



Therapeutic Drug Monitoring of 5-Fluorouracil in Head and Neck Cancer Patients: An Interventional Pilot Study

P. Sharmila Nirojini¹ N.K. Bhuvaneshwari² N. Dharsshini² S. Dhivya Bharathi² K. Velavan³

¹Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy (Affiliated to the Dr. M.G.R. Medical University), Namakkal, Tamil Nadu, India

²Pharm D Intern, Swamy Vivekanandha College of Pharmacy (Affiliated to the Dr. M.G.R. Medical University), Namakkal, Tamil Nadu, India

³Radiation Oncologist, Erode Cancer Centre, Erode, Tamil Nadu, India

Address for correspondence P. Sharmila Nirojini, M.Pharm., PhD, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal (dt), Tamil Nadu, 637205, India (e-mail: sharmilapractice@gmail.com).

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Abstract

Introduction 5-fluorouracil (5-FU) is a crucial agent in treating various types of cancer, particularly recurrent head and neck cancers (HNCs). According to prior studies, individuals who underwent therapeutic drug monitoring (TDM) based 5-FU dosage adjustments showed significantly higher response rates and experienced fewer adverse events compared with those who received the standard 5-FU administration. This study aims to enhance our understanding of the overall clinical outcomes in patients with recurrent HNCs who received 500 mg of 5-FU through a pharmacokinetic (PK) analysis.

Objectives Our objectives are to conduct TDM in selected HNC patients and observe individual PK responses, efficacy, tolerability, and drug toxicity.

Materials and Methods We enrolled a total of 12 patients with recurrent metastatic HNC, and all of them received a fixed dose of 500 mg with cisplatin in a 21-day cycle. During cycle II or III, we analyzed the blood concentrations and PK parameters of 5-FU using the liquid chromatography and mass spectrometry (LC–MS) technique. Notably, we calculated the Concentration maximum (C_{max}), time at which the concentration reaches maximum (T_{max}), Half life of the drug ($T_{1/2}$), and area under the curve (AUC) for the 500-mg dose of 5-FU, as the PK data for this particular dose were unavailable, making our study uniquely valuable for assessing efficacy and toxicity.

Results Within the study group, 83.33% obtained an average AUC range of 1,000 to 3,000 h/μg/mL. Out of this group, 41.66% showed a partial response, 33.33% experienced disease progression, and 25% remained stable during the therapy. One patient had an AUC below the expected value (832.21 h/μg/mL), while another had an overexposed AUC value (5726.87 h/μg/mL), resulting in a poor clinical outcome. After interpreting the results, suggestions for dosage adjustments were made to the clinician.

Conclusion From our interventional study, it is evident that at a flat dose of 500 mg, PK-based individual dosage regimens play a superior role in managing advanced cancer patients with minimal toxicities. This PK analysis showed us clarity on the outcomes of 5-FU at a 500-mg dose.

Keywords

- ▶ 5-fluorouracil
- ▶ therapeutic drug monitoring
- ▶ head and neck cancer
- ▶ dosage adjustments

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Introduction

An antimetabolite chemotherapeutic molecule, 5-fluorouracil (5-FU), has been used in the last six decades to treat multiple cancers, including gastrointestinal (GI), breast, ovarian, and head and neck cancers (HNCs). Head and neck squamous cell carcinoma (HNSCC) refers to the majority of head and neck malignancies, which are generated from the mucosal epithelium in the oral cavity, pharynx, and larynx. In most of these, quantifying the efficacy and establishing an individualized dose is still challenging for health care professionals and researchers. 5-FU is the primary component of combination chemotherapy in patients with metastatic HNCs. Like other anticancer drugs, 5-FU is administered by body surface area (BSA) based dosing in most practices.¹ Numerous studies have clinically proven suboptimal and poor outcomes in colorectal cancers (CRCs) treated with 5-FU in different regimens, such as folinic acid, fluorouracil and oxaliplatin chemotherapy drugs (FOLFOX)² and folinic acid, fluorouracil and irinotecan chemotherapy drugs (FOLFIRI).³ But evaluating the efficacy of 5-FU in HNC has been stated in very few studies. Notably, stage III and IV locoregionally progressed tumors were found in roughly 60% of HNC patients.^{4,5} Many patients had stage IV (stage IVA) tumors out of the two stages. The typical patient survival time for stage IV HNC patients with metastatic and locoregionally progressed HNC was approximately 10 months, whereas nonmetastatic stage IV HNCs were treatable.⁶

