RESEARCH ARTICLE

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Association between Area under the Curve Estimated from Carboplatin Dose and Incidence of Severe Thrombocytopenia in Patients with Non-Hodgkin's Lymphoma on DeVIC Therapy

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Abstract

Background: The degrees of adverse effects with carboplatin (CBDCA) are influenced by interindividual differences in the area under the curve (AUC), whereas renal function is not considered in the CBDCA dose design for dexamethasone, etoposide, ifosfamide, and CBDCA (DeVIC) therapy. We conducted this study to evaluate the association between the AUC and incidence of severe thrombocytopenia in patients treated with DeVIC with or without rituximab (DeVIC ± R). **Methods:** We retrospectively analyzed clinical data for 36 patients with non-Hodgkin's lymphoma who received DeVIC ± R between May 2013 and January 2021 at the National Hospital Organization Hokkaido Cancer Center. The AUC of CBDCA (AUC_{actual}) was calculated backward using a variant of the Calvert formula. **Results:** The median AUC_{actual} was 4.6 (interquartile range: 4.3–5.3) min mg/mL and AUC_{actual} was negatively correlated with the nadir platelet count ($r = -0.45$; $P < 0.01$). Multivariate analysis showed that $AUC_{actual} \geq 4.3$ versus < 4.3 was an independent factor predictive of severe thrombocytopenia (odds ratio: 19.3, and 95% confidence interval: 1.45–258; $P = 0.02$). **Conclusion:** This study suggests that the CBDCA dosing design considering renal function can reduce the risk of severe thrombocytopenia in DeVIC ± R therapy.

Keywords: Carboplatin- area under the blood concentration time curve- severe thrombocytopenia

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Introduction

Carboplatin (CBDCA) is a platinum-containing drug, which was developed to reduce adverse effects such as nephrotoxicity, nausea, and vomiting without reducing the antitumor activity of cisplatin (McKeage, 1995). The kidneys are the primary routes of excretion of CBDCA, and the amount of excretion correlates with the glomerular filtration rate (GFR) (Calvert et al., 1985). The toxicity which limits an increase of the CBDCA dose is thrombocytopenia, (Oun et al., 2018) and the area under the curve (AUC) for CBDCA and rate of thrombocytopenia were reported to be positively correlated (Chatelut et al., 2000; Egorin et al., 1984). Interindividual differences in the incidence of adverse effects with CBDCA can be explained by interindividual differences in the AUC influenced by renal function; (Harland et al., 1984) therefore, setting a target AUC and determining the dose based on GFR is believed to eliminate interindividual differences in AUC, and reduce the risk of serious adverse events (Calvert et al., 1985). In a model analysis of patients with ovarian cancer, the antitumor effect of CBDCA was shown to plateau at an AUC of 5–7, while a degree of side effects increased in conjunction with an increased AUC (Jodrell et al., 1992). Therefore, the target AUC is generally set at 5–7 for standard treatments of many solid tumors, and the Calvert formula is widely used for the CBDCA dosing design (Calvert et al., 1989; Ozols et al., 2003).

GDC therapy (comprising 21-day cycles of gemcitabine, CBDCA, and dexamethasone [DEX]) and ICE therapy (comprising 21-day cycles of etoposide [VP-16], CBDCA, and ifosfamide [IFO]) are known therapies that include CBDCA in salvage therapy for

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relapsed or refractory malignant lymphoma (Gopal et al., 2010; Hagberg and Gisselbrecht, 2006; Kewalramani et al., 2004; Moskowitz et al., 1999). In each case, the CBDCA dosing design is based on the Calvert formula; however, the CBDCA dosing design in DeVIC therapy (21-day cycles of DEX, VP-16, IFO, and CBDCA) uses the body surface area method (300 mg/m^2), (Okamoto et al., 1994) and no prospective clinical trials have been reported using the AUC and Calvert formula for the CBDCA dosing design. In a retrospective study, Tomono et al. reported that while an AUC of 4 or more for CBDCA improved therapeutic efficacy, it increased the incidence of thrombocytopenia and neutropenia (Tomono et al., 2016).

