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MOLECULAR MARKERS FOR CAPECITABINE THERAPY: A REVIEW

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ABSTRACT: Capecitabine an oral prodrug of 5- fluorouracil is widely used for the treatment of variety of solid tumors, particularly colorectal cancer. However it is not devoid of toxicities and may limit therapy. A little is known about predictors of toxicity, response and survival in patients treated with capecitabine. The pharmacogenetic testing methods can identify such variants and thus indicate those patients who are at risk for adverse effects with capecitabine. Various studies have been carried out to assess the various genetic predictive and prognostic markers with treatment. The purpose of this review is to describe the comprehensive reports and draw conclusion with the available information on capecitabine pharmacogenetics and future directions on ongoing research. An extensive literature search was carried out on the genes encoding the enzymes involved in the metabolism of capecitabine. Overall, evidence indicates multiple genes associated with the response/toxicity with capecitabine therapy, however majority of reports indicate DPD deficiency as a source of life-threatening toxic effects. Hence, prospective studies correlating the enzymes and the concentration of the drug and its metabolites in the body are needed before validated SNP tests can enter routine clinical practice.

INTRODUCTION: Capecitabine (CAP), carbomate of fluropyrimidine is an orally administered anti neoplastic agent. It was synthesized in 1990s by Japanese researchers as an oral formulation designed to overcome the toxicity of 5'-deoxy-5-fluorouridine (5′d5-FUrd) [1].

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This 5′d5-FUrd is related to GI toxicity, attributed to the liberation of 5FU in the small intestine under the action of thymidine phosphorylase (TP) [2]. Thus CAP was designed as a prodrug of 5′d5-FUrd that crosses the GI barrier intact and is rapidly and almost completely absorbed [3].

The anti tumor activity is related to fluorouracil which is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis [4]. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

Capecitabine is FDA-approved for: Adjuvant in colorectal cancer Stage III Dukes' C & used as first-line monotherapy and in metastatic colorectal cancer as well. If appropriate, it is used in combination with docetaxel, after failure of anthracycline-based treatment in metastatic breast cancer. It is also used as monotherapy, if the patient has failed paclitaxel-based and anthracycline-based treatment has failed or cannot be continued for other reasons (i.e., the patient has already received the maximum lifetime dose of an anthracycline).

In the UK, capecitabine is approved by the National Institute for Health and Clinical Excellence (NICE) for colon and colorectal cancer, and locally advanced or metastatic breast cancer.[5] On March 29, 2007, the European Commission approved Capecitabine, in combination with platinum-based therapy (with or without epirubicin), for the first-line treatment of advanced stomach cancer. Unlabeled it is used in the treatment of CNS lesions for metastatic breast cancer, esophageal cancer, gastric cancer, hepatobiliary cancers (advanced), neuroendocrine (pancreatic/islet cell) tumors (metastatic or unresectable), ovarian cancer (platinum-refractory), pancreatic cancer (metastatic), unknown primary cancer.

Dosing:

The first line treatment of metastatic colorectal cancer patients on whom single agent capecitabine therapy is preferred, the approved FDA dose is 1,250 mg/m^2 which is given orally twice daily, over 12 hours interval for 14 days followed by a period of rest for 1 week. The FDA has also approved the same dose as colorectal cancer for metastatic breast cancer patients who have developed resistance to both anthracycline and taxane based regimens or in whom any further anthracycline therapy is contraindicated, as single agent therapy. Additionally, the approved combination regimen with docetaxel 75 mg/m^2 as a 1-hour IV infusion on the first day for metastatic breast cancer patients, in whom prior anthracycline therapy has failed and 1,250 mg/m^2 capecitabine administered orally twice a day for the first 2 weeks of every 3-week cycle. In prostate, renal cell, ovarian and pancreatic cancers, the majority of evidence is from smaller, Phase II trials, and efficacy has been mostly in the form of partial response and stable disease. Combination therapy in these patients appears to be more beneficial than single-agent capecitabine. [6] Further, based on tolerability dosage modifications are recommended. [7] The ideal dosing of capecitabine varies as regional differences have been seen in the tolerance of oral fluoropyrimidines.[8] The product data recommends the tablets should be administered within 30 minutes of a meal; this may decrease gastrointestinal discomfort.

