Toxicity analysis of docetaxel, cisplatin, and 5-fluorouracil neoadjuvant chemotherapy in Indian patients with head and neck cancers

Vijay M Patil, MBBS, MD, DM,[a] Vanita Noronha, MBBS, MD, DM,[a] Amit Joshi, MBBS, MD, DM,[a] Anuradha Majumdar, PhD,[b] Nilambari Sawardekar, BPharm,[b] Anant Ramaswamy, MBBS, MD, DM,[a] and Kumar Prabhash, MBBS, MD, DM[a]

[a]Department of Medical Oncology, Tata Memorial Hospital, and [b]Department of Pharmacology, Bombay College of Pharmacy, Mumbai, India

Background There is a lack of data that systematically address toxicity with docetaxel, cisplatin, and 5-fluorouracil (TPF) regimen in routine care.
Objective To detect, profile, and quantify the toxicity in Indian patients with head and neck cancers who received neoadjuvant TPF chemotherapy in a routine clinical practice (non-trial setting).
Methods 58 patients with locally advanced head and neck cancer who received TPF chemotherapy were selected for this analysis. They received 2 cycles of TPF chemotherapy every 21 days. The patients were monitored for the occurrence of adverse drug reactions in accordance with Common Terminology Criteria for Adverse Events (version 4.03) during the hospitalization (median length of stay in cycle 1, 10 days), daily (at least until day 8 after chemotherapy initiation), then at days 15 and 20. Descriptive statistics was done and factors predicting for toxicity were identified using logistic regression analysis.
Results The cumulative rate of grade ≥3 anemia, neutropenia, and thrombocytopenia were 12.1%, 56.9%, and 5.2%, respectively. The cumulative incidence of febrile neutropenia was 20.7% (12 of 58 patients). The cumulative incidences of mucositis and diarrhea were 67.2% and 74.1%, respectively. There was no mortality associated with induction chemotherapy, and all of the patients completed the planned 2 cycles of TPF. None of the tested factors predicted for any of the adverse events considered in the study.
Limitations Small, single-center study
Conclusion The incidence of TPF-related toxicity in Indian patients in routine practice is high, and the toxicities differ substantially from the toxicities seen in trial settings.

Docetaxel, cisplatin, and 5-fluorouracil (TPF) neoadjuvant chemotherapy is an established standard regimen in patients with head and neck cancer.[1,2] Although the efficacy of TPF combination chemotherapy has been well established through clinical trials, the regimen is toxic.[3-6] The most common adverse drug effects reported with this regimen are neutropenia, anemia, thrombocytopenia, fatigue, mucositis, diarrhea, nausea, and vomiting. The incidence of febrile neutropenia (FN) reported in clinical studies varies from that seen in routine clinical practice. The incidence of FN reported in the TAX 323 & 324 studies was 5.2% and 4.8%, respectively.[2,7] However, higher rates of FN (34.6%-58.3%) have been reported from Indian series.[3,5] Similarly, a high mortality rate of 14.0% was reported in a study from California with the routine use of TPF in patients with a low socioeconomic status.[6]

In India, concerns about morbidity and mortality associated with the TPF regimen resulted in oncologists using modified versions of TPF or conversion of the regimen to a 2-drug combination of platinum and taxane as a neoadjuvant chemotherapy.[8,9] To the best of our knowledge, we are not aware of any national or international data that systematically characterize the TPF toxicities associated with the regimen in routine non-trial practice. We planned this study to detect, profile, and quantify the toxicity of TPF in Indian patients with head and neck

Accepted for publication August 16, 2016. Correspondence: Kumar Prabhash, MBBS, MD, DM; kumarprabhashtmh@gmail.com. Disclosures: The authors report no disclosures or conflicts of interest. JCSO 2016;14(10):412-419. doi: 10.12788/jcso.0292.

cancer who received neoadjuvant chemotherapy in routine clinical practice.

Patients and methods

Study population

Patients with locally advanced head and neck cancers who had been assigned to receive TPF combination chemotherapy as standard care were enrolled in the study if they fulfilled the following criteria: they were older than 18years; they had received a histological diagnosis of squamous cell carcinoma of the head-neck region; they had an ECOG performance status 0-1; they were willing to participate in follow-up; and they had not previously received induction chemotherapy outside of the center.