Therapeutic drug monitoring (TDM) is a part of clinical therapy in which a patient's drug level is continuously monitored for the concentration of a specific medicine to ensure that their dose regimens are working as effectively as possible.⁷ TDM should be considered and recommended for improving the safety and efficacy of drugs with a narrow therapeutic index.⁸

The typical routine for administering 5-FU in concomitance with many anticancer drugs has been based on BSA, regardless of the regimen used.⁹ Sadly, BSA dosing cannot fit the needs of different body types and leads to a wide range of 5-FU exposure. A study with 81 patients with metastatic CRC documented a lack of association between BSA and 5-FU.¹⁰ An algorithm for 5-FU dosage adjustments was introduced by Wilhelm et al¹¹ in a study conducted in 14 HNC patients administered with cisplatin and a 5-day continuous infusion of 5-FU. Hillcoat et al reported a strong association between 5-FU plasma concentrations and tumor response in patients with GI malignancies in the 1970s.⁹ All the patients got nitrosourea 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) 150 mg/m² on the first day, followed by a 5-day continuous infusion of 5-FU at a rate of 1,200 mg/m²/d on days 1 to 5, delivered every 6 weeks. Measurements of plasma 5-FU concentrations revealed significant interpatient variability. Furthermore, the area under the curve (AUC) was found to be considerably larger in patients with either partial response (PR) or stable disease (SD) compared with those who did not have a tumor response. This first instance linked clinical data on 5-FU plasma exposure to clinical action. 5-FU is a highly saturable, narrow therapeutic index with a very

short half-life of 8 to 20 minutes. This favors the trend to adopt a pharmacokinetic (PK) based dosing in cancer patients. Clinical investigations from the past few decades have demonstrated that individual 5-FU dose titration with PK monitoring results in a high and effective survival rate, a high positive response, and good tolerability in CRC and HNC patients.^{12,13} The adverse event system of voluntary post-marketing reporting reviewed data from the U.S. Food and Drug Administration (FDA) suggested severe toxicities. Nausea, diarrhea, vomiting, mucositis, neutropenia, and palmar-plantar erythrodysesthesia (PPE) are examples of systemic Fluoropyrimidines (FP)-associated toxicities (FP-TOX).¹⁴

This pilot investigation enhances comprehension of disease progression, survival rate, and efficacy of chemotherapy in certain populations while providing updated information to clinicians on the safe and effective utilization of 5-FU. The main focus of this study is to examine the correlation between PK data and its impact on both treatment effectiveness and potential side effects when administering a constant 500-mg dose of 5-FU through intravenous infusion over 8 hours.

It is important to note that the actual treatment regimen involves a 2-day intravenous infusion of 5-FU + cisplatin, repeated every 21 days, with cisplatin playing a significant role in overall clinical outcomes. However, this evaluation specifically concentrates on observing the PK data of 5-FU at a flat dose of 500 mg.

Materials and Methods

Study Design

This is a prospective interventional study. Twelve patients diagnosed with advanced squamous cell carcinoma of the head and neck were studied in the Department of Clinical Research, Erode Cancer Centre, Tamil Nadu, India.

Inclusion and Exclusion Criteria

Recurrent HNC patients with normal renal, hepatic, and cardiac functions and good hematological status were included. Patients with renal failure or hepatic impairment, vulnerable populations (pediatrics and age above 75 years), obesity patients, medication histories, and those using drugs and alcohol that interfere with 5FU were excluded.