We considered that interindividual differences in the AUC of CBDCA on DeVIC therapy with or without rituximab (DeVIC ± R) could affect thrombocytopenia; however, to date, there are no reports regarding renal function in DeVIC ± R. Therefore, we conducted a retrospective study in patients with malignant lymphoma treated with DeVIC ± R to assess the relationship between the AUC calculated from the actual dose of CBDCA designed by the body surface area method and the incidence of severe thrombocytopenia.

Materials and Methods

Subjects

We performed a retrospective study of 41 patients with malignant lymphoma who received DeVIC therapy (IFO: 1500 mg/m^2, day 1–3; VP-16, 100 mg/m^2, day 1–3: CBDCA: 300 mg/m^2, day 1; DEX: 40 mg/body, day 1–3) every 3 weeks, with or without rituximab (375 mg/m^2), at the National Hospital Organization Hokkaido Cancer Center between May 1, 2013 and January 31, 2021. Thirty-six patients were evaluable; five patients with fewer than 5.0×10^4 platelets per μL at the start of treatment were excluded. The observation period was from the start of DeVIC ± R therapy to the day before the start of the next course, or 28 days after the start of the first course if the treatment was discontinued.

Data collection

In this retrospective study, we used the physician's electronic medical chart, nursing records, drug administration instruction records, and ordering systems to collect information; age (years) at the start of induction chemotherapy, sex, height (cm), body weight (kg), the dose of anticancer drugs (mg), treatment line, and laboratory data (serum creatinine [Scr] using the enzyme method [mg/dL], platelet count [$\times 10^4$/μL], hemoglobin count [g/dL], neutrophil count [$\times 10^3$/μL], and lactate dehydrogenase [LDH] [IU/L]).

Assessments

Body surface area (m^2) was calculated using the DuBois formula (Formula 1), the estimated creatinine clearance (Ccr) (mL/min) was calculated using the Cockcroft-Gault formula (Formula 2), and the AUC was calculated via modification of the Calvert formula. Variant of the Calvert formula was defined as the dose of CBDCA divided by "25+GFR" equals AUC (Formula 3). GFR in the Calvert formula is known to substitute the estimated Ccr calculated via the Cockcroft-Gault formula, using Scr measured by the Jaffe method (Calvert et al., 1989). Since Scr is measured via the enzymatic method in Japan, it was corrected to the Jaffe method by adding 0.2 to the Scr of the enzymatic method (Ando et al., 2000). Therefore, in this study, the estimated Ccr calculated by the Cockcroft-Gault formula was substituted for the GFR by substituting the corrected Scr for the Jaffe method. Adverse events were evaluated using the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0.

Formula 1: Dubois formula

Body surface area (m^2) = body weight (kg)$^{0.425}$ × height (cm)$^{0.725}$ × 0.007184

Formula 2: Cockcroft-Gault formula

Ccr (mL/min) = ((140-age) × body weight (kg)) / (72 × Scr (mg/dL)) × (1: male; 0.85: female)

Formula 3: Variant of the Calvert formula

AUC (min mg/mL) = dose of CBDCA (mg) / (25+GFR)

