



# Clinical pharmacokinetics and drug exposure-toxicity correlation study of docetaxel based chemotherapy in Chinese head and neck cancer patients

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**Background:** Area under time-concentration curve (AUC) of docetaxel is related with its toxicity and efficacy. The aim of this study is to investigate the target range of docetaxel AUC in Chinese head and neck cancer (HNC) patients.

**Methods:** Eligible HNC patients were enrolled and received at least 2 cycles of docetaxel-based chemotherapy. A simplified pharmacokinetic (PK) strategy (2 monitored samples) was developed to simulate docetaxel AUC using the nonlinear mixed-effect modelling program. Preliminary target range of AUC was pre-set as 2.5–3.7 µg·hr/mL according to pooled analysis from 8 previous studies. Fisher exact test was used to analyze the relationship between AUC with neutropenia and efficacy, and to verify the target range.

**Results:** Thirty-nine eligible patients were enrolled. Grade 3–4 and grade 4 neutropenia rate in 1<sup>st</sup> cycle was 64% and 36%, respectively. AUC simulation by simplified PK strategy was acceptable compared to full sampling method from the analysis of archived 300 patients' data, with –5.67% of mean prediction error (MPE). Median AUC of all patients was 2.58 µg·hr/mL (range from 1.28 to 9.39). A significant correlation (P=0.007) was detected between AUC and body surface area (BSA)-dosage, but BSA contributed only 18.3% of AUC inter-individual variability. Docetaxel AUC was significantly related with the severity (grade 3–4) of neutropenia (correlation of coefficient was 0.452, P=0.004). Fourteen patients (36%) were within the target AUC range. Patients with AUC above the target experienced more severe neutropenia (grade 3–4 rate 100% vs. 56%, P=0.036; grade 4 rate 86% vs. 25%, P=0.005). No significant difference of response rate was found between patients within the target or not.

**Conclusions:** A simplified samples PK strategy was developed for docetaxel AUC simulation. The target range of docetaxel AUC in Chinese HNC patients was suggested at 2.5–3.7 µg·hr/mL for reduced toxicity without compromising efficacy of docetaxel treatment.

**Keywords:** Docetaxel; area under time-concentration curve (AUC); Chinese; head and neck cancer (HNC); neutropenia

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## Introduction

Docetaxel is a commonly used anti-neoplastic agent of the taxoid family with broad activity in a variety of solid tumors, such as breast, non-small-cell lung, head and neck, ovarian, and prostate cancers (1). As with most cytotoxic agents, docetaxel has a narrow therapeutic window (2,3). Notably, severe hematologic toxicity, mostly neutropenia, is the major dose limiting side effect of docetaxel, especially for short courses of treatment, such as induction chemotherapy in head and neck cancer (HNC) (4-7).

Traditionally, the dosage of docetaxel has been based on body surface area (BSA), which is believed to reduce the inter-patient variability of drug exposure (8). However, previous studies have indicated that BSA had a limited effect on predicting drug clearance, and only 15–35% of metabolic variability could be accounted for by BSA adjusted dosing (9,10). Rudek demonstrated a 35% coefficient of variation (CV) in clearance when docetaxel was administered in six different regimens. Normalization of clearance based on BSA reduced the variation by only 1.7% in this study (11).

The most important limitation of docetaxel treatment is its unpredictable toxicity due to large inter-individual variability of drug exposure based on BSA dosing (12-14). The large PK variability could result in a proportion of patients being under-dosed, resulting in lower efficacy, or overdosed, resulting in increased toxicity (13). Previous studies have indicated that docetaxel exposure measured by area under time-concentration curve (AUC) was significantly correlated with its toxicity (mainly neutropenia) (5,15-21). Bruno's researches in 640 Caucasian patients demonstrated a positive correlation between AUC and grade 4 neutropenia and febrile neutropenia (16). A change in AUC from 4.2 to 6.5  $\mu\text{g}\cdot\text{hr}/\text{mL}$  was predictive of an approximate 2-fold increase in the odds of severe adverse events (AEs). In Asian population, Goh and Minami's researches also demonstrated a similar relationship between AUC and reduction in absolute neutrophil count (5,17).

The standard dosage of docetaxel in Caucasian populations is 75 to 100  $\text{mg}/\text{m}^2$ . The previous research by Engels suggest the target AUC values are 3.68 and 4.90  $\mu\text{g}\cdot\text{hr}/\text{mL}$  for 75 and 100  $\text{mg}/\text{m}^2$ , respectively (21). However, the dosage of docetaxel for Chinese patients is generally lower (60  $\text{mg}/\text{m}^2$ ) because of higher hematological toxicity than Caucasian population (22,23). No optimal AUC range has been established in Chinese populations (5,15-21). Therefore, the objectives of this study are to

analyze the correlation of AUC and neutropenia or efficacy in docetaxel chemotherapy and to find the optimal target AUC range in Chinese HNC patients.

