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Treatment Outcome of Pharmacokinetics-Based Dosing of Docetaxel and Fluorouracil in Advanced Head and Neck Cancer Patients

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Abstract

Introduction: Docetaxel, Cisplatin and 5-Fluorouracil (DPF) became the standard induction chemotherapy in advanced Head and Neck Cancer (HNC) but associated with high toxicity rate. Several studies reported higher response rates with better tolerability when chemotherapy dose is calculated based on Pharmacokinetics (PK) versus conventional Body Surface Area (BSA). **Patients and Methods:** Thirty nine patients with stage III and IV HNC who received induction DPF were included in the study. Dose of cycle 1 was BSA-based then Docetaxel and 5-FU doses were PK-adjusted starting from cycle 2 whereas Cisplatin dose was BSA-based throughout the study. **Results:** After median follow up period of 14 months the median overall survival (OS) and progression free survival (PFS) were 15.1 and 10.6 months respectively. Twenty nine patients were available for response assessment. Seven patients (24.1%) achieved complete response while partial response encountered in 19 patients (65.5%) with and Overall response rate of 89.6%. Both treatment related side effects and mortality significantly decreased after the application of PK dose adjustments (p-value 0.007 and 0.01 respectively). **Conclusion:** PK-guided dose adjustments of 5-FU and Docetaxel in DPF regimen can significantly decrease the treatment related side effects and mortality without compromising the tumor response rate. A randomized clinical trial is needed to compare the PK-guided dose adjustment with the standard BSA based protocol.

Keywords

Head and Neck Cancer, DPF, Docetaxel, Fluorouracil, Pharmacokinetics Dose Adjustment

1. Introduction

Head and Neck Cancers (HNCs) are heterogeneous group of cancers. That may differ in location, pathogenesis, tumor biology, treatment, prognosis and effect on quality of life [1]. It was estimated that HNCs comprise 2% - 3% of all cancers in the United States and account for 1% - 2% of all cancer deaths [2]. In Egypt, HNC represents about 5% of all malignant tumors [3].

The Docetaxel, Cisplatin and 5-fluorouracil (5-FU) regimen (DPF) is the standard induction regimen in advanced HNC since the publication of the TAX323 [4] and TAX324 studies [5]. On the other hand, they are associated with high hematologic toxicity and a high complication rate [4] [5].

Chemotherapy dosing is based on body surface area (BSA). The BSA-based dose for any drug is recommended by the manufacturer according to the maximum tolerated dose (MTD) achieved during phase I studies. But there is actually no exact scientific basis for the use of BSA for chemotherapeutic drugs, and several studies have shown that this approach is not valid. BSA-based dosing is associated with drug plasma level variability up to 30-fold. Solid evidence exists that this inter- and intra-patient pharmacokinetic (PK) variability of anticancer-agents is a major contributor to toxicity and treatment failure [6].

Former studies reported that 20% - 30% of patients treated with BSA-based 5-FU dosing have drug exposure levels within a previously established therapeutic range [area under the concentration-time curve (AUC) 20 - 25 mg/h/L], whereas approximately 40% - 60% and 10% - 20% are under and over this therapeutic AUC threshold respectively. PK-guided 5-FU dosing has not been widely incorporated into clinical practice, because of the lack of data that support this approach [7]. Also there is lack of prospective studies that clarify the concept of modifying the Docetaxel dose based on drug PKs to achieve the target AUC. We proposed this study aiming to investigate the application of PK-guided 5-FU and Docetaxel dosing and to evaluate its effect on treatment outcome and toxicity profile.

