Simple predictors for the completion of scheduled gemcitabine-cisplatin regimens based on real-world urothelial cancer data

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Abstract. Gemcitabine plus cisplatin (GC) is the standard first line of chemotherapy for urothelial carcinoma. However, it is often difficult to complete scheduled GC therapy because of real-world adverse events. Therefore, the reasons behind delays, scheduled cancelations and determined predictive factors for completing scheduled GC therapy were retrospectively analyzed. Patients diagnosed with locally advanced or metastatic urothelial carcinoma from 2009 to 2020 received a 4-week GC therapy schedule in Oita University Hospital. Information was retrospectively extracted from medical records and all cycles were divided into two groups: One wherein all treatments were administered and completed on schedule and the other wherein treatment was either delayed or canceled in during the treatment schedule. Predictive factors were then statistically extracted between the two groups. In total, 70 patients received 201 cycles of a 4-week scheduled GC therapy. Of the 201 cycles, a total of 68 (33.8%) completed all scheduled treatments, while 133 (66.1%) did not complete the treatment as scheduled. In the group where administration was not completed on schedule, the factors of male, ureteral cancer, lower stage, <90% of gemcitabine and cisplatin dosage, solitary kidney, high creatinine level, low estimated glomerular filtration rate level, low platelet count and high alkaline phosphatase level at the initiation of each cycle were more significant. Additionally, the lowest anticancer drug percentage administration was on day 15. From these results, predictive factors for patients with various backgrounds who completed the scheduled 4-week GC therapy based on real-world data were identified. This information can be useful for clinical physicians when deciding the course of treatment.

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Abbreviations: GC, gemcitabine plus cisplatin

Key words: chemotherapy, cisplatin, gemcitabine, real-world data, urothelial cancer

Introduction

Gemcitabine plus cisplatin (GC) therapy is a chemotherapy frequently used to treat urothelial carcinoma, biliary tract cancer, pancreatic cancer (1) and germ cell tumors (2). Lately, immune-checkpoint inhibitors and an antibody-drug conjugate (3) were approved as next-generation urothelial carcinoma therapies. However, GC therapy is currently the standard first-line chemotherapy for urothelial carcinoma. Additionally, it provides an improved safety profile and tolerability than the combination of methotrexate, vinblastine, doxorubicin and cisplatin, with similar survival benefits (4).

In a previous clinical study (4), a favorable performance status (PS) and adequate laboratory data, including blood cell counts and renal function, were required from included patients. These patients had bladder cancer that was measurable and histologically proven as locally advanced or metastatic transitional cell carcinoma of the urothelium, excluding prior treatment with systemic therapy. Patients received gemcitabine (1,000 mg/m^2) on days 1, 8 and 15, plus cisplatin (70 mg/m^2) on day 2, based on the treatment schedule. Ultimately, the aforementioned study revealed that GC therapy had efficacy against specific patients. However, in clinical practice, GC therapy is widely used for numerous patients with various backgrounds, including the primary site, histological type, the aim of therapy, prior systemic therapy, age, PS and renal function. It is now receiving increased attention since the results of these clinical trials differ from real-world data, and yet both are the most reliable sources of evidence for research (5).

As physicians treating urothelial carcinomas, the authors have often faced the dilemma that doses defined in previous gemcitabine and cisplatin clinical trials (4) could not be provided to the patients they treat on schedule because of their backgrounds and various adverse events. There has

been no report of the details for when, which and how numerous adverse events cause delays and cancelations in GC therapy. There is also a lack of information regarding the prognoses of patients who could not complete their scheduled GC therapy. Nevertheless, it may be possible to predict whether the schedule can be completed before the start of GC therapy by clarifying which background and adverse events can affect it. The cause of delays and cancelations for the standard 4-week GC therapy schedule and predictive factors for completing the schedule were assessed retrospectively as real-world evidence.

Patients and methods

Patient studies. Urothelial carcinoma patients who were assigned the 4-week GC regimen (Oita University Hospital; Yufu, Japan) between January 2009 to December 2020 (12 years) were selected for the present study. Cases of bellini duct carcinoma and urethra adenocarcinoma were excluded because of the rarity of these tumors. Additionally, prior therapy was allowed in the present study as long as it only consisted of local intravesical therapy, radiation, or immunotherapy completed more than 4 weeks ago, adhering to the previous clinical trial (4).