## Methods

### Patients

This trial was conducted between January 2013 and June 2014 (data cutoff). Eligibility criteria included (I) 18–75 years old, (II) no history of systemic chemotherapy, and (III) diagnosis with pathologically confirmed HNC, (IV) indication for docetaxel based systemic chemotherapy, (V) an Eastern Cooperative Oncology Group performance score of 0-1, and (VI) at least one lesion measurable by CT scan or MRI according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1). Patient screening was conducted at the Sun Yat-sen University Cancer Center (SYSUCC) and conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. The study was approved by the Ethical Committee of SYSUCC (B2013-008-01). Written informed consent was obtained for each patient individually prior to enrollment in the study. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) (NCT01891123).

### Study design

Eligible patients were enrolled and received at least 2 cycles of docetaxel-platinum double or plus 5-Fu triple regimens, platinum was chosen from cisplatin or carboplatin according to investigator. In this 3-weekly regimen, docetaxel was administered at a dose of 60  $\text{mg}/\text{m}^2$  by intravenous infusion after standard premedication for 1.5 h (infusion started around 10–11 am), followed by cisplatin at a dose level of 60  $\text{mg}/\text{m}^2$  (or carboplatin at dose of AUC 5) by intravenous infusion. 5-fluorouracil was transfused afterwards by constant speed continuous intravenous infusion for 120 h at a dose level of 3  $\text{g}/\text{m}^2$  (infusion started around 3–4 pm). Primary G-CSF prophylaxis was not permitted in the first cycle, but allowed in subsequent cycles. Patients experiencing grade 4 neutropenia or febrile neutropenia were allowed to receive therapeutic G-CSF treatment. The primary endpoint of this trial was toxicity (mainly neutropenia) after 1 cycle, and the secondary endpoint was efficacy after 2 cycles. This study was discontinued after 2 cycles of chemotherapy, whether patients still receive

further cycles of docetaxel regimen chemotherapy or turn to other treatment was determined by investigators.

### **Toxicity and response assessment**

AEs were assessed and documented by investigators according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For neutropenia, grade 0–2 was considered moderate, 3–4 was considered severe, according to national comprehensive cancer network (NCCN) guideline for hematopoietic growth factors. Patients were evaluated for safety by laboratory tests and physical examination. To determine the severity of neutropenia, a recommended plan of additional peripheral complete blood count tests was set at days 5, 8, 11, 14, 17 and 20 after each chemotherapy cycle. Tumor imaging was performed at screening and after 2<sup>nd</sup> cycle using either CT scan or MRI, and assessed by investigators according to RECIST v1.1.

### **Pharmacokinetic (PK)**

Two peripheral blood samples were collected in first cycle of chemotherapy. The feasibility of a limited sampling strategy with only two monitored samples has been shown (24). In this trial, two monitored samples at end of infusion (EOI) and 1 h after EOI were collected and centrifuged within 2 hours, and the plasma was separated and frozen at –80 °C for PK analysis of docetaxel levels at the Sun Yat-sen University Cancer Center laboratory. The concentration of docetaxel in plasma was determined utilizing the MyDocetaxel™ Assay (Saladax Biomedical Inc., Bethlehem, PA, USA), an automated homogeneous two-reagent nanoparticle agglutination immunoassay for the detection of docetaxel in human plasma (25). AUC was calculated using the nonlinear mixed-effect modelling program (NONMEM) version V (double precision, level 1.1) using previously validated PK parameters (16) and the published residual variability (24).

### **Preliminary determination of target AUC from pooled 8 docetaxel PK studies**

Before the PK analysis of this trial, a systemic literature survey was performed using PubMed (Table 1). Relevant publications reporting docetaxel PKs and toxicity or efficacy were retrieved. Twenty-two studies were included, 7 were excluded for lacking of AUC data (26–32), 3 were

