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Clinical impact of standardized creatinine on dose adjustment of capecitabine

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ABSTRACT

Although the Cockcroft-Gault equation is still used for the dose adjustment of many drugs that have been approved prior to creatinine standardization, the clinical impact of standardized creatinine in the dose adjustment of capecitabine is poorly understood. We focused on patients with borderline renal function and evaluated the tolerability and safety of capecitabine in patients who received capecitabine plus oxaliplatin (Cape-Ox). We retrospectively identified patients with resected colorectal cancer who had received adjuvant therapy with Cape-Ox regimen. Creatinine clearance (CrCL) was calculated by the Cockcroft–Gault equation with standardized creatinine measured using enzymatic methods, and adjusted CrCL was estimated by adding 0.2 (mg/dL) to the serum creatinine in the equation. We defined patients with "pseudo-normal" renal function as those who had an adjusted CrCL of ≤50 mL/min in patients with normal renal function (CrCL >50 mL/min). We evaluated the tolerability and grade 2 or severer adverse events of capecitabine treatment. One hundred four patients had normal and 10 had impaired renal function (CrCL <50 mL/min). Among the 104 patients with normal renal function, 23 (22.1%) had pseudo-normal renal function. Seventeen patients completed the eight cycles of Cape-Ox therapy without treatment delay or dose reduction, and all of them had truly normal renal function. The patients with pseudo-normal renal function were more likely to have grade 2 or severer thrombocytopenia than those with truly normal renal function. We should recognize correctly the clinical impact of standardized creatinine in the treatment of borderline renal function with Cape-Ox regimen in patients.

Keywords: capecitabine, creatinine clearance, renal function

Abbreviations:
CrCL: creatinine clearance
Cape-Ox: capecitabine plus oxaliplatin

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INTRODUCTION

Adjustment of the starting dose of anticancer drugs is the mainstay of oncology practice. In particular, when treating patients who have impaired renal function with renally cleared drugs, the starting dose is usually reduced on the basis of the patient's renal function. The Cockcroft-Gault equation is a simple equation for estimating creatinine clearance (CrCL) using serum creatinine and, this equation has long been the standard for assessing renal function in drug development as well as in clinical practice.[1] The equation is still involved in the interpretive criteria and dose adjustment in the package inserts of many drugs that are cleared by the kidneys.

Creatinine measurement has been standardized in the United States (US) and Japan.[2,3] Prior to creatinine standardization, a traditional colorimetric assay with the Jaffe reaction was used to measure serum creatinine and accordingly in the development of the Cockcroft-Gault equation. Whereas, in Japan, the enzymatic method is used to measure serum creatinine. It has been reported that the level of creatinine measured using the Jaffe method is approximately 0.2 mg/dL higher than that measured through the enzymatic method.[4] At present, because the old assay is no longer used, estimating glomerular filtration rate (eGFR) with standardized serum creatinine has been substituted for the Cockcroft-Gault equation in the past few decades. Although the Cockcroft-Gault equation with standardized creatinine should not be used to estimate CrCL in theory, the Cockcroft-Gault equation is still used for the dose adjustment of many drugs that were approved before creatinine standardization. Fortunately, whether or not standardized creatinine is used, a discrepancy in estimated CrCL that occurred with various assays was negligible for dose adjustment in most patients and with most drugs.[5] However, little is known about the impact of standardized creatinine on treatment with drugs that have a narrow therapeutic index such as anticancer drugs, which might cause unexpected severe toxicity when given even in a small overdose.

Capecitabine is an oral fluoropyrimidine that is designed to be finally metabolized to an active metabolite, 5-fluorouracil (5-FU), and is commonly used to treat breast, colorectal, and gastric cancers. Because of a higher incidence of adverse events in patients with renal impairment in previous studies, the package insert of capecitabine recommends a 25% reduction in the starting dose for patients with moderate renal impairment (baseline CrCL= 30 to 50 mL/min).[6] Surprisingly, the clinical impact of standardized creatinine in the dose adjustment of capecitabine is poorly understood. In particular, patients with renal function on the borderline between normal (CrCL >50 mL/min) and impaired (CrCL ≤50 mL/min) might suffer from unnecessary toxicity due to overdosing. In this analysis, focusing on patients with borderline renal function, we evaluated the tolerability and safety of capecitabine in patients with resected colorectal cancer who had received adjuvant treatment with capecitabine plus oxaliplatin (Cape-OX).

