C-41

Novel Use of a CLIA-Certified CDKN2C Loss Assay in Sporadic Medullary Thyroid Carcinoma

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BACKGROUND: The cyclin-dependent-kinase inhibitors (CDKN)/retinoblastoma pathway has been implicated in sporadic medullary thyroid carcinoma (sMTC) tumorigenesis. Somatic CDKN2C loss has been associated with decreased overall survival in MTC patients, independent of RET status. We evaluated CDKN2C loss in a prospective clinical environment using a novel CLIA-certified assay to confirm its association with aggressive disease and interrogate response to targeted therapy.

METHODS: Patients with advanced sMTC underwent tumor genotyping for the purpose of management of targeted therapy and prognostication.

RESULTS: Tumors from 83 patients with advanced sMTC were evaluated for CDKN2C loss from 5/2017 to 5/2019. Thirty-three patients had haploid loss (1n) (51%), 32 (49%) were diploid wildtype (2n), and the test was indeterminate in 15 cases (18%). Forty-five patients (70%) had a somatic RET mutation and 38% had alteration of both genes. Thirteen (20%) patients presented with M1 disease and 47 (73%) eventually developed distant metastasis. Patients with CDKN2C loss had a shorter time-to-distant-metastasis compared to those with wildtype CDKN2C (1.7 versus 6.6 years; p=.01). Patients with fewer genetic alterations had longer time-to-distant-metastasis, but this did not reach statistical significance (p=.06; Table). Of the 34 patients treated with targeted therapies, median time from diagnosis to initiating therapy was 1.8 years in those with CDKN2C loss versus 6.1 years in wildtype patients (p=.02).

CONCLUSION: This is the first evaluation in the clinical setting of CDKN2C haploinsufficiency in sMTC. Although a larger cohort and longer follow-up will be required, loss of CDKN2C is frequent and loss seems to be associated with more aggressive disease. Additionally, loss may indicate patients that might receive benefit from treatment with a CDK inhibitor.

Table 1. Time-to-distant metastasis examined by combination of genetic alteration

	RET mutation	RET wildtype
CDKN2C loss	1.69 years (0.9 - 5.6 years)	1.4 years (1.1 - NR)
CDKN2C wildtype	4.8 years (1.5 - NR)	7.34 years (6.6 - NR)