

Impact of relative dose intensity in gemcitabine–cisplatin chemotherapy for metastatic urothelial carcinoma

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Abstract

Objectives: To evaluate the impact of relative dose intensity for gemcitabine–cisplatin chemotherapy in patients with metastatic urothelial carcinoma.

Methods: We retrospectively reviewed the medical records of 18 patients with metastatic urothelial carcinoma, who received gemcitabine–cisplatin regimen as the first-line chemotherapy between 2009 and 2015. The doses of gemcitabine and cisplatin were reduced or the intervals between treatment cycles were prolonged according to the treatment efficacy and adverse events during the first and second cycles. The individually optimal relative dose intensity was set as the actual dose per the standard dose in the first and second cycles. From the third course onward, patients received the gemcitabine–cisplatin chemotherapy with the same relative dose intensity. Overall survival was compared with the groups according to the value of relative dose intensity.

Results: The median age was 72.5 (range, 56–79) years and 15 men and 3 women were enrolled in the study. The median number of cycles of first-line gemcitabine–cisplatin chemotherapy was 8 (range, 2–17), and the median survival time from initiation of first-line chemotherapy was 20.1 (range, 3.5–32.8) months. The total median relative dose intensity of gemcitabine–cisplatin chemotherapy was 56.1%. The median survival time of 10 patients in the group with the relative dose intensity of less than 60% was significantly longer than that of 8 patients in the group with the relative dose intensity of more than 60% (19.2 and 11.0 months, respectively, $p=0.04$).

Conclusion: Individual low relative dose intensity management in the first-line gemcitabine–cisplatin chemotherapy may be an acceptable option for patients with metastatic urothelial carcinoma.

Keywords

Metastatic urothelial carcinoma, relative dose intensity, urology, chemotherapy, dose reduction

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Introduction

Metastatic urothelial carcinoma (UC) is rarely curable and its prognosis remains poor. Approximately 10% of patients with UC already have metastatic disease at the time of diagnosis,¹ requiring systemic chemotherapy. For UC, cisplatin (CDDP)-based chemotherapy regimens, such as methotrexate/vinblastine/adriamycin/cisplatin (MVAC) and gemcitabine–cisplatin (GC), are currently effective first-line regimens, because these regimens were reported to prolong the median survival of advanced UC up to 14.8 and 13.8 months, respectively.² However, systemic chemotherapy with CDDP-based regimens has been traditionally restricted to a limited number of chemotherapy cycles

because of toxic adverse events.^{1,3} In fact, regimens for locally advanced or metastatic UC with GC and MVAC are usually suspended within six cycles.^{4,5} Long-term duration is an important issue for those regimens because outcomes in patients with metastatic UC are mainly dependent on the response to the first-line chemotherapy.⁶

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One feature in patients with metastatic UC is advanced age, which induced severe organ damage leading to an impediment to full dose of chemotherapy. Therefore, dose reduction in chemotherapy is often an option to reduce adverse events; however, it may have a disadvantage for patients due to limited efficacy. If both efficacy and safety can be achieved with dose adjustment, long-term maintenance with lower-dose chemotherapy could be an option to secure long-term survival and quality of life.⁷

Relative dose intensity (RDI) is the ratio of the actually delivered dose intensity of chemotherapy to the standard dose intensity, which reflects the process to reduce adverse events.⁸ Several studies on malignant lymphoma and breast cancer have shown that patients receiving chemotherapy in the curative setting at higher RDI had better clinical outcomes than those at lower RDI.^{8,9} However, the impact of RDI in metastatic UC remains unclear, and to the best of our knowledge, few previous studies have addressed this issue.

In this study, we established the significance of RDI in GC chemotherapy for metastatic UC.

