Molecular Variations in Uterine Carcinosarcomas: Are There Therapeutic Opportunities?

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Levine Cancer Institute is the destination for leading clinical trials and breakthrough treatments at 25 locations across the Carolinas.

OBJECTIVE

To perform comprehensive molecular profiling (CGP) on a large cohort of patients with uterine carcinosarcomas to identify potential therapeutic targets.

BACKGROUND

Uterine carcinosarcomas—also known as malignant mixed mesodermal tumors (MMMTs)—comprise only 5% of uterine cancers, yet account for disproportionately more uterine cancer-related deaths owing to their aggressive behavior. Uterine carcinosarcomas present with extrauterine disease in 60% of patients. In patients with early-stage disease (I or II) who receive adjuvant treatment, recurrence rates approach 50%(1).

In advanced stages of disease, the mainstay of treatment remains chemotherapy but cure rates are suboptimal. In a series of 121 patients with uterine carcinosarcomas, five-year stage-specific survival rates were 59, 22, and 9 percent for women with stage I/II, III, or IV disease, respectively(2). Standard treatment options are inadequate, and studies attempting to identify more effective agents have been disappointing. More research is needed to elucidate the aggressive nature of these cancers, as well as identify treatment targets.

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METHODS

- Tumor samples that underwent CGP by Caris Life Sciences (Phoenix, AZ) with clear indication as uterine MMMT were examined for mutations using NextGen DNA sequencing (NextSeq on 592 genes), protein expression by immunohistochemistry (IHC), copy number amplification using NGS or in situ hybridization (CNA or CISH), and fusion events using NextGen RNA sequencing (FusionPlex on 52 genes).

- Tumor mutational load (TML) was calculated based on the total number of somatic non-synonymous missense mutations identified per megabase of genome coding area. Threshold for TML-high was set at ≥17.

- Microsatellite (MS) instability was evaluated on over 7,000 known MSI loci in target regions. The threshold to determine MSI by NGS was determined to be 46 or more loci with insertions or deletions to generate a sensitivity of > 95% and specificity of > 99%.
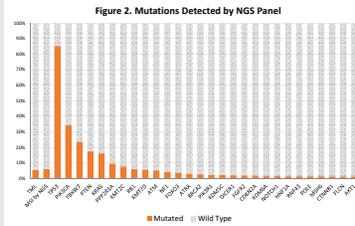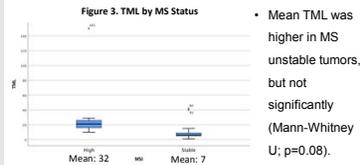
RESULTS

Figure 1. Specimen Site
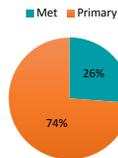
- Out of approximately 4000 uterine tumors, we identified a total of 168 patients with primary MMMT with CGP results. Median age was 67 years. The majority of specimens, n=124 (74%), were obtained from the uterus; the remaining n=44 (26%) were from metastatic sites (Figure 1).

RESULTS (CONT'D)

**Figure 2. Mutations Detected by NGS Panel**

- In a 592 gene panel, the following aberrations were observed in mutational analyses: *TP53* (86%), *PIK3CA* (34%), *FBXW7* (23%), *PTEN* (18%), *KRAS* (16%), *PPP2R1A* (10%). Other genes (e.g. *ATM, RB1, KMT2D, NF1, KMT2C, BRCA2, DICER1, FGFR2*) were mutated at ≤ 6% frequency (Fig. 2).

- Tumor mutation load (TML) was low in most cases (50%), 45% were moderate, and 5% were high; two TML-high tumors (1.3%) harbored POLE mutations. Most tumors were MS stable (94%). In a subset analysis, a significant association was seen between TML and MS instability (Fisher's Exact; p=0.000) (Fig 3).
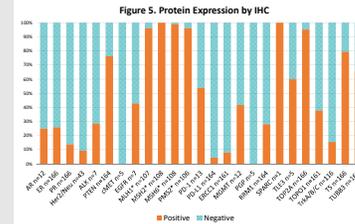
Figure 3. TML by MS Status

Mean: 32 | Mean: 7
High | Stable

- Mean TML was higher in MS unstable tumors, but not significantly (Mann-Whitney U; p=0.08).

RESULTS (CONT'D)

Figure 4. CNA Detected by NGS Panel
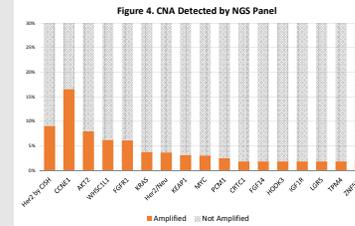
- CNA was observed for *CCNE1* in 16% of specimens and *AKT2* in 8% (Fig. 4). *HER2* was amplified by CISH in 9% (n=3/33) of tumors.

Figure 5. Protein Expression by IHC

- A majority (95%) of patients were *TOP2A* positive by IHC, while *TS* (80%), *PTEN* (76%), and *TUBB3* (66%) also had high expression (Fig. 5). ER and PR staining was generally low (26 and 14%, respectively). *PD-L1* expression was also low, detected in only 5% of cases. Mismatch repair deficiency (negative result for MLH1, MSH2, MSH6, or PMS2) was seen in 4% of tumors.

RESULTS (CONT'D)

- A single low frequency in-frame fusion event was detected, however the clinical relevance is unknown at this time.

Gene 1	Gene 2	Breakpoint
NOTCH1: exon 2	PRPSAP2: exon 7	chr9:139438476:-/chr17:18814416:+

- An additional out of frame fusion event was detected between ESR1: exon 4 and c6orf211: exon 3.

CONCLUSIONS

To our knowledge, this is the largest cohort of uterine MMMTs to be molecularly profiled. Multiple somatic mutations and copy-number alterations in genes that are therapeutic targets were identified. Our data suggests CGP may inform treatment, for example, targeting the PI3K/AKT pathway with mTOR inhibition, chromatin remodeling therapies including EZH2 or PARP inhibition, or VEGF inhibition. PD-1/PD-L1 inhibition may be useful in a subset of patients with high TML/MS instability. Clinical trials are needed to validate these observations.

REFERENCES

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