

## Factors that Predict Neutropenia in Korean Patients with Advanced Urothelial Cancer after Cisplatin-Based Systemic Chemotherapy

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**Purpose:** The aim of this study was to identify factors that can be used to predict severe neutropenia (grade 3 or higher) in patients with advanced urothelial cancer after cisplatin-based systemic chemotherapy.

**Materials and Methods:** The study examined 79 Korean patients with advanced urothelial cancer who were treated with several cycles of cisplatin-based systemic chemotherapy from May 2006 to May 2015. Risk factors for neutropenia (grade 3 or higher) and for the occurrence of neutropenia (grade 3 or higher) during the first cycle of chemotherapy were examined.

**Result:** Thirty-six out of the 79 patients (45.6%) developed neutropenia at grade 3 or higher during the first cycle of cisplatin-based systemic chemotherapy: 18 (22.7%) of these experienced grade 3 neutropenia and 18 (22.7%) experienced grade 4. Multivariate analysis identified pretreatment neutrophil counts ( $P = .001$ ) as the only significant factor predictive for severe neutropenia.

**Conclusion:** The pretreatment neutrophil count was found to be the factor that poses a significant and independent risk in development of severe neutropenia induced by applying cisplatin-based systemic chemotherapy to patients with advanced urothelial cancer.

**Keywords:** bladder cancer; cisplatin; metastasis; neutropenia; predictive factor.

### INTRODUCTION

There are several different types of urologic cancer. Patients with metastatic urologic cancer usually undergo some form of anticancer chemotherapy.<sup>(1)</sup> Recently, several regimens for urologic anticancer chemotherapy have been reported, including combination anticancer chemotherapy using gemcitabine and cisplatin (GC); indeed, this has come to be the standard treatment option for locally advanced and metastatic urothelial carcinoma.<sup>(2)</sup> Until studies of GC were reported, methotrexate, vinblastine, doxorubicin, plus cisplatin (MVAC) was the most used regimen in metastatic urologic cancer.<sup>(3)</sup> Several studies suggested GC as the standard treatment for locally advanced and metastatic urothelial carcinoma because of its similar efficacy and lower toxicity compared with MVAC.<sup>(4)</sup> A phase III trial was designed to compare GC and MVAC. The initial goal of this study was to show the superiority of GC. However, the results showed similar overall survival (OS) (MVAC: 14.8 months vs. GC: 13.8 months) and objective response rates (MVAC: 45.7% vs. GC: 49.4%).<sup>(2,5)</sup> Importantly, the GC group experienced significantly fewer side effects such as neutropenic sepsis (MVAC: 12% vs. GC: 1%) and grade 3–4 mucositis (MVAC: 22% vs. GC: 1%) than the MVAC group.<sup>(2,5)</sup> Thus, due to lower toxicity, GC was considered the standard treatment for locally advanced and metastatic urothelial carcinoma. Platinum-based agents such as cisplatin and carbopla-

tin are the first-line chemotherapy agents for advanced urothelial cancer.<sup>(6)</sup> In vivo, neutrophils serve as the first-line defense against infection, by playing a crucial role at early stages of an inflammatory response and by overseeing the innate immunity. As such, invading bacteria is allowed to multiply when neutropenia weakens inflammatory responses against an infection. And, because the signs and symptoms of an infection are suppressed by neutropenia, patients may display a fever as the only indicative.<sup>(7)</sup>

Neutropenia following the application of cytotoxic anticancer drugs is inevitable. Several studies identified factors that predict the occurrence of febrile neutropenia (FN) in patients receiving systemic chemotherapy based on an assortment of anticancer drugs.<sup>(8,9)</sup> The risk factors for febrile neutropenia included old age, serum albumin, baseline neutrophil count, hepatic disease and non-use of granulocyte colony-stimulating factors. Neutropenia is defined as an absolute neutrophil count of less than  $0.5 \times 10^9/L$ .<sup>(10)</sup>