excluded for the lack of toxicity data (neutropenia) (33–35), 2 were excluded for liver dysfunction enrollment (36,37), and 2 were excluded for the lack of correlation analysis (38,39). Totally, 8 studies were enrolled into this pooled analysis (5,15–21). Two studies in Caucasian populations have indicated that a docetaxel dosage of 100 mg/m<sup>2</sup> leads to a median AUC of about 4.81–5.62 µg·hr/mL, such high docetaxel AUC also lead to severe hematologic toxicities (16,18). The reported grade 4 neutropenia rate was 64%, and >90% decrease rate of ANC in total courses. The suggested target AUC of 75 mg/m<sup>2</sup> dosage from Engel's research on Caucasian population was 3.68 µg·hr/mL (21). However, the same dosage of docetaxel in Asian population leads to an average AUC of 5.1 µg·hr/mL, also with 74% rate of grade 3 or 4 neutropenia rate according to Goh's research (17). Two Japanese studies show that the median docetaxel AUC with an acceptable toxicity, which is 34.8% grade 4 neutropenia rate or 4.5% febrile neutropenia rate, is around 2.68–3.03 µg·hr/mL with a lower dosage at 60 mg/m<sup>2</sup> (5,20).

An optimal AUC range from previous studies was set at 2.5–3.7 µg·hr/mL accordingly. The upper limit at 3.7 µg·hr/mL was set as the suggested target AUC in Baker's research (18), the lower limit at 2.5 µg·hr/mL was set as the median AUC in neutropenia grade 1–3 patients according to Minami's research (5). Based on the data from 3 previously reported docetaxel PK studies in Asian populations (5,17,20), the estimated neutropenia rates within the pre-set optimal AUC range (2.5–3.7 µg·hr/mL) were moderate and tolerable, with grade 3–4 neutropenia around 50–70% and grade 4 neutropenia around 20–40%.

### **Statistics**

Descriptive statistics for quantitative variables, such as means, standard deviations, medians, and percent coefficients of variation (%CV), and counts and proportions for categorical variables were calculated and listed. Pairwise spearman rank correlation between docetaxel AUC values and neutropenia grades were performed to determine the correlation coefficient and significance level. Scatter plots were presented to graphically describe the relationship of BSA adjusted dosages and AUC, and simple linear regression analysis was also conducted. Fisher's exact test was utilized to compare the proportions of neutropenia grades and efficacy among patients with different docetaxel AUC grouped by pre-set AUC range. Sample size was calculated by estimated the grade 3–4 neutropenia rate

**Table 1** The basic information and the results of AUC-outcome analysis from pooled 8 docetaxel pharmacokinetic studies

Study	Population	Indication	Number	Regimen dosage (Q3W)	AUC $\mu\text{g}\cdot\text{hr}/\text{mL}$	Outcomes
Extra 1993 (15)	Not mentioned	Solid tumors (OC, BC, SCLC, etc.)	23	20–115 $\text{mg}/\text{m}^2$	2.79 $\pm$ 0.85 for 70 $\text{mg}/\text{m}^2$	Grade 4 neutropenia is 57% in $\geq 85$ $\text{mg}/\text{m}^2$ (AUC 4.10–5.93), and 16% in 70 $\text{mg}/\text{m}^2$ ; AUC correlated with the percentage decrease of neutrophils
Bruno, 1998 (16)	Mostly Caucasian	Breast cancer, non-small cell lung cancer	640	640 (5% 75 $\text{mg}/\text{m}^2$ , 95% 100 $\text{mg}/\text{m}^2$ )	4.81 median (2.93–9.52) for all	Severe hematologic toxicity, with 64% grade 4 neutropenia. AUC is a strong predictor of neutropenia ( $P < 0.0001$ ), 4.8 as threshold; AUC at first cycle is a significant predictor of time to progression
Goh, 2002 (17)	Asian	Solid tumor indicated for docetaxel	31	75 $\text{mg}/\text{m}^2$ (N=23); 100 $\text{mg}/\text{m}^2$ (N=8)	5.1 $\pm$ 1.6; 5.5 $\pm$ 1.6	Grade 3 or 4 neutropenia rates are 74% (17/23) and 63% (5/8) in 75 and 100 $\text{mg}/\text{m}^2$ , respectively; AUC significant correlated with ANC nadir ( $P = 0.001$ )
Baker, 2004 (18)	Mostly Caucasian	Solid tumors indicated for docetaxel	46	60 $\text{mg}/\text{m}^2$ (N=10); 75 $\text{mg}/\text{m}^2$ (N=9); 100 $\text{mg}/\text{m}^2$ (N=7)	2.85 $\pm$ 1.40; 3.05 $\pm$ 0.85; 5.62 $\pm$ 2.12	Safety and efficacy not mentioned
ten Tije, 2005 (19)	Mostly Caucasian	Histologically confirmed solid tumor	51	75 $\text{mg}/\text{m}^2$ , 1 hour infusion every 3 weeks	Age <65 =5.69; age $\geq$ 65 =6.01	Grade 4 neutropenia; age <65 =30%; Age $\geq$ 65 =63%; febrile neutropenia; age <65 =0%; age $\geq$ 65 =16%
Minami, 2006 (5)	Asian	Solid tumors (BC, NSCLC, HNC, <i>et al.</i> )	69	60 $\text{mg}/\text{m}^2$ (range, 20–60)	Median 2.68 (range, 1.35–12.20)	Toxicity: 34.8% patients (24/69) experienced grade 4 neutropenia, efficacy data not mentioned; median AUC with neutrophils <500 =2.73, range, 1.49 to 5.99; median AUC with neutrophils $\geq$ 500 =2.49, range, 1.35 to 12.17
Ozawa, 2008 (20)	Asian	Solid tumors (GC, CRC, SCLC, NSCLC, NPC, <i>et al.</i> )	200	60 $\text{mg}/\text{m}^2$ (range, 20–60, mostly reduced dosage)	Median 3.03 (range, 1.99–4.29) for FN (N=9); median 1.78 (range, 0.451–7.58) for no FN (N=191)	Toxicity is mild with 4.5% FN rate, efficacy data not mentioned; logistic regression for AUC for FN coefficient =1.29, $P < 0.001$
Engels, 2011 (21)	Caucasian	Solid tumors indicated for docetaxel	30	Mostly 100 $\text{mg}/\text{m}^2$ (decreased dosage 75 $\text{mg}/\text{m}^2$ )	Target 4.90 for 100 $\text{mg}/\text{m}^2$ ; target 3.68 for 75 $\text{mg}/\text{m}^2$	Severe hematologic toxicity, with >90% decrease rate of ANC in total courses; PK-guided dosing decreased the inter-individual variability of percentage decrease in WBC and ANC