The present study was conducted in accordance with ethical standards of the Declaration of Helsinki (2013 revision) and Good Clinical Practice guidelines (6). Patients received gemcitabine (Eli Lilly) (600-1,000 mg/m^2) on days 1, 8 and 15, plus cisplatin (Pfizer, Inc.) (42-70 mg/m^2) on day 2, based on the treatment schedule. Almost all factors that were assessed before the initiation of each GC course have been analyzed, regardless of whether they were related to cancer treatment in previous studies. This is because some factors such as serum lactate dehydrogenase (7) and C-reactive protein (8) are related to patient prognosis even if they are not related to cancer treatment. The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 was used to evaluate all adverse events.

Statistical analysis. Patients who completed the scheduled GC treatment were compared with patients with a delay or canceled administration in the middle of treatment. Pearson's chi-square test (or Fisher's exact test) and multifactor analyses, by SPSS version 25 (IBM Corp.), were used to analyze factors, such as blood counts and serum chemistry, at the beginning of each cycle. The logistic regression analysis (the forced entry method) was used for multifactor analyses. Statistical significance was set at $P<0.05$.

Results

Patient characteristics. Patient characteristics (including sex and age distribution; n=70) are shown in Table I. A total of 201 courses, scheduled to 70 patients, were analyzed. The median age of patients was 69 (29-87) years old. Most had a PS of 0 (91.4%), but only two patients had PSs of 2-3 (2.8%). Regarding disease breakdown, most patients had bladder cancer (66.7%), and >50% were stage IV (58.6%). A total of 74 courses (36.8%) were performed as neoadjuvant and adjuvant therapy, and 127 courses (63.2%) were for metastatic or locally advanced disease. In total, four stage I patients underwent GC therapy for recurrence with distant metastasis after primary therapy. In addition, one patient with stage II bladder cancer underwent GC therapy as neoadjuvant chemotherapy and the ypT classification was ypT1. The patient was classified as stage II due to obvious muscle-invasive cancer before neoadjuvant chemotherapy.

Table I. Patient characteristics.

Patient characteristics	Number	Percentage (%)
Sex (n=70)		
Male	54	77.1
Female	16	22.9
Median age, years (n=70)	69 (range 29-87)	
Performance status		
0	64	91.4
1	4	5.7
2	1	1.4
3	1	1.4
Diabetes		
Yes	12	17.1
No	58	82.9
Hypertension		
Yes	26	37.1
No	44	62.9
Cancer type (n=72)		
Bladder cancer	48	66.7
Ureteral cancer	15	20.8
Renal pelvic cancer	9	12.5
Stage (n=70)		
I	4	5.7
II	13	18.6
III	12	17.1
IV	41	58.6
Purpose (n=201)		
Neo-adjuvant therapy	47	23.4
Adjuvant therapy	27	13.4
Treatment for metastatic or advanced tumor	127	63.2
Outcome (n=70)		
Alive	27	38.6
Dead	36	51.4
Unknown	7	10.0
Median number of courses/persons	3 (1-9)	

Laboratory data at the initiation of each cycle showed that patients had white blood cell counts ≥2.5x10^9/l, platelet counts ≥8.8x10^9/l, hemoglobin levels ≥8.0 g/dl and creatinine clearance levels ≥40 ml/min at the initiation of each cycle (data not shown). A total of 130 cycles were given to patients with bilateral kidneys, while other cycles were not given