The patients who met the criteria (58 of 512) had undergone a staging contrast-enhanced, axial computed-tomography (CT) scan of head and neck region and a chest X-ray. Neck nodes that were radiologically more than 1 cm in short axis dimension or that had a round shape and central necrosis were considered as positive. Neck nodes that were radiologically indeterminate but suspicious were confirmed by fine-needle aspiration. The results of these scans and imaging were subsequently discussed at a multidisciplinary clinic, and 58 patients were referred for neoadjuvant chemotherapy. The referral pattern for neoadjuvant chemotherapy at our institute has been reported by us.[10]

Procedure

The patients received 2 cycles of standard TPF chemotherapy every 3 weeks. The protocol consisted of docetaxel 75 mg/m^{2}on day 1, cisplatin 75 mg/m^2 or carboplatin (area under the curve calculated by Calvert formula) 5 on day 1, and 5-fluorouracil 750 mg/m^2 a day on days 1-5 as a continuous 24-hour intravenous infusion. All of the patients received routine premedication with antiemetics, including 5HT3 anatagonists, aprepitant, and dexamethasone. Granulocyte-colony stimulating factor (G-CSF) was administered daily to the patients on days 7-10. Dose reductions and modifications were done during the induction chemotherapy according to previously published reports.[11] Patients who had a partial response to induction TPF received a third cycle of TPF before definitive local therapy. We have reported the method of selection of definitive treatment and its outcomes in our setting.[12]

All the patients were admitted for TPF. Patients were monitored by a pharmacologist (NS) for the occurrence of adverse drug reactions during the period of hospitalization daily (at least until day 8 after initiation of chemotherapy) then on days 15 and 20. NS monitored the patients for the development of adverse events and documented them daily during the period of hospitalization on a predesigned case report form. NS also did the charting on days 15 and 20. Toxicity was graded using the Common Terminology Criteria for Adverse Events (version 4.03).

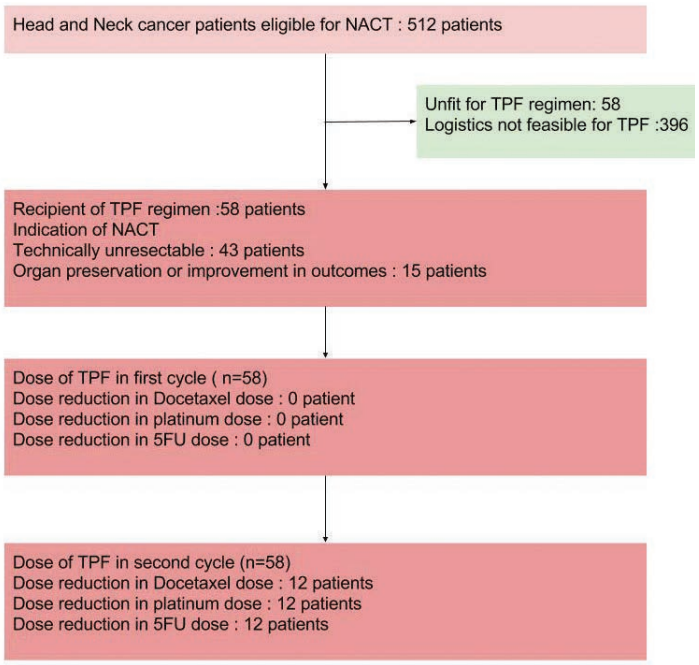

FIGURE 1 Flow diagram of patient selection and treatment processes.

Analysis

The case report form data were entered and analyzed (using SPSS version 16) for demographic details, baseline nutritional parameters, drug details, and severity of adverse drug reactions. Descriptive statistics were also done. Predictive markers for toxicity were sought. They were: age (younger or older than 60 years), gender (male or female), ECOG performance status (0 or 1), body-mass index (below or above 16.0 kg/m^2), albumin level (below or above 3.5 g/dL), hemoglobin (below or above 11.5 g/dL), presence of comorbidities, and serum creatinine clearance (below or above 60 ml/min). Binary logistic regression analysis was performed to identify possible predictive factors.