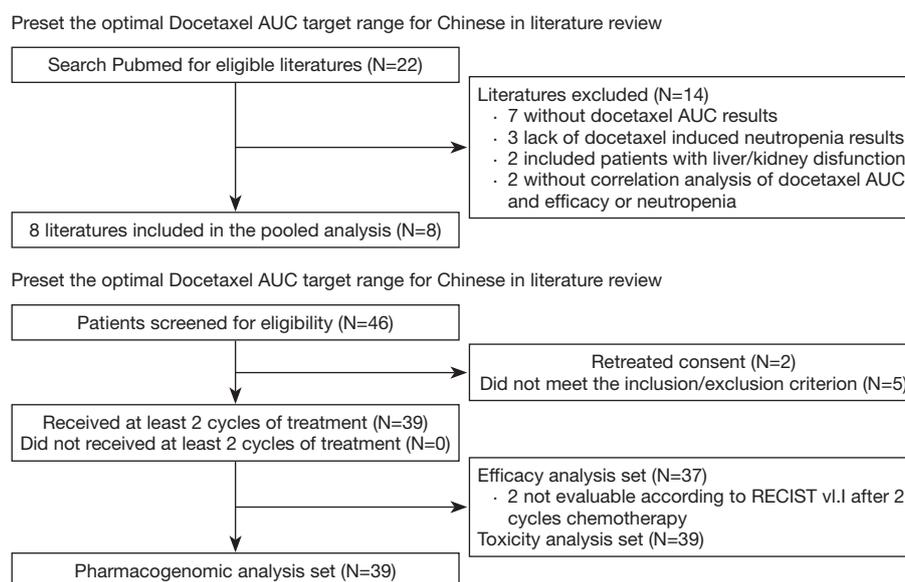
AUC, area under time-concentration curve; Q3W, every 3 weeks; OC, ovarian cancer; BC, breast cancer; SCLC, small cell lung cancer; ANC, absolute neutrophil count; HNC, head and neck cancer; GC, gastric cancer; CRC, colorectal cancer; NPC, nasopharyngeal carcinoma; FN, febrile neutropenia; PK, pharmacokinetics; WBC, white blood cell.

above target limit (75%) versus below target limit (35%) from literature review, with type I error 0.05 and type II error 0.2. All statistical analyses were performed using Stata v13.1 (Stata Corp LP, College Station, TX, USA). A significance level of  $P < 0.05$  (two-sided) was considered to be statistically significant.

## Results

### Patient characteristics and results

Thirty-nine eligible patients (38 nasopharyngeal carcinoma and 1 tongue carcinoma) were enrolled in this study (Figure 1). Thirty-seven patients received a triple-agent



**Figure 1** Patients' flowchart and study design.

chemotherapy regimen (docetaxel, plus cisplatin, plus 5-Fluorouracil), and most of the patients were male and with measurable lesions in the local nasopharynx or regional lymph nodes. The detailed characteristics are shown in *Table 2*. All patients received docetaxel treatment at a dosage of approximately 60 mg/m<sup>2</sup>. The incident rates of grade 3 and 4 neutropenia rate were 28% and 36%, respectively. Nineteen patients achieved partial remission (PR) (49%), 17 patients achieved stable disease (SD) (44%), and only 1 patient had disease progression after treatment (*Table 2*).

