STK11 mutated cervical carcinoma

Zoran Gatalica¹, Kara Bui¹, Jeffrey Swensen¹, Joanne Xiu¹ and Alexandra Leary²

¹Caris Life Sciences, Phoenix, AZ. ²Gustave Roussy Cancer Center, Paris, France.

Introduction and Objectives: Pathogenic germline mutations in STK11, a tumor suppressor gene, lead to development of Peutz-Jeghers syndrome (PJS). PJS is associated with increased rates of tumors that include cervical adenocarcinoma, specifically adenoma malignum. The impact of STK11 germline and somatic mutations in an unselected cervical cancer population is unknown. The role of HPV infection and potential therapeutic targets, including immuno-oncology (I-O) were evaluated in a cohort of STK11-mutated cervical cancers.

Methods and Patients: The study set consisted of 31 cases of primary cervical/endocervical malignancies with STK11 pathogenic mutations, detected using a 592 gene NGS panel. Additional biomarkers included IHC for PD-L1 and steroid receptors (ER, PR and AR), and in-situ hybridization (ISH) for HR-HPV. Microsatellite instability (MSI) and total mutational burden (TMB) were calculated from NGS data. The tumor was considered TMB-H when ≥ 10 mutations/Mb were detected, excluding known germline variants. MSI was calculated from NGS data as recently described (*Vanderwalde A et al. Cancer Medicine 2018* and *Le DT et al. Science 2017*); MSI-H threshold was set at ≥ 46 altered microsatellite loci (95.8% sensitivity, 99.4% specificity, 94.5% PPV, and 99.2% NPV). Patients' age range was 29-64 (mean 47.6) years.

Results: STK11 mutated cervical carcinoma represented 4% of all cervical malignancies. Pathogenic mutations were identified in exons 1 and 3-8, and included splice site (3), frameshift (17) missense (4) and nonsense (9) mutations (two cases had 2 and one case had 3 concurrent mutations). Mutated gene variant frequencies (VF) varied from 7% to 82%. In 3 cases with a STK11 mutation and VF near 50% (W239C at 42%, N181fs at 59% and I192fs at 48%) clinical presentation and germ line testing confirmed PJS. 18 cases had evidence of metastasis at the time of testing. Histologically, STK11 mutant cancers were classified as: squamous (11), adenosquamous (3) or adenocarcinomas (16). One patient had squamous cell carcinoma with an STK11 mutation (Y60fs at 9% VF) and a separate focus of adenocarcinoma without an STK11 mutation. A second patient presented with neuroendocrine cervical carcinoma (negative for STK11 mutation) and adjacent adenocarcinoma (with somatic Y118X mutation with VF of 7%). Other commonly mutated genes included: PIK3CA (4), KRAS (4) and CDKN2A (4). 2 cases (1 PJS) had additional MDM2 gene amplification. All tested cases were microsatellite stable (24/24), while TMB varied between from 1 to 19/Mb. PD-L1 was positive in 4/29 cases. HR-HPV was detected in 17/28 cases, including 1/3 adenocarcinomas in PJS patients. Steroid receptors were consistently negative (ER and PR 0/29; and AR 0/7).

Discussion/Conclusions

STK11 mutated cervical carcinomas are rare (4% of all cervical cancers), and associated with various histologic types. Majority of the cases present with somatic STK11 mutations. Confirmed cases of PJS (germline STK11 mutations) were all adenocarcinomas. Rare cases (N=2 in our series) may present with two concurrent, distinctly different, histologic phenotypes and STK11 mutation may be present in one, but not both tumor types. Biomarkers of potential usefulness of I-O therapy included PD-L1 overexpression (4 cases) and, potentially, TMB-H (9/26 cases had TMB ≥ 10 /Mb). None of the tested cases exhibited MSI-H. HPV infection can occur concomitantly with STK11 mutations (17/28 cases). All STK11 mutated cervical carcinomas were consistently negative for all 3 steroid receptors.