Results

Demographic characteristics

In all, 58 patients were enrolled in the study during July 2014-June 2015 (Figure 1). The median age was 43.5 years (range, 21-64 years), 36 patients (62.07%) had a history of tobacco use and of those,10 (17.25%) were smokers (Table 1). The median BMI was 23.16 kg/m^2 (range, 14.53-45.14 kg/m^2). The median baseline hemoglobin and serum albumin levels were 13.8 g/dL (range, 9.4-16.5 g/dL) and 4.15 g/dL (range, 3.4-4.9 g/dL), respectively.

Tumor details

The sites of tumor were oral cavity in 39 patients (67.24%), nasopharynx in 13 (22.39%), oropharynx in 2 (3.45%), hypopharynx , larynx maxillary sinus, and unknown pri-

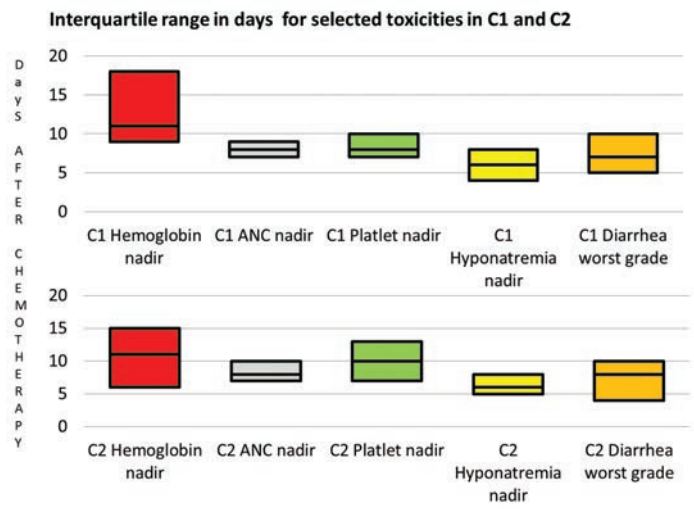

FIGURE 2 Occurrence of worst grade toxicity after start of first and second cycles of chemotherapy.

ANC, absolute neutrophil count; C1, cycle 1; C2, cycle 2

TABLE 1 Patient characteristics and tumor features

Variable	n (%)
Median age, y (range): 43.5 (21-64)	—
Gender	
Male	48 (82.75)
Female	10 (17.25)
ECOG PS	
0	48 (82.75)
1	10 (17.25)
Comorbidities	
None	53 (91.38)
Type II diabetes	2 (3.45)
Hypertension	3 (5.17)
Site of tumor	
Oral cavity	39 (67.24)
Nasopharynx	13 (22.39)
Oropharynx	2 (3.45)
Hypopharynx	1 (1.73)
Larynx	1 (1.73)
Maxillary sinus	1 (1.73)
Unknown primary	1 (1.73)
Indication of neoadjuvant chemotherapy	
Tumor classification	
1-2	8 (13.79)
3	3 (6.9)
4a	31 (53.45)
4b	15 (25.86)
Node classification	
0	5 (8.62)
1	11 (18.97)
2	36 (62.07)
3	6 (10.34)
Stage	
IVA	40 (68.97)
IVB	18 (31.03)

ECOG PS, Eastern Cooperative Oncology Group Performance Score

mary in 1 patient (1.73%) each, respectively. The of the total, 40 patients (68.97%) had stage IVA disease, and 18 (31.03%), stage IVB (see Table 1).

Chemotherapy compliance and dose reductions

All of the patients completed 2 cycles of induction chemotherapy. Dose reduction was required in 12 patients in second cycle, with 11 patients getting 20% dose reductions in all 3 drugs, and 1 patient getting a 25% dose reduction in all 3 drugs. The third cycle was received by 28 patients.

Toxicity

The incidence of hematological, biochemical, and clinical toxicities during cycle 1 (C1) and cycle 2 (C2) are shown in Table2. The cumulative incidence of highest grade of common toxicities during the whole regimen is shown in Table 3. There was no mortality during this period.

Hematological toxicity. The rates of grade 3-4 anemia, neutropenia, and thrombocytopenia in C1 were 5.2%, 41.4%, and 3.4 % respectively. The rates of grade 3-4 anemia, neutropenia, and thrombocytopenia in C2 were 8.6%, 37.9%, and 3.4 % respectively. The cumulative rates of grade 3-4 anemia, neutropenia and thrombocytopenia over the 2 cycles were 12.1%, 56.9% and 5.2 % respectively. The median time to recovery of hematological events in C1 andC2 is shown in Figure 2.