Toxicities with capecitabine:

Capecitabine is not devoid of toxicities. It poses a risk of adverse effects, some of which can be serious and dose limiting. The predominant adverse effects observed with capecitabine include hand and foot syndrome, Stomatitis, nausea, vomiting and diarrhoea. The Toxicity Profile of Capecitabine monotherapy is tabulated in the **Table 1.**

TABLE 1: TOXICITY PROFILE CAPECITABINE MONOTHERAPY IN COLON AND RECTAL CANCERS

Study	No of patients, Cancer type	Place of study	setting	Toxicities
Twelves et al.[9]	1004 ,CRC Phase III	164 centers worldwide	Adjuvant Colon Cancer	Diarrhoea (11%), nausea vomiting (3%), Stomatitis (2%), hand and foot syndrome (17%), neutropenia (2%), hyperbilirubinemia (20%)
Hoff et al.[10]	302,CRC Phase III	US, Canada, brazil and Mexico	Metastatic Colorectal Cancer	Diarrhoea(15.4%),vomiting(3.6%), Stomatitis(3%), hand and foot syndrome(18.1%),neutropenia(2.6%), hyperbilirubinemia(17.3%)
Van Custem et al.[11]	297,CRC Phase III	59 centers in Europe, Australia, New Zealand, Taiwan, and Israel	Metastatic Colorectal Cancer	Diarrhoea10.7%, Stomatitis1.3%, hand and foot syndrome16.2%, neutropenia 2%, hyperbilirubinemia 28.3%
Chi-Ching Law et al[12]	58,single arm	China	Adjuvant colon cancer	Diarrhoea (0), nausea vomiting (0), Stomatitis(1.7%), hand and foot syndrome(41.4%), neutropenia (1.7%),

Janneke Baan et al[13]	9CRC,28breast cancer, single centre	Netherland	Metastatic and adjuvant setting	hyperbilirubinemia (1.7%) Nausea/Vomiting(16.2%), Mucositis (e.g. stomatistis, gastritis) (27.0%), Diarrhoea (24.3%), Hand and foot Syndrome (10.8%), Bone marrow suppression (8.1%), Thromboembolic event (2.7%)

In its standard dose schedule of capecitabine is 2000 mg/ m^2 per day (days 1–14) and oxaliplatin 130 mg /m^2 (day 1) every 3 weeks (CAPOX 2000), the reported rate of grades 3 and 4 diarrhoea rate was about 20% [14-17]. This severe diarrhoea rate further increased when CAPOX 2000 was combined with cetuximab [18]. Differential reports of toxicities by patients from different racial groups were observed. Regional differences in tolerability of capecitabine as adjuvant therapy was noted with toxicities being worse in the US population compared with rest of the world [19, 20] and whereas in Chinese population a much higher incidence of serious hand-foot syndrome and a lower rate of severe diarrhoea were observed[12].

Pharmacogenetics:

Although in recent years, there has been a vast improvement in the outcome of patients, present day protocols are still limited by the unpredictable response to the drug and to its severe toxic effects. The different responses to a particular drug are not only due to the specific clinic pathological features of the patients but also ethnic origins and particular genotype of a single individual. Here, we provide an overview of the known polymorphism present in the genes which codify for key metabolic factors involved in the mechanism of action of the drugs responsible for significant toxicity with capecitabine