Statistical analysis

Continuous variables were expressed as the median and interquartile range (IQR), and categorical variables as the number of patients and percentage. The correlation coefficient between the nadir of platelet count (PLT_{nadir}) and dose of each anticancer drug was calculated using the Pearson product-moment correlation coefficient. The correlation strength was interpreted based on the size of the absolute value of r, and the following general standards were commonly used: $0.0 \leq |r| \leq 0.2$, almost no correlation; $0.2 \leq |r| \leq 0.4$, weak correlation; $0.4 \leq |r| \leq 0.7$, considerable correlation; and $0.7 \leq |r| \leq 1.0$, strong correlation. The correlation coefficient of each group was compared using the Bonferroni correction for multiple comparisons. Univariate analysis was performed using logistic regression analysis, with a grade 3 or higher thrombocytopenia as the objective variable, and the odds ratio was determined. Multivariate analysis was performed when $P < 0.2$ in univariate analysis; to exclude the influence of confounders, we considered excluding a combination with a variance inflation factor >10 from the explanatory factors. Additionally, factors with a first-order dependent variable relationship and multicollinearity, or a linearly dependent variable relationship and multicollinearity, were excluded as factors in the multivariate analysis. Continuous variables were subjected to receiver operating characteristic (ROC) curve analysis to determine the cutoff value for grade 3 or higher thrombocytopenia. A significance level <5% was considered statistically significant in all tests. Statistical analyses were performed using the Bell Curve for Excel software (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Ethical considerations

This study was performed in compliance with the ethical guidelines for medical research on human subjects and was approved by the Ethics Committee of

Hokkaido Cancer Center (Approval No: 03-27). Due to the retrospective nature of the study, written or oral consent was not obtained from the research subjects. Information regarding the study was made available to the research subjects (posted on the hospital or on the hospital website), who were guaranteed the opportunity to refuse participation in the study. Patient data were anonymized prior to handling, ensuring that confidential information was protected.

Results

The background characteristics of the 36 patients are shown in Table 1. Most of the patients underwent DeVIC ± R as a second or later line treatment. The median anticancer drug doses administered were almost 80% of the reference doses. The estimated Ccr was less than 60 mL/min in more than half of the patients. The median (IQR) AUC calculated backward via the modified Calvert formula (Formula 3) using the actual CBDCA dose administered (AUC_{actual}) was 4.6 (4.3–5.3). The correlations between each anticancer drug dose administered and PLT_{nadir} were then analyzed to evaluate the effect of each drug on platelet count. The correlation coefficients were -0.26 (P = 0.12) between IFO_{dose} and PLT_{nadir} (Figure 1 A), -0.25 (P = 0.13) between $VP\text{-}16_{dose}$ and PLT_{nadir} (Figure 1 B), and -0.25 (P = 0.14) between $CBDCA_{dose}$ and PLT_{nadir} (Figure 1 C), indicating a weak negative correlation. The correlation coefficient between the AUC_{actual} and PLT_{nadir} was -0.45 (P < 0.01), indicating a negative correlation (Figure 2).

Multiple comparisons of the correlation coefficients for each group were performed through the Bonferroni correction. Specifically, the significance level (α') adjusted by Bonferroni correction was obtained, and the probability values of the significance test (Pearson product-moment correlation coefficient) for each comparison were compared with the probability value of α' (0.017) and used to make a judgment. The analysis showed that the correlation between AUC_{actual} and PLT_{nadir} was significantly stronger than between IFO_{dose} or $VP\text{-}16_{dose}$ with PLT_{nadir}. Next, we analyzed the relationship between AUC_{actual} and the grade of thrombocytopenia (Figure 3). We found that the higher the AUC_{actual}, the greater the incidence of grade 3 or higher thrombocytopenia.

The ROC curve of the AUC_{actual} for incidence of grade 3 or thrombocytopenia is shown in Figure 4. The cutoff value for the AUC_{actual} was 4.3 (AUC on the ROC curve: 0.70, sensitivity 88%, specificity 55%, P = 0.04). We classified the patients into four quadrants based on an AUC_{actual} of 4.3 and grade 3 thrombocytopenia (Figure 3), there were 21 patients (58%) in the group with an AUC_{actual} ≥4.3 and grade 3 or higher thrombocytopenia, 5 (14%) in the group with an AUC_{actual} ≥4.3 and grade 2 or lower