2. Patients and Methods

2.1. Patients

This prospective study was conducted at the Medical Oncology department, National Cancer Institute of Egypt, Cairo University. All the patients with HNC stages III & IV who were candidate for induction chemotherapy (DPF) during the period from April 2013 to April 2014 and approved to participate in the trial were included in the study. The study included 39 patients and they were fol-

lowed till December 2016. Eligibility criteria were: Age 18 - 70 years, histologically confirmed diagnosis of stage III & IV HNC (excluding hematopoietic, lymphoprolefrative, sarcoma, thyroid and primary skin cancer), Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, with adequate bone marrow, liver and kidney functions. Ineligibility criteria were: pregnancy or lactation, serious illnesses like myocardial infarction within 6 months prior to study entry, history of significant neurologic or psychiatric disorders including dementia or seizures and patients with active uncontrolled infection.

2.2. Treatment and PK-Based Dose Adjustments

All of the patients were planned to receive three cycles of DPF regimen. At the first cycle, the doses of the drugs were prescribed based on the patient's body surface area. The dose of Docetaxel and Cisplatin was 75 mg/m^2 for each drug and both of them were delivered on day 1 of the cycle while as regards 5-FU the dose was 1000 mg/m^2/day and it was delivered as continuous intravenous infusion (CIVI) over 24 hours from day 1 to 4 of the cycle. Subsequent cycles were repeated every 3 weeks. Docetaxel and 5-FU CIVI doses were adjusted starting from the second cycle and onwards using a PK-guided dose-adjustment algorithm based on plasma concentration results of the preceding cycle that was expressed as AUC dose/h/L (Table 1). Cisplatin dosage remained the same throughout the treatment as there were no available kits to perform PK-guided

Table 1. 5-FU and docetaxel dose adjustment algorithm.

5-FU adjustment [9]	
AUC (mg/h/L)	**Dose adjustment**
≥45	Reduce by 30%
42 - 44	Reduce by 25%
39 - 41	Reduce by 20%
36 - 38	Reduce by 10%
25 - 35	**NO CHANGE NEEDED**
22 - 24	Increase by 10%
19 - 21	Increase by 20%
16 - 18	Increase by 25%
8 - 15	Increase by 30%
Docetaxel adjustment [10]	
AUC (mg/h/L)	**Dose adjustment**
>5.5	Reduce by 25%
4.5 - 5.5	Reduce by 10%
3.5 - 4.5	**NO CHANGE NEEDED**
1.5 - 3.5	Increase by 10%
<1.5	Increase by 25%

Cisplatin dose adjustment. Further treatment after the induction DPF was tailored according to response *i.e.* those who achieved good response received local therapy (surgery or concomitant chemoradiotherapy) while non-responders received palliative treatment.

During cycles 1 - 3, a peripheral blood sample was obtained for the measurement of the plasma level (mg/L) of 5-FU and Docetaxel which was used later on to calculate the plasma concentration or AUC (dose/h/L) of the drugs. The plasma level of both drugs was measured carefully using the following steps: Regarding 5-FU at least 18 hours after the start of CIVI 2 ml blood sample was withdrawn into an ethylene diamine tetra acetic acid (EDTA) tube. A stabilizing agent [derivative of uracil with properties that irreversibly inhibit Dihydropyrimidine dehydrogenase (DPD)] was added to the sample immediately. The sample was used for AUC analysis using immunoassay-based technique. ForDocetaxel, two 2 ml samples were withdrawn into an EDTA tubes, first was in the last 5 minutes of infusion, whereas second was 1 hour after end of infusion. AUC for 5-FU was calculated by multiplying the steady-state concentration (CSS) by time of continuous infusion (TCI): AUC = Css × TCI. AUC for Docetaxel was calculated using limited samples strategy where the AUC was estimated from two samples, one of them during and one other after the infusion [8].

2.3. Follow up, Response and Toxicity Assessment

Patients were considered eligible for response analysis if they completed three cycles of planned DPF. Disease response was assessed at the end of cycle three then every 3 months. Responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST V1.1) criteria [11]. During follow up complete physical examinations was performed and local imaging (CT or MRI) was requested. Toxicity assessment was done using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [12]. Patients were followed-up for a minimum period of 12 months for survival assessment.