Primary and Secondary Objective

The primary objective was to perform TDM in selected HNC patients and to observe individual PK responses to the drug. The secondary objective is to assess the efficacy and tolerability based on PK values and monitor for toxicity and evaluate the overall clinical outcomes for the given dose.

Selection of Patients

Patients were selected based on the following criteria: (1) histologically confirmed and diagnosed with HNC; (2) recurrent metastatic disease; (3) no prior chemotherapy with 5-FU, and prescription of a 500-mg dose of 5-FU in cycles I and II; (4) WHO performance status of 0 to 2; and (5) tumor evaluations done with computed tomography (CT) scan,

magnetic resonance imaging (MRI), and biopsy. The sample size was determined based on the availability of patients during the study period.

Selected Patients and Sample Collection

Twelve recurrent metastatic HNC patients (8 males, 4 females) with a mean age of 55 years (range: 45–75 years) with histologically proven active stage III and IV cancers confirmed using TNM (tumor size, node involvement, and metastasis status) staging and with a history of past radiotherapy for primary tumors were enrolled for the study. Tumors were localized in the oropharynx ($n=4$), tongue ($n=4$), buccal mucosa ($n=2$), and esophagus ($n=1$). The performance status of all the patients was ≤ 2 . All the patients were given 5-FU and cisplatin throughout the study. Everyone was thoroughly evaluated based on a detailed history and HNC diagnostic and treatment criteria. We conducted relevant investigations, including positron emission tomography (PET) scans, CT and MRI, complete blood count (CBC), renal function test (RFT), liver function test (LFT), and electrocardiogram (ECG), frequently. A fine-needle aspiration cytology (FNAC) was done previously. A professional team of oncologists, pharmacists, nurses, and bioanalysts were involved throughout the study.

On day 0, patients were well hydrated with 5% dextrose (1 L), sodium chloride (NaCl; 6 g/L), and potassium chloride (KCl; 3 g/L). On day 1, 500 mL of dextrose was given with ondansetron (4 mg) and dexamethasone (8 mg). Later, 500 mg of 5-FU was mixed in 500 mL of normal saline (NS) and infused through an infusion pump at a rate of 1.41 mL/min (85 mL/h) for 6 hours. Blood samples were collected to estimate the drug concentration.¹⁵ Then 20 to 60 mg of cisplatin in NS was given as a 5-hour infusion. On day 2, 1 g of 5-FU was given as a 12-hour infusion, followed by the same dose of cisplatin.

Blood Sampling and PK Analysis

The optimization of extraction trial for 5-FU was done with a bioanalytical team. As a result, the mobile phase, flow rate, column, and internal standards were fixed. Accordingly, six time points for sample collection were framed, which included predose (5 minutes before dosing) and 00.50, 01.00, 02.00, 04.00, and 08.00 hours on day 1. More than 80% of 5-FU elimination was done by the catabolic process of the rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD).^{15,16} So the addition of DPD inhibitors is important for plasma separation. 5-FU has a short half-life of 10 to 15 minutes and would attain steady-state concentration in a few hours. In this, approximately 3 mL of venous blood was transferred to K2 EDTA (ethylenediaminetetraacetic acid) tubes and centrifuged in the laboratory immediately at 4,000 rpm for 10 minutes. The supernatant portion after precipitation was then transferred to respective aliquots and stored at -70°C until analyzed. All the samples were sent for PK analysis using the liquid chromatography and mass spectrometry (LC-MS) technique under controlled conditions.

Pharmacokinetic Investigation and Assessment

PK investigations were done. The AUC at 0 to 8 hours was calculated by the trapezoidal rule. Along with that, C_{max} , T_{max} , concentration of drug at last (Clast), time where concentration of drug is last (Tlast), volume of distribution (Vd), Concentration at steady state (C_{ss}), $T_{1/2}$, elimination rate constant (Ke), and clearance of drug (CL) for the flat dose of 500 mg for all the patients were recorded. For each patient, the 5-FU exposure based on AUC was compared with the average. The RECIST (response evaluation criteria in solid tumors) criteria were assessed for overall PK response.