An occurrence of neutropenia induced by chemotherapy is the most common type of neutropenia, and such occurrence can be used to define a toxicity line limiting a dose of cytotoxic anticancer treatments.<sup>(11)</sup> A Western study shows that the incidence of docetaxel-induced grade 3–4 neutropenia in patients with castration-resistant prostate cancer is about 25%,<sup>(12)</sup> whereas a Korean study reports an incidence of 17%.<sup>(13)</sup>

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**Table 1.** Patient characteristics and pharmacokinetic parameters of cisplatin in the groups with or without severe neutropenia

| Variables   | Without severe neutropenia (n = 43) | With severe neutropenia (n = 36) | Total (n = 79)    | P Value |
|---|-------------------------------------|----------------------------------|-------------------|---------|
| Mean age (years)  | 68.7 ± 8.76                         | 69.8 ± 7.84                      | 69.2 ± 8.29       | .474    |
| Body mass index (kg/m <sup>2</sup> )                    | 23.2 ± 3.19                         | 22.8 ± 3.16                      | 22.9 ± 3.15       | .599    |
| Mean serum Hg level (g/dL)                              | 9.6 ± 1.61                          | 9.6 ± 1.28                       | 9.6 ± 1.44        | .600    |
| Pretreatment WBC count (/mm <sup>3</sup> )              | 8152.97 ± 2134.27                   | 6431.67 ± 1618.40                | 7304.11 ± 2074.04 | < .001  |
| Posttreatment WBC count (/mm <sup>3</sup> )             | 3959.7 ± 1811.86                    | 1944.4 ± 783.52                  | 6928.7 ± 1978.24  | < .001  |
| Pretreatment neutrophil count (/mm <sup>3</sup> )       | 5250.81 ± 2218.56                   | 4005.83 ± 1434.19                | 4636.85 ± 1963.08 | < .001  |
| Posttreatment neutrophil count (/mm <sup>3</sup> )      | 2067.3 ± 1647.58                    | 500.0 ± 258.67                   | 1294.3 ± 1418.55  | < .001  |
| Pretreatment serum albumin level (g/dL)                 | 3.84 ± 0.71                         | 4.02 ± 0.59                      | 3.92 ± 0.65       | .188    |
| Serum creatinine level                                  | 1.40 ± 0.64                         | 1.43 ± 0.42                      | 1.41 ± 0.53       | .198    |
| Pretreatment serum platelet count (/mm <sup>3</sup> )   | 277.5 ± 84.66                       | 255.6 ± 74.94                    | 266.7 ± 80.22     | .229    |
| Pretreatment serum ALP level (g/dL)                     | 252.9 ± 125.45                      | 196.4 ± 77.28                    | 225.9 ± 108.25    | .030    |
| Pretreatment serum lymphocyte count (/mm <sup>3</sup> ) | 1933.5 ± 785.94                     | 1611.2 ± 614.87                  | 1774.5 ± 720.38   | .101    |
| NL ratio  | 1.3 ± 1.26                          | 0.4 ± 0.63                       | 0.85 ± 1.07       | < .001  |
| PL ratio  | 170.9 ± 99.30                       | 198.4 ± 160.66                   | 184.4 ± 132.92    | .395    |
| Charlson comorbidity index                              | 1.8 ± 2.08                          | 1.7 ± 1.36                       | 1.7 ± 1.75        | .483    |
| Geriatric index   | 13.6 ± 2.10                         | 13.9 ± 2.01                      | 13.7 ± 2.04       | .627    |
| N stage   |                                     |                                  | .990              |         |
| 0   | 23                                  | 22                               | 45                |         |
| 1   | 10                                  | 10                               | 20                |         |
| 2   | 4                                   | 3                                | 7                 |         |
| 3   | 1                                   | 1                                | 2                 |         |
| Performance status (ECOG)                               |                                     |                                  |                   | .378    |
| 0   | 35                                  | 35                               | 70                |         |
| 1   | 2                                   | 0                                | 2                 |         |
| 2   | 1                                   | 1                                | 2                 |         |
| Hydronephrosis  |                                     |                                  |                   | .486    |
| No  | 21                                  | 23                               | 44                |         |
| Yes   | 17                                  | 13                               | 30                |         |