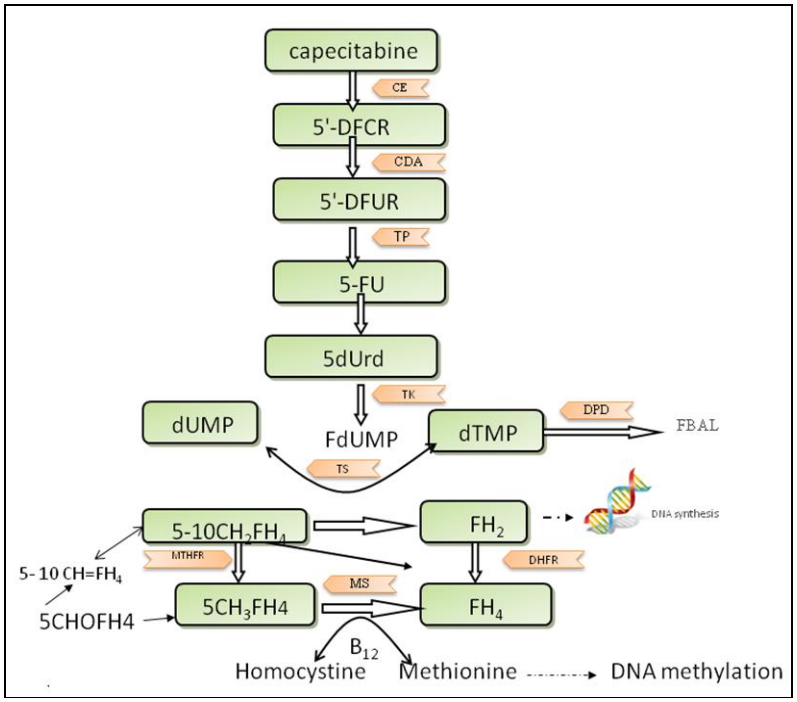

FIG. 1: CAPECITABINE IN ITS METABOLIC PATHWAY

5'-DFUR ,5'-deoxy-5-fluorouridine ; 5'-DFCR, 5'-Deoxy-5-fluorocytidine; *5-dUrd*, 5-fluorodeoxyuridine ; 5-10 CH=FH4, 5-10 methenyltetrahydrofolate; 5-10 CH2FH4, 5-10 methylene-tetrahydrofolate; 5-CH3FH4, 5-methyltetrahydrofolate; 5-CHOFH4 (FA), 5-formyltetrahydrofolate; DHFR, dihydrofolate reductase; FdUMP, 5-fluorodeoxyuridine 5′-monophosphate; FdUrd, 5-fluorodeoxyuridine; FH2, dihydrofolate; FH4, tetrahydrofolate; MS, methionine synthase; TK, thymidine kinase; TP, thymidine phosphorylase.

Carboxylesterases:

Carboxylesterases (CES) are members of the α/β hydrolase fold family and are a group of enzymes that function in the metabolism of ester and amide prodrugs to their free acid forms [21]. They are ubiquitously expressed, but levels are highest in the small intestine, liver, and lungs. There are five genes of carboxylesterases reported in humans, named CES1-CES5. CES1 substrates generally contain a large acyl and a small alcohol group, while substrates for CES2 contain a small acyl and a large alcohol moiety. Carboxylesterases hydrolyze capecitabine's carbamate side chain to form 5′-deoxy-5-fluorocytidine (5′-DFCR). Both CES1A1 and CES2 are responsible for the activation of capecitabine, whereas CES3 plays little role in 5′-DFCR formation. For the first time N Ribelles et al reported an association between a polymorphism in the CES2 gene(CDD 943insC and CES 2 Exon 3 6046 G/A) and the efficacy of capecitabine with a non-statistically significant higher incidence of grade 3 hand-foot syndrome (HFS) (p=0.07) and grade 3-4 diarrhoea (p=0.09), respectively.

It was also observed that the patients heterozygous or homozygous for the polymorphism CES 2 5UTR 823 C/G exhibited a significantly greater response rate to capecitabine, and time to progression of disease (59%, 8.7 months) than patients with the wild type gene sequence (32%; 5.3 months) [22].

Thymidine phosphorylase:

Thymidine phosphorylase (TP), also known as platelet-derived endothelial cell growth factor (PD-ECGF), is an enzyme expressed in many normal tissues and cells with a key role in pyrimidine salvage pathway that recovers pyrimidine nucleosides formed during RNA or DNA degradation [23]. TP catalyzes the conversion of thymidine, deoxyuridine and their analogs to their respective bases and 2-deoxyribose-1-phosphates. Furthermore, TP is often overexpressed in tumor sites. The high TP activity in the tumor can selectively activate the 5FU prodrug 5'-deoxy-5-fluorouridine to 5FU. [24] Thymidinephosphorylase is located at chromosome 22 in the region of q13.33. cDNA is approximately 1.8 kb long, consisting of 10 exons in a 4.3 kb region .[25, 26] TP is highly expressed in liver tissues.

