Molecular characterization of 361 cases of uterine carcinosarcomas reveal alterations in the DNA repair and PI3K pathways as potential therapeutic targets

Nathaniel L Jones1, Joanne Xiù2, Sandee K. Reddy2, Ana I. Tergas1, William M. Burke1, Jason D. Wright1, June Y. Hou1
1Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital 2Caris Life Sciences

Abstract
Background: Uterine carcinosarcomas (malignant mixed Müllerian tumors or MMMTs) are rare endometrial cancers composed of epithelial and mesenchymal components. MMMTs exhibit aggressive behavior with poor prognosis. We aim to evaluate patterns of molecular, genomic and protein changes in a large cohort of uterine carcinosarcomas and identify potential treatment options.

Methods: 361 out of 3133 (11.5%) of EC submitted to Caris Life Sciences from March 2011 to July 2014, were identified as MMMT. A combination of sequencing (Sanger or next generation sequencing, protein expression [immunohistochemistry], and/or gene amplification [FISH/CISH]) was performed.

Results: Of 47 genes sequenced 26 genes were mutated, including TP53 (69%) and PIK3CA (22%). Within the PI3K pathway, the most common alteration was cMET mutation 1.4%, amplification 1.2%, and 4.7% for PIK3CA. In the DNA repair pathway, the loss of ERCC1 (84%) and MGMT (68%) protein expression, suggesting benefit of alkylating agents in a subset of MMMT tumors. In addition, alkylating agents and anthracyclines may have benefit in a selected subset of patients.

Conclusions: Our retrospective data analysis of a large cohort (n=361) of uterine carcinosarcomas contributes to the increased understanding of the molecular drivers within this heterogeneous and rare cancer.

References: