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Dihydropyrimidine dehydrogenase mutation in neoadjuvant chemotherapy in head and neck cancers: Myth or reality?

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Abstract

Purpose: The docetaxel, 5-fluorouracil (5-FU), and cisplatin (TPF) regimen in India is associated with high percentages of Grade 3–4 toxicity. This analysis was planned to evaluate the incidence of dihydropyrimidine dehydrogenase (DPD) mutation in patients with severe gastrointestinal toxicity, to assess whether the mutation could be predicted by a set of clinical criteria and whether it has any impact on postneoadjuvant chemotherapy response. **Methods:** All consecutive patients who received TPF regimen in head and neck cancers between January 2015 and April 2015 were selected. Patients who had predefined set of toxicities in Cycle 1 were selected for DPD mutation testing. Depending on the results, C2 doses were modified. Postcompletion of two cycles, patients underwent radiological response assessment. Descriptive statistics has been performed. The normally distributed continuous variables were compared by unpaired Student's *t*-test, whereas variables which were not normally distributed by Wilcoxon sum rank test. For noncontinuous variables, comparison was performed by Fisher's exact test. **Results:** Out of 34 patients, who received TPF, 12 were selected for DPD testing, and 11 (32.4%, 95% confidence interval [95% CI]: 19.1–49.3%) had DPD mutation. The predictive accuracy of the criteria for the tested DPD mutations was 81.3% (95% CI: 62.1–100%). Of the 11 DPD mutation positive patients, except for one patient, all others received the second cycle of TPF. The dose adjustments done in 5-FU were 50% dose reduction in 9 patients and no dose reduction in one patient. The response rate in DPD mutated patients was 27.3% (3/11) and that in DPD nonmutated/nontested was 39.1% (9/23) ($P = 0.70$). **Conclusion:** In this small study, it seems that the incidence of DPD mutation is more common in Indian then it's in the Caucasian population. Clinical toxicity criteria can accurately predict for DPD mutation. Postdose adjustments of 5-FU from C2 onward, TPF can safely be delivered in the majority of patients with DPD heterozygous mutations without decrement in efficacy.

Key words: 5-fluorouracil, dihydropyrimidine dehydrogenase mutation, head and neck cancers, neoadjuvant chemotherapy, toxicity

Introduction

Neoadjuvant chemotherapy (NACT) is one of the treatment options considered in multimodality management of locally advanced head and neck cancers.[1] Three drug regimen consisting of docetaxel, 5-fluorouracil (5-FU), and cisplatin (TPF) is the recommended regimen in this setting.[1] This regimen, though standard, is associated with considerable amount of morbidity and even mortality. A mortality of 15.3% was reported with this regimen in routine practice from a center in the Western world.[2] Similar concerns regarding toxicity of this regimen has been raised by us in previous publications.[3] This concern for toxicity has led to reservations among oncologists for using this regimen. As a result, two drug combination of platinum and taxane or a modified dose reduced TPF regimen is been administered in certain centers in India.[3-7] These regimens are likely to be associated with inferior outcomes than the standard TPF regimen. Mucositis and diarrhea, two common toxicities associated with this regimen, are either not seen or are seen at a considerably lower frequency when two drug regimen of platinum and taxane is administered.[3,8] Infusional 5-FU seems to be the major culprit responsible for these morbidities.

Dihydropyrimidine dehydrogenase (DPD) enzyme is the rate-limiting enzyme responsible for metabolism of 5-FU.[9] Point mutations in DPD gene can lead to varying functional forms of DPD enzyme. Homozygous or heterozygous mutations affecting DPD gene activity can lead to increased toxicity of 5-FU.[9-11] DPD gene mutation testing facilities were not available at our center. The cost and time required for doing the DPD mutation analysis by outsourcing the sample prohibit its routine use at our center. However, we started testing for DPD mutation in our patients, who had a certain set of toxicities post the first cycle of TPF regimen to address the impact of DPD mutation on these toxicities. To the best of our knowledge, we do not have data from India on the incidence of DPD mutation in head and neck cancer patients. This analysis was planned to study the predictability of certain clinical toxicity-based criteria for the prediction of the presence of DPD gene mutations, incidence of DPD mutation in patients with severe toxicity, and the impact of DPD mutation on response to NACT.

Methods

Treatment delivery

All locally advanced head and neck cancer patients who underwent NACT with TPF regimen between January 10, 2015, and April 30, 2015, at Tata Memorial Hospital, Mumbai, Maharashtra, India, were included in this analysis. All of these patients received TPF regimen in standard doses (75 mg/m^2 for docetaxel on D1, 75 mg/m^2 for cisplatin on D1 and 750 mg/m^2 for 5-FU 24 h continuous venous infusion from D1 to D5) with standard premedications and antiemetic prophylaxis. All of these patients received TPF indoors, with pegylated granulocyte colony-stimulating factor prophylaxis provided on D7.

Patients who had the following toxicities were selected for DPD mutation analysis:

- Early mucositis: Oral mucositis Grade 2 or above seen within 4 days of starting TPF regimen
- Prolonged mucositis: Oral mucositis Grade 2 or above persisting after 14 days of starting TPF regimen
- Severe mucositis: Grade 3 or above oral mucositis at any time postdelivery of TPF regimen

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- Severe diarrhea: Grade 3 or above diarrhea at any time postdelivery of TPF regimen.

Postcompletion of C1, patients who had DPD mutations, underwent dose reduction in 5-FU as per the recommendations of clinical pharmacological consortium guidelines.[12] Patients who had Grade 3–4 toxicities but did not have DPD mutations underwent dose reduction in each individual drug of TPF regimen, according to the toxicities.

Postcompletion of two cycles of NACT axial imaging was done for response assessment. Depending on the response and the Eastern cooperative oncology group (ECOG) performance status (PS), patients were planned for further therapy. The details of the local treatment protocol following two cycles of NACT have been detailed by us in our previous publications.[3,6,7] Patients who had favorable response and had PS 0–2 were planned for radical intent treatment (surgery + adjuvant radiation/chemoradiation or radical chemoradiation), whereas patients who had disease progression or deterioration in PS (PS 3–4) were planned for palliative intent treatment (palliative chemotherapy or palliative radiation therapy [RT] or supportive care).

Clinical data collection

For the purpose of this study (VP, SD, SZ) collected the demographic details, NACT toxicity details, DPD mutation testing details, dose reduction details, and response assessment details. The details were collected from a prospectively maintained NACT database and electronic medical record system.

Dihydropyrimidine dehydrogenase testing

The DPD mutation testing was done on peripheral blood in a commercial laboratory (Metropolis India, Mumbai, Maharashtra, India) by polymerase chain reaction-sequencing method. One splice site point mutation IVS14+ G/A along with 10 other mutations could be detected using this test- 85T/C, 61 T/C, 496 A/G, 601 A/C, 632 A/G, 1601 G/A, 1627 A/G, 1678 T/G, 2194 G/A, and 2846 A/T.[12]

Statistical analysis

R studio version 3.0 (2015, Boston, MA) was used for analysis. The demographic features and response rate were compared between DPD mutation positive cohort and DPD mutation negative/not tested cohort. The continuous variables were tested for normal distribution by QQ plot and Shapiro–Wilkinson test. The continuous variables normally distributed were tested by unpaired Student's *t*-test, whereas variables which were not normally distributed were tested by Wilcoxon sum rank test. For noncontinuous variables, Fisher's exact test was performed. The predictive value of clinical toxicity-based criteria was tested by the following formula:

Predictive value = (number of patients with DPD mutation leading to nonfunctional or dysfunctional DPD enzyme×100)/(number of patients in whom DPD mutation was suspected on the basis of clinical toxicity criteria).

Results

Demographic details

Thirty-four patients received TPF regimen during the stipulated period. The median age of the whole cohort was 43 years (range: 21–59 years). There were 25 males (73.5%) and 9 females (26.5%). All patients had squamous cell carcinoma. The site of malignancy was oral cavity in 22 patients, nasopharynx in 10 patients, larynx in one patient, and unknown primary in one patient. The median body mass index was 22.6 kg/m^2 (range: 18.2–32.5 kg/m^2). The median albumin was 4.0 g/dl (3.2–4.6 g/dl). The comparison of clinical, demographic, and biochemical details between two cohorts is shown in Table 1. The mean age of DPD mutated patients was 47.3 years which was statistically more than nonmutated/nontested cohort (P = 0.03). Rest all factors were comparable between the two groups.

Predictive accuracy of clinical criteria

Twelve patients had DPD testing done on the basis of clinical toxicity-based criteria. Table 2 gives the detail of toxicity in Cycle 1 for which DPD mutation was suspected. Out of these patients, 11 patients had DPD mutation (32.4%, 95% confidence interval [95% CI]: 19.1–49.3%). The predictive accuracy of the criteria for the tested DPD mutations was 81.3% (95% CI: 62.1–100%).

Details of C2 dose adjustments in dihydropyrimidine dehydrogenase mutation positive cohort

Out of the 11 DPD mutation positive patients, except for one patient, all others received the second cycle of TPF. This patient had Grade 4 mucositis, took 35 days for recovery. Disease progressed within this period with deterioration in nutritional and ECOG PS-3. Hence, she was planned for palliative intent treatment only.

The dose adjustments done in 5-FU were 50% dose reduction in 9 patients and no dose reduction in 5-FU in one patient. The dose was not reduced in patient who had delayed mucositis recovery [patient number 5 in Table 1]. This patient did not have any other indication of dose reduction; hence, he was given chemotherapy in full dose. Further, the DPD mutation was ordered on D15 of C1 in this patient and hence the report came after C2 was delivered.

Toxicity in dihydropyrimidine dehydrogenase mutated patients

The toxicity of DPD mutated patients in C1 and C2 of TPF are shown in Table 3. All types of life-threatening toxicities seen in C1, postdose reduction of 5-FU were seen a lower proportion. The maximum decline was seen in Grade 3–4 mucositis which decreased from 70% to 10% (P = 0.0198). The incidence of Grade 3–4 hematological toxicities in C1 was 80% while it was 30% in C2 (0.0697).

Response postneoadjuvant chemotherapy

The response rate in DPD mutated patients was 27.3% (3/11) and that in DPD nonmutated/nontested was 39.1% (9/23) (P = 0.70). All nasopharyngeal patients except one, both laryngeal and CUP patient underwent radical chemoradiation. One nasopharyngeal patient in whom DPD was unknown succumbed C1 TPF toxicity. She had hematemesis and aspiration pneumonia during TPF treatment.

In patients with oral cancer primary, out of the 8 DPD mutation positive patients, six patients were resectable, whereas two patients failed to achieve resectability. The resectable patients were offered surgery followed by chemoradiation. Out of two unresectable patients, one patient was the above-mentioned patient who had Grade 4 mucositis and took 35 days for its recovery and was offered palliative RT. The second patient had

Table 1: Baseline characteristics of dihydropyrimidine dehydrogenase mutated and other patients

	DPD mutation positive cohort (*n*=11)	DPD mutation negative or nontested cohort (*n*=23)	*P* (test used)
Age (mean) (years)	47.3	40.7	0.03798 (Student's *t*-test)
Gender (%)			
Male	8 (72.7)	17 (73.9)	1 (Fisher's exact test)
Female	3 (27.3)	6 (26.1)	
Site (%)			
Oral	8 (72.7)	14 (60.9)	0.705 (Fisher's exact test)
Nonoral	3 (26.3)	9 (34.1)	
State (%)			
North East	5 (45.5)	4 (17.4)	0.1108 (Fisher's exact test)
Rest of India	6 (54.5)	19 (82.6)	
BMI (median) (kg/m^2)	21.9 (18.2-32.5)	22.7 (18.9-27.9)	0.3201 (Wilcoxson rank sum test)
Serum albumin (mean) (g/dl)	4.0	4.0	0.8132 (Student's *t*-test)

DPD=Dihydropyrimidine dehydrogenase, BMI=Body mass index

Table 2: Details of all patients in whom dihydropyrimidine dehydrogenase mutation was suspected

Patient number	Clinical toxicity criteria for which DPD mutation was done	DPD testing result	Type of mutation or mutation seen
1	Severe mucositis	Heterozygous	2194 G/A, 1601 G/A
2	Severe diarrhea	Heterozygous	2194 G/A
3	Severe mucositis	Heterozygous	1627 G/A
4	Severe diarrhea	Heterozygous	2194 G/A, 85 T/C, 496 A/G
5	Prolonged mucositis	Heterozygous	2194 G/A
6	Severe mucositis	Heterozygous	85 T/C, 496 A/G
7	Severe mucositis	Heterozygous	2194 G/A, 1627 G/A
8	Severe mucositis	Heterozygous	2194 G/A
9	Severe mucositis	Heterozygous	2194 G/A, 85 T/C, 496 A/G
10	Early mucositis	Heterozygous	85 T/C
11	Severe diarrhea	Heterozygous	85 T/C
12	Severe mucositis	Negative	-

DPD=Dihydropyrimidine dehydrogenase

Table 3: Comparison of C1 and C2 toxicity in dihydropyrimidine dehydrogenase mutated patients

Toxicity (Grade 3-4)	C1 (*n*=10) (%)	C2 (*n*=10) (%)	*P*
Anemia	2 (20)	0 (0)	0.4737
Neutropenia	7 (70)	3 (30)	0.1789
Diarrhea	5 (50)	0 (0)	0.0325
Mucositis	7 (70)	1 (10)	0.0198
TPN requirement	6 (60)	2 (20)	0.1698
Drop in serum albumin			
Median drop (range) (g/dl)	1.20 (0.57-2.8)	0.22 (0.0-0.7)	0.0006

TPN=Total parenteral nutrition

stable disease, was fit for radical treatment hence was planned for radical chemoradiation.

