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Clinical Suspicion &Dihydropyrimidine Dehydrogenase (DPD) Mutation Positivity In Patients Receiving Chemotherapy With Capecitabine / 5 Fluorouracil (5 FU)

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I. Introduction

5FU and capecitabine based chemotherapeutic regimens form the mainstay of chemotherapeutic treatment in multiple gastrointestinal malignancies including Colorectal, Gastroesophageal junction and stomach, both in the adjuvant and metastatic settings.(1,2,3)5FU and Capecitabine based chemotherapy is also used in Head & Neck and Breast malignancies. 5 FU based chemotherapy is used as Neoadjuvant chemotherapy in head & neck cancers.(4) Fluoropyrimidine treatment is associated with several serious adverse side effects including myelosuppression, cardiac toxicity, mucositis, hand-foot syndrome (HFS), and diarrhoea.

Rate-limiting enzyme in metabolism of 5-FU is Dihydropyrimidine dehydrogenase (DPD) .(5)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.(5,6,7)Patients with a complete or near-complete deficiencyof the enzyme may have severe toxicity following theadministration of standard doses of fluoropyrimidines, due to significantly increased and prolonged plasmalevels of 5-FU.(8,9) The DPD deficiency syndrome, which is a familial syndrome as a result of the allelic mutations within the DPD gene.(10) Complete DPD deficiency is rare and occur in about 0.1% of patients, whereas partial DPD deficiency have an incidence of 3% to 5%.(11)

In our clinical practice we investigate for DPD mutation analysis when we have clinical suspicion. With this study we want to know the clinical suspicion and DPD mutation positivity in patients receiving chemotherapy with 5 FU and Capecitabine.

II. Aims & Objectives

- To note the proportion of clinically suspicious patients who had positive DPD mutations.
- To note the frequencies of different mutations observed.

III. Materials & Methods

This was a retrospective analysis.The details of DPD mutation analysis report of clinically suspicious cases from the period 01/01/2016 to 31/12/2016 was analysed.

In clinical practice, patients with adverse side effects on 5 FU and Capecitabine chemotherapy would have been investigated for DPD mutation analysis based on treating physician's discretion. DPD mutation analysis is not done in our hospital.For DPD mutation analysis5ml peripheral blood sample is sent to outside commercial laboratory (Oncquest).Reports of DPD mutation analysis was retrieved from case records.

IV. Results

Total number of patients in whom DPD mutation analysis was done during the study period was 40. Among the 40 patients, 26 were males and 14 were females.Among 40 patients, 29 had Colorectal malignancy, 7 had Ca Stomach, 1 had Ca Tongue, 1 had unknown primary with neck Lymph node metastasis, 2 had Ca Breast.

Table 1 shows patient characteristics

Age	Range (24-77) Median 57
Gender	Male26 (65%) Female14 (35%)
Type of primary	Colorectal 29 (72.5%) Stomach 7 (17.5%) Breast 2 (5%) Ca Tongue 1 (2.5%) Unknown primary with neck node metastasis 1 (2.5%)

Among the 40 patients, 24 patients had positive DPD mutation that is 60% of patients.16 out of 26 males had positive mutation and 8 out of 14 females had positive mutation.11 patients had multiple mutation.13 patients had single mutation.Total of 37 mutations were observed.

Table 2 shows proportion of mutation positivity and number of mutations.

DPD mutation	Present 26 Absent 14
Total no. of mutation	37
Multiple mutations	13 patients
Single mutation	11 patients

Among the 37 mutations, 3 were homozygous mutation and 34 were heterozygous mutation
Different mutations observed were 1. Exon 2 Heterozygous 85 T>C in 16 patients 2. Exon 2 Homozygous 85 T> C in 3 patients, 3. Exon 6 Heterozygous 496 A>G in 7 patients, 4. Exon 13 Heterozygous 1627 A>G in 7 patients, 5. Exon 18 Hetetrozygous 2194G>A in 3 patients, 6. Exon 14 Heterozygous 1905+1 G>A in 1 patient.