2.4. Statistical Methods

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to compare toxicity between different cycles. Survival analysis was done using Kaplan-Meier method and comparison between survival curves was done using log-rank test. All tests were two-tailed. A p-value < 0.05 was considered significant. Progression free survival (PFS) was defined as the time measured in Months from starting first cycle of treatment until disease progression or death from any cause. Overall survival (OS) was calculated from the date of starting first cycle of treatment until death or last visit.

3. Results

3.1. Patients Characteristics

Thirty nine patients were enrolled in this study. The mean age of the patients was 46.7 ± 9.7 years (range 24 - 68). More than half of the patients were females (53.8%). The majority of the patients at the study entry had PS 1 (97.4%) and the smoking history was depicted in 30.8% of them. Presentation with head and neck lump was the most common presenting complaint (66.7%). Patient characteristics were summarized at (Table 2).

3.2. Tumor Characteristics

The tumor characteristics at the time of diagnosis are shown in (Table 3). Nasopharyngeal cancer was encountered in 11 patients (28.2%). Squamous cell carcinoma was the predominant histological subtype found in 58.9% of cases. G II tumors were the dominant grade found in 46.2% of cases. The majority of our cases presented with advanced tumor (T) and nodal (N) stage where T3 & T4 encountered in 69.3% while N2 & N3 in 51.2%.

Table 2. Characteristics of the study patients.

Parameter	Number (%)
Age	
Mean ±Standard deviation	46.7 ± 9.7
Median (Range)	47 (24 - 68)
Gender	
Female	21 (53.8%)
Male	18 (46.2%)
Comorbidity	
Diabetes	2 (5.1%)
Hypertension	3 (7.7%)
Smoking	12 (30.8%)
Performance Status	
1	38 (97.4%)
2	1 (2.6%)
Presenting Complaint	
Headache	9 (23.1%)
Pain	10 (25.6%)
Blurring of vision	2 (5.1%)
Nasal obstruction	8 (20.5%)
Mass	26 (66.7%)
Dysphagia	9 (23.1%)
Hoarseness of voice	7 (17.9%)

Table 3. Tumor characteristics of the study patients.

Parameter	Number (%)
Site	
Nasopharynx	11 (28.2%)
Oropharynx	4 (10.3%)
Hypopharynx	1 (2.6%)
Supraglottic larynx	1 (2.6%)
Glottic larynx	4 (10.3%)
Postcricoid	6 (15.4%)
Mandible	5 (12.8%)
Maxilla	3 (7.7%)
Tongue	3 (7.7%)
Sino-nasal	1 (2.6%)
Pathological type	
Squamous cell carcinoma	23 (58.9%)
Adenocarcinoma	14 (35.9%)
Mucoepidermoid	1 (2.6%)
Adenomucinous	1 (2.6%)
Grade	
I	4 (10.3%)
II	18 (46.2%)
III	7 (17.9%)
IV	10 (25.6%)
T-stage	
T1	2 (5.1%)
T2	10 (25.6%)
T3	14 (35.9%)
T4a	9 (23.1%)
T4b	4 (10.3%)
N-stage	
N0	11 (28.2%)
N1	8 (20.6%)
N2	10 (25.6%)
N3	10 (25.6%)
TNM stage	
III	5 (12.8%)
IVA	19 (48.7%)
IVB	15 (38.5%)

3.3. Treatment

Three cycles of induction DPF were prescribed to all of the patients who were included in the study. The first cycle was delivered successfully to all of them however only 30 and 29 patients were able to receive the second and third cycles respectively. Eight of the ten patients who did not complete the treatment died and the other two patients lost follow up before the subsequent cycles.

3.4. Drug Pharmacokinetic Characteristics and Dose Adjustments

Docetaxel:

After the first cycle, the patients who had low, high and targeted plasma concentration of Docetaxel were 13, 14 and 9 respectively. Three patients did not get their results due to lab error (*i.e.* beyond stability blood sample). Thirty patients were able to receive the second cycle of DPF and their plasma concentration of Docetaxel was re-assessed. The patients who had low, high and targeted plasma concentration of Docetaxel were 9, 4 and 15 respectively while it couldn't be measured for 2 patients due to lab error. The third cycle was received by 29 patients. Twenty three patients had target plasma concentration, three patients had low plasma concentration and another three patients had high plasma concentration of Docetaxel.