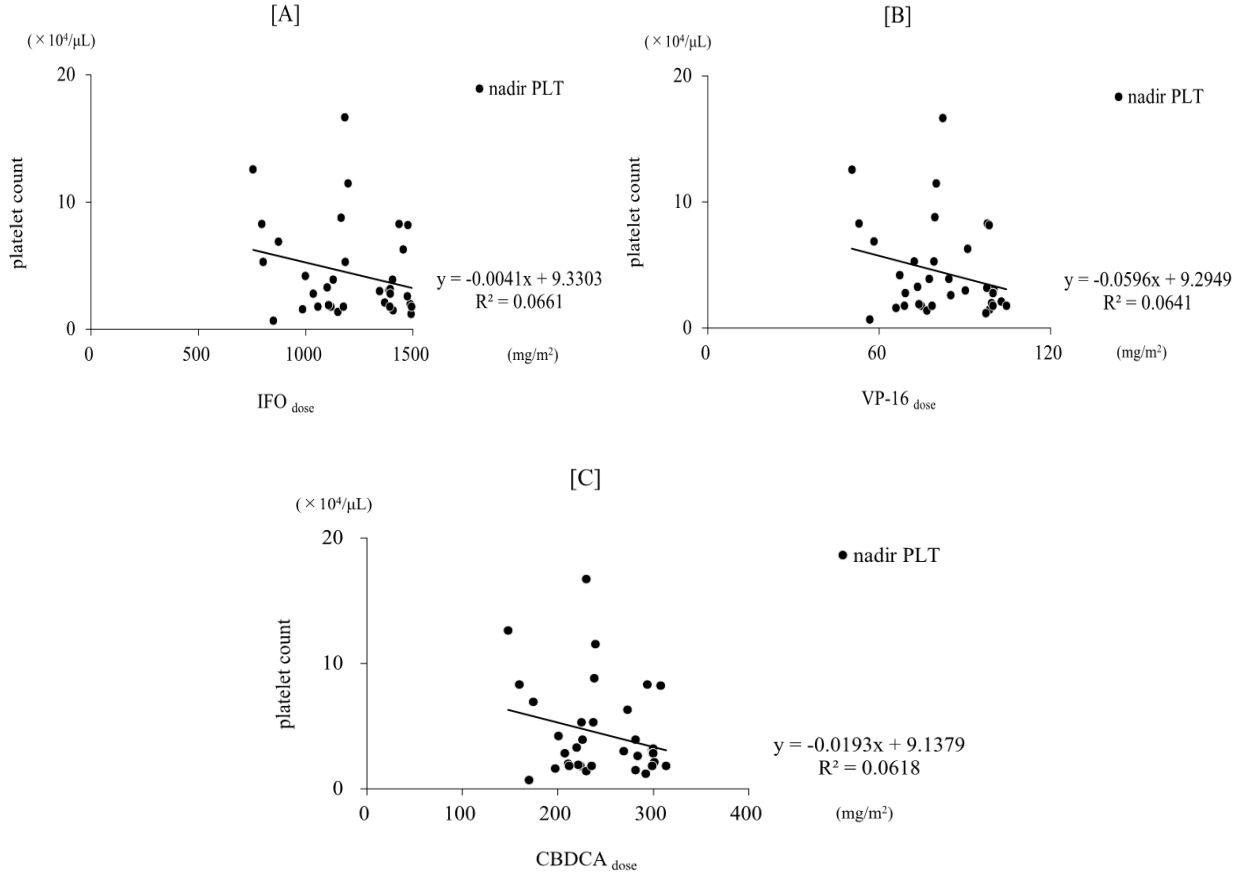

Figure 1. Correlation of Dose (A: ifosfamide, B: etoposide, C: carboplatin) and platelet nadir value. Correlation coefficient of earch anticancer drug dose and platelet nadir value; A: correlation coefficient: -0.26, P = 0.12, B: correlation coefficient: -0.25, P = 0.13, C: correlation coefficient: -0.25, P = 0.14, indicating a weak negative correlation. Abbreviation: platelet; PLT, dose of ifosfamide; IFO_{dose}, dose of etoposide; $VP\text{-}16_{dose}$, dose of carboplatin; $CBDCA_{dose}$. Pearson product-moment correlation coefficient.