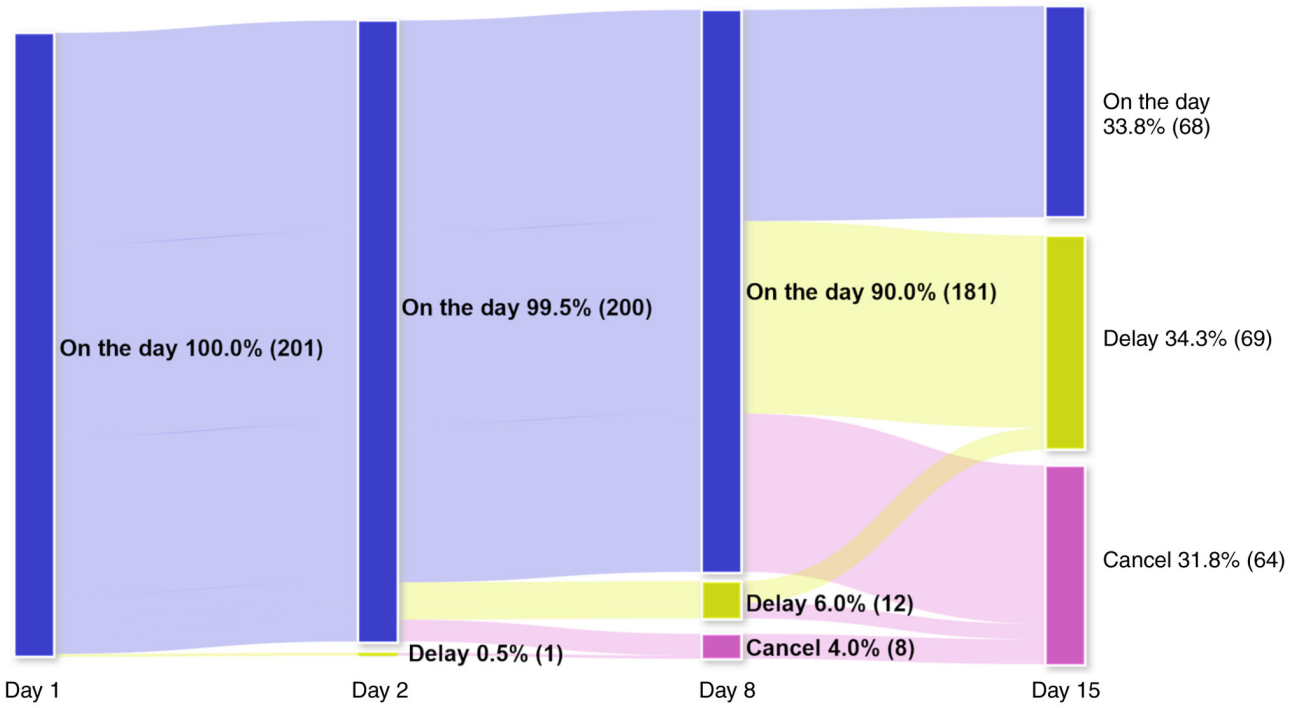

Figure 1. Sankey diagram of the distribution of the gemcitabine plus cisplatin therapy schedule. Gemcitabine was administrated on days 1,8 and 15. Cisplatin was administrated on day 2. This shows the number of cycles those could be given anticancer drug on schedule or not.

due to nephrectomy or nephroureterectomy from primary disease.

Distribution of chemotherapy schedule. Patient distributions receiving GC therapy (Figs. 1 and S1) indicated that only 68 courses (33.8%) were performed on schedule. The remaining were canceled or delayed in the middle of treatment. GC therapy was delayed and/or canceled in 1 course (0.5%) on day 2, 20 courses (10.0%) on day 8 and 133 courses (66.1%) on day 15. Day 15 had the lowest percentage of anticancer drug scheduled administration. Only 37.6% (68/181) of GC therapy courses scheduled on day 8 were performed on day 15.

Adverse events and chemotherapy schedule. Myelosuppression was the most common of all hematologic adverse events. The focus of the present study was on CTCAE grade 3 and 4 toxicities (Table II); thrombocytopenia was the most common (52 cycles, 25.9%) and neutropenia was the second (32 cycles, 15.9%) of hematologic adverse events. Febrile neutropenia was the most common of all non-hematologic adverse events. In clinical practice, heavier toxicities (>grade 3) are considered to directly prevent scheduled GC treatments.

In univariate analyses (Table III), male, ureteral cancer, lower stage (stage I/II), receiving less than 90% of the gemcitabine and cisplatin dosage, solitary kidney, high creatinine level, low estimated glomerular filtration rate (eGFR) level, low platelet count, and high alkaline phosphatase (ALP) level, at the initiation of each cycle, were significantly associated with not receiving GC chemotherapy on schedule.

In the multivariate analysis, receiving more than 90% of the cisplatin dosage and having bilateral kidneys were significant and independent factors for receiving GC chemotherapy on schedule. Age and PS were included in the analysis because they are clinically important factors in chemotherapy decision making. eGFR level is highly associated with serum creatinine, therefore, creatinine levels were adopted for this assessment, which had a higher association in Table II and is easier to use clinically. The type of cancer is highly associated with the purpose of treatment, and most neoadjuvant/adjuvant chemotherapy treatments were performed for bladder cancer. Therefore, the purpose of treatment, considered a potentially more generalizable factor (as to other cancers), was included in the analysis.

Discussion

The present study revealed several risk factors that interfered with scheduled GC therapy for urothelial carcinomas by using real-world data rather than controlled clinical trials. The data of the present study demonstrated that receiving more than 90% of the scheduled cisplatin dosage and having bilateral kidneys are the most important predictive factors. Renal function was one of the most important factors, as other renal factors such as serum creatinine and eGFR were also associated with whether scheduled GC therapy was completed. Patient conditions that allow tolerance of sufficient amounts of cisplatin may contribute to the success of receiving the complete schedule of GC therapy. The present study focused on the completion rate for each cycle of GC therapy. Patients with UC typically require 3-4 cycles of chemotherapy and the median cycles per patient of GC therapy was also 3 cycles in the present study.