Hemoglobin recovery. A drop in hemoglobin level in C1 (drop from baseline hemoglobin) was seen in 51 patients (87.9%). The median hemoglobin drop in C1 was 2.5 g/dL (interquartile range [IQR], 1.7-3.3g/dL). The median day of nadir hemoglobin drop was day 11 (IQR,days 9-18) in C1. A drop in hemoglobin level in C2 (drop from C1 hemoglobin) was seen in 40 patients (68.9%). The median hemoglobin drop in C2 was 0.9 g/dL (IQR, 0.5-2.0g/dL). The median day of nadir hemoglobin drop was day 11 (IQR,days 6-15) in C2. None of the tested factors pre-

TABLE 2 Hematologic, biochemical, and clinical toxicities for cycles 1 and 2 of chemotherapy.

Toxicity	Grade, no. of patients			
	1	2	3	4
Cycle 1				
Anemia	17	15	3	0
Neutropenia	5	4	9	15
Febrile neutropenia	NA	NA	3	8
Thrombocytopenia	26	6	1	1
Hyponatremia	20	NA	34	2
Hypokalemia	0	15	17	1
Hypomagnesemia	17	1	0	3
Transaminitis				
Rise in SGOT	21	6	1	0
Rise in SGPT	13	1	0	0
Bilirubin elevation	11	5	0	0
Creatinine elevation	6	0	0	0
Nausea	13	2	0	0
Vomiting	12	6	1	0
Anorexia	12	1	0	0
Fatigue	8	7	0	0
Myalgia	4	0	0	0
Fever	14	3	0	0
Mucositis	15	11	9	0
Constipation	02	3	0	0
Diarrhea	15	10	11	3
ACS	0	3	0	0
Dyspepsia	5	1	0	0
Allergic reaction	0	0	0	0
Cycle 2				
Anemia	27	13	4	1
Neutropenia	4	5	13	9
Febrile neutropenia	NA	NA	1	2
Thrombocytopenia	23	6	1	1
Hyponatremia	31	NA	23	0
Hypokalemia	0	24	9	4
Hypomagnesemia	29	2	3	0
Transaminitis				
Rise in SGOT	10	1	0	0
Rise in SGPT	22	2	2	0
Bilirubin elevation	3	4	0	0
Creatinine elevation	4	0	0	0
Nausea	5	4	0	0
Vomiting	6	3	1	0

Continued on next page

Continued from previous page

Toxicity	Grade, no. of patients			
	1	2	3	4
Anorexia	2	1	0	0
Fatigue	5	1	0	0
Myalgia	3	1	0	0
Fever	8	0	0	0
Mucositis	9	3	4	0
Constipation	6	2	0	0
Diarrhea	11	7	4	0
ACS	0	0	0	0
Dyspepsia	3	1	0	0
Allergic reaction	0	0	0	0

ACS, acute coronary syndrome; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

dicted for grade 3-4 anemia in C1.

Neutrophil recovery. The drop in absolute neutrophil count (ANC) of at least grade 1 was seen in 36 patients (62.1%) in C1 and in 31 patients (53.4%) in C2. The median nadir ANC in C1 was 0.63 x 10^9/L (IQR, 0.2-1.2 x 10^9/L) and 0.67 x 10^9/L (IQR, 0.5-1.1 x 10^9/L) in C2. The median day of attainment of nadir ANC was on day 8 after chemotherapy initiation (IQR, days 7-9) in C1. In C2 as well, the median day of nadir ANC was on day 8 after chemotherapy initiation (IQR, days 7-10). None of the tested factors predicted for the development of grade 3-4 neutropenia in C1.

Platelet recovery. Any grade thrombocytopenia was seen in 34 patients (58.6%) in C1 and in 31 patients (53.4%) in C2. The median day of nadir platelet drop was day 8 (IQR, days 7-10) in C1, and day 10 (IQR, days 7-13) in C2.

Febrile neutropenia. The incidence of FN in C1 and C2 was 19.0% (11 patients) and 5.2% (3 patients), respectively. The cumulative incidence of FN over the whole regimen was 20.7% (12 patients). None of the tested factors predicted for occurrence of FN.