### *The verification of two samples simplified PK methods*

Baille's research have shown that with only two monitored samples (first at EOI, and second at 6 hours after EOI), an accurate AUC could be simulated (24). We conducted a PK simulation analysis using archived data base of 300 patients taking one sample at the EOI and the second sample from 0.25 to 5 h after the EOI compared to full sampling method (start of infusion 0, 0.25, 0.5 h, EOI 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 7, 9, 11, 23 h). The results were shown in *Table 3*. As compared to full sampling method, two samples AUC simulation with EOI time-point and 0.25 to 5 hours after EOI time-point showed satisfactory results. The mean prediction error (MPE) and root mean square error (RMSE) range from -1.03% to -5.70% and 11.07% to 17.28%, respectively. For the record, Baille's results showed that two sample with EOI+6 hours were 1.37% and 12.3% for

MPE and RMSE respectively, RMSE less than 20% was considered good (24). With the relatively satisfactory and clinical practical two samples AUC simulation strategy, this trial collected the end of docetaxel infusion and 1 hour after EOI samples (MPE -5.67% and RMSE 15.67%).

### *PK results*

At the dose level of 60 mg/m<sup>2</sup>, the median docetaxel AUC of all 39 patients was 2.58 µg·hr/mL (95% CI, 2.38–3.34), range from 1.28 to 9.39, and median value was within the preliminary target range. The CV in cycle 1 was 52%. Seven patients (18%) with an AUC higher than the upper limit of target range, 14 patients (36%) in the target range, and 18 patients (46%) were below the lower limit of the target range (*Figure 2*).

A scatter plot of dosages adjusted by BSA and docetaxel AUC is presented in *Figure 3*. As shown, the regression analysis showed that the BSA adjusted dosage was significantly related with docetaxel AUC, with a regression coefficient of 0.328 and a P value of 0.007. However, the R<sup>2</sup> value was low, and the adjusted effect by BSA contributed only 18.3% of the inter-individual variability of the docetaxel AUC.

### *The relationship of AUC and toxicity and efficacy*

The rate of grade 3-4 and 4 neutropenia in all 39 patients

**Table 2** Patients' demographics and clinical characteristics (N=39)

Characteristic	Patients, N (%)
Age (years, range)	49 [22–72]
Sex	
Male	32 [82]
Female	7 [18]
Disease	
Nasopharyngeal carcinoma	38 [97]
Tongue carcinoma	1 [3]
Dose per body surface area (mg/m <sup>2</sup> )	
55–60	30 [77]
60–62	9 [23]
ECOG performance status	
0	35 [90]
1	4 [10]
Stage (AJCC 8th)	
II	2 [5]
III	21 [54]
IV	16 [41]
Site of lesion (measurable)	
Local nasopharynx	24 [62]
Regional lymph nodes	30 [77]
Remote lymph node	6 [15]
Lung	3 [8]
Liver	3 [8]
Others	2 [5]
Treatment setting	
Induction	31 [79]
Palliative	8 [21]
Combination chemotherapy	
Cisplatin + 5-Fu	37 [95]
Cisplatin	1 [3]
Carboplatin	1 [3]
Neutropenia (assessed by CTC AE v4.03)	
Grade 0–2	14 [36]
Grade 3	11 [28]
Grade 4	14 [36]

**Table 2** (continued)**Table 2** (continued)

Characteristic	Patients, N (%)
Objective response rate (assessed by RECIST v1.1)	
PR	19 [49]
SD	17 [44]
PD	1 [3]
NE	2 [5]

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; CTC AE, Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial remission; SD, stable disease; PD, progressive disease; NE, not evaluable.

