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4520 DPYD genotype-guided dose individualization of fluoropyrimidine therapy: A prospective safety and cost-analysis on DPYD variants DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A

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Background: Fluoropyrimidines are generally well tolerated drugs, but can result in severe, potentially fatal toxicity in up to 30% of patients. The major cause of toxicity is reduced activity of the key metabolizing enzyme dihydropyrimidine dehydrogenase (DPD), most often the result of genetic DPYD variants. In this prospective clinical trial we determined whether toxicity of fluoropyrimidine treatment can be reduced by upfront screening for 4 relevant DPYD variants and DPYD genotype-guided dosing.

Methods: Prospective genotyping for DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A was performed in patients prior to start of fluoropyrimidine-based therapy. Heterozygous DPYD variant carriers received an initial dose reduction of 25% (c.2846A>T, c.1236G>A) or 50% (DPYD*2A, c.1679T>G). Incidence of severe (grade ≥ 3) toxicity in DPYD variant carriers was compared to a historical cohort of DPYD variant carriers treated with full dose.

Results: A total of 1,103 evaluable patients was enrolled, of whom 85 were heterozygous DPYD variant carriers (7.7%). In DPYD variant carriers the overall frequency of grade ≥ 3 toxicity was 39%. When comparing to the historical cohort, DPYD genotype-guided dosing markedly reduced the risk of grade ≥ 3 toxicity for DPYD*2A and c.1679T>G carriers, moderately reduced risk for c.2846A>T carriers, and resulted in a similar risk for c.1236G>A carriers. Pharmacokinetic analyses showed that fluoropyrimidine exposure after dose reductions in DPYD variant carriers was comparable to wild-type patients. A cost-analysis showed that the reduced risk in toxicity resulted in average total treatments costs per patient that were even lower for the screening strategy (€2599) compared to non-screening (€2650).

Conclusions: Upfront DPYD genotyping improves patient safety during fluoropyrimidine chemotherapy, is feasible in routine practice, and is cost saving. For heterozygous DPYD*2A and c.1679T>G carriers, a 50% initial dose reduction is recommended. For c.1236G>A and c.2846A>T carriers the applied dose reductions of 25% in this study were not enough to lower the risk of severe toxicity in this group, so more cautious dose reductions of 50% are recommended.

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