Study design and patients

The internal ethics review board of Shizuoka General Hospital approved this study. Patients with unresectable metastatic UC between April 2009 and December 2015, who were treated at our institution, were evaluated. Blood examinations were performed within 2 weeks before beginning chemotherapy. Body surface area was calculated using the Mosteller formula. Cases of non-UC and recurrence cases after total cystectomy or nephroureterectomy were excluded. The charts of included patients were reviewed retrospectively.

In the original regimen, GC consisted of 1000 mg/m² gemcitabine on days 1, 8, and 15 and 70 mg/m² cisplatin on day 2 of a 28-day cycle.² Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (ver. 4.0).¹⁰ If Grade 2 or higher adverse events were observed, the dose reduction of GC chemotherapy was controlled to be within grade 1 adverse events in the next cycle. Even if within the grade 2 adverse events, gemcitabine on days 8 or 15 was omitted according to patient's demand for the quality of life. Subsequent therapy was determined according to the response or adverse events during the first and second treatment cycles. Tumor size and new lesions were measured on computed tomography (CT) scans at baseline and every two or three cycles. Responses were evaluated by the New Response Evaluation Criteria in Solid Tumors: Revised RECIST guidelines (ver. 1.1). If the response was stable disease (SD) or a favorable response such as a partial response (PR) or a complete response (CR), the same regimens were continued without RDI modification until disease progression, occurrence of unacceptable toxicity, or a patient's request for suspension of the treatment. If the response was progressive disease (PD) or the development of any new lesion was observed, chemotherapy was ended followed by best supportive care (BSC) or other chemotherapy regimens.

There was no re-challenge of GC chemotherapy with increased RDI. Second- and third-line chemotherapies were methotrexate, epirubicin, and cisplatin (MEC); gemcitabine and carboplatin (GCa); gemcitabine and paclitaxel (GT); or paclitaxel, ifosfamide, and nedaplatin (TIN).^{11–15}

We calculated RDI by averaging the RDI of all individual agents within a regimen, according to previous studies.^{16,17} The RDI of omitted cases was calculated as follows: if a patient received a full dose of GC chemotherapy on days 1 and 2, and which was then omitted on days 8 and 15, that patient was administered the full dose of cisplatin and a 33% dose of gemcitabine, resulting in RDI of 66.7%. The RDI of extended cases was calculated as follows: if a patient received a full dose of GC chemotherapy on days 1, 2, 8, and 15 and the interval to the next GC treatment cycle was extended by 1 week, it means that treatment took 5 weeks and the RDI was 80%. Age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), primary origin, metastatic sites, serum creatinine, creatinine clearance, duration of chemotherapy, median survival time, and adverse events were assessed. The impacts of the RDI for the first and second cycles of GC treatment (low RDI; less than 60% vs high RDI more than 60%) on overall survival were analyzed.

The non-parametric Mann–Whitney U-tests were performed for continuous variables and chi-square tests were performed for categorical variables to compare groups. The duration of survival was calculated from the initiation of first-line chemotherapy to the date of death or the last follow-up. Survival rate curves were constructed using the Kaplan–Meier method. The log-rank test was used to test associations between chemotherapy and survival. A p-value of less than 0.05 was considered statistically significant.

Results

There were 54 patients with unresectable metastatic UC. Of them, 31 selected BSC without surgery or systemic chemotherapy, and 5 patients who were unfit for CDDP because of renal insufficiency underwent other chemotherapy regimens. Thus, 18 patients who were treated with GC for the first-line chemotherapy were enrolled in this study.

Patient characteristics are shown in Table 1. The median age was 72.5 (range, 56–79) years and their ECOG-PS 0/1/2 score distribution was 16/2/0. There were 15 male patients and 3 female patients. The primary cancer origin was the renal pelvis in 3 (16.7%) patients, the ureter in 4 (22.2%), and the urinary bladder in 11 (61.1%). Lymph node, pulmonary, hepatic, osseous, and cerebral metastases were observed in 14 (77.8%), 5 (27.8%), 3 (16.7%), 3 (16.7%), and 1 (5.6%) patient, respectively. Moreover, 6 (33.3%) patients had decreased renal function, with a creatinine clearance <60 mL/min. The median cycles of GC treatment were 8 (range, 2–17) cycles, and the median RDI was 56.1%. The median survival from initiation of GC treatment was 20.1 months (Figure 1). Survival rates at 12, 24, and 36 months were 71.8%, 36.3%, and 14.5%, respectively. The median survival

Table 1. Characteristics of patients with metastatic UC receiving first-line GC chemotherapy.