Statistical Analysis

Descriptive statistics were deemed necessary to observe the percentages, mean standard deviation (SD) range, and median range for all patient demographic characteristics. The regression statistics were used for a comparison of the PK parameters. The level of significance was set at $p=0.05$. The software PK=SOLVER was used for most of the analyses (version 2.0; Microsoft Excel USA Software, Inc).

Ethics

This study was approved by the institutional ethical committee before the study began (approval reference number: SVCP/IEC/SEP/2021/09). All the procedures followed were under the ethical standards of the responsible committee on human experimentation and in compliance with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all the patients for inclusion in the present study.

Results

Patient Characteristics

The study performed TDM of 5-FU in 12 patients, comprising 8 males (66.6%) and 4 (66.6%) females, mostly falling under normal body mass index (BMI) and mean age of 45 to 55 (92.7%) and receiving 500 mg of 5-FU on day 1. In all, six (50%) and seven (58.3%) patients had no past medical and medication history, respectively. Of these, 5 (41.6%) were smokers and alcoholics in the past. Four of 12 (33.3%) patients had oropharyngeal cancer, and another 4 (33.3%) had tongue cancer. Seven patients (58%) had multiple metastatic lymph nodes. Toxicity was mild. Nausea experienced by 11 (91.66%) patients and there was grade 1 stomatitis in 1 (8.3%) patient. All the patients were coded between Therapeutic drug monitoring of 5-Fluorouracil of first patient (TDM5FU001) and TDM5FU012. Their basic characteristics of the patients are summarized in ► **Table 1**.

Pharmacokinetic Parameters

Overall, individual PK response from the selected population was appreciable (► **Table 2**). A considerable difference in disease progression with better therapeutic tolerance was noted with the flat dose of 500 mg of 5-FU. The target was not achieved by only two patients (► **Figs. 1** and **2**). Laboratory investigations were done pre- and postdosing and the corresponding observations for toxicity were done. Postdosing,

Table 1 Patient demographics

Patient characters		No. of patients (maximum, $n = 12$)
Gender	Male	8 (66.6%)
	Female	4 (33.3%)
Age (y)	45–55	7 (58.3%)
	56–65	4 (33.3%)
	66–75	1 (8.3%)
WHO performance status	0	3
	1	9
	2	0
Social History	Smoker	1 (8.3%)
	Alcoholic	1 (8.3%)
	Smoker and alcoholic	5 (41.6%)
	Betel nut	2 (16.6%)
	Smoking and betel nut	2 (16.5%)
	No social history	1 (8.3%)
BMI	Underweight	3 (25%)
	Normal	2 (16.6%)
	Overweight	7 (58.3%)
Diagnosis	Oropharyngeal cancer	4 (33.3%)
	Tongue cancer	4 (33.3%)
	Buccal mucosa cancer	2 (16.66%)
	Tonsil and esophageal cancer	2 (16.6%)

Abbreviation: BMI, body mass index.

Table 2 Observed pharmacokinetic (PK) values

PK parameters	Observed range	Deviated samples	
		Therapeutic drug monitoring of 5-Fluorouracil of fifth patient (TDM5FU005)	Therapeutic drug monitoring of 5-Fluorouracil in sixth patient (TDM5FU006)
Area under the curve	1,000–3,000 h/ μ g/mL	5.726.878	832.217
C_{max}	500–1,000 ng/mL	1819.322	335.056
T_{max}	00.50–01.00 h	02.00 h	00.50 h
Clearance	0.100–0.300 L/h	0.086	0.5536

hematological parameters (hemoglobin, RBC, platelet, lymphocytes, polymorphs, etc.) showed reduced count to pre-dosing blood count. There was an increase in the blood glucose range compared to the range before intervention. Nausea was predominantly seen in all samples and stomatitis with grade 1 was observed in one patient (**► Fig. 3**).

Comparison of Pharmacokinetics

Deviated samples: The AUC and tumor reduction were plotted in a normal probability plot using regression statistics (**► Fig. 4**). The R -value from the correlation using regression statistics was 0.16, that is, the R -value is progressing toward a positive factor. In the case of a large sample

population, the relation between AUC and tumor size reduction will be clearer.