MATERIALS AND METHODS

Patients and treatment

We retrospectively identified Japanese adult (aged >20 years) patients with resected colorectal cancer who had consecutively received adjuvant treatment with a Cape-OX regimen in our university hospital between July 2014 and December 2018. The protocol has been approved by the institutional ethics committee (approval number 2020-0619). Any patients with a performance status of 2 or worse were excluded. The Cape-OX therapy consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1,000 mg/m^2 twice daily from days 1 to 14, every 3 weeks for a total of eight cycles.[7,8] Patients generally received dexamethasone and

a serotonin receptor 5-HT3 antagonist as antiemetic prophylaxis. Adverse events were assessed at baseline and at each visit for treatment (usually every 3 weeks) after starting Cape-Ox therapy according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0.

Assessment of patient's renal functions

CrCL (mL/min) was calculated by the Cockcroft-Gault equation with standardized creatinine measured using an enzymatic method, and adjusted CrCL was estimated by adding 0.2 (mg/dL) to serum creatinine in the equation.[9]

$$\text{CrCL (mL/min)} = \frac{\text{weight (kg)} \times \{140 - \text{age (years)}\}}{72 \times \text{serum creatinine}} \ (\times 0.85 \text{ if female})$$

$$\text{Adjusted CrCL (mL/min)} = \frac{\text{weight (kg)} \times \{140 - \text{age (years)}\}}{72 \times (\text{serum creatinine} + 0.2)} \ (\times 0.85 \text{ if female})$$

In this analysis, we defined patients with "pseudo-normal" renal function as those who had an adjusted CrCL of ≤50 mL/min among patients who had normal renal function (CrCL >50 mL/min). These patients had apparently normal renal function (CrCL >50 mL/min), but had an adjusted CrCL of ≤50 mL/min, estimated by adding 0.2 (mg/dL) to the standardized serum creatinine level in the Cockcroft-Gault equation. If patients with pseudo-normal renal function had received capecitabine treatment prior to creatinine standardization, the starting dose of capecitabine should have been reduced by 25% according to the recommendation in package inserts.

Statistical analysis

We evaluated the tolerability and adverse events of capecitabine treatment by assessing whether patients who had treatment delay or dose reduction owing to adverse events, completed the eight cycles of adjuvant Cape-Ox therapy with or without treatment delay or dose reduction, and had grade 2 or severer adverse events. All statistical analyses were performed using EZR software version 1.33 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). *P* values of <0.05 were considered to indicate statistical significance.

RESULTS

Baseline clinical characteristics

We identified a total of 114 patients, comprising 104 patients with normal renal function (CrCL >50 mL/min) and 10 with impaired renal function (CrCL <50 mL/min). Among the 104 patients with normal renal function, 23 patients (22.1%) had pseudo-normal renal function (adjusted CrCL <50 mL/min) with the non-adjusted CrCL ranging from 50.9 to 65.6 mL/min. All patients had a performance status of 0 or 1 (Table 1).

Table 1 Baseline clinical characteristics

		Total n= 114	Truly normal n= 81	Pseudo-normal n= 23	Impaired n= 10
CrCL (mL/min)	median	76.5	89.5	57.2	44.9
	range	36.6–172.9	62.8–172.9	50.9–65.6	36.6–49.2
Adjusted CrCL (mL/min)	median	60.7	68.2	44.8	37.7
	range	31.0–134.0	50.2–134.0	39.3–49.8	31.0–41.1
Sex (male / female)		66 / 48	49 / 32	10 / 13	7 / 3
Age (years)	median	64	61	68	73
	range	25–80	25–80	61–78	42–80
Body weight (kg)	mean ± SD	55.9 ± 10.4	58.6 ± 10.2	49.7 ± 8.3	48.0 ± 5.7
Total dose oxaliplatin (mg/m^2)	median	839	881	610	454
	range	126–1067	127–1067	127–1023	126–1038

CrCL: creatinine clearance
SD: standard deviation

Tolerability

Among the 23 patients with pseudo-normal renal function, the initial dose of capecitabine was reduced in one patient (Table 2). The other 22 patients (95.7%) received the standard dose initially, but all underwent treatment delay or dose reduction during the entire treatment owing to adverse events. The 23 patients with pseudo-normal function were slightly lower the completion rates of eight cycles of Cape-OX therapy (56.5%) than 81 patients with truly normal renal function (75.3%), but there was no significant difference. The rate of treatment delay or dose reduction were similar in patients with pseudo-normal renal function (82.6%) and those with truly normal renal function (70.4%).