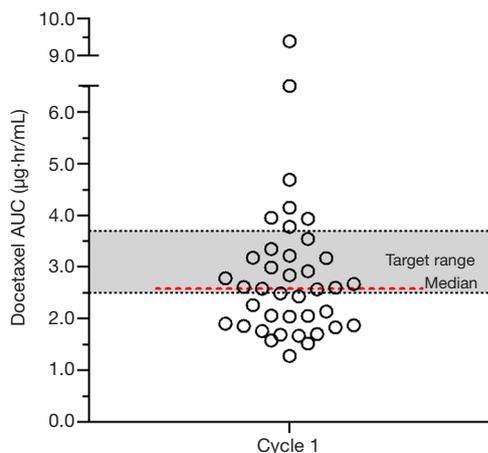
was 64% and 36%. The distribution of AUC's in cycle 1 by different grades of neutropenia showed that as the AUC increased, the neutropenia became more severe (*Figure 4*). The median AUC in grade 4 and 3 neutropenia patients were 3.17 and 2.60  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , in grade 2 and 1 were 2.04 and 1.83  $\mu\text{g}\cdot\text{hr}/\text{mL}$ . The average AUC in patients experience severe neutropenia (grade 3-4) was significant higher than those with moderate neutropenia (grade 0-2), which was 3.23 *vs.* 2.21  $\mu\text{g}\cdot\text{hr}/\text{mL}$  ( $P=0.038$ ). The correlation analysis indicated a significant relationship between docetaxel AUC and neutropenia ( $P$  value =0.004, correlation coefficient =0.452). However, no statistically difference was found between the average AUC of patients achieved PR (2.64  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) and average AUC of patients with SD or PD (3.16  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ),  $t$ -test  $P$  value 0.304.

The correlation analysis of docetaxel AUC, neutropenia, and efficacy is presented in *Figure 5*. Using the preliminary target AUC range, patients were grouped by the upper and lower limits according to their docetaxel AUC value in cycle 1. Patients with docetaxel AUC above 3.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$  experienced more severe neutropenia (grade 3-4 rate 100% *vs.* 56%,  $P=0.036$ ; grade 4 rate 86% *vs.* 25%,  $P=0.005$ ) than patients with docetaxel AUC under 3.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$ . Four patients (10%) received a docetaxel dose reduction at cycle 2 (20% off compared to cycle 1) due to hematological toxicities, 3 patients experienced grade 4 neutropenia, 1 patient experienced grade 3 neutropenia and related fever. Three of them were with docetaxel AUC above target, 1 was within the target. No significant differences in response rate was found between patients with AUC above and below 2.5  $\mu\text{g}\cdot\text{hr}/\text{mL}$  (50% *vs.* 53%,  $P=1.000$ ), or above and below 3.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$  (43% *vs.* 53%,  $P=0.693$ ).

**Table 3** simulation of AUC according to two samples strategy (EOI and time-point after EOI) compared to full sampling method

Compare	Full sampling	EOI + 0.25 h	EOI + 0.5 h	EOI + 0.75 h	EOI + 1 h	EOI + 5 h	EOI + 6 h Baille (25)
Bias absolute	MPE (h)	-0.4	-0.39	-0.4	-0.4	-0.17	NA
	Median error (h)	-0.09	-0.11	-0.15	-0.17	-0.02	NA
Bias relative	MPE (%)	-5.13%	-5.38%	-5.70%	-5.67%	-1.03%	1.37%
	Median error (%)	-2.97%	-3.31%	-4.67%	-4.91%	-0.74%	NA
Precision absolute	RMSE (h)	1.07	1.01	0.98	0.97	0.63	NA
	Absolute median error (h)	0.27	0.23	0.25	0.24	0.21	NA
Precision relative	RMSE (%)	17.28%	16.50%	15.88%	15.67%	11.07%	12.3%
	Absolute median error (%)	8.37%	7.00%	7.82%	7.67%	6.49%	NA

AUC, area under time-concentration curve; EOI, end of infusion; MPE, mean prediction error; RMSE, root mean square error; NA, not applicable.

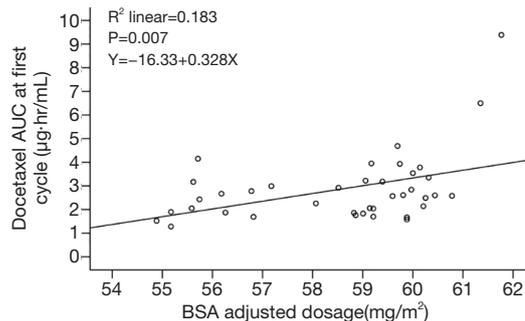


Patients No.	39
AUC Median	2.58
AUC Average (95% CI)	2.86 (2.38–3.34)
CV%	52%
AUC >3.7 No.(%)	7 (18)
AUC [2.5–3.7] No.(%)	14 (36)
AUC <2.5 No.(%)	18 (46)

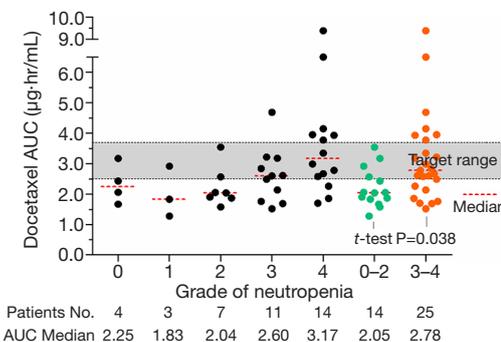
**Figure 2** The distribution and descriptive statistics of docetaxel AUC of all patients (N=39).