		No.	(%)
Age		72.5 (56–79) ^a	
Sex	Male	15	83.3
	Female	3	16.7
ECOG-PS	0	16	88.9
	1	2	11.1
	2	0	0
Origin	Renal pelvis	3	16.7
	Ureter	4	22.2
	Bladder	11	61.1
Metastatic sites	Lymph node	14	77.8
	Lung	5	27.8
	Liver	3	16.7
	Bone	3	16.7
	Brain	1	5.6
Creatinine clearance (mL/min)		65.5 (44.6–126.2) ^a	
GC Cycles		8 (2–17) ^a	
RDI of GC		56.1 (39.7–97.0) ^a	

UC: urothelial carcinoma; GC: gemcitabine–cisplatin; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; RDI: relative dose intensity.

^aMedian (range).

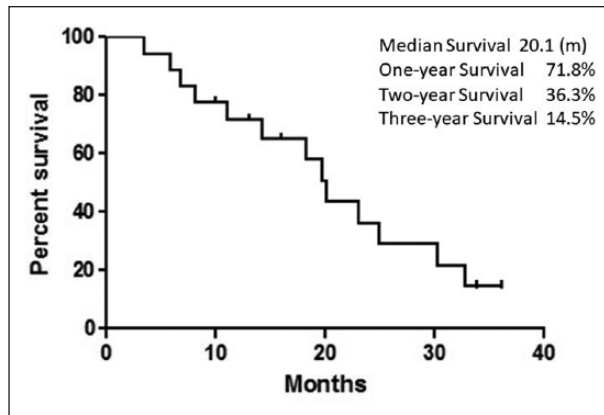


Figure 1. Survival outcomes of all patients with metastatic UC who underwent first-line GC chemotherapy.

in patients with urinary bladder cancer was 19.7 months and that in upper urinary tract cancer was 20.1 months, showing no significant difference. Two (11.1%) patients were still on GC chemotherapy at the last follow-up, 12 (66.7%) patients had switched to second-line chemotherapy, and 4 elected to undergo BSC. Second-line chemotherapies were GT in 8 (44.4%) patients, MEC in 3 (16.7%), and GCa in 1 (5.6%). Third-line chemotherapies were TIN in 3 (16.7%) patients and GCa in 1 (5.6%).

Figure 2 shows the duration of GC, second-line and third-line chemotherapies, and BSC in each of the 18 cases. The median duration of GC chemotherapy and subsequent regimens were 8.8 and 1.9 months, respectively.

Adverse events at the time of the first and second treatment cycles of GC chemotherapy are shown in Table 2. Grade 3 hematological adverse events at the time of first or second

treatment cycle were observed in three (17%) patients, but no other Grade 3 adverse events were observed. Although approximately two-thirds of patients showed Grade 1 or 2 hematological toxicities, they were successfully treated with blood transfusions, granulocyte-colony stimulating factor, and/or omitting day 8 or day 15 of administration. All of the gastrointestinal symptoms were transient. There was no adverse event of peripheral neuropathy in this study population. From the third cycle of GC treatment, there was one patient who suffered a Grade 2 drug eruption and could not continue the GC treatment, and there were four (25%) patients who had hematological toxicity or gastrointestinal Grade 1 adverse events, but no Grade 2 or more adverse events.

