Annals of Oncology 27 (Supplement 4): iv59–iv76, 2016
doi:10.1093/annonc/mdw337.29

breast cancer

F29 5-fluorouracil degradation rate (5-FU-DR) could predict toxicity in breast cancer patients treated with capecitabine

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Background: Fluoropyrimidines are commonly used in metastatic breast cancer after anthracyclines and/or taxanes failure or in frail patients. The identification of a toxicity predictive biomarker could help to avoid severe toxicities and consequent dose reduction or treatment discontinuation. We analyzed the predictive role on toxicity of 5-FU-DR and polymorphisms in TSER, DPYD and MTHFR genes.

Materials and methods: We collected blood samples of metastatic breast cancer patients before starting capecitabine-based treatment. 5-FU-DR was determined by measuring the decrease of a known dose of 5-FU incubated with peripheral blood mononuclear cells in a time unit. Patients were classified as: poor metabolizers (PM: 5-FU-DR $\leq$ 0.85 ng/ml/10^6cells/min); normal metabolizers (NM: 0.85< 5-FU-DR > 2.2 ng/ml/10^6cells/min); ultra-rapid metabolizers (UM: 5-FU-DR $\geq$ 2.2 ng/ml/10^6cells/min). Gene polymorphisms of MTHFR, DPYD and TSER were detected using DNA pyrosequensing. Toxicities were classified according to CTCAE v 3.0. SPSS2 software was used to perform statistical analysis. Gene polymorphisms and the 5-FU-DR were correlated with toxicities through Pearson's Chi Square test.

Results: We analyzed 40 metastatic breast cancer patients treated with capecitabine alone or in combination regimens. 3 patients were PM, 35 were NM and 2 were UM. Grade 3-4 toxicities were observed in 20% of patients: 50% hematopoietic, 50% gastrointestinal, 12.5% hepatic and 12.5% hand-foot symdrome. PM and UM showed a higher incidence of G3-4 toxicities (p = 0.05) and PM required dose reduction due to toxicity more frequently than NM (66.7% vs 20%). No statistically significant association between gene polymorphisms and toxicities were observed.

Conclusions: 5-FU-DR could be considered a useful toxicity predictive biomarker in breast cancer patients treated with capecitabine-based regimens, although larger and perspective studies are required to implement this results.

Table: F29

	Patients N (%)	Dose reduction (%)	G 3-4 Toxicity (%)	P value
Type of treatment				
Capecitabine alone	20 (50)	4 (20)	5 (25)	
Capecitabine combination regimens	20 (50)	5 (25)	3 (15)	
TSER				
2R/2R	7 (17.5)	3 (42.9)	2 (28.6)	
2R/3R	16 (40)	3 (18.8)	3 (18.8)	
3R/3R	14 (35)	3 (21.4)	2 (14.3)	NS
DPYD				
GG	40 (100)	9 (22.5)	8 (20)	
GA	-	-	-	NS
MTHFR C677T				
CC	13 (32.5)	3 (23.1)	4 (30.8)	
CT	20 (50)	3 (15)	4 (20)	
TT	6 (15)	1 (16.7)	-	NS
MTHFR A1298C				
AA	18 (45)	2 (11.1)	4 (22.2)	
AC	17 (42.5)	5 (29.4)	2 (11.8)	
CC	5 (12.5)	2 (40)	2 (40)	NS
5-FU-DR				
PM	3 (7.5)	2 (66.7)	2 (66.7)	
NM	35 (87.5)	7 (20)	5 (14.3)	
UM	2 (5)	-	1 (50)	0.05