Thymidine phosphorylase is upregulated in a wide variety of solid tumors such as breast, bladder, gastric, colorectal, pancreatic, lung and esophageal cancer [27-31]. Several literatures shows a correlation between the TP expression level with tumor angiogenesis, growth and progression illustrating that TP promotes tumor growth and metastasis by preventing apoptosis and inducing angiogenesis.[32, 33]

As TP is the rate-limiting enzyme for the activation of capecitabine, it might be a useful predictor of tumor response to capecitabine-based chemotherapy. Reports of a study by bokos et al confer that Median ratio TP/DPD of patients with proven pathological "response" (downstaging of the disease) was higher than the "no response" group, 4.40 and 1.42, respectively (P = 0.0001) indicating that Thymidine phosphorylase to dihydropyrimidine dehydrogenase ratio as a predictive factor of response to preoperative chemoradiation with capecitabine in patients with advanced rectal cancer [34].

Similarly, Meropol *et al.* assessed in the tissues from primary and metastatic sites for TP protein expression in patients with previously untreated metastatic CRC on irinotecan plus capecitabine chemotherapy and concluded that the objective tumor response to chemotherapy was associated with high TP expression in primary tumors (OR: 4.77; 95% CI: 1.25-18.18), with a similar trend in metastases (OR: 8.67; 95% CI: 0.95-79.1). These reports seem to indicate that TP expression might be a predictive marker for response. In addition, overall survival (OS) was also based on TP expression. The median survival in TP-expressing primary tumors was 28.2 months (95% CI: 15.5--39.8 months) compared to 14.9 months (95% CI: 9.0--20.5) in patients with TP-negative primary tumors. [35]

Another study by Petrioli R et a indicated a significant associated with high TP expression in metastatic tissue with response to treatment (P=0.019), and also with a trend towards a better median progression-free survival and overall survival compared with patients expressing low TP (P=0.056; P=0.073) suggesting that patients with high levels of intratumoral TP expression were the

ideal candidates for capecitabine-based chemotherapy patients with metastatic colorectal cancer treated with continuous oral capecitabine and biweekly oxaliplatin [36]. Lindskog EB et al reports that high TP gene expression in non-microdissected tumour tissues of patients with advanced colorectal cancer correlates with longer time to progression.[37]

Several studies report a correlation between elevated TP (as measured by either IHC or ELISA) and benefit with high response rate in gastric cancer patients and breast cancer on capecitabine based therapy as well.[38-43] These findings support the potentially predictive role of TP and a promising marker that can give helpful information to benefit from capecitabine-based chemotherapy.
Palmar-plantar erythordysesthesia (PPE) is the most common toxicity of capecitabine. Saif M W *et al* showed no significant association of PPE with higher tumor thymidine phosphorylase in patients receiving capecitabine. [44]

With an extensive literature survey, it was observed that TP plays a dual role in cancer development and therapy. On the one hand, TP activity is necessary for the activation and in contrast, high levels of TP in tumor tissues are correlated with a poor prognosis because of higher tumor aggressiveness. This apparently opposite effect of TP illustrates the complexity of this marker in tumor progression and in the clinical response to capecitabine therapy and strongly suggesting the involvement of other markers.