Since the median RDI was 56.1%, it was analyzed in two groups of less than 60% RDI (low RDI group) and more than 60% RDI (high RDI group) in the first and second cycles of GC treatment. In total, 10 patients underwent GC with low RDI and 8 patients with high RDI. There was a significant difference in survival between these two groups (median survival; 19.2 months in low RDI group, 10.5 months in high RDI group; $p=0.04$, Figure 3). The patient characteristics of the two groups are shown in Table 3. There were no differences between them regarding sex, age, or origin. In GC cycles, there was an increasing trend in cycles in the group with low RDI, but the difference was not significant.

Discussion

Our study revealed two important points: namely, the low tolerability of the GC regimen due to adverse events and a prolonged survival rate in the low RDI group. The interesting point is the latter, because several studies for other cancers have shown controversial data indicating

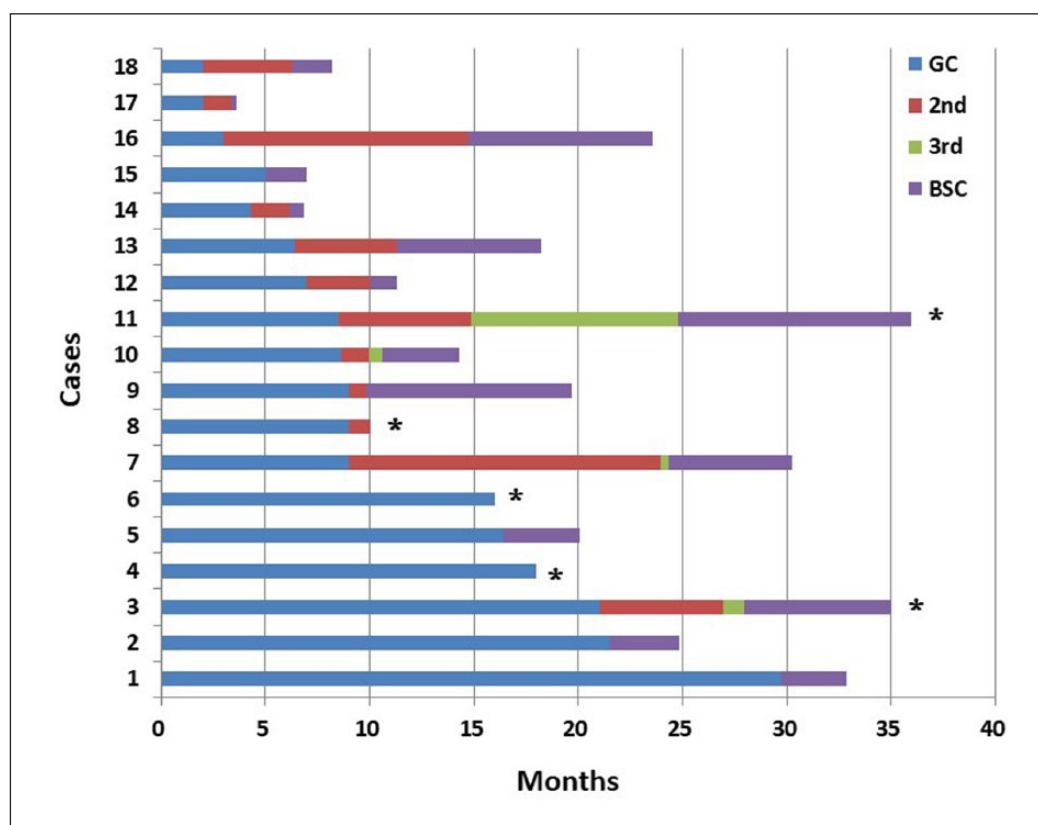


Figure 2. Duration of GC, second-line and third-line chemotherapies, and BSC in 18 patients. Median duration of GC chemotherapy and second-line plus third-line chemotherapy were 8.8 and 1.9 months, respectively. *Ongoing.

Table 2. Adverse events at the time of the first and second treatment cycles of GC chemotherapy.