Discussion

DPD gene mutations were found in 81.3% (95% CI: 62.1–100%) of patients who were selected for DPD testing. The clinical criteria used in this study seem to be fairly accurate. These criteria were selected on the basis of discussion between the investigators (VP and KP) and extrapolation of available literature of DPD mutation and 5-FU toxicity in colon cancers.[9] The criteria heavily focused on mucositis and related toxicity as the investigators felt that hematological toxicity seen in TPF regimen is contributed largely by docetaxel. This assumption stems from the fact that the dose-limiting toxicity (DLT) of continuous infusion 5-FU is mainly mucositis and related complications, whereas the DLT for docetaxel is mainly hematological toxicity.[13,14]

Out of the cohort of 34 patients, at least 11 patients (32.4%) were DPD mutation positive. Although whole cohort was not tested for DPD mutation, we can assume from this study that the incidence of DPD mutation in our locally advanced head and neck cancer patients is at least 32.4% (95% CI: 19.1–49.3%). This incidence of DPD mutation positivity seems to be high in comparison to the studies done in the Caucasian population, in whom it is around 3–5%.[10,15,16] Although incidence of DPD mutation has not been consistently reported to differ between ethnic groups, Indian patients have never been part of such analysis.[17] The Indian population is an ethnically and genetically diverse population. Hence, it would not be a surprise if the DPD mutation status differs according to the region and ethnicity in the country. Our center mainly caters to the population from Western India, Central India, and Northeast India. Hence, this cohort can be a representative sample of the whole country. Most of the data of DPD mutation comes from colon cancer and not from head and neck cancer. In an interesting study of DPD enzyme deficiency reported by Yang *et al*. in head and neck cancer patients, the incidence of mild and marked DPD deficiency was 28% and 20%, respectively.[18] It may be a possibility that DPD deficiency is common in head and neck cancers than in colon cancers at least in some ethnic groups.

DPD mutation predicts for severe toxicity associated with 5-FU administration.[9,10,19,20] The high incidence of DPD mutation in our study may be the reason for high morbidity, especially mucositis and diarrhea, seen in our head and neck cancer patients treated with TPF regimen as compared to that reported in TAX 323 and TAX 324 studies.[21,22]

Dose adjustments done in this study were in accordance with the clinical pharmacology consortium guidelines.[12] Out of 11 patients with DPD mutation 10 patients had received C2. The C2 in adjusted doses were completed by all patients. Life-threatening Grade 3–4 toxicity postdose adjustment was seen in 20% patients (2 out of 10 patients). These results testify that though these recommendations at present give guidance for dose adjustment, but they are not completely accurate. Similar

concern regarding arbitrary dose adjustments has been raised by Magnani *et al*.[23] Hence, we would recommend giving such dose-adjusted cycles in indoor settings, preferably with patients monitored daily for toxicity before each dose of 5-FU. It is a heartening fact though that dose adjustments done did lead to a decrement in toxicity. Furthermore, an equally important finding was that the response seen in DPD mutated patients did not differ from DPD nonmutated/nontested patients. Similar results regarding no difference in response rate between dose reduced 5-FU given in DPD deficient patients and DPD nondeficient patients in head and neck cancers have been reported by Yang *et al*.[18]

Practice of personalized medicine has logistic issues.[24] The DPD done in this study was from an outside commercial laboratory. The reports were available only after 10–14 days. This hampers our ability to do DPD upfront in the present setting as our indication for NACT in head and neck cancers largely differs from the literature.[25] Majority of our NACT indications are in technically unresectable tumors in whom waiting for such long period may render the disease and patient condition unsuitable for further treatment. To overcome this, we have decided to do an in house of DPD mutation testing by sequencing. In addition, in near future, we plan to study the sensitivity, specificity, and negative predictive value of DPD mutation for prediction of life-threatening 5-FU toxicity.

This analysis is not without limitations. Its preliminary hypothesis-generating report. Not all patients have undergone DPD testing. Hence, negative predictive value cannot be calculated. The DPD testing was limited to common 10 DPD mutations known in Asians and sequencing of the whole DPD gene was not done, so novel mutations would have been missed.

Conclusion

In this small study, it seems that the incidence of DPD mutation is more common in Indian then it is in the Caucasian population. Clinical toxicity criteria's can accurately predict for DPD mutation. Postdose adjustments of 5-FU C2 of TPF can safely be delivered in the majority of patients without decrement in efficacy. There is a need for a large study to confirm sensitivity, specificity, and predictive value of DPD mutation for TPF toxicity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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