Based on plasma concentrations of Docetaxel, the following adjustments in Docetaxel dose in the subsequent cycle were done: No dose change for the patients with either target plasma concentration or lab error, dose reduction for the patients with high plasma concentrations and dose escalation for those patients with low plasma concentrations.

The median doses of Docetaxel given in the first cycle, second and third cycle were 127, 127.5 and 134 mg respectively and the Docetaxel dose necessary to successfully achieving the target AUC at cycle 3 ranged from 44.9% to 137.8% of the standard dose (75 mg/m^2).

5-FU:

After the first cycle, the patients who had low, high and targeted plasma concentration of 5-FU were 10, 9 and 7 respectively. Thirteen patients did not get their results due to lab error (*i.e.* beyond stability blood sample). Thirty patients were able to receive the second cycle of DPF and their plasma concentration of 5-FU was re-assessed. The patients who had low, high and targeted plasma concentration of 5-FU were 5, 7 and 11 respectively while it couldn't be measured for 7 patients due to lab error. The third cycle was received by 29 patients. Twenty patients had target plasma concentration, two patients had high plasma concentration and none of the patients had low plasma concentration of 5-FU. Again, seven patients did not get their results due to lab error (*i.e.* beyond stability blood sample).

Based on plasma concentrations of 5-FU, the following adjustments in 5-FU dose in the subsequent cycle were done: No dose change for the patients with either target plasma concentration or lab error, dose reduction for the patients

with high plasma concentrations and dose escalation for those patients with low plasma concentrations.

The median doses of 5-FU given in the first cycle, second and third cycle were 1700, 1685 and 1700 mg, respectively and the 5-FU dose necessary to achieve the target AUC at cycle 3 ranged from 31.2% to 147% of the standard dose.

Cisplatin:

Cisplatin dosage was based on BSA in the three cycles and was given as 75 mg/m2 on day 1.

Toxicity

The treatment related toxicity was evaluated after each cycle. Two patients lost follow up after the first cycle and were not included in the toxicity assessment. Diarrhea, mucositis and neuropathy were the most frequent toxic events and occurred mainly after the first cycle of treatment. Treatment related deaths was encountered in 8 patients and were due to febrile neutropenia and septic shock and all of them had high plasma concentrations to Docetaxel and/or 5-FU. Both severe (grade III & IV) treatment related side effects and mortality significantly decreased after the application of PK dose adjustments compared to the first cycle which was prescribed based on the patients' BSA (Table 4, Figure 1).

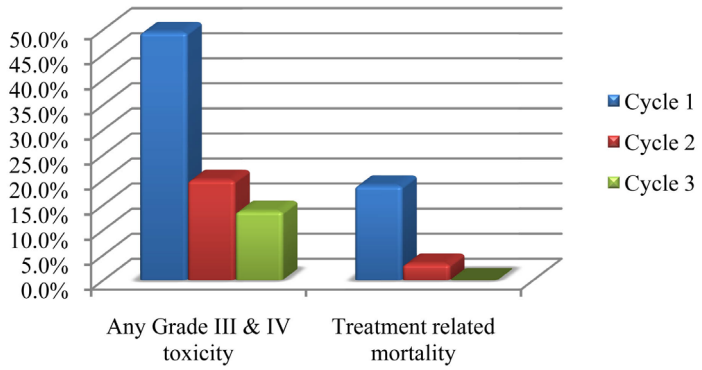

Figure 1. Toxicity and treatment related mortality in relation to each cycle.

Table 4. Adverse events observed for the 3 cycles of treatment.