	Hematological toxicity	Renal dysfunction	Gastrointestinal symptoms	Liver dysfunction	Infection	Peripheral neuropathy	Dermatitis
G1	3 (16.7)	2 (11.1)	9 (50.0)	1 (5.56)	1 (5.56)	0	1 (5.56)
G2	8 (44.4)	1 (5.56)	2 (11.1)	0	1 (5.56)	0	0
G3	3 (16.7)	0	0	0	0	0	0
G4	0	0	0	0	0	0	0

G: grade of the adverse event.
Values are shown as N (%).

prolonged survival rates in higher RDI groups.¹⁸ One study for early-stage breast cancer showed that RDI equal to or more than 85% was associated with longer disease-free survival and overall survival.¹⁹ Another study for diffuse large B-cell lymphoma showed that average RDI more than 90% was associated with longer overall survival.²⁰ The purpose of systemic chemotherapy in unresectable metastatic cancer excluding testicular cancer is not to cure but to control disease, so it is quite different from that of adjuvant chemotherapy for early-stage cancer. Our data suggest the possibility that chemotherapy with low RDI may be beneficial in the maintenance of unresectable metastatic cancer.

The major concern is that dose reduction of GC chemotherapy might easily shorten the prognosis for patients with metastatic UC. Von der Maase et al. reported that the median overall survival in the GC treatment group for advanced or metastatic UC was 10.3 months.² Phase II studies of GC treatment for advanced UC showed that the median survival with visceral metastases was 9.9 months.²¹ On the other hand, Kaufman et al.²² reported that the median overall survival was 14.3 months, but 35 of 164 CDDP doses and 146 of 487 gemcitabine doses were reduced or omitted. Survival in our study seemed to be longer than that in these previous studies. In addition, our data indicated that number of regimen cycles was more in the low RDI than high RDI group.

Taking these data into account, a low RDI, leading to more cycles, might contribute to an improvement in the prognosis of patients with unresectable metastatic UC.

Individual dose management with optimal balance of acceptable adverse events and cancer control is desirable for unresectable UC.

One study that attempted to clarify the optimal RDI for unresectable metastatic UC demonstrated that low-dose GCa chemotherapy following first-line chemotherapy could be beneficial in terms of reducing severe adverse events, minimizing hospitalization, and maintaining quality of life for patients with unresectable metastatic UC.⁷ Their protocol of low-dose maintenance GCa chemotherapy consisted of a 50% dose of gemcitabine and a 66.7% dose of carboplatin in

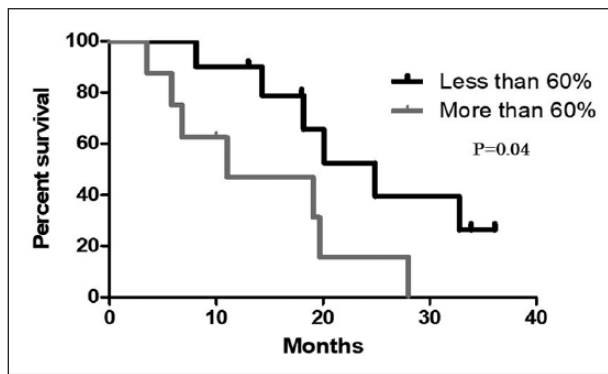


Figure 3. Survival curve of the two groups. A group of patients receiving GC chemotherapy with less than 60% of RDI at the first and second course GC chemotherapy, and the other group received that of more than 60% of RDI.

a 42-day cycle, indicating that the actual RDI was 30.6%. Their study protocol with dose adjustment was quite different from ours because the administered dose was set in each case in our study. In their study, median survival from initiation of first-line chemotherapy was about 12 months but it included a median 2 months of first-line chemotherapy, indicating shorter survival than our results. Reduction in RDI could lead to pursuing chemotherapy in patients with severe adverse events, but excessive reduction might diminish the effects of cancer control and decrease survival time. Therefore, it is important to adjust optimal RDI individually and a balance in the treatment effects and adverse events should be considered in the setting of RDI. Sufficient RDI should be evaluated in the future study.