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; WBC, white blood cell.; N ratio, neutrophil to lymphocyte ratio; PL ratio, platelet to lymphocyte ratio. The Mann-Whitney U test and Fisher’s exact test were used to compare continuous and categorical variables, respectively, between groups.

astatic urothelial carcinoma, GC has a certain degree of adverse effects such as FN, despite having lower toxicity than MVAC. A study of GC reported that the most frequent grade 3–4 hematologic toxicity was neutropenia in 45.4% for GC.<sup>(14)</sup> Therefore, clinicians must understand the infectious adverse events that may occur during and after chemotherapy for urologic cancer. However, to the best of our knowledge, few studies have identified factors that predict neutropenia in patients with advanced urothelial cancer after cisplatin-based systemic chemotherapy. Thus, this study aims to identify factors that can be used to predict neutropenia in patients treated with cisplatin-based systemic chemotherapy and to determine an incidence rate of neutropenia in such patients.

**MATERIALS AND METHODS**

**Ethics and informed consent**

This study was conducted at Wonkwang University Hospital. Written informed consent was obtained from all subjects before enrollment in the study. Study protocols and informed consent forms were approved by the institutional review board.

**Study Population**

Patients whose medical records show a diagnosis of an advance urothelial cancer and who received one or more cycles of cisplatin-based systemic chemotherapy at Wonkwang University Hospital, located in Iksan, South Korea, from May 2006 to May 2015 were reviewed retrospectively. Baseline demographic, clinical, and laboratory data including the hemoglobin level, white blood cell (WBC) count, neutrophil count, platelet count, lymphocyte count, neutrophil to lymphocyte ratio (NL ratio), and platelet to lymphocyte ratio (PL ra-

tio) before chemotherapy were collected retrospectively for all patients. This retrospective study was approved by the Institutional Review Board of Wonkwang University Hospital.

**Treatment protocol**

The following common urological anticancer chemotherapy regimens were examined: GC and MVAC (methotrexate, vinblastine, doxorubicin hydrochloride, and cisplatin). All subjects must have required at least one cycle of chemotherapy and none had received prophylactic granulocyte-colony stimulating factor (G-CSF) until completion of the first cycle. However, if neutropenic events had occurred, the administration dose of chemotherapy was reduced to 75%.

The Common Terminology Criteria for Adverse Events Version 3.0 recommends that neutropenia is defined as a neutrophil count < 1500/mm<sup>3</sup>. In the present study, the state of neutropenia was divided in four separate grades: grade 1, < 1500/mm<sup>3</sup>; grade 2, < 1500–1000 /mm<sup>3</sup>; grade 3, < 1000–500 /mm<sup>3</sup>; and grade 4, < 500 /mm<sup>3</sup> (National Cancer Institute, 2006). Then, incidences of neutropenia (≥ grade 3) and potential risk factors for incidences of neutropenia were examined and evaluated during the first cycle of chemotherapy.