No. of assessed patients	Cycle 1	Cycle 2	Cycle 3	
	37	30	29	
Events	**Number (%)**	**Number (%)**	**Number (%)**	**P-value**
Any Grade III & IV toxicity	17 (49.5%)	6 (20%)	4 (13.8%)	**0.007**
Diarrhea	8 (21.6%)	4 (13.3%)	2 (6.9%)	0.236
Mucositis	9 (24.3%)	3 (10%)	1 (3.4%)	**0.038**
Myelosuppression	12 (32.4%)	2 (6.7%)	3 (10.3%)	**0.01**
Neuropathy	2 (5.4%)	1 (3.3%)	1 (3.4%)	0.89
Nausea & Vomiting	2 (5.4%)	2 (6.7%)	0 (0.0%)	0.392
Treatment related mortality*	7 (18.9%)	1 (3.3%)	0 (0.0%)	**0.01**

*Treatment related mortality were due to febrile neutropenia and septic shock.

Response

Twenty nine patients completed full 3 cycles of DPF and were assessed for response using RECIST criteria. Seven patients achieved complete response (CR), whereas 19 had partial response (PR), accounting for 24.1% and 65.5%, respectively, with an objective response rate (ORR) of 89.6%. Only 3 patients did not respond well to the treatment, 2 of them had stable disease and the last one had progression of his disease. Since most of the patients (89.6%) achieved good response to the treatment no further analysis was done to define prognostic factors for response.

Survival

After a median follow up period of 14 months (range 1.0 - 43.9), the median PFS for the whole group was 10.6 months (95% confidence interval (CI): 6.2 - 14.9) and the OS was 15.1 months (95% CI: 10.9 - 19.2). Cumulative PFS and OS at the end of study (36 months) were 29.7% and 31.1% respectively (Table 5 & Figure 2).

Patients with nasopharyngeal tumors had significantly superior PFS and OS compared to the patients with HNC at other sites (p-value 0.01 and 0.006 respectively). Early T-stage had a borderline significance as a good prognostic factor for PFS (p-value 0.05) while developing G III & IV toxicity at any cycle also had a borderline significant poor impact on OS (p = 0.05).