Cytidine Deaminase:
The human CDA spans approximately 30 kB and consists of 4 exons. No splice variant was reported. The *CDA* gene encodes an enzyme involved in the pyrimidine salvage pathway and catalyzes irreversibly the hydrolytic deamination of cytidine and deoxycytidine into uridine and deoxyuridine, respectively [45]. In addition, *CDA* plays an essential role in the metabolism of a number of antitumor cytosine nucleoside analogues, leading to their pharmacologic activation to 5-FU.Few case reports indicate the association of *CDA* with toxicity. A report by Mercier at al suggests severe toxicity with capecitabine linked to *CDA* without the deficiency Of *DPD*. [46] A study by Caronia et al. investigated the association between grade 3 HFS and the genes involved in capecitabine metabolism and found that the deleted allele of rs3215400 showed an increased allele-specific expression and was significantly associated with an increased risk of capecitabine-induced HFS. [47]

Thymidylate Synthase:
The prime target for 5FU is thymidylate synthase (TS). TS in association with a methyl cofactor, catalyses the conversion deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). by methylation.

In a trial by Uchida K et al involving predominantly pre-treated colorectal cancer patients, higher levels of TS mRNA expression appeared to have a predictive value in identifying those subjects with a greater probability of early disease progression during treatment with XELOX [48]and a study by lee et al reports that the median PFS was significantly lower in patients with high TS (6.6 vs. 3.0 months; P = 0.017) [42]. Another study by Lee S et al showed that high expression of TS and TP was associated with a higher RR than was low expression of TS and TP (54.1 vs 40.5%, P=0.022) in advanced oesophageal squamous cell carcinoma with capecitabine and cisplatin therapy.[49] Study reports of Agustin A. Garcia, et al indicated severe nausea/vomiting associated with TS expression (P = 0.039), but not with other severe toxicities[50]. The results of a recent study presented by Martinez-Balibrea et al and Spindler K L et al reported a less pronounced impact of the *TS* and *ERCC1* genotypes on XELOX efficacy compared with the outcome of an 5-FU-oxaliplatin infusional regimen (FUOX) [51, 52].

Among the three common polymorphisms associated with altered *TS* gene expression the variable number of tandem repeats (VNTR) polymorphism in 5'untranslated region mainly leads to double or triple tandem repeats (2R or 3R) of a 28-bp sequence. These repeats are found in Caucasians, Asians and Africans. The Four, five or nine tandem repeats have also been described for this polymorphism. A low TS levels *in vitro* and in tumour tissue samples were observed with homozygous 2R/2R genotype.[53, 54] A deletion of 6 bp in the *TS* gene has been associated with

decreased TS expression [55]. Several studies indicate association between treatment outcome and TS polymorphism which is depicted in **Table 2** .[57-59]

TABLE 2: SUMMARY OF PUBLISHED LITERATURE ON TS POLYMORPHISM WITH CAPECITABINE

Publication	No of patients	Type of cancer	Genotype	Response	Toxicity	survival
David J. Park et al,2002[56]	24	Colorectal cancer patients	5' untranslated region	75% (3/4) of individuals with the S/S variant responded to capecitabine, compared to 8% (1/12) and 25% (2/8) of those with the S/L and L/L variants, respectively	100% S/S variant reported toxicity level of grade 3 and 56% of those with S/L and 37.5% with L/L	
Rémy Largillier et al,2006[57]	**105**	**Breast cancer**	TS 5' genotype 28 bp tandem repeats	(3RG3RG genotype) were prone to rapid disease progression was not related to toxicity	a higher global toxicity grade 3 and 4 was observed in patients homozygous for the TS 3RG allele compared with patients heterozygous for the 3RG allele or patients not carrying the 3RG allele (50% versus 19% versus 13% respectively, P = 0.064).	
J. Gao et al,2012[58]	**123**	Advanced gastric cancer patients	TS 3′-UTR			TS ins6/ins6 genotype was the independent poor OS predictor (*P* = 0.001, HR = 3.182)

In the second repeat of the 3R allele, a SNP resulting in a G>C change has been observed. Increased gene expression and protein levels have been associated with the G allele of this SNP. Another common polymorphism has been reported at position 1494 in the 3'UTR of TS [59]. 3'UTRs modulate gene regulation at a posttranscriptional level through control of mRNA stability. A 6-bp insertion/deletion (indel) polymorphism in TS 3'R is associated with decreased TS mRNA stability in vitro and reduced expression of TS protein in colorectal tumor tissue [60]. According to a study by A Loganayagam et al the presence of a homozygous del/del genotype approximately doubled the risk of grade 3–4 toxicity [61]. However, other studies have failed to show an association between a homozygous del/del genotype and severe toxicity [62-64].