Non-hematological toxicity

Electrolyte imbalance. The cumulative incidence of any grade hyponatremia during the regimen was 98.3% (57 patients). The rates of grade 3-4 hyponatremia were 62.1%in C1 and 39.7% in C2. The median day of the nadir drop in sodium was day 6 (IQR, days 4-6) in C1 and day 6(IQR, days 5-8) in C2. The 95% percentile for the day of nadir drop in sodium in C1 was day 10 and day 13 in C2.

The cumulative incidence of hypokalemia during the regimen was 79.3% (46 patients). The rates of grade 3-4 hypokalemia were 31.3 %.in C1 and 22.4% in C2. The median days of nadir drop in potassium were day 8(IQR, days 7-12) in C1 and day 9 (IQR, days 7-12) in C2.

Diarrhea and mucositis. The cumulative incidence of mucositis during the course of the 2 cycles of chemotherapy was 67.2%. The rates of grade 2-4 mucositis were 34.5% in C1 and 12.1% in C2. The worst grade of mucositis was on day 7 (IQR, days 5-10) in C1 and day 9 (IQR, days 5-10) in C2.None of the tested factors predicted for the occurrence of mucositis.

The cumulative incidence of diarrhea during the course of 2 cycles of chemotherapy was 74.1%. The rates of grade 2-4 diarrhea were 41.4% in C1 and 19.0% in C2. The worst grade of diarrhea was on day 6 (IQR, days 4-9) in C1 and on day 8 (IQR, days 4-10) in C2. None of the tested factors predicted for the development of diarrhea.

Vomiting. The rates of grade 2-4 vomiting were 12.1% in C1 and 6.9% in C2. The worst grade of vomiting was on day 8 (IQR, days 5-10) in C1 and on day 5 (IQR, days 3-8) in C2.

Discussion

Neoadjuvant chemotherapy is one of the important components in the armamentarium of head and neck cancer medical oncologists. When used appropriately, it has the ability to improve organ preservation rates and probably improve overall survival as well.[11] In India, neoadjuvant chemotherapy is commonly used to treat borderline resectable or technically unresectable tumors to improve local control and survival.[20] However, in both India and Western countries there are concerns about the toxicity of TPF che-

TABLE 3 Selected common cumulative toxicities for cylces 1 and 2. Only the highest grade of toxicity is shown. Each patients is been represented only once

Toxicity	Grade, no. of patients			
	1	2	3	4
Anemia	24	17	6	1
Neutropenia	3	7	15	18
Febrile neutropenia	NA	NA	3	9
Thrombocytopenia	28	09	1	2
Hyponatremia	16	NA	39	2
Hypokalemia	23	0	18	5
Hypomagnesemia	30	0	2	6
Creatinine elevation	10	0	0	0
Transaminitis				
Rise in SGOT	18	2	0	0
Rise in SGPT	28	7	2	0
Bilirubin elevation	11	8	0	0
Mucositis	15	14	10	0
Diarrhea	16	10	14	3

NA, not applicable; SGOT, serum glutamic oxaloacetic transaminase;SGPT, serum glutamic pyruvic transaminase

motherapy, which in turn leads to poor compliance with local definitive treatment following induction chemotherapy. Hence, the ability to predict which patients will develop excessive toxicity from induction chemotherapy is very important.

We attempted to identify simple clinical features that might help predict toxicity in our patients, but were not able to identify any clinical factor associated with toxicity. This might have been because of the systematic selection process we follow before assigning patients to the TPF regimen. Before assignment, we evaluate performance status, nutritional status, comorbidities, organ function, and whether they are able to pay for the therapy. Patients as assigned to TPF only if they have a performance status of 0-1, adequate organ function, no uncontrolled comorbidities, and can afford to pay for the regimen. Each of these selection criterion predispose not only to morbidity but to mortality associated with induction chemotherapy.[6,9] Possibly because of this strict selection process, we had 0% mortality and 100% compliance to induction chemotherapy.

The importance of hospitalization and monitoring was highlighted in this study. It is important to understand that TPF leads to a high rate of grade 3-4 complications in

TABLE 4 Comparison of toxicity of TPF regimen in published literature with present series. Only grade 3-4 toxicities are shown.