Interpretation of the R value is as follows:

- 0: relation cannot be predicted.
- +1: positive relation between variables.
- -1: negative relation between variables.

The underdosed sample showed reduced C_{max} , T_{max} , and AUC and increased clearance, while the overdosed sample showed increased C_{max} , T_{max} , and AUC and reduced clearance. We have attained the expected target in 10 samples (84.4%).

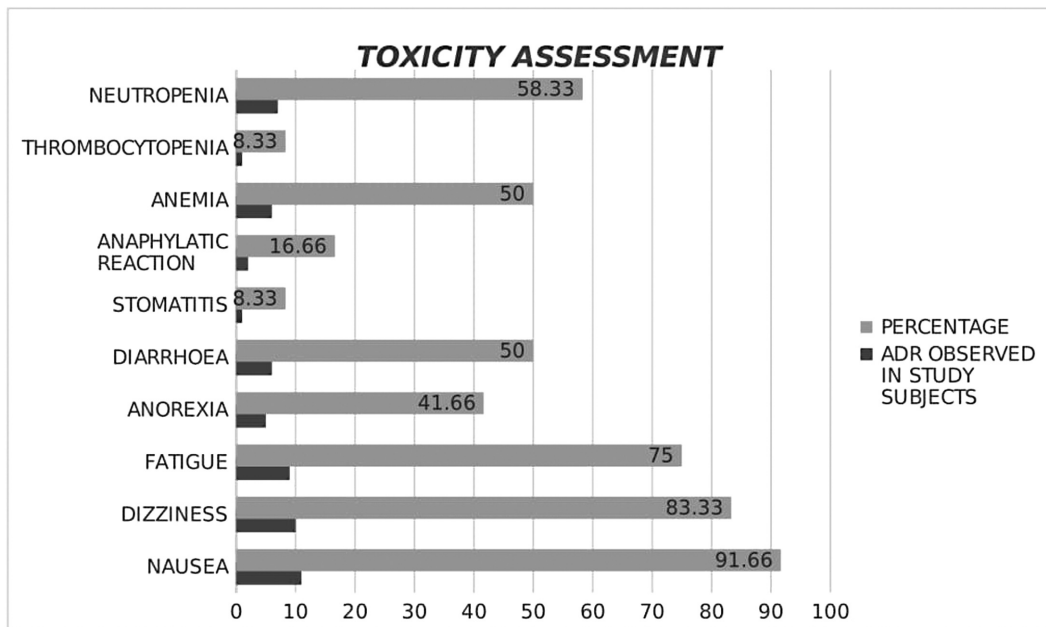


Fig. 1 Toxicity assessment of study population. Toxicity changes occurred in patient while on 5-fluorouracil treatment. Nausea and dizziness were predominant. ADR, adverse drug reaction.

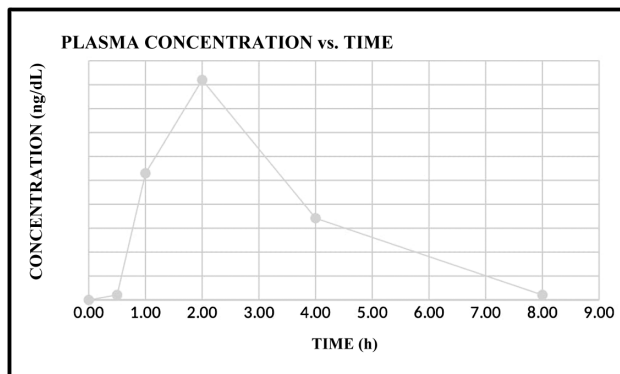


Fig. 2 Concentration versus time graph. A 64-year-old female patient of was on 5-fluorouracil treatment. Samples were collected and the concentration versus time graph was plotted and displayed. The graph shows the area under the curve concentration is increased, indicating the patient requires low dose.