Table 1. Baseline Characteristics of Patients Received DeVIC Therapy (n=36).

		N=36
Sex, number (%)	Male	16 (44)
	Female	20 (56)
Age (years), median (IQR)		72 (64-75)
Treatment line, number (%)	First line	3 (8)
	Second line or more	33 (92)
Dose (mg/m^2), median (IQR)	Ifosfamide	1,192 (1,089-1,414)
	Etoposide	81 (73-98)
	Carboplatine	238 (218-295)
Body surface area (m^2), median (IQR)		1.53 (1.44-1.68)
Renal function before administration, median (IQR)	Ccr (mL/min)	56 (45-68)
Blood cell count before administration, median (IQR)	Neutrophil (×10^3 /μL)	3.58 (2.80-4.81)
	Hemoglobin (μg/dL)	11.1 (9.9-11.9)
	Platelet (×10^4 /μL)	21.7 (15.3-31.6)

Abbreviation: interquartile range; IQR, creatinine clearance; Ccr

thrombocytopenia, 4 (11%) in the group with an AUC_{actual} <4.3 and grade 3 or higher thrombocytopenia, and 6 (17%) in the group with an AUC_{actual} <4.3 and grade 2 or lower thrombocytopenia.

The IFO_{dose} and $VP\text{-}16_{dose}$ were not associated with the grade of thrombocytopenia (data not shown). Logistic regression analysis of the incidence of grade 3 or higher thrombocytopenia was performed. In univariate analysis, $P < 0.20$ was observed for the platelet count before starting treatment, Ccr, treatment line, AUC_{actual}, IFO_{dose}, $VP\text{-}16_{dose}$, and LDH (Table 2). Next, we performed a multivariate analysis of the categories with $P < 0.20$ in the univariate analysis (Table 3). Among pairs with a variance expansion coefficient >10, one was excluded as an explanatory factor. Additionally, since IFO_{dose} and $VP\text{-}16_{dose}$ had a weaker correlation with PLT_{nadir} than AUC_{actual}, factors related to dose (other than CBDCA) were excluded as explanatory factors. Although the Ccr had a $P < 0.20$ in univariate analysis, it was excluded as a factor in multivariate analysis because Ccr and AUC had a first-order dependent variable relationship; additionally, multicollinearity was observed because Ccr was calculated using age, Scr, and weight when determining the AUC. In the multivariate analysis, only an $AUC_{actual} \geq 4.3$ was considered a significant factor (versus <4.3; OR: 19.3, 95% CI: 1.45–258; P = 0.02).

Next, we performed univariate and multivariate analyses of factors other than AUC_{actual} that affected the incidence of grade 3 or higher thrombocytopenia in the group with an $AUC_{actual} > 4.3$. In the univariate analysis, $P < 0.2$ was observed for LDH (OR: 6.75, 95% CI: 0.83–54.7; P = 0.07), treatment line (OR: 5.78, 95% CI: 0.55–60.6; P = 0.14) and body surface area (OR: 7.00, 95% CI: 0.66–73.9; P = 0.11). However, multivariate analysis showed that neither category was a factor in the development of grade 3 or higher thrombocytopenia (data not shown).