In a phase III study of GC therapy reported by von der Maase *et al* (4), prior systemic chemotherapy was excluded.

Table II. Grade 3/4 adverse events by day 15.

	Grade 3		Grade 4		Grade 3/4	
Hematologic	No. of cycles	%	No. of cycles	%	No. of cycles	%
Thrombocytopenia	36	17.9	16	8.0	52	25.9
Anemia	9	4.5	0	0	9	4.5
Leucopenia	13	6.5	0	0	13	6.5
Neutropenia	20	10.0	12	6.0	32	15.9
Creatinine increased	2	1.0	0	0	2	1.0
eGFR decreased	1	0.5	0	0	1	0.5
ALT increased	0	0	1	0.5	1	0.5
Hyponatremia	1	0.5	0	0	1	0.5
Hyperamylasemia	1	0.5	0	0	1	0.5
	Grade 3		Grade 4		Grade 3/4	
Non-hematologic	No. of cycles	%	No. of cycles	%	No. of cycles	%
Febrile neutropenia	3	1.5	0	0	3	1.5
Acute upper respiratory inflammation	1	0.5	0	0	1	0.5
Gastric ulcer	0	0	1	0.5	1	0.5
Acute kidney injury	1	0.5	1	0.5	2	1.0
Allergic reaction	1	0.5	0	0	1	0.5
Urinary tract infection	1	0.5	0	0	1	0.5
Gingivitis	1	0.5	0	0	1	0.5
Fever	0	0	1	0.5	1	0.5
Headache	0	0	1	0.5	1	0.5
Pelvic infection	1	0.5	0	0	1	0.5
Pulmonary infection	1	0.5	0	0	1	0.5

eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase.

However, clinicians often encounter patients with myelosuppression caused by primary diseases and prior chemotherapy before scheduling GC therapy in the real world. Therefore, it would be necessary for clinicians to explain why patients with these risk factors may not complete their scheduled cycles on schedule. Regarding adverse events that might delay and/or lead to cancelled GC therapy, neutropenia was the most common hematologic toxicity in the previous phase III study (4), but in the present study, thrombocytopenia was the most common hematologic toxicity. In non-hematologic adverse events, nausea was the most common in the previous study (9), but febrile neutropenia was the most common in the present study.

This meant that adverse events varied between patients with the same background and good laboratory data, and patients with various backgrounds in clinical practice. Therefore, the differences between real-world data and controlled clinical trials is important information for patients and clinicians.

It was expected that patients with higher stages (stage III/IV) would not complete the scheduled GC treatment. In fact, patients with lower stages (stage I/II) were those who were unable to complete it. Stage I/II was significantly correlated with solitary kidney and abnormal renal function (serum creatinine, creatinine clearance rate and eGFR) in the present study. Patients with stage I/II tended to receive a lower dose of both cisplatin and gemcitabine compared with stage III/IV. This may have been because surgery is the main therapy for stage I/II patients and chemotherapy is the primary treatment for stage III/IV.

Myelosuppression is a very common adverse event in patients receiving chemotherapy, and thrombocytopenia was the most common hematologic adverse event in the present study (Table III). This result indicated that having a normal platelet count before initiating GC chemotherapy could enhance the likelihood of completing all scheduled cycles.

Problems related to the kidneys negatively affected GC therapy scheduling (Tables III and IV). Urothelial tumors are more likely to be associated with having a solitary kidney and high serum creatinine levels, due to the primary disease and resulting surgery, compared with other tumor regions (10). Having a solitary kidney and low eGFR-related renal dysfunction could lead to a reduced dose of cisplatin.

The present study is also consistent with another previous study that reported an association between elevated ALP

Table III. Univariate analysis based on patient characteristics. Blood exam at the initiation of each cycle and dosage of anti-cancer drugs.