$p = 0.615$ ($p > 0.05$): The p value calculated for the AUC range and intercept was greater than 0.05. So the AUC range and the outcome were not statistically significant. The result shows nonsignificance of the p value due to small sample size and disease progression. The results indicated that one (8.3%) patient was underdosed and showed decreased maximum concentration (C_{max}) and below the AUC range. One (8.3%) patient showed increased maximum concentration (C_{max}) and AUC range. Ten (84.4%) patients were under an optimum range.

Response Rate

The response evaluation was represented using the RECIST criteria for 12 subjects. PR was observed in five (41.66%) patients, disease progression in four (33.33%) patients, and stable response in three (25%) patients. No complete responses were observed.

Discussion

In advanced HNC, the main goal of chemotherapy is to relieve symptoms. Slightest increase in their response rate can improve their quality of life. In general, when administered as first-line therapy, combination chemotherapy has response rates that are 10 to 15% greater than those of single-agent chemotherapy (15–40%).^{17,18} Only a tiny proportion of patients with stage III or IV locoregionally progressed HNCs are treated by radiation or surgery. Concurrent radiation and chemotherapy treatment may yield better outcomes in terms of lifespan and disease-free life expectancies.¹⁹

Numerous studies have shown that an individual's response to chemotherapy is significantly influenced by the PK heterogeneity of 5-FU in them.^{2,20} Age-related changes in physiology and biological traits may affect the PK of medicines, alter plasma concentrations, and ultimately influence the acceptability and efficacy of chemotherapy. The variability in the steady-state concentration may also be due to changes in the infusion pump or drug collection. When therapy is based on BSA or a flat dose, the clearance of 5-FU exhibits significant intersubject variability that is not diminished. The BSA-based dose was personalized for individual patient dosing of chemotherapy drugs.²¹ Another major point is that the drug is unstable in blood and plasma at room temperature, while the catabolism of 5-FU is handled by the DPD enzyme.^{11,22–24} Many studies have been conducted to evaluate the efficacy of a dose-modifying algorithm and demonstrate the advantages of a 5-FU PK-guided dosing pattern for reducing toxicity and enhancing therapeutic outcomes, although BSA is an accepted method for determining 5-FU dosage. TDM and adjustment of the

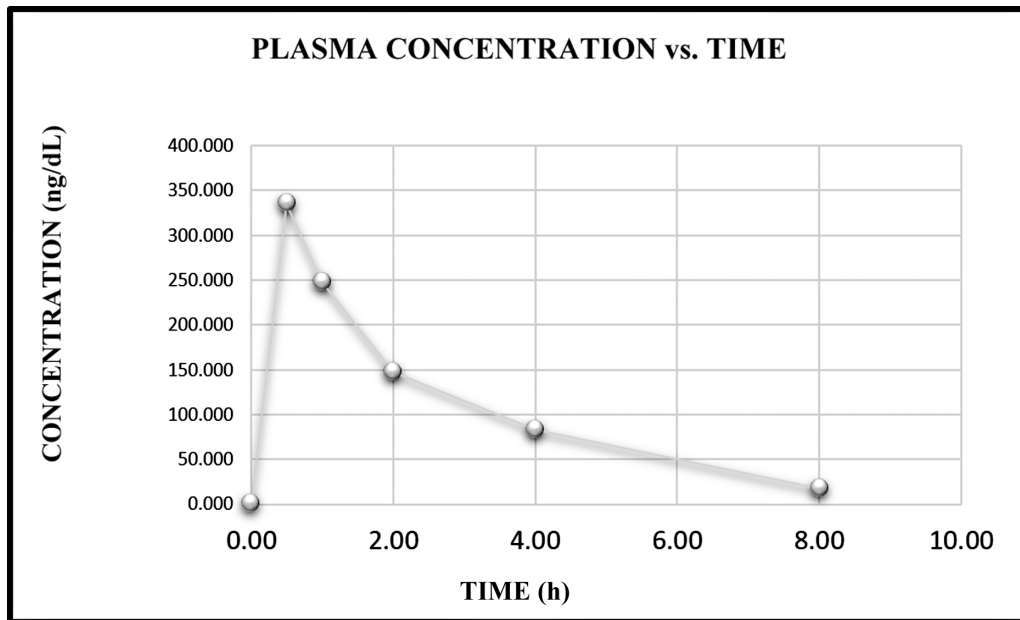


Fig. 3 Concentration versus time graph. A 53-year-old male patient was on 5-fluorouracil treatment. Samples were collected and the concentration versus time graph was plotted and displayed.