Methylenetetrahydrofolate Reductase:

An important enzyme in the folate pathway is Methylenetetrahydrofolate reductase (MTHFR) which converts 5,10-Methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate.An increased levels of 5,10-MTHF available for inhibiting TS has been linked to reduction in enzyme activity and therefore leading to increased efficacy of 5-FU.[65]

The two common polymorphism of MTHFR gene are 677c>T and 1298A>C are known to reduce the enzyme activity leading to a decreased pool of methyl THF and associated with

hyperhomocysteine particularly in folate deficiency [66]. The 677c>T transition at exon 4 causes an amino acid substitution from alanine to valine at codon 222 within the catalytic region of the enzyme.the677c>T variants MTHFR TT genotype show-30% of the enzyme activity found among those with wild type(CC). While individuals who are heterozygous for mutation CT have -65% of wild type enzyme activity. Individuals with the TT genotype, particularly if combined with a diet low in folate, have elevated plasma homocysteine levels.

The A1298C polymorphism, resulting in an amino acid change of glutamine to alanine, also leads to reduced enzyme activity of the minor allele; however, this is to a lesser extent than for the 677T allele.[65] Studies related to the association of these genotypes with reponse/toxities with capecitabine is represented in the **Table 3.**

TABLE 3: SUMMARY OF PUBLISHED LITERATURE ON MTHFR POLYMORPHISM WITH CAPECITABINE

Study	No of patients	Type of cancer	Genotype	Response	Toxicity	survival
van Huis-Tanja LH et al 2013[67]	127	CRC	MTHFR 1298A>C 677C>T	No significant association	MTHFR 1298CC homozygotes showed a borderline significantly higher incidence of grade 3-4 diarrhoea compared with MTHFR 1298AC or AA individuals	-
J. Dimovskiet al, 2010 et al [68]	136	Colon cancer	677C>T		The MTHFR 677 TT genotype was predictive of absence of side effects (OR 0.094, 95% CI 0.01-0.87, p = 0.014).	MTHFR 677TT genotype are predictive for mid-term relapse-free survival
Rohini Sharma et al, 2008[62]		CRC			MTHFR c.677C>T and c.1298A>C genotypes and diplotypes predicted for grade 2/3 Toxicities	MTHFR c.677 genotype tended to predict overall survival (P = 0.08)
Remy Largillier et al,2006[57]	105	Breast cancer			MTHFR genotypes 677C>T and 1298A>C were not related to toxicity	
Lei-zhen Zheng et al[69]	93	Gastric cancer				MTHFR 1298C/A had marginally significant correlation with the survival of patients (χ2=3.447,P=0.062),

Dihydropyrimidine Dehydrogenase:

Dihydropyrimidine dehydrogenase (DPD) acts in the degradation of 5-FU and a rate limiting enzyme accounting for more than 80% in its catabolism. The clearance of 5FU depends on DPD activity. Hence, reduced DPD activity leads to both increased toxicity and efficacy of the drug [70]. Till date at atleast 30 polymorphism in DPD gene have been described [71]. In two studies Common genetic polymorphisms in the DPD gene (DPD-C1896T, DPD-T85C, DPD-A496G, DPD-A557G, DPD-A1627G, DPD-T3351C, DPD-G3649A, DPD-A3844G and DPD-T3856C) leading to altered enzyme activity were examined. These studies reveal no significant associations between DPD genotype and toxicity or response. [72, 73]. The most common polymorphism is DPYD*2A,G>A splice site transition that causes skipping of exon 14 has been found in upto 40-50% of people with partial or complete DPD deficiency. The point mutation G to A in the invariant slice donor site leads to skipping of exon 14 immediately upstream of the mutated splice donor site in the process of DPD prem RNA splicing segment coding the aminoacid 581-635[74]. Patients heterozygous for this polymorphism have low DPD activity and

developing toxicity is represented in **Table 4** and several case reports also indicate toxicity with DPD deficiency [81-85].