Characteristics	On schedule	Not on schedule	P-value
Sex			0.024
Male	47	109	
Female	21	23	
Type of disease			0.020
Bladder cancer	42	68	
Ureteral cancer	9	41	
Renal pelvis cancer	17	23	
Diabetes			0.221
Yes	12	31	
No	55	99	
Hypertension			0.204
Yes	19	46	
No	49	86	
Purpose			0.009
NAC/AC	33	40	
Treatment	35	92	
Stage			<0.001
I/II	7	43	
III/IV	61	86	
Age			0.297
≥70	39	69	
<70	29	63	
Performance status			0.451
0	65	124	
1/2/3	3	8	
Dosage of gemcitabine			0.003
≥90%	57	85	
<90%	11	47	
Dosage of cisplatin			0.017
≥90%	53	82	
<90%	15	50	
Kidney			<0.001
Bilateral	55	75	
Solitary	11	53	
CCr (ml/min/1.73 m^2)			0.091
≥60	20	44	
<60	5	26	
Cr			0.008
Normal	52	80	
High	13	49	
eGFR			0.014
≥60	34	45	
<60	23	66	
WBC			0.669
Normal	66	128	
High	2	4	
Neutrophils			0.294
Normal	58	111	
Low	9	12	
Hb			0.448
Normal	7	16	
Low	61	116	
PLT			0.012
Normal	65	111	
Low	3	21	
Alb			0.067
Normal	7	28	
Low	47	88	
AST			0.131
Normal	63	116	
High	4	16	
ALT			0.344
Normal	65	126	
High	1	5	
ALP			<0.05
Normal	52	99	
High	4	21	
LDH			0.148
Normal	42	98	
High	14	20	
Na			0.512
Normal	55	107	
Low	12	25	
K			0.389
Normal	53	108	
Low/high	14	24	
CRP			0.403
Normal	21	40	
High	39	85	
Ca			0.339
Normal	50	98	
High	3	3	
P			0.406
Normal	27	55	
Low/high	2	7	

NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; CCr, creatinine clearance rate; Cr, creatinine; eGFR, estimated glomerular filtration rate; WBC, white blood cells; Hb, hemoglobin; PLT, platelet count; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

levels and adverse pathologic features of upper tract urothelial carcinomas (11). The present study also suggested that

Table IV. Multivariate analysis based on patient characteristics. Blood exam at the initiation of each cycle and dosage of anticancer drugs.

		95% Confidence interval		
Characteristics	Hazard ratio	Lower bound	Upper bound	P-value
Age	1.134	0.512	2.512	0.756
Sex	0.766	0.303	1.94	0.574
Performance status	1.694	0.263	10.916	0.579
Purpose	2.193	0.93	5.17	0.073
Stage	0.577	0.205	1.624	0.298
Dosage of gemcitabine	4.171	0.977	17.802	0.054
Dosage of cisplatin	4.651	21.27	1.003	0.049
Kidney	3.512	1.212	10.176	0.021
Creatinine	1.746	0.637	4.783	0.279
Platelet	2.407	0.596	9.721	0.218
Alkaline phosphatase	2.478	0.716	8.577	0.152

elevated ALP levels may be associated with the completion of chemotherapy for urothelial carcinomas.

The current study has certain limitations. First, as a retrospective study, data was collected from patient medical records and blood test results were lacking in a few patients. Hence, it is possible that not all adverse events were accounted for, particularly with low-grade non-hemorrhagic events. A second limitation is related to the focus on GC treatment schedules in each course, and that only initial laboratory data before each cycle were used for the analysis. Therefore, survival curves could not be created since most patients received multiple GC courses. Imaging tests were usually performed between every few courses; therefore, the effectiveness of each GC course individually could not be evaluated. Additionally, the present study could not show efficacy in terms of patient survival and therapy evaluations based on response criteria in solid tumors. Third, the current study focused on whether all anticancer drugs were administered on schedule during one 15-day cycle, therefore, adverse events after day 16 were not evaluated. While the anticancer drugs in the current study could be provided to patients with low-grade adverse events before day 15, any severe adverse events after day 16 could have influenced the next course of chemotherapy. Finally, the present study had a small sample size and was not randomized. Besides these limitations, there have been no other studies of real-world data on GC therapy in a scale comparable to that of the present study.

In conclusion, the present study reported how cycle percentages are completed on scheduled GC therapy, the type of adverse events that prevented it, and predictors that aided in the completion of the schedule against various patient backgrounds. This evidence has been disseminated to clinicians in this field to recognize the difference between clinical trials and real-world situations. In addition, based on real-world data, predictive factors for patients with various backgrounds who completed the scheduled 4-week GC therapy have been identified. This information can be productive for clinical physicians to decide the course of treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MS, SH, HM and ToS contributed to the concept and design of the present study. MS, TI, TaS and TA contributed in the data collection. MS and SH contributed to the analysis and interpretation of data and all authors confirm the authenticity of all the raw data. MS, SH and ToS drafted the article. All authors critically revised the article for important intellectual content. HM and ToS provided administrative, technical and material support. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the of Oita University (approval no. 2358; Oita, Japan). All study participants provided informed consent (or a formal waiver of consent). Informed consent was obtained in the form of opt-out on the website (https://oita-urol.jp/exam/).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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