Tumor microenvironment biomarkers as therapeutic strategies for TNBC

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Background: Patients with triple negative breast cancer (TNBC) comprise a heterogeneous and poor-prognosis subgroup. Biomarkers for targeted therapy development remains a challenge. Progression of TNBC is associated with extracellular matrix (ECM) remodeling and reactivation of the paracrine Hedgehog (Hh) pathway, highlighting the relevance of tumor microenvironment (TME) in tumorigenesis. We investigated whether TME biomarkers could determine clinical response in TNBC patients treated with the Hh pathway inhibitor sonidegib in combination with docetaxel.

Methods: Patients enrolled in GEICAM/2012-12 (EDALINE) trial were included (n = 12). To evaluate Hh pathway activation, the expression of SHH and GLI1 was centrally examined by immunohistochemistry in pre-treatment primary tumors. A Hh Pathway Activation Signature (HPAS) was defined when SHH expression in epithelium and GLI1 in stroma were high (> median). Biomarkers involved in formation and degradation of ECM (C1M, C3M, C4M, pro-C3, pro-C6, CRP,M, Loric-2 and VCANM) were evaluated by ELISA (Protein FingerprintTM) in sequential plasma samples. ECM signature (ECMS) was defined when C4M and VCANM were high at baseline (> median).

Results: Related to Hh pathway activation, only 10 tumors had IHC results. Three patients had high HPAS, 2 of them experienced a clinical benefit, 1 complete response (CR) and 1 stable disease (SD) lasting 7.3 and 5.5 months, respectively. All patients with low HPAS expression progressed. An additional patient had clinical benefit but the status of Hh pathway activation was unknown. For ECM biomarkers, a maintained reduction was observed in the expression along treatment (C2D1-6.3B, C2D2-25B and C4D1) vs baseline for pro-C3 (12.8, 10.2 and 9.4 vs 16.6, p = 0.05, p = 0.03, p = 0.25, respectively), and pro-C6 (9.2, 7.5 and 8 vs 9.95, p = 0.13, p < 0.01, p = 0.03, respectively). Interestingly, patients with high ECMS had better Progression Free Survival (p = 0.02). Moreover, 4 patients out of 12 had high ECMS, 3 of them experienced a clinical response, 1 CR and 2 SD. All patients with low ECMS progressed.

Conclusions: Hh pathway activation and ECM remodeling might be associated with improved benefit to sonidegib in combination with docetaxel in TNBC metastatic patients.

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