Table 3 shows frequency of different mutations observed among the total 37 mutations

Exon 2 Heterozygous 85 T>C	16 mutations (43.2%)
Exon 6 Heterozygous 496 A>G	7 mutations (20.6%)
Exon 13 Heterozygous 1627 A>G	7 mutations (20.6%)
Exon 2 Homozygous 85 T> C	3 mutations (8%)
Exon 18 Hetetrozygous 2194G>A	3 mutations (8%)
Exon 14 Heterozygous 1905+1 G>A	1 mutation (2.7%)

Different toxicities which evoked clinical suspicion of DPD mutation were, 1.Diarrhoea Grade III in 22 patients & Grade IV in 4 patients, 2. Hematological Grade IV (neutropenia + thrombocytopenia) in 2patients, Grade III neutropenia in 5 patients, Grade II neutropenia in 1 patient, 3. Hand foot syndrome Grade III in 1 patient , Grade II in 1 patient, 4. Grade III fatigue in 2 patients, 5. Grade III mucositis in 2 patients, 6. Grade IV electrolyte imbalance (Hyponatremia,Hypokalemia) in 1 patient.

Table 4 shows different toxicities which evoked clinical suspicion

Diarrhoea	Grade III 22 patients (55%) Grade IV 4 patients (10%)
Hematological toxicity	Grade II neutropenia in 1 patient (2.5%) Grade III neutropenia in 5 patients (12.5%) Grade IV (neutropenia + thrombocytopenia) in 2patients (5%)
Hand foot syndrome	Grade II in 1 patient (2.5%) Grade III in 1 patient (2.5%)
Mucositis	Grade III mucositis in 2 patients (5%)
Electrolyte imbalance	Grade IV electrolyte imbalance (Hyponatremia,Hypokalemia) in 1 patient (2.5%)
Fatigue	Grade III fatigue in 2 patients (5%)
Hematuria	1 patient (2.5%)

Table 5 shows chemotherapeutic regimens that were used for DPD mutation positive patients

Chemotherapy regimens used in DPD mutation positive patients	1.CAPOX 10 patients (41.7%) 2.EOX 3 patients (12.5%) 3.FOLFOX 3 patients (12.5%) 4.Concurrent Capecitabine with radiotherapy 3patients (12.5%) 5. FOLFOX +Panitumumab2 patients (5%) 6. Single agent Capecitabine 1 patient (2.5%) 7.Cisplatin + 5FU 1 patient (2.5%) 8.Cisplatin + 5FU + Cetuximab 1 patient (2.5%)

V. Discussion

Clinical suspicion has correlated with positive DPD mutation in 60% cases. In males and females positivity was almost similar.Most common mutation observed was Exon 2 Heterozygous 85 T>C, that is around 43% of mutations. Next common mutations were Exon 6 Heterozygous 496 A>G , Exon 13 Heterozygous 1627 A>G, both constituting 20% each.

Most common toxicity which evoked clinical suspicion for DPD mutation analysis was diarrhea (Grade III & Grade IV) in 60% of cases. Next common was hematological toxicity inaround 22% of cases. Less common toxicities were mucositis, hand foot syndrome, fatigue and electrolyte imbalance.

Investigating for DPD mutation is not uniform in clinical practice among treating physicians. At present there are no strict guidelines for investigating for DPD mutation.From the results of this study,we would suggest to do DPD mutation analysis for patients who are having Grade III & IV toxicities on chemotherapy with 5 FU and Capecitabine.

Since in this study we have only looked for DPD mutations in clinically suspicious cases, it is difficult to comment on incidence in our population. In, Indian population exact incidence of DPD mutation has not yet been reported. From the results of this study, it seems that the incidence of DPD mutation could be higher than that in Caucasian population. Study by V M Patil et al also have observed that incidence of DPD mutation could be higher in Indian population.(12) A properly conducted prospective study would be essential to find out the exact incidence of DPD mutation in Indian population.

VI. Conclusion

From this retrospective data analysis it is evident that in around 60% of cases clinical suspicion had correlated with DPD mutation positivity.At present there is no standard guidelines for ordering DPD mutation analysis.From this analysis we would suggest to order for DPD mutation analysis in patients with Grade III & IV toxicities (diarrhoea, hematological, hand foot syndrome, mucositis), who are receiving chemotherapy with Capecitabine/ 5FU. Incidence of DPD deficiency in Indian population is not well studied.

Based on the result of this retrospective study we are planning for future prospective study in patients undergoing chemotherapy with 5FU & Capecitabine to find out the incidence of DPD deficiency or DPD mutation positivity in Indian population.

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