### Discussion

The current study examines the population PKs of docetaxel based chemotherapy and analyzed the exposure-neutropenia relationship of docetaxel in Chinese patients. Thirty-nine patients with HNC were enrolled and a limited-sample strategy (2 samples) was performed for the calculation of docetaxel AUC by NONMEM (24). The optimal target of AUC for Chinese HNC population was suggested as 2.5–3.7 µg·hr/mL.

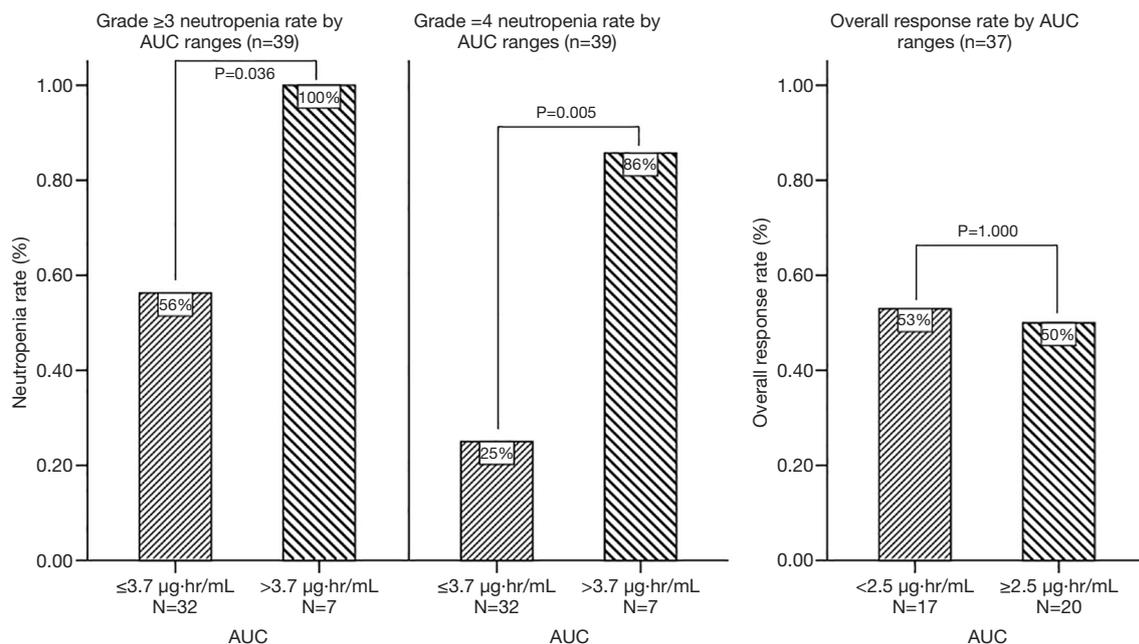


**Figure 3** The scatter plot and best fitted line of Docetaxel AUC and BSA adjusted dosage in first cycle.



**Figure 4** The scatter plot of docetaxel AUC and neutropenia grade in first cycle.

Our study indicated that variability of docetaxel exposure by BSA based dose determination is substantial (over 7-fold). BSA adjustment contributed only 18.3% of the inter-individual variability of docetaxel AUC. Correlation analysis



**Figure 5** Correlation analysis of 1st cycle Docetaxel AUC, neutropenia rate, and overall response rate.

in this study confirm that docetaxel AUC is significantly correlated with neutropenia, correlation of coefficient is 0.452, which is consistent with previous findings (2,14-21). We pre-set an optimal AUC range for Asian populations according to pooled analysis of several PK and toxicity researches (5,15-21). The optimal AUC range was pre-set to 2.5–3.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$  to minimize the rate of severe neutropenia, which is verified in our study. Patients over-exposed (AUC above 3.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) to docetaxel experienced significant higher grade 3–4 and grade 4 neutropenia, the upper limit of target is successfully verified. Efficacy analysis shows no significant relationship was found between AUC and objective response rate, no difference between responders and non-responders neither. These results suggested that docetaxel at the dosage of 60  $\text{mg}/\text{m}^2$  is probably still overdosed for East Asian population. Lower limit set at 2.5  $\mu\text{g}\cdot\text{hr}/\text{mL}$  would not damage the treatment efficacy in the first place, and closed to the median value (2.58  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) to ensure dose intensity. This therapeutic range of docetaxel AUC might fit the therapeutic dose monitoring (TDM) attempt in future studies for Chinese patients.

