A single-center experience on tolerance to chemotherapy with adjusted dosing of capecitabine in breast cancer patients with altered variants in the dihydropyrimidine dehydrogenase gene. Illarramendi J, Arraras JI, Salgado J, Valiente A, García-Solaesa V, Salgado JE, De La Cruz S, Illarramendi JJ. Services of Hematology, Genetics and Medical Oncology. University Hospital of Navarra. Pamplona. Spain.

Background: Capecitabine (CPB) remains as a useful fluoropyrimidine drug for chemotherapy of breast cancer (BC). Current guidelines establish the pharmacogenomic study of dihydropyrimidine (DPYD) for patients scheduled for treatment with this drug in order to ascertain the risk of life threatening toxicity. Some guidances of alternative dosing in patients with altered DPYD genotypes are available for fluoropyrimidines in general, but there is limited real-world information on the tolerance to reduced dosing of CPB in this context.

Methods: Review of DPYD genotyping and practice of dose adjustment of CPB in patients with altered genotypes. Study setting: Large academic center. Study period: April 2021-March 2024. DPYD studies and chemotherapy with CPB were all performed at our center. Data were retrospectively retrieved from the electronic health record, covering all information on diagnostic tests, laboratory studies, drug therapy and clinical evaluations.

Results: 92 patients (p.) with advanced BC have been evaluated. Altered DPYD was found in 4/86 p. (4.3%). 1 p. had an homozygous Hap B3 haplotype and was not treated with CPB after this finding. 2 p. had an heterozygous hap B3 haplotype, and 1 p. was heterozygous for D949V. Starting CPB dose was halved to 500 mg/sqm every 12 hours for 14 consecutive days in 3 p. Median age: 54 years (47-68). Previous therapy: palbociclib (2), alpelisib (1). Organ function was adequate and none used concurrent drug therapy with potential impact on DPYD. Tolerance was fair in 2/3 p. 1 p. stopped CPB after 2 cycles, due to progression. 1 p. had evidence of early tumor response but abandoned CPB due to progression after 9 cycles. Doses were not increased in these p. Toxicity was severe in 1 p. with the D949V variant, with grade 4 cytopenia, skin damage and mucositis, and therapy was stopped in the first cycle. She was studied by whole genome sequencing, displaying a concurrent pathogenic variant in BRCA2 without other significant findings.

Conclusions: Despite current guidelines, dose management of CPB may be complex in BC p. with altered DPYD genotypes in clinical practice, and further knowledge is needed on this subject.

Keywords: breast cancer, DPYD, capecitabine.