MOLECULAR AND CLINICAL CHARACTERISTICS OF SLOVENIAN PATIENTS WITH SMALL CELL CARCINOMA OF THE OVARY, HYPERCALCEMIC TYPE

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Description Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) is rare and usually affects young women with median age at diagnosis of 241. It has a poor prognosis with long-term survival of 30% in early-stage disease [1]. Germline and somatic variants in SMARCA4 gene, which encodes a catalytic subunit of the SWI/SNF chromatin-remodelling complex, are associated with SCCOHT. Penetrance of *SMARCA4* germline pathogenic variants (PV) and incidence of SCCOHT is currently unknown. The aim of our study was to identify all cases of SCCOHT in Slovenia from 1991 to 2021 and present their genetic testing results, histopathological and clinical characteristics. We also aimed to estimate the incidence of SCCOHT and assess the penetrance of germline *SMARCA4* PVs in Slovenian families.

First, we analysed medical records and data from the Slovenian Cancer Registry. In patients suspected of having SCCOHT, histopathological review with immunohistochemical staining for SMARCA4/BRG1 was undertaken to confirm the diagnosis. In cases of confirmed SCCOHT, both germline and somatic genetic analyses using next-generation sequencing were performed. We identified 7 patients who developed SCCOHT aged 21-41 in a population of two million during a 30-year period and estimate the minimal incidence of SCCOHT to be 0.12/million/year [2]. Two cases were sporadic, with presumably biallelic *SMARCA4* variants in their tumours not seen on germline testing. In one patient, a *SMARCA4* PV and loss-of heterozygosity was identified in tumours tissue, but germline testing was unfeasible. In four cases from two different families, two novel germline loss-of-function variants in SMARCA4, c.1423_1429delTACCTCA p.(Tyr475Ilefs*24) and c.3216-1G>T were identified. Based on pedigree analysis,

they appear to be associated with relatively high penetrance. In all tested tumours, tumour mutational burden was low. Five tumours consisted of small cells with scant cytoplasm. In two cases, there was a predominance of large cells with eosinophilic cytoplasm, i.e. large cell variant of SCCOHT. Patients included in our study were diagnosed with stage FIGO IA-III disease and died due to SCCOHT within 36 months. In one case, temporary disease stagnation was achieved using immunotherapy.

In conclusion, our study presents all known cases of SCCOHT diagnosed in Slovenia between 1991 and 2021. We offer a first estimate of SCCOHT incidence in the non-paediatric population, but expect studies in larger populations will lead to more accurate assessments.

References:

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