Clinical Research (Excluding Clinical Trials)

Abstract 3795: Dynamic acquisition of HER2 expression on circulating tumor cells in gastric cancer patients correlates to developing therapeutic resistance

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Abstract

Introduction: It has been hypothesized that molecular characters of circulating tumor cells (CTCs) is dynamically evolved during cancer development. However, how the evolutive CTC subtypes support tumor progression and drug resistance remains unclear. In this study, converted phenotypic HER2 expression and karyotypic chromosome 8 ploidy of CTCs in gastric cancer patients who developed therapeutic resistance were systematically investigated.

Methods: Ninety-eight prospectively enrolled patients with diagnosis of advanced gastric cancer (AGC) were histo-pathologically classified into 2 cohorts of $HER2^+$ ($hHER2^+$, 53 patients, subjected to the combined chemo- and anti-HER2 targeted therapy), and $HER2^-$ ($hHER2^-$, 45 patients, subjected to chemotherapy alone). Integrated EpCAM-independent subtraction enrichment and immunostaining-fluorescence in situ hybridization (SE-iFISH) was applied to monitor and characterize HER2 expression and chromosome 8 ploidy of CTCs in patients following multiple courses of therapy until disease progression.

Results: HER2 expression on CTCs was heterogeneous and interconverted compared to its relatively stable status on primary tumor. Among those prior-to-therapy patients, $HER2^+$ CTCs were only detected in 30.2% (16/53) $hHER2^+$ patients, which whereas can also be detected in 29.5% (13/44) $hHER2^-$ cohort. Following several courses of therapy, additional 34% (18 out of 53, total: 34% + previous 30.2% = 64.2%) in $hHER2^+$ and 15.9% (7 out of 44, total: 15.9% + previous 29.5% = 45.4%) in $HER2^-$ cohort revealed acquired HER2 expression on CTCs. Acquired $HER2^+$ phenotype on CTCs closely correlated to the decreased therapeutic efficacy. Twenty one patients in $hHER2^+$ and 8 in $hHER2^-$ cohorts have developed therapeutic resistance at the time of analysis. Among those patients, $HER2^+$ CTCs were identified in 19 of $hHER2^+$ (19 out of 21, 90.5%) and 6 of $hHER2^-$ cohorts (6 out of 8, 75%), respectively. Further karyotyping of CTCs in those patients developing therapeutic resistance indicated that most of the CTCs with acquired HER2 expression had multiploid (≥5) chromosome 8, implying that aneuploid chromosome 8 in acquired $HER2^+$ CTCs were likely relative to development of therapeutic resistance, both chemotherapy alone and the combined chemo- and targeted therapy. Genomic profiling of the single CTC subtyped by iFISH upon phenotypic HER2 expression and karyotypic chromosome 8 ploidy is currently under investigation.

Conclusion: Dynamic profiling gene signature and molecular characterization of CTCs might be significant in terms of predicting therapeutic resistance, and further help select an alternative effective intervention to overcome the acquired therapeutic resistance.

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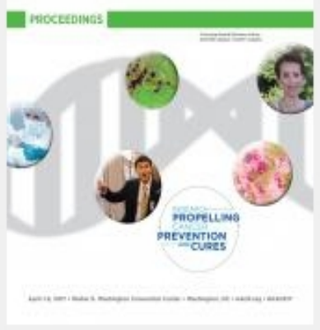

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