Discussion

In this study, our results indicate that CBDCA $AUC_{actual} \geq 4.3$ is an independent risk factor for the development of grade 3 or higher thrombocytopenia with the CBDCA dosing design for DeVIC ± R therapy using

Table 2. Univariate Analysis of Facter Associated the Incidence of Grade 3 or Higher Thrombocytopenia to Patients Received DeVIC Therapy

	Odds ratio	95% CI	P-value
Platelet count before administration (×10^4/μL)	0.95	0.90-1.00	0.1
Body surface area (m2)	0.1	0.001-8.66	0.3
Ccr before administration (mL/min)	0.97	0.93-1.01	0.15
Age (years)	0.95	0.86-1.05	0.28
Sex, male	0.94	0.23-3.92	0.94
Treatment line	1.37	0.87-2.17	0.17
AUC actual	1.05	1.00-1.10	0.02
Ifosfamide dose (mg/m^2)	1	1.00-1.00	0.08
Etoposide dose (mg/m^2)	1.04	0.99-1.09	0.11
LDH	1	0.99-1.01	0.08
With rituximab	1.53	0.37-6.35	0.56

Abbreviation: confidence interval; CI, creatinine clearance; Ccr, area under the curve; AUC, AUC estimated from the actual carboplatin dose; AUC_{actual}

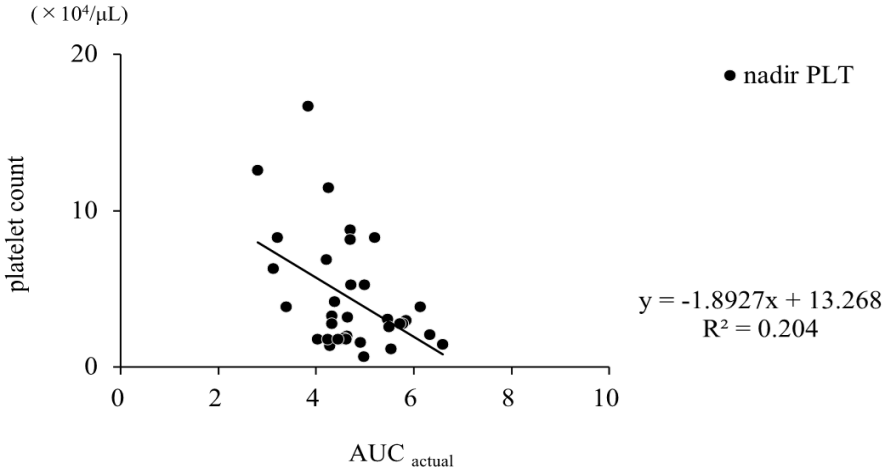

Figure 2. Correlation of AUC_{Actual} and Platelet Nadir Value. Correlation of AUC_{actual} and platelet nadir value; correlation coefficient: -0.45, $P < 0.01$, indicating a negative correlation. Abbreviation: area under the curve; AUC, platelet; PLT, AUC estimated from the actual carboplatin dose; AUC_{actual}. Pearson product-moment correlation coefficient.

Table 3. Multivariate Analysis of Facter Associated the Incidence of Grade 3 or Higher Thrombocytopenia to Patients Received DeVIC Therapy

	Odds ratio	95% CI	P-value
Platelet count before administration (×10⁴ /μL)			
< 15.8	36	0.93-1,389	0.05
≥15.8	1		
Treatment line			
≥4	2.96	0.36-24.2	0.31
< 4	1		
AUC actual			
≥4.3	19.3	1.45-258	0.02
< 4.3	1		
LDH, (IU/L)			
≥236	6.27	0.76-51.9	0.09
< 236	1		

the body surface area method. This is consistent with a previous study reporting an increase in the incidence of thrombocytopenia associated with increasing AUC; (Calvert et al., 1985) therefore, we considered that interindividual differences in AUC would also affect thrombocytopenia in DeVIC ± R therapy. The doses of IFO, VP-16, and CBDCA per body surface area were reduced from the reference dose, as shown in Table 1. If the dose of CBDCA calculated by the body surface area method was administered without dose reduction, the median (IQR) AUC_{actual} was 5.8 (5.3 - 6.3), including 4 patients with an AUC of 7 or greater (data not shown). However, since the median age of the patients was over 70 years and the median Ccr was 60 mL/min before the introduction of treatment, the dose was reduced by the attending physician based on the patient condition. As a result, the median AUC_{actual} (IQR) was 4.6 (4.3 - 5.3). Although this study indicated the usefulness of a dosing

