Capecitabine-induced adverse events: a pharmacogenetic study beyond *DPYD*

**INTRODUCTION**

- About 25-75% of patients treated with capecitabine develop hand-foot syndrome (HFS)\(^1\)
- HFS can limit activities of daily living and can seriously impact patients' quality of life\(^2\)
- Occurrence of HFS during capecitabine often results in treatment interruptions (26%) or treatment discontinuations (17%)\(^1\)
- Screening for DPYD deficiency by testing for common single nucleotide polymorphisms (SNPs) in *DPYD*, the gene encoding DPYD, followed by a dose reduction significantly reduced the incidence of fluoropyrimidine-related toxicity\(^3\)
- However, the overall incidence of HFS is still high in patients treated with capecitabine

**PRIMARY OBJECTIVE**

To investigate whether SNPs in genes encoding for capecitabine metabolizing enzymes (*CES1, CES2, and CDA*) can be used to predict the occurrence of HFS in patients treated with capecitabine.

**METHODS**

- 446 patients treated with capecitabine at the Erasmus MC Cancer Institute were included for analysis
- Prospectively collected blood samples were genotyped for 8 SNPs in 3 genes:
  - *CES1* 1165-C>A (rs2244613)
  - *CES1* 1165-T>C (rs2244614)
  - *CES1* 690>T>G (rs3217164)
  - *CES2* 1613-A>G (rs2244109)
  - *CES2* -823C>G (rs11075646)
  - CDA 79-A>C (rs2072671)
  - CDA 205G (rs603412)
  - CDA 266+242A>G (rs10916825)
- HFS was graded according to the Common Terminology Criteria for Adverse Events version 5.0
- Associations between SNPs or baseline factors (age, sex, performance status) and HFS with *P* ≤ 0.50 were tested multivariably by logistic regression and internally validated by bootstrapping

**RESULTS**

**CONCLUSION AND FUTURE PERSPECTIVES**

- Carriers of *CES1* 1165-C>A and CDA 266+242A>G polymorphisms are at higher risk of developing HFS ≥ grade 2 during capecitabine treatment. This is in line with previous research.\(^4\)
- Prospective studies should investigate if preemptive screening for these SNPs can be used to individualize systemic cancer treatment.
- Additionally, *CES2* -823C>G was associated with a reduced risk on developing HFS. Replication of this association is needed.