Overall, 17 patients completed the eight cycles of Cape-Ox therapy without treatment delay or dose reduction, and all of them had truly normal renal function. The patients with pseudo-normal renal function and impaired renal function didn't continue the eight cycles of Cape-Ox therapy without treatment delay or dose reduction.

Table 2 Tolerability of capecitabine treatment according to renal function

	Total n= 114	Truly normal n= 81	Pseudo-normal n= 23	Impaired n= 10	*P* value [a]
Initial dose reduction (%)	10 (8.8)	1 (1.2)	1 (4.3)	8 (80.0)	0.395
Treatment delay or dose reduction (%)	84 (73.7)	57 (70.4)	19 (82.6)	8 (80.0)	0.296
Completed eight cycles of Cape-OX (%)	79 (69.3)	61 (75.3)	13 (56.5)	5 (50.0)	0.116
Completed eight cycles of Cape-OX without treatment delay or dose reduction (%)	17 (14.9)	17 (21.0)	0 (0)	0 (0)	0.021*

[a]: *p* values as calculated by Fisher's exact test (Truly normal vs Pseudo-normal)
P values of < 0.05 are considered to indicate statistical significance and are flagged with one asterisk (*).

Adverse events

The patients with pseudo-normal renal function were more likely to have grade 2 or severer thrombocytopenia than those with truly normal renal function (Table 3). No apparent differences were detected in the severity or frequency of other adverse events between patients classified according to renal function.

Table 3 Grade 2 or worse adverse events of capecitabine treatment according to renal function

	Total n= 114		Truly normal n= 81		Pseudo-normal n= 23		Impaired n= 10		*P* value [a]
	≥ grade 2	≥ grade 3	≥ grade 2	≥ grade 3	≥ grade 2	≥ grade 3	≥ grade 2	≥ grade 3	
All (%)	106 (93.0)	53 (46.5)	75 (92.6)	35 (43.2)	21 (91.3)	14 (60.9)	10 (100.0)	4 (40.0)	1.000
Leukopenia (%)	42 (36.8)	1 (0.9)	28 (34.6)	0 (0)	13 (56.5)	1 (4.3)	1 (10.0)	0 (0)	0.089
Neutropenia (%)	70 (61.4)	30 (26.3)	51 (63.0)	23 (28.4)	14 (60.9)	7 (30.4)	5 (50.0)	0 (0)	1.000
Thrombocytopenia (%)	33 (28.9)	4 (3.5)	19 (23.5)	2 (2.5)	11 (47.8)	2 (8.7)	3 (30.0)	0 (0)	0.037*
Anemia (%)	11 (9.6)	4 (3.5)	7 (8.6)	1 (1.2)	3 (13.0)	2 (8.7)	1 (10.0)	1 (10.0)	0.688
AST/ALT increased (%)	11 (9.6)	7 (6.1)	8 (9.9)	4 (4.9)	2 (8.7)	2 (8.7)	1 (10.0)	1 (10.0)	1.000
Blood bilirubin increased (%)	11 (9.6)	0 (0)	11 (13.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.117
Palmar-plantar erythrodysesthesia (%)	15 (13.2)	2 (1.8)	14 (17.3)	2 (2.5)	1 (4.3)	0 (0)	0 (0)	0 (0)	0.181

[a]: *p* by Fisher's exact test (AEs ≥ grade 2, Truly normal vs Pseudo-normal)

P values < 0.05 are considered statistically significant and are flagged with one asterisk (*).

AEs were evaluated using the CTCAE ver. 4.0.

AEs: adverse events

AST: aspartate aminotransferase

ALT: alanine aminotransferase

DISCUSSION

The patients with pseudo-normal renal function in this analysis appeared to be unable to tolerate eight cycles of adjuvant Cape-OX therapy with the standard dose of capecitabine. All the patients with pseudo-normal renal function ultimately required treatment delay, dose reduction or interruption, and frequently experienced grade 2 or severer adverse events, such as thrombocytopenia, as compared with patients who had truly normal renal function. The patients with pseudo-normal renal function couldn't identify with the patients with truly normal renal function. These findings suggest that patients with pseudo-normal renal function should receive capecitabine in the same way as those with impaired renal function; they require reduction of the starting dose. Given that the completion rate of eight cycles of the adjuvant treatment was similar in patients with pseudo-normal and those with truly normal renal function, an appropriate reduction in the starting dose is absolutely essential to avoid unnecessary toxicity and complete the planned adjuvant treatment in patients with pseudo-normal renal function.