The major obstacle for cytotoxic drug is the unexpected toxicity caused by large inter-individual variability of drug exposure (12-14). Traditional BSA based dosing method has limited contribution for reducing inter-individual variability.

For patients over-exposed to docetaxel, severe toxicity is one of the reasons for early discontinued treatment. Patients under-exposed to the drug rarely require doses to be increased to achieve an intra-patient maximum tolerated dose (MTD). Such dose escalations are difficult to execute in practice due to concerns over the potential to cause severe side effects. Using AUC based TDM to minimize toxicity or achieve better efficacy is a promising direction of cytotoxic drug research (40). Gamelin's researches indicated that the therapeutic range of 5-fluorouracil (5-FU) for colorectal cancer patients is 20–25  $\text{mg}\cdot\text{hr}/\text{L}$ , dose adjustment according to this range will significantly improve 5-FU efficacy and reduce incident rate of diarrhea (41). Joerger's researches also indicated paclitaxel exposure ( $T_c > 0.05$ , time above a plasma concentration of 0.05  $\mu\text{M}$ ) is related with its toxicity and efficacy,  $T_c > 0.05$  between 26–31 hours should be set as the target range. The results of a randomized phase III trial show that dosing according to the target range could significant reduce paclitaxel-associated neuropathy (42). In order to accomplish this goal, a target AUC range must be established. Before the randomized phase III trial of 5-FU in colorectal cancer, Gamelin had launched several PK studies using weekly 8 hours continuous infusion or 5-FU, the results showed a relationship of AUC and both efficacy and toxicity of treatment. An  $\text{AUC}_{0-8}$  of 20 to 25  $\text{mg}\cdot\text{hr}/\text{L}$  as the optimal

level (43). Joerger also using pooled data to conclude that  $T_c > 0.05$  was the ideal candidate for TDM, which was significantly correlated with paclitaxel-related absolute neutrophil count nadir. A prospective trial was proposed and verified that target range of  $T_c > 0.05$  was 26–31 hours and individual dosing accordingly would significantly reduce grade 4 neutropenia (44). As to docetaxel, AUC was proved an effective metric for TDM (5,15–21). Engels reported a randomized PK study of TDM for the individualization of docetaxel dosing in Caucasian population. The target of AUC was set at 3.68 and 4.90  $\mu\text{g}\cdot\text{hr}/\text{mL}$  for 75 and 100  $\text{mg}/\text{m}^2$ , respectively. Dosing guided by this target, the inter-individual variability of AUC was reduced by 35%, so was percentage decrease in white blood cell and absolute neutrophil count variability. In our study, due to the small sample size (39 patients enrolled) and lack of docetaxel PK data in East Asian population. So, it's more appropriate to analyze AUC data and toxicity or efficacy data and establish a preliminary target AUC range according to previous similar docetaxel PK studies, and further verify this target in our study. Lower AUC might further reduce the incident rate of grade 3–4 neutropenia, but it might also damage the efficacy which requires larger sample size to confirm. So, the lower limit of the range was decided at 2.5  $\mu\text{g}\cdot\text{hr}/\text{mL}$  to ensure adequate dose intensity. Our data suggest this AUC range in Chinese head and neck patients receiving docetaxel based chemotherapy is reliable and may be verified and utilized in future randomized clinical trials of TDM. Further prospective PK studies are needed to verify that target AUC range.

## Conclusions

Our study suggested a target docetaxel AUC (2.5–3.7  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) for Chinese head and neck patients receiving docetaxel based chemotherapy. Patients with an AUC within the target range, severe toxicity can be statistically reduced without compromising efficacy. Sampling at EOI and about 1 h after introduces slight but acceptable bias in the AUC calculation compared to full sampling.

Current study included patients received cisplatin and 5-Fu triplet chemotherapy. These drugs could have a proportion of influences on neutropenia which is considered invariant. Instead of launching a large scale phase II trial to conclude the target AUC range, we chose to preset a range from literature review and verified it in a small sample size prospective phase II trial. The estimated optimal AUC range was mainly based on toxicity data. So,

this target range should be further validated in a prospective randomized clinical trial.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethical Committee of Sun Yat-Sen University Cancer Center (B2013-008-01). Informed consent written informed consent was obtained from all participating subjects. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) (NCT01891123).

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