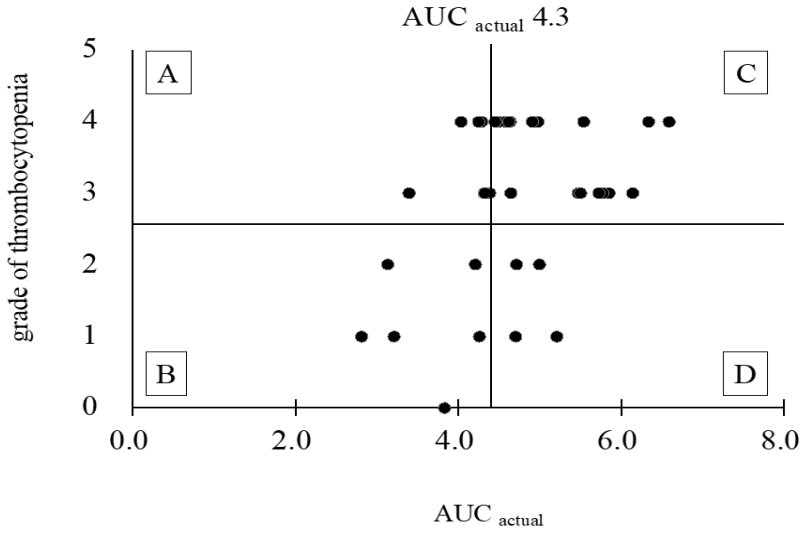

Figure 3. Relationship between AUC Actual and Grade of Thrombocytopenia. A: 6 patients (17%) in the group with an AUC_{actual} <4.3 and thrombocytopenia grade 1 or 2, B: 4 patients (11%) in the group with an AUC_{actual} <4.3 and thrombocytopenia grade 3 or higher, C: 21 patients (58%) in the group with an AUC_{actual} ≥4.3 and thrombocytopenia grade 3 or higher, D: 5 patients (14%) in the group with an AUC_{actual} ≥4.3 and thrombocytopenia grade 1 or 2, indicating the higher the AUC_{actual}, the greater the incidence of grade 3 or higher thrombocytopenia.

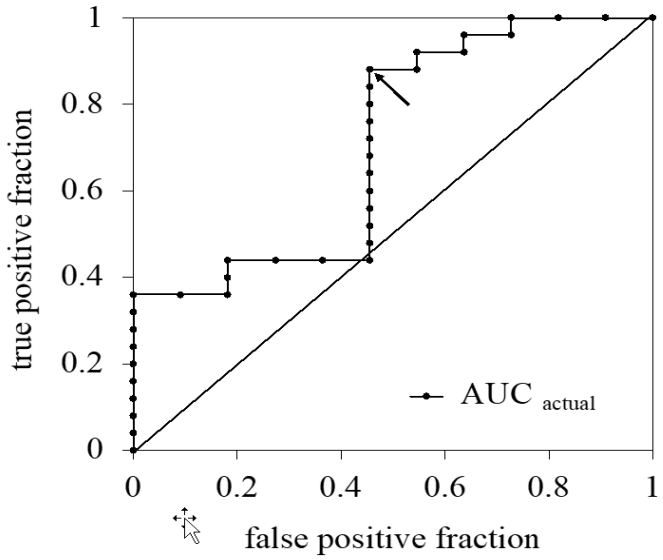

Figure 4. ROC Curve of AUC_{actual} in Thrombocytopenia Grade 3 or Higher. AUC_{actual}: cutoff value 4.3, AUC 0.70, sensitivity 88%, specificity 55%, P = 0.04. Abbreviation: receiver operatorating characteristic curve; ROC, area under the curve; AUC, AUC estimated from the actual carboplatin dose; $AUC_{actual.}$