Creatinine standardization has progressed firstly in the field of nephrology to normalize the diagnosis of chronic kidney disease. In the US, under the Creatinine Standardization Program led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The clinical laboratories switched to standardized methods using Isotope Dilution Mass Spectrometry (IDMS) or those traceable to IDMS by the end of 2010.[2] In Japan, enzymatic methods with calibration traceable to IDMS have replaced the old colorimetric assays since the middle of the 1990s.[3] Unfortunately, because creatinine standardization is not well known in the field of clinical oncology, most oncologists and pharmacists involved in cancer chemotherapy did not recognize the impact of creatinine calibration until recently. The dose of carboplatin, a platinum-based anticancer drug used to treat many types of cancer, is usually determined on the basis of a patient's GFR to achieve the target area under the plasma concentration-time curve: dose (mg) = target AUC (mg⁄mL × min) × [GFR (mL⁄min) + 25].[3] The GFR in the formula is usually replaced by CrCL in practice for convenience. However, because standardized serum creatinine is lower by 0.1 to 0.3 mg/dL than that measured with obsolete methods, the dose of carboplatin is overestimated when CrCL is calculated with standardized serum creatinine, potentially leading to unneeded toxicity. In 2010, the US Food and Drug Administration and Gynecologic Oncology Group alerted investigators who were participating in clinical trials of carboplatin that the incidence of carboplatin-related toxicity increased after the introduction of standardized creatinine.[10]

One limitation of this analysis is its retrospective single-institution design. Of the 114 patients, 35 (30.7%) did not complete the planned eight-cycle treatment and 84 (73.9%) required treatment delay or dose reduction, which is comparable to the findings of a pivotal study of adjuvant chemotherapy with Cape-Ox; in which 31% did not receive the complete planned treatment, and 30% and 56% required dose reduction and treatment delay, respectively.[7] Therefore, we consider that the treatment given to the patients in this analysis is fairly representative of standard practice. In addition, the relative dose intensity of capecitabine could not be calculated because of retrospective study. The dose reduction might reduce treatment intensity, but the patients with pseudo-normal renal function complete the treatment by dose reduction. So that, we thought that the risk of recurrence could be reduced. In a future prospective study, we should increase the sample size and evaluate the therapeutic efficacy of Cape-OX using overall survival and/or progression-free survival.

Another limitation is that the tolerability and safety of capecitabine could not be completely separated from those of oxaliplatin. There were no patients with CrCL <20 mL/min who should be treated with a reduced dose of oxaliplatin in this study.[11] The total dose of oxaliplatin in pseudo-normal renal function was significantly lower than in normal renal function (normal renal function: 881 mg/m^2, pseudo-normal renal function: 610 mg/m^2, P=0.004, Mann-Whitney U test). Because, patients with pseudo-normal renal function were lower the completion of Cape-OX therapy. In addition, drug interactions between capecitabine and oxaliplatin have not been reported so far.[12] Therefore, we consider that the possible involvement of oxaliplatin to be negligible.

Many anticancer drugs, as well as capecitabine and carboplatin, were approved prior to creatinine standardization. Approximately 96% of capecitabine and its metabolites are excreted through the kidneys,[13] and previous studies have indicated that renal dysfunction increased the level of capecitabine metabolites in the plasma, and incidence of grade 3–4 AEs.[6] Therefore, the pharmacokinetics of capecitabine and its metabolites are significantly dependent on the renal function of patients. The dose adjustment of these old drugs is usually based on the CrCL which is supposed to be calculated with the serum creatinine measured with old colorimetric assays using the Cockcroft-Gault equation. When standardized creatinine is used in the equation without caution, patients with pseudo-normal renal function might suffer from unnecessary toxicity by missing the necessary reduction in the starting dose. It is not realistic to redetermine the

optimal dose for patients with renal impairment as defined by standardized creatinine for each drug. Instead, oncologists and pharmacists involved in cancer chemotherapy should correctly recognize the clinical impact of standardized creatinine when using those older drugs in patients with borderline renal function.

CONFLICT OF INTEREST

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