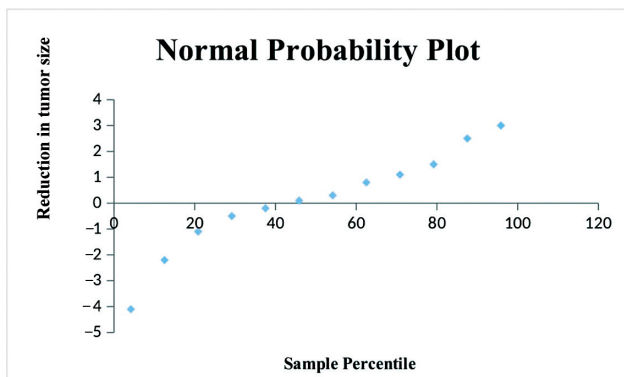


Fig. 4 The normal probability by regression statistics. The plot shows the regression graph of area under the curve concentration and tumor size reduction. The regression value is 0.16. It shows that the plot is moving toward a positive correlation.

5-FU concentration significantly improved the efficacy of chemotherapy.²⁵

In our study, we chose 12 recurrent HNC patients diagnosed with tongue cancer (4), oropharyngeal cancer (4), buccal mucosa cancer (2), tonsil cancer (1), and esophageal cancer (1) in palliative care who underwent combination chemotherapy of cisplatin and 5-FU. The age range was between 45 and 75 years. We found that increasing dosage in underdosed individuals may assist in minimizing toxicities and complaints from the present cycle to subsequent cycles in progressing malignancies. At the initial cycle, a flat 5-FU dose of 500 mg was administered. No difference in terms of the 5-FU combination was observed. However, all the patients received 500 mg of 5-FU + cisplatin on day 1 and 1,000 mg of 5-FU + cisplatin on day 2 as a cumulative total regimen for a 21-day cycle. As a reminder, for this study, individual dose adjustment was based on systemic exposure

measured from TDM. An average AUC range of 1,000 to 3,000 h/ μ g/mL was obtained in 83.33% of the group, with two exceptions. One was under the expected AUC (832.21 h/ μ g/mL) and one had an overexposed AUC value (5,726.87 h/ μ g/mL). Both cases showed wide variability in PK parameters.

This result led to an important variability in 5-FU steady-state concentrations, ranging from 130 to 541 mg/L for an identical total dose of 500 mg. The C_{ss} in two cases (16.66%) showed a significant change in their AUC and was subjected to poor clinical outcomes (i.e., disease progression). Similarly, the PK parameters of all the patients were interpreted according to the clinical outcome. PR was observed in 41.66% of the patients, disease progression in 33.33% patients, and SD in 25% patients. Suggestions for dosage adjustments were made to the clinician after interpreting the results. In Saam et al,² the 5-FU AUC was recorded for 4 cycles in 64 CRC patients prescribed with any regimen in which 5-FU was administered throughout 44 to 48 hours. The first measurement indicated that 68% of patients were underexposed, 13% were under the therapeutic range, and 19% had a superior AUC target level. A clinical trial conducted by Macaire et al focused on assessing the benefit-to-risk ratio in elderly individuals. The study investigated the relationship between 5FU exposure and toxicity while also comparing the effectiveness of 5FU therapeutic drug monitoring (TDM). The drug was monitored on cycle 1, and blood samples were drawn. Further dosage adjustments were made. Results showed a percentage difference between older and younger patients. The AUC of 5-FU at cycle 2 was 64% in older and 68% in younger patients. The toxicity level decreased compared with the first cycle after dose adjustment. Their results demonstrate that the vast majority of patients are not in the expected therapeutic range after receiving a standard 5-FU BSA-based dose. The high interindividual variability after dose adaptation testifies to a very limited interest in 5-FU

