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Titel des Beitrags:
Somatic copy number changes in DPYD are associated with lower risk of recurrence in triple-negative breast cancers.

Abstract:
Background: Genomic rearrangements at the fragile site FRA1E may disrupt the dihydropyrimidine dehydrogenase gene (DPYD) which is involved in 5-fluorouracil (5-FU) catabolism. In triple-negative breast cancer (TNBC), a subtype of breast cancer frequently deficient in DNA repair, we have investigated the susceptibility to acquire copy number variations (CNVs) in DPYD and evaluated their impact on standard adjuvant treatment. Methods: DPYD CNVs were analysed in 106 TNBC tumour specimens using multiplex ligation-dependent probe amplification (MLPA) analysis. Dihydropyrimidine dehydrogenase (DPD) expression was determined by immunohistochemistry in 146 tumour tissues. Results: In TNBC, we detected 43 (41%) tumour specimens with genomic deletions and/or duplications within DPYD which were associated with higher histological grade (P=0.006) and with rearrangements in the DNA repair gene BRCA1 (P=0.007). Immunohistochemical analysis revealed low, moderate and high DPD expression in 64%, 29% and 7% of all TNBCs, and in 40%, 53% and 7% of TNBCs with DPYD CNVs, respectively. Irrespective of DPD protein levels, the presence of CNVs was significantly related to longer time to progression in patients who had
received 5-FU- and/or anthracycline-based polychemotherapy (hazard ratio=0.26 (95% CI: 0.07-0.91), log-rank P=0.023; adjusted for tumour stage: P=0.037). Conclusion: Genomic rearrangements in DPYD, rather than aberrant DPD protein levels, reflect a distinct tumour profile associated with prolonged time to progression upon first-line chemotherapy in TNBC.