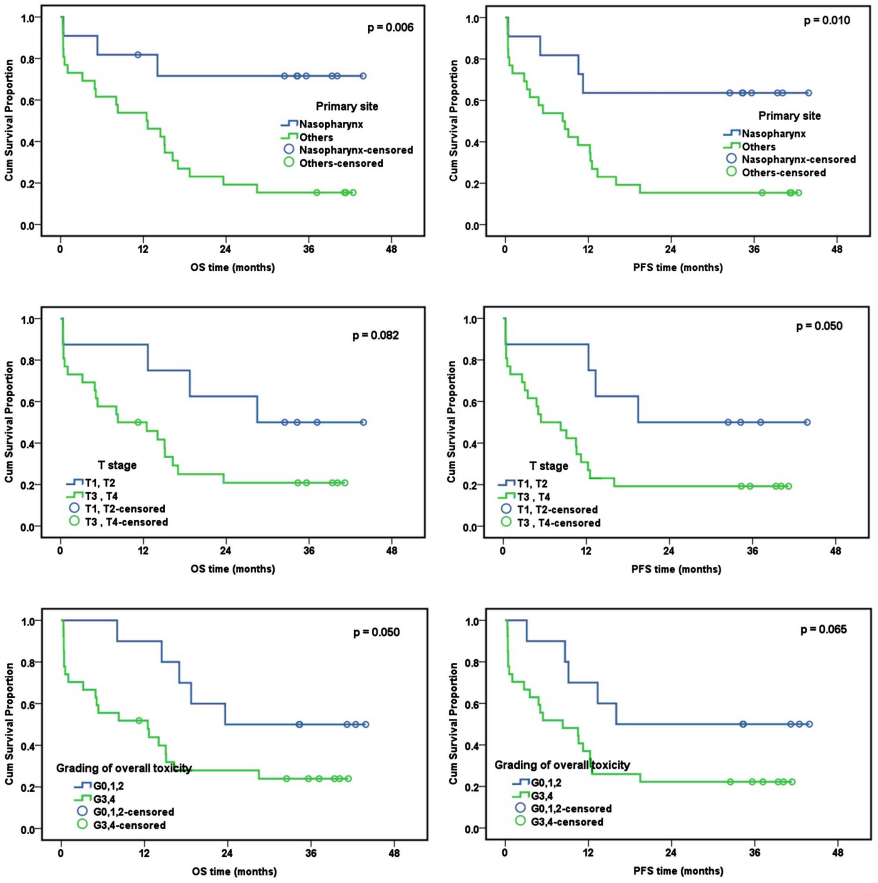

Figure 2. Relation between clinicopathological factors, toxicity with PFS and OS.

Table 5. Relation between clinicopathological factors, toxicity with PFS and OS.

		PFS				OS			
Prognostic factors	**Number of patients**	**PFS at 18 months**	**PFS at 36 months**	**Median PFS months**	**P-value**	**OS at 18 months**	**OS at 36 months**	**Median OS months**	**P-value**
Whole group	39	32.4%	29.7%	10.6		39.6%	31.1%	15.1	
Age									
≤47	20	25.0%	25.0%	8.6	0.45	33.0%	27.5%	14.0	0.604
>47	19	35.3%	35.3%	12.5		47.1%	35.3%	16.3	
Sex									
Male	18	17.6%	17.6%	10.5	0.22	25.9%	19.4%	14.0	0.258
Female	21	40.0%	40.0%	12.3		50.0%	40.0%	15.0	
Smoking									
Non-smoker	27	34.6%	34.6%	9.1	0.65	45.3%	37.1%	15.0	0.486
Smoker	12	18.2%	18.2%	10.6		27.3%	18.2%	14.5	
Primary site									
Nasopharynx	11	63.6%	63.6%	-	**0.01**	71.6%	71.7%	-	**0.006**
Other	28	15.4%	15.4%	8.2		26.9%	15.4%	12.7	
Histology									
SCC	23	18.2%	18.2%	8.6	0.089	31.8%	18.2%	12.6	0.071
Others	16	46.7%	46.7%	16.0		51.9%	51.9%	-	
Grade									
I and II	22	21.1%	21.1%	5.4	0.061	31.6%	21.1%	8.3	0.072
III and IV	17	41.2%	41.2%	13.3		50.7%	44.3%	18.7	
T-stage									
T1 and T2	12	50.0%	50.0%	19.5	**0.05**	62.5%	50.0%	28.5	0.082
T3 and T4	27	19.2%	19.2%	5.4		25.0%	20.8%	8.3	
N-stage									
N0 and N1	19	23.5%	23.5%	8.3	0.41	29.4%	23.5%	12.5	0.374
N2 and N3	20	35.0%	35.0%	11.2		43.1%	37.7%	16.3	
Grade 3 - 4 Toxicity*									
No	12	50.0%	50.0%	16.0	0.065	60.0%	50.0%	23.6	**0.05**
Yes	25	25.9%	22.2%	8.3		27.9%	23.9%	15.0	

*Analysis was done on the 37 patients who were assessed for toxicity. Patients who developed toxicity at any cycle where grouped together. Abbreviations: OS = overall survival; PFS = progression free survival; SCC = squamous cell carcinoma.

4. Discussion

While therapeutic options for HNCs have improved over the past 30 years, the survival for patients with advanced HNCs remained poor with high treatment related toxicity [13]. The DPF regimen is associated with extensive hematologic

toxicity and a high complication rates resulting in treatment delays and delivery of less number of planned cycles with subsequent impairment of treatment outcome [4].

Santini *et al.* [14], Fety *et al.* [15] and Gamelin *et al.* [16] prospectively studied 5-FU dose adjustment based on PK aiming to predict safe dose intensification with less toxic adverse effects; however, there is lack of prospective studies that tried to clarify the concept of modifying the dose of Docetaxel-based PKs to improve its therapeutic index [10]. To the best of our knowledge, our study is the first to prospectively investigate PK-based dose adjustment of both Docetaxel and 5-FU in DPF regimen used in advanced HNC.