design of CBDCA considering renal function for the incidence of thrombocytopenia in DeVIC ± R therapy, but because this study was based on the first course only, the efficacy of the treatment could not be evaluated because this study examined the data in the first course only. Tomono et al. reported that an AUC of 4 or higher for CBDCA improves therapeutic efficacy but did not assess the upper limit of the AUC (Tomono et al., 2016). The ICE therapy used in Europe and the United States as salvage therapy for relapsed and refractory non-Hodgkin's lymphoma consists of the same drug combinations as the DeVIC therapy with slightly different dosing schedules and doses, and the dose of CBDCA is set at the AUC of 5. In a report on ICE therapy for relatively young patients eligible for autologous transplantation, the incidence of grade 3 or higher thrombocytopenia was 29.4%, a lower frequency than in the present study but still a noteworthy level (Moskowitz et al., 1999). The incidence of chemotherapy-induced thrombocytopenia (CIT) in hematologic malignancies has been reported to be as high as 75%, (Liou et al., 2007) and the incidence and severity of CIT vary by regimen, with 92.3% reported for DHAP, 89.7% for ICE, and 89.7% for GDP being the most likely regimens to cause CIT (Lu et al., 2020). Since CIT can cause delays in the treatment schedule of antitumor drugs and bleeding events, reducing the risk of CIT is very important for continuing treatment in hematologic malignancies, where CIT is more frequent than in solid tumors (Shaw et al., 2021). In solid tumors, the antitumor effect of CBDCA was shown to plateau at an AUC of 5–7, while hematologic toxicity such as thrombocytopenia increased along with AUC (Jodrell et al., 1992). Our results indicate that an upper limit of less than the AUC_{actual} of 4.3 for DeVIC ± R therapy reduces the risk of incidence of grade 3 or higher thrombocytopenia. Therefore, in the dosing design of CBDCA in DeVIC ± R therapy, we propose that the AUC be kept in the range of 4 or greater and less than 4.3 to maintain efficacy and reduce the bleeding risk due to the severe thrombocytopenia for undergoing treatment safely. The CBDCA dosing design considering renal function is used based on the assumption that Scr is stable and overestimating renal function could lead to overdose of CBDCA when renal function fluctuates widely, such as during the acute phase of renal failure, or when muscle mass is extremely reduced, such as in sarcopenia or undernourished states (Hudson and Nolin, 2018). In such cases, it is necessary to estimate accurate GFR, such as by substituting a GFR estimation formula based on cystatin C according to patient conditions (Horio et al., 2013). This study has several limitations. First, it is a single-center, retrospective study with a small number of patients; thus, the findings cannot be generalized. Further prospective studies under uniform conditions are needed to identify the target AUC accurately. Second, we were unable to exclude the influence of other factors as causes of grade 3 or higher thrombocytopenia (such as underlying disease, which was not investigated in this study). However, the current study provides a new perspective on the CBDCA dosing design using the body surface area method for DeVIC therapy with regard to the management of severe thrombocytopenia.

Author Contribution Statement

All authors discussed the results and commented on the manuscript. K.U., S.T., K.Y., K.Y., K.O., T.S., M.K., H.S. and K.F. confirmed medical judgment and designed this study. K.U., S.T., M.K., H.S. and K.F. provided advice on statistical analysis. K.U., H.S. and K.F. edited the manuscript.

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Ethics approval and consent to participate

This study was performed in compliance with the ethical guidelines for medical research on human subjects and was approved by the Ethics Committee of Hokkaido Cancer Center (Approval No: 03-27). Due to the retrospective nature of the study, written or oral consent was not obtained from the research subjects. Information regarding the study was made available to the research subjects (posted on the hospital or on the hospital website), who were guaranteed the opportunity to refuse participation in the study.

Consent for publication

Not Applicable.

Data availability

The data supporting the findings of this study are available from the corresponding author, [K.U.], upon reasonable request.

Conflict of interest

There are no conflicts of interest associated with this paper.

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