**Statistical analysis**

Clinicopathological data obtained for two groups of patients were compared: 1) a group of patients who developed ≥ grade 3 neutropenia during the first cycle of chemotherapy; and 2) a group of patients who did not. In order to compare continuous and categorical parameters between two groups, the Mann-Whitney U test and Fisher’s exact test were used respectively. Potential risk factors for grade 3–4 neutropenia in patients with advanced urothelial carcinoma were identified in a uni-

**Table 2.** Multivariate analysis to identify factors that predict severe neutropenia in patients with advanced urothelial cancer

| Variables                     | 95% confidence interval (CI) | P Value |
|-------------------------------|------------------------------|---------|
| Pretreatment WBC count        | 0.999–1.005                  | 0.213   |
| Pretreatment neutrophil count | 0.967–0.996                  | 0.012   |
| Pretreatment ALP              | 0.956–1.004                  | 0.108   |
| Pretreatment NL ratio         | 0.166–681.026                | 0.265   |

**Abbreviations:** WBC, white blood cell; ALP, alkaline phosphatase.

variate analysis. Variables with a *p*-value > 0.05 were eliminated from the model. Significant associated variables from the univariate were entered in a multivariate logistic analysis using backward elimination process. Accordingly, a *p*-value of < .05 was considered significant. SPSS software, version 15.0, was used in all statistical analyses (SPSS Inc., Chicago, IL, USA).

## RESULT

Seventy-nine patients met the inclusion criterion, i.e., all had histologically confirmed urothelial carcinoma of the urinary tract. The origin site of the tumor was the bladder in 31 patients (39.2%), the ureter in 17 patients (21.5%), and the renal pelvis in 26 patients (32.9%). They were all chemotherapy-naïve patients, but four patients had received radiotherapy previously. Cancer had infiltrated the bone marrow in 14 patients before they received chemotherapy. Fourteen patients achieved a complete response (17.7%) and nine patients achieved a partial response (11.3%).

The mean age of the 79 patients was 69.2 years (range, 46–87 years). The most common chemotherapy regimen was GC (*n* = 76); only three cases received MVAC. Median overall survival was 21.7 months (range, 1–66 months). Forty-three patients were classified into the “without ≥ grade 3 neutropenia” group (54.4%) and 36 into the “with ≥ grade 3 neutropenia” group (45.6%). The latter developed ≥ grade 3 or more neutropenia during the first cycle of cisplatin-based systemic chemotherapy. Thirteen patients (16.5%) experienced grade 1 neutropenia, 20 (16.5%) experienced grade 2, 18 (22.8%) experienced grade 3, and 18 (22.8%) experienced grade 4. Of 14 patients who had bone metastasis, 13 experienced neutropenia. Six patients (42.9%) experienced grade 1 neutropenia, one (7.1%) experienced grade 2, four (28.6%) experienced grade 3, and two (14.3%) experienced grade 4. However, there was no significant difference between the without and with ≥ grade 3 neutropenia groups among patients who had bone marrow infiltration of cancer (*p* = .57).

There were significant differences between the without and with ≥ grade 3 neutropenia groups in terms of the pretreatment WBC counts (8152.97 ± 2134.27/mm<sup>3</sup> vs. 6431.67 ± 1618.40/mm<sup>3</sup>, *p* < .001), pretreatment neutrophil counts (5250.81 ± 2218.56/mm<sup>3</sup> vs. 4005.83 ± 1434.19/mm<sup>3</sup>, *p* < .001), pretreatment serum alkaline phosphatase (ALP) levels (252.9 ± 125.45 g/dL vs. 196.4 ± 77.28 g/dL, *p* = .030), and pretreatment neutrophil/lymphocyte (NL) ratio (1.3 ± 1.26 vs. 0.4 ± 0.63, *p* < .001). The complete set of results for the two groups is presented in **Table 1**. Multivariate logistic analysis identified pretreatment neutrophil counts (*P* = .012) as the only significant predictive factor for neutropenia (**Table 2**).