Author	No. of cycles	Neutropenia (%)	Febrile neutropenia (%)	Diarrhea (%)	Mucositis/ Stomatitis (%)	Hyponatremia (%)
Pointerau[13]	3	31.5[a]	10.9	NR	7.8	NR
Paccagnella[14]	3	52.0	8.0	NR[b]	6.0	NR[b]
Vermorken[7]	4	76.9	5.2	2.9	4.6	NR
Posner[2]	4	83.0	12.0	7.0	21.0	NR
Hitt[15]	3	15.7	17.0	7.2	9.1	5.3
Cohen[16]	2	11.0	NR	5.1	8.8	5.1
Present series	2	56.9	20.7	29.3	17.2	70.7

NR, not reported; TPF, docetaxel, cisplatin, and 5-fluorouracil

[a]Only grade 4 toxicity reported. [b]Only toxicity above 2% were reported.

Indian patients (> 80%) and hence it is prudent to monitor for these complications as an inpatient. In the majority of the patients, the nadir drop in ANC, platelet, and hemoglobin had occurred by day 10 after TPF initiation. The common non-hematological side effects such as mucositis and diarrhea (worst grade) had also appeared by day 10. On the basis of these findings, we would recommend inpatient admission and monitoring of patients clinically and by laboratory parameters until at least day 10 after TPF initiation. The laboratory parameters of complete blood count, renal function test, and serum electrolytes should be done daily from day 4until day 10so that laboratory abnormalities can be promptly addressed.

In Table 4, we have compared the toxicity noted in this series to that reported in other studies. It is expected that the cumulative highest grade toxicities that have been reported in various studies would vary depending on the doses of each individual drug, the number of cycles delivered and the supportive care available. All of the series that we have selected for comparison have reported on TPF toxicity and have used the same doses of TPF as used in our series. However it can be appreciated from table 4 that the number of cycles of chemotherapy varied between 2-4 across different series.[2,11,13–16]Further the supportive care provided also differed between these series. Prophylactic antibiotics were used in TAX 323 study, TAX 324 study and in the study reported by Paccagnella and colleagues.[2,7,14] Both primary G-CSF prophylaxis and prophylactic antibiotics used in the study reported by Hitt and colleagues.[15] However, only primary G-CSF prophylaxis was used in the DeCIDE study.[16] In comparison to these, we used only primary G-CSF prophylaxis only in our current series. The use of primary G-CSF prophylaxis is mandated by guidelines when the incidence of FN is 20% or above.[17]In our previous experiences with the TPF regimen, our incidence of FN was higher than this and hence we routinely use primary G-CSF prophylaxis.[5] Interestingly even in the study reported by Hitt and colleagues, primary G-CSF prophylaxis was not a part of initial protocol but the protocol had to be amended to include primary G-CSF prophylaxis, as the incidence of FN was high.[15] Although most of the series have used prophylactic antibiotics, the use of this is not supported by the American Society of Clinical Oncology (ASCO) guidelines and additionally, the use of prophylactic antibiotics for gram positive coverage may not be very relevant in countries like India where the predominant bacteria causing FN are still gram negative.[18,19] Hence in our patients, prophylactic antibiotics were not used but there might be a case for use of gram negative antibiotic prophylaxis.

However, the lack of prophylactic antibiotics cannot be the reason for the differences in toxicity that we have reported in our present series as compared to other trials reported in the literature. In spite of primary G-CSF prophylaxis and use of only 2 cycles of TPF in our present series, we had an FN rate of 20.7%. The corresponding numbers in the TAX studies without primary growth factor prophylaxis were 5.2 to 12.0%.[2,7] Similarly, we noted a higher rate of diarrhea, mucositis and hyponatremia. Consistently, the incidence of these toxicities was reported below 10% in international studies. It is possible that these 3 toxicities are interrelated, potentially due to 5FU-induced gastrointestinal toxicity, which leads to mucositis and diarrhea and manifests as hyponatremia. It is interesting that the incidence of grade 3-4 hyponatremia has been found to be very low amongst a majority of published data. However, in a retrospective series reported from Japan by Izawa, hyponatremia was one of the commonest side effects noted following TPF induction.[20]Probably the difference lies in the pharmacogenomics of the Asian population. Recently we have noted a high incidence of DPD (dihydropyrimidine dehydrogenase enzyme) mutation in our series of head and neck cancer patients receiving induction chemotherapy (unpublished data).DPD mutations are known to be associated with an increased incidence of myelosuppression and gastrointestinal side effects.[21] However this finding alone probably cannot explain the difference in the toxicity spectrum and hence we are planning a detailed pharmacogenomic analysis of these patients in future.