BSA-based dosing. Upon 5-FU PK-guided dose adjustment in subsequent cycles, a significant decrease in this variability was observed.²³ The clinical outcome was evaluated through imaging studies at the end of chemotherapy, and the interpretation revealed some publications describing increased rates of nausea, diarrhea, stomatitis, leukopenia, or neutropenia.^{11,23} In our investigation, after a standard flat dose of 500 mg, the following common toxicity symptoms were observed: nausea (91.66%), vomiting (25%), dizziness (83.33%), fatigue (75%), anorexia (41.66%), diarrhea (50%) and moderate stomatitis (8.33%), anaphylactic reaction (16.66%), anemia (50%), thrombocytopenia (8.33%), and neutropenia (58.33%). However, both toxicity and clinical outcome depend on the activity of 5-FU given with cisplatin as a combination therapy. We observed that grade III and IV toxicities were associated with a higher AUC range than grade I and II toxicities. Conversely, almost twice as many toxicities were observed among overexposed patients compared to patients who were underexposed or well exposed.

The results show that the flat dose gives a significant positive response in most cases along with lower toxicity. All 12 recurrent HNC patients in the study underwent TDM, and all the PK parameters were assessed. The target AUC was obtained in approximately 83.33 %. Dose alterations were made for the under- and over-exposed patients. Toxicities were mild and moderate with manageable conditions. Out of 12 subjects, 41.66 % showed PR, 33.33 % showed disease progression, and 25% were stable.

The main limitations of our study are the small sample size and the short study time. A multi-centered study with a large sample size might give more detailed and confirmatory reports of the relationship between dose and clinical response of 5-FU at a flat dose.

Future studies should come up with preemptive pharmacogenetic testing that confidently enhances 5-FU exposure in a significant number of patients. Despite the abundance of positive shreds of evidence supporting the 5-FU TDM, the clinical routine of PK tests has not been widely established. To fully enter the era of precision medicine, a model framework incorporating the PK and pharmacodynamics of 5-FU will be necessary. The use of model applications may also help clinicians determine the appropriate dose before beginning chemotherapy.

Conclusion

From our interventional study, it is evident that at a flat dose of 500 mg, PK-based individual dosage regimens play a superior role in managing advanced cancer patients with minimal toxicity. The study population involving 12 recurrent HNC patients underwent TDM, and all the PK parameters were assessed. The target AUC was obtained in approximately 83.33% of patients. Two patients who deviated from the expected therapeutic window were considered for dosage adjustments. The dose was increased to 750 mg + 1 g in patient 6 in the next cycle and patient 5 was prescribed 350 mg + 750 mg by the clinician. PR was observed in 41.66% patients, disease progression in 33.33%,

and SD in 25% patients. This PK analysis showed clarity on the outcomes of 5-FU at a 500-mg dose.

A small sample size and a non-PK-based dosage regimen before TDM may be the cause of the nonsignificance of our results. However, the significance of a sample size of 12 showed positive progress with a regression value of 0.16. Increasing the sample size to more than 30 with extended follow-up can have a greater impact by establishing a detailed PK response for 500 mg of 5-FU. This single-center pilot study gives hope for managing advanced HNC patients with flat doses for better tolerability while reducing toxicity. Its precise role in the management of HNC remains to be determined at a larger scale.

Author Contributions

N.K.B, N.D., and S.D.B. were responsible for the concept and design of the study, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and literature search. Critical revision of the manuscript for important intellectual content was done by K.V. and P.S.N. They also provided administrative, technical, or logistic support. PSN contributed to design the study protocol and supervised the study.

Statement

The manuscript has been read and approved by all the authors, and the requirements for authorship have been met.

Patient Consent

The consent from the patient has been taken to participate on this study.

Funding

None declared.

Conflict of Interest

None declared.

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