## DISCUSSION

Here, we showed that 45.6% of patients that underwent urologic anticancer chemotherapy experienced neutropenia of grade 3 or higher. Multivariate analysis identified pretreatment neutrophil counts as the sole independent predictor of grade 3 or higher neutropenia during the first cycle of chemotherapy. Other studies identified factors that predict subsequent complications in patients diagnosed with FN<sup>(15-17)</sup>, as well as independent predictive factors for bacteremia and sepsis.<sup>(18-20)</sup> In a previous study, we showed that pretreatment WBC counts, pretreatment neutrophil counts, pretreatment serum creatinine levels, and pretreatment serum albumin levels were significant predictive factors for neutropenia in patients with castration-resistant prostate cancer after docetaxel-based systemic chemotherapy.<sup>(21)</sup> To the best of our knowledge, the present study is the first to identify a factor that predicts the occurrence of neutropenia (grade 3 or higher) in patients with advanced urothelial cancer. Matsumoto et al. observed infectious complications in 93 patients with urologic cancer during 207 courses of anticancer chemotherapy. Thirty (14.5%) neutropenic events occurred. Risk factors were urinary diversion, hydronephrosis, and the duration of severe neutropenia (< 500/mm<sup>3</sup>).<sup>(22)</sup> Several factors increase the risk of neutropenia, including older age, advanced stage of disease, previous episodes of neutropenia, no treatment with G-CSF, lack of antibiotic prophylaxis, a low pretreatment absolute neutrophil count, diabetes, and prior chemotherapy.<sup>(11,23,24)</sup> However, these risk factors were identified in studies of hematologic malignancies, although some are applicable to patients with solid cancers. No previous study has focused on urothelial cancer patients.

Here, we found that the pretreatment neutrophil count was the only significant independent risk factor for grade 3 or higher neutropenia induced by cisplatin-based systemic chemotherapy. Further, several studies identified additional patient-related factors that, although not identified in this study, predisposed the afflicted individuals to either FN<sup>(25,26)</sup> or excessive myelosuppression.<sup>(27)</sup> These included age > 65 years, advanced disease, anemia, poor performance status, prior chemotherapy treatment, combined chemo-radiotherapy, bone marrow infiltration, and medical comorbidities (particularly renal disease). However, many of these pretreatment risk factors were identified in studies that included patients with hematological malignancies. Thus, the cogency or relevance of those factors are still questionable as to the adjuvant treatment of prostate cancer. Other studies demonstrate that the first cycle absolute neutrophil count nadir is a predictive factor for subsequent neutropenic events.<sup>(28-30)</sup> Indeed, we found similar results in the present study. There may be several reasons as to why there are differences between the results of this study and those of many previous stud-

ies. First, we examined only histologically confirmed urothelial carcinoma, whereas previous studies examined a variety of tumor types (i.e., lymphomas and solid tumors). Secondly, our cohort was relatively small (n = 79) compare to the population of patients examined in previous studies. The small sample number is a major limitation of the present study.

In cancer treatment, therapeutic strategies for cancer management keep evolving, and chemotherapy regimens continue to serve important roles. Our future work will focus on evaluating the incidence of, and factors that predispose to, FN during other types of urologic chemotherapy, and setting up further necessary guidelines for this purpose.

Due to several limitations this study had in addition to the small sample size, drawing definitive conclusions from this study would be difficult. For example, the study was performed retrospectively rather than being prospective in nature. Further, a larger study may have led use to identify other factors that can be used to predict neutropenia induced by cisplatin-based systemic chemotherapy in patients with advanced urothelial cancer. Nonetheless, in this study, the patients were treated in single, not separate, institution with a limited number of attending physicians, and follow-up periods were relatively long.

## CONCLUSIONS

In conclusion, the results of this study identified only the pretreatment neutrophil count as an independent risk factor for grade 3 or higher neutropenia induced by cisplatin-based systemic chemotherapy in Korean advanced urothelial cancer patients. This predictive factor helps better to make the therapeutic strategy during chemotherapy. For patients who have low pretreatment neutrophil counts, it is suggested that the dose of chemotherapy is reduced or prophylactic G-CSF is given to prevent severe neutropenia. To the best of our knowledge, this study first identified such a significant independent risk factor in this patient group. However, to confirm these results, a large cohort and prospective study would be required.

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