Conclusion

The toxicity of TPF in Indian patients differs substantially from that in the western population. Strict selection criteria similar to that seen in clinical trials thereby preempting adverse events, prompt treatment of toxicity and adequate supportive care can ensure high compliance to completion of induction chemotherapy with low mortality. In view of the high incidence of grade 3-4 toxicity, high rate of febrile neutropenia, we recommend administering ofTPF as an indoor event and to monitor these patients for toxicity for at least 5 days after the completion of TPF regimen. Pharmacogenomics of Indian patients need to be performed to address the differential toxicity noted in our patients.

References

1. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013;14(3):257-264.
2. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007;357(17):1705-1715.
3. Patil VM, Chakraborty S, Shenoy PK, et al. Tolerance and toxicity of neoadjuvant docetaxel, cisplatin and 5 fluorouracil regimen in techni-

cally unresectable oral cancer in resource limited rural based tertiary cancer center. Indian J Cancer. 2014;51(1):69.
4. Noronha V, Patil VM, Joshi A, et al. Induction chemotherapy in technically unresectable locally advanced carcinoma of maxillary sinus. Chemother Res Pract. 2014;2014:487872.
5. Patil VM, Noronha V, Joshi A, et al. Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: does it make a difference? Indian J Cancer. 2013;50(1):1-8.
6. Caudell JJ, Hamilton RD, Otto KJ, Jennelle RL, Pitman KT, Vijayakumar S. Induction docetaxel, Cisplatin, and 5-Fluorouracil precludes definitive chemoradiotherapy in a substantial proportion of patients with head and neck cancer in a low socioeconomic status population. Am J Clin Oncol. 2014;37(4):332-336.
7. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007;357(17):1695-1704.
8. Somani N, Goyal S, Pasricha R, et al. Sequential therapy (triple drug-based induction chemotherapy followed by concurrent chemoradiotherapy) in locally advanced inoperable head and neck cancer patients – single institute experience. Indian J Med Paediatr Oncol. 2011;32(2):86-91.
9. Patil VM, Noronha V, Joshi A, et al. Weekly chemotherapy as Induction chemotherapy in locally advanced head and neck cancer for patients ineligible for 3 weekly maximum tolerable dose chemotherapy. Indian J Cancer. 2014;51(1):20-24.
10. Patil VM, Noronha V, Joshi A, et al. Referral pattern for neoadjuvant chemotherapy in the head and neck cancers in a tertiary care center. Indian J Cancer. 2014;51(2):100-103.
11. Schrijvers D, Van Herpen C, Kerger J, et al. Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I–II feasibility study. Ann Oncol. 2004;15(4):638-645.
12. Patil VM, Prabhash K, Noronha V, et al. Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. Oral Oncol. 2014;50(10):1000-1004.
13. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst. 2009;101(7):498-506.
14. Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol. 2010;21(7):1515-1522.
15. Hitt R, Grau JJ, López-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol. 2013:mdt461.
16. Cohen EEW, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014;32(25):2735-2743.
17. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33(28):3199-3212.
18. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013;31(6):794-810.
19. Prabhash K, Medhekar A, Ghadyalpatil N, et al. Blood stream infections in cancer patients: a single center experience of isolates and sensitivity pattern. Indian J Cancer. 2010;47(2):184-188.
20. Izawa N, Onozawa Y, Hikosaka T, et al. Efficacy and feasibility of docetaxel, cisplatin, and 5-fluorouracil induction chemotherapy for locally advanced head and neck squamous cell carcinoma classified as clinical nodal stage N2c, N3, or N2b with supraclavicular lymph node metastases. Int J Clin Oncol. 2015;20(3):455-462.
21. Van Kuilenburg ABP, Meinsma R, Zoetekouw L, Van Gennip AH. Increased risk of grade IV neutropenia after administration of 5-fluorouracil due to a dihydropyrimidine dehydrogenase deficiency: high prevalence of the IVS14+1g>a mutation. Int J Cancer. 2002;101(3):253-258.