TABLE 4: SUMMARY OF DPD POLYMORPHISM AND ASSOCIATED TOXICITIES WITH CAPECITABINE

Publication	No of patients	Type of cancer	Genotype	Toxicity
Maarten J. et al [75]	568	Advanced Colorectal Cancer	IVS14+1G>A, 1236G>A, 2846A>T, 2194G>A, or 496A>G	IVS14+1G>A and 1236G>A were strongly associated ($P < 0.05$; FDR < 0.3) with grade 3 to 4 diarrhea.
M. Wasif et al [76]	23	GI malignancies	(IVS14+1 G>A, DPYD	severe leucopenia demonstrated
M. Del Re et al,[77]	450 patients Italy	with gastrointestinal , breast and pancreas cancers	IVS14+1G>A and 2846T>C DPD variants	Toxicities in all subjects were G3/4 diarrhea (100%), G3/4 mucositis (48%), febrile neutropenia (45%), G3/4 thrombocytopenia (38%), G3/4 anemia (24%), G2/3 hand-foot syndrome (14%), G3 dermatitis (7%) and G2/4 alopecia (7%).
Timur Ceric et al [78]	50 subjects	GI malignanacy	IVS14 +1 G>A,	Diarrhea, neutropenia, mucositis
Muhammad Wasif Saif et al,2013 [79]	colon (n=871, 62%)breast (n=184, 13%)227 patientsUSA	Colon cancer, breast cancer	IVS14 +1 G>A, D949V	hand-foot syndrome 9%, myelosupression-9%
Loganayagam A et al [80]	47 patients	GI malignanacy	1905+1G>A, 2846A>T,1679 T>G	1905+1G>A developed severe diarrhoea

The simultaneous presence of variants DPYD*2A and 2846A>T was shown to be lethal in several cases shortly after initiation of treatment with fluoropyrimidine. [86, 87] Deenen et al. found that 100% of patients carrying the IVS14+1 polymorphism developed severe toxicity.[88] Measuring DPYD activity has been suggested to be a better biomarker for fluoropyrimidine-induced toxicity than DPYD genotyping, although recent findings confirm that genotyping and haplotyping could be acceptable options for stratifying patients according to risk of toxicity [89] or establishing dose recommendations for capecitabine and as shown by the Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association.[90]

Recently Recommended dosing of fluoropyrimidines by DPD phenotype has been laid [91], Hélène Blasco et al indicated that, once this deficiency has been identified on the basis of both DPD genotype and phenotype with capecitabine, it is possible to tailor 5-FU dose in DPD-deficient patients, using TDM [92]. However a study by Garcia AA et al expression of DPD was not associated with any of the severe toxicities.[93] Saif MW et al reports discoloration of his palms consistent with HFS, contrary to the pattern and degree of HFS reported in the current guidelines as proposed in the drug insert. This case suggests that the pattern of cutaneous manifestations varying in patients with different ethnic backgrounds, especially whites Versus non-whites with the normal limits of DPD.[94]

A study by Vallböhmer D et al reports a Higher gene expression levels of DPD were associated with resistance to capecitabine (P=0.032). Patients with a lower mRNA amount of DPD (<or=0.46) had a longer progression-free survival compared with patients that had a higher mRNA amount (8.0 vs. 3.3 months; adjusted P=0.048; log-rank test).[95] Nishimura G et al reports patients with high TP but low DPD had the best disease-free survival, whereas the low TP but high DPD group had the worst survival in colorectal cancer patients on capecitabine.[96]

CONCLUSION: Predicting response and limiting drug induced toxicity are two important challenges faced by clinicians in the treatment of colorectal cancer. The introduction of genetic testing individualize treatment regimens will hope fully allow better response prediction and limit drug induced toxicity leading to improved patient outcomes. Determination of polymorphisms in metabolizing enzymes before the administration of chemotherapy could offer new strategies for optimizing the treatment of individual patients. However, phase wise studies on large population simultaneously accounting for other co variables should be carried out for predicting and confirming the effects of multiple genetic factors.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST:

No potential conflicts of interest were disclosed.

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