Novel Combinatorial Drug Therapy for MTC

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Background: Medullary thyroid carcinoma (MTC) originates from the thyroid gland parafollicular cells. Treatment options for progressive, metastatic MTC patients are limited to the recently FDA-approved tyrosine kinase inhibitors (TKIs), Vandetanib and Cabozantinib, which target multiple receptor tyrosine kinases, including VEGFR2. However, the efficacy of TKIs is limited and development of TKI resistance is common. Here we examined, the effect of a combinatorial drug therapy using the TKI, Nintedanib, and the histone deacetylase (HDAC) inhibitor, Romidepsin, on MTC growth and mouse survival.

Methods: We used the NSE/p25-gfp bi-transgenic mouse line, which is an inducible mouse model for MTC. Mice were dosed with either Nintedanib (100 mg/kg/day) or Romidepsin (0.75 mg/kg/day) or [Nintedanib (35 mg/kg/day) + Romidepsin (0.37 mg/kg/day)] or vehicle. Drugs were administered intraperitoneally for a 3-week period. For survival studies, mice were left untreated for 3 more weeks. Tumor progression was monitored weekly using a T2 weighted magnetic resonance imaging on a 7 Tesla system. Tumor tissues were analyzed for oncogenic signaling pathways by immunoblotting. Proliferation and microvessel density were determined by immunostaining tumors with Ki-67 and CD-31 antibodies respectively.

Results: Romidepsin, alone, has no effect on tumor growth. However Nintedanib slows down tumor growth by 50% by disrupting tumor vasculature. This is demonstrated by a 75%, and a 54% reduction in microvessel density in Nintedanib- and [Nintedanib + Romidepsin]-treated mouse tumors, respectively. Importantly Nintedanib has no effect on proliferation. However combining Nintedanib with Romidepsin reduced proliferation by 70%. Mechanistically Nintedanib or the combination of Nintedanib and Romidepsin inhibit RET and VEGFR2 signaling as well as AKT and mTor.

Conclusion: Nintedanib or combinatorial treatments of [Nintedanib + Romidepsin] represent valid strategies to stop MTC progression. We are currently evaluating the effect of these drugs on mouse survival and development of drug resistance.

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