In our study, a standard GC regimen chemotherapy showed low tolerability because severe adverse events were observed in the first or second cycle of the non-adjusted GC regimen. However, these severe adverse events during the first and second cycle were controlled with dose adjustment since the third cycle. For gemcitabine, the omitted dose on day 8 or day 15 improved the hematological toxicity. For CDDP, reduction in single doses and extension of the course interval averted neurotoxicity. Thus, a higher rate of severe adverse events in the GC regimen might result in lower RDI. Our data suggest the importance of controlling severe adverse events in the first and second cycles of the GC regimen in setting the optimal RDI.

This study had several limitations. First, the population was very small and non-randomized study. We have to admit that this report only states a preliminary result and it is difficult to reach definitive conclusions from our data, as there were a limited number of cases available at the

Table 3. Characteristics of patients receiving GC chemotherapy with less than 60% of RDI at the first and second course GC chemotherapy and more than 60% of RDI.

		Less than 60%	More than 60%	p
		N = 10	N = 8	
RDI	(%)	46.9 (24.3–59.6) ^a	68.4 (61.1–91.0) ^a	
Sex	Male	9	6	0.40
	Female	1	2	
Age	Median	74 (59–79) ^a	66 (56–77) ^a	0.17
Creatinine clearance (mL/min)	Median	65.4 (56–83) ^a	68.4 (44.6–126.2) ^a	0.21
PS	Median	0 (0–1)	0 (0–1)	0.80
Origin	Upper tract	2	5	0.07
	Bladder	8	3	
Metastatic sites	Lymph node	8 (80) ^b	6 (75) ^b	0.85
	Lung	3 (30) ^b	2 (25) ^b	
	Liver	2 (20) ^b	1 (12.5) ^b	
	Bone	1 (10) ^b	2 (25) ^b	
	Brain	0 (0) ^b	1 (12.5) ^b	

GC: gemcitabine–cisplatin; RDI: relative dose intensity; PS: performance status.

^aMedian (range).

^bNumber (%).

time we executed our study. However, our study showed that dose reduction in the GC regimen could have the possibility of few disadvantages and some benefit. Further studies with large population are necessary to establish the advantage of lower RDI in the GC regimen. Second, there was no comparison with other protocols with dose adjustment, such as GCa or MVAC treatment. Dose adjustment depends on adverse events in each regimen. Thus, it is possible that higher RDI might be better for other regimens with a lower rate of adverse events. Third, there are variations in the ways to estimate RDI. Some studies have calculated RDI for a selected agent and then averaged the RDI of individual agents within a regimen.¹⁵ Other studies have calculated RDI for all agents within the regimen and estimated the dose intensity according to standard protocols.¹⁸ We used the latter method to estimate the actual dose intensity of all individual agents according to the previous studies,^{7,8} but conclusions might differ with the different ways to calculate RDI.

We showed the possibility of some benefits with low RDI of the GC regimen for metastatic UC. Outcomes in patients with metastatic UC are dependent on a good response to first-line chemotherapy and prolonged duration of first-line chemotherapy.⁷ In future studies, it will be important to investigate how low RDI is acceptable in the GC regimen for prognosis of unresectable metastatic UC and to standardize RDI calculations on the impact of maintaining planned dose intensities.

Conclusion

Although the small sample size and retrospective design were major limitations of this study, low RDI for GC chemotherapy is high tolerability and may be beneficial in the maintenance of metastatic UC.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the review board of Shizuoka General Hospital. Ethics approval number: 14-09-34.

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Informed consent

Verbal informed consent was obtained from legally authorized representatives before the study. Since it was retrospective and nonrandomization study, and most patients died at the time of the analysis, it was judged that written informed consent was unnecessary by the review board of Shizuoka General Hospital.

Trial registration

This study was not registered because it was retrospective study and unrandomized clinical trial.

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