Santini *et al.* [14] and Fety *et al.* [15] compared the effect of PK-based 5-FU dose adjustment in Cisplatin/5-FU (PF) regimen in advanced HNC to BSA-based PF (two arm studies).In the former study the CR in PK arm was 47.0 vs 31.0% in the BSA arm ($P < 0.050$), whereas in the second study ORR in PK arm was 81.7 vs 77.2% in BSA arm ($P = 0.030$), while in our study ORR was 89.6%. ORR in our study was higher than that achieved by Vermorken *et al.* [4] (67.8%) and Posner *et al.* [5] (72.0%) who used BSA-based DPF dosing in advanced HNC. Our results concur with that reported in the meta-analysis done by Fang *et al.* [17] and indicated that PK-guided strategy significantly improved the ORR compared with BSA-guided strategy ($P < 0.0001$). Matching with these results; Gamelin *et al.* [16] reported ORR in the PK arm was 33.6% vs 18.3% in the BSA arm ($P = 0.0004$).

In respect to DPF-associated toxicities observed in our study, they were consistent with that reported in other literature used BSA-based dosing including myelosuppression, diarrhea, mucositis, hand and foot syndrome, nausea, vomiting, neuropathy and febrile neutropenia. In the current study the treatment related serious side effects (G III & IV) and treatment related mortality after second and third cycles(PK-based) were significantly lowered when compared to that occurred after first cycle (BSA-based) ($P = 0.007$ and 0.01, respectively). These findings again are similar to the work of Santini *et al.* [14] and Fety *et al.* [15] where the incidence of GIII & IV toxicities were significantly lower in PK arm vs BSA arm. The frequency of G III & IV myelosuppression (neutropenia) after the third cycle in our study was lower in patients treated with PK-guided DPF dosing when compared with BSA-guided DPF dosing used in Vermorken *et al.* [4] and Posner *et al.* [5] (10.3% vs 76.9% vs 83%, respectively).

The correlation between age and PK dose adjustment was presented in ASCO 2005 by ten Tije *et al.* [18] and they found that Docetaxel plasma PKs are unaltered in elderly patients, yet they appeared to be more sensitive to Docetaxel-induced neutropenia. In our trial this correlation was not done due to the percentage of patients aged ≥ 65 years was only 2.6%.

In our study the Docetaxel dose necessary to successfully achieving the target AUC at cycle 3 ranged from 44.9% to 137.8% of the standard dose (75 mg/m^2). While the 5-FU dose necessary to achieve the target AUC at cycle 3 ranged from 31.2% to 147% of the standard dose (1000 mg/m^2). We attributed this finding to

the large intra-patient variability in Docetaxel and 5-FU exposure and this finding underline that no standard dose could be applied for all patients due to different plasma levels of drugs in each patient. The intra-patient variability may be due to administration time (circadian rhythm), PK sampling time, diet, concomitant medications and other environmental factors [9].

The main limitation of our study is the single-arm design, which did not allow for direct comparison of BSA& PK dosing strategies (in 2 different arms) regarding toxicity, tolerance and efficacy.

Also, the number of non evaluable (beyond stability) samples throughout the course of the study was high and this may be due to samples being withdrawn before or after the exact time of infusion and infusion time error reflecting the challenges of conducting this dosing approach. This suggests that experience and training would be necessary to correctly implement this dosing approach.

5. Conclusion

PK-based dose adjustment of Docetaxel and 5-FU in DPF regimen in advanced HNC significantly lowered serious toxicities and treatment related mortality with excellent response to treatment. We suggest that this strategy may be promising in effectively and safely delivering more cycles of chemotherapy without unneeded dose delay or reductions particularly in the setting of metastatic cancers where chemotherapy is the main line of treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

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