metastatic bladder cancer, Masse et al. reported equivalent long-term overall and progression-free survival of patients receiving GC compared to MVAC[8]. Decreased toxicity is very important with neoadjuvant chemotherapy prior to cystectomy in patients with MIBC. GC has become the most commonly used regimen based on extrapolation of data from patients with metastatic bladder cancer, owing to a better toxicity profile than MVAC [8,17]. In this study,

toxicity during GC neoadjuvant chemotherapy manifested as hematological AEs. Grade 3 or 4 neutropenia, thrombocytopenia, anemia, and febrile neutropenia were observed in 37.8%, 10.8%, 5.4%, and 2.7% of all GC cycles, respectively. No patient had a delay in surgery due to AEs, and there were no remarkable AEs in the early postoperative phase. In this study, the median age was 70.5 years old (range: 44-81), showing that three cycles of GC neoadjuvant chemotherapy were well tolerated by elderly patients.

Indeed, almost 80% of Bladder Cancer Advocacy Network oncologists offer neoadjuvant chemotherapy with GC, which is the most used regimen (90%), followed by MVAC (30%) [18]. However, the efficacy of GC for neoadjuvant chemotherapy has not been evaluated as fully as that of MVAC. In addition, many studies of GC as a neoadjuvant chemotherapeutic agent were retrospective analyses, and the reported pathological response outcomes are conflicting. For example, the Cleveland Clinic used a standard administration of three cycles of GC and reported that only 7% of patients achieved pT0 [19]. On the other hand, Kaneko et al. reported a good pathological response to GC neoadjuvant chemotherapy using a standard administration of 3 cycles of GC, with 50.0% and 63.6% of patients achieving pT0 and ≤pT1N0, respectively [20]. For GC, the reported rate of pCR among published series is within the range of 10%–50% [19-23]. In this study, we used a 28-day schedule of neoadjuvant GC therapy for three cycles. The mean number of cycles performed was 2.48 cycles, and 24.3% and 51.4% of patients achieved a pCR and pR at cystectomy, respectively. Kaneko et al. hypothesized the manner of transurethral resection influenced pathological response, especially in cT2 cases [20]. In this study, there were 21 cT2 cases (N0:19, N1:1, N2:2), and 66.6% achieved pR after GC neoadjuvant chemotherapy. On the other hand, of the 16 >cT2 cases, 31.2% achieved pR. Our protocol of TURBT in patients with clinical T2 was visually completed TUR. According to several studies of selective organ treatment of MIBC with radiation plus chemotherapy, the completeness of TURBT is an important predictor of survival and pathological response. Further, the resection volume of the tumor at TUR may affect the pathological response of GC neoadjuvant chemotherapy in cT2 cases. [24,25].

A previous study suggested worse overall survival in MVAC neoadjuvant chemotherapy patients with residual pTa/pTis/pT1 when compared with that of pT0 patients [26]. However, in this study, the outcomes of patients with pT0 stage were not shown to be superior to pTis/pT1 patients. A recent retrospective study reported that residual pTa, Tis, or pT1 disease after GC neoadjuvant chemotherapy had a similar DSS to that of pT0 patients and that residual non–muscle-invasive disease was a significantly meaningful pathologic benchmark in the neoadjuvant chemotherapy setting [27]. Our results support this hypothesis.

Platelets can secrete several growth factors including platelet derived growth factor (PDGF) [28], platelet-activating factor (PAF) [29], and vascular endothelium growth factor (VEGF) [30]. These growth factors could further support tumor growth, angiogenesis and metastasis [31]. In tumor-derived inflammatory responses, lymphocytes show antitumor activity by inducing cytotoxic cell death and inhibiting tumor proliferation [32]. Therefore, increased PLR have negative effects on patient survival. Platelet and lymphocyte counts are routinely measured blood-based parameters, therefore PLR can be evaluated easily in clinical practice.

We found that a high pretreatment PLR was associated with a poor pathological response in GC neoadjuvant chemotherapy for MIBC. Previous studies have identified that PLR has a role in many malignant tumors [33-36]. NLR, which is defined as the absolute neutrophil count divided by the absolute lymphocyte count, is another predictor of prognosis in many tumors. Several studies reported that NLR was superior to PLR as a predictor of prognosis in urothelial carcinoma [37]. However, other studies concluded the opposite. Our present study also found that PLR was a predictor of the response to GC neoadjuvant chemotherapy. However, further research is still needed to confirm whether NLR is more useful than PLR in MIBC patients undergoing GC neoadjuvant chemotherapy.

The limitations of this prospective study were the small sample size and short follow-up period. The main reason for the poor accrual in this study was the difference in the perceived benefits of neoadjuvant chemotherapy between physicians and Japanese patients. Many candidates rejected neoadjuvant chemotherapy due to severe anxiety. The benefits of cisplatin-based neoadjuvant chemotherapy were obvious to physicians, but patients had anxieties, for example delayed cystectomy, progression during neoadjuvant chemotherapy, and AEs of neoadjuvant chemotherapy.

In conclusion, this phase II prospective multicenter study demonstrates that GC neoadjuvant chemotherapy is safe and well tolerated. A good pathological response was obtained in organ confirmed disease (cT2) and low pretreatment PLR cases. Without level I evidence, neoadjuvant GC has been widely used worldwide; therefore, a larger, well-designed, randomized study is recommended to establish the clinical benefit of neoadjuvant GC chemotherapy.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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