Molecular Profiling of Aggressive Variant Urothelial Carcinoma

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Background

- The WHO recognizes multiple variant histologies of urothelial carcinoma (vUC), many of which have been associated with poor outcomes compared with UC (UC).
- Prior studies have identified molecular differences between variant vUC and UC through targeted techniques, for example, *HER2* gene amplification in micropapillary histology or CDH1 loss is plasmacytoid histology.
- We aimed to explore molecular differences between aggressive vUC and UC using multiplatform profiling.

Methods

- 23 micropapillary (MP), 16 plasmacytoid (P), 23 sarcomatoid (S), 7 nested (N), 6 clear cell (CC), and 2 giant cell (GC) variant UC specimens were tested between 2012 to 2018 via a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ) consisting of gene sequencing (Sanger or next generation sequencing [NGS]), gene amplification (CISH or FISH), and protein expression (immunohistochemistry [IHC]).
- 84% of samples were from the primary tumor, and 16% from a metastatic site. Upper tract or lower tract was not specified. Histologic subtype was determined from referring pathology report.
- PD-L1 IHC was performed using the Ventana SP142 assay, reading tumor cell only. HER2 IHC was performed using the Ventana 4B5 assay.
- The specific NGS assay used evolved over time from a 47-gene hotspot assay to a 592 gene panel.
- Findings were compared to 435 control UC specimens using the Chi square test.
- Genes were grouped together by pathway for descriptive analysis. Percentages of aberrations were calculated using both the rates from the hotspot and NGS analyses. DNA damage repair genes with mutations included: *FANC* family, *ATM, PALB2*, *ERCC*, *BRCA1/2*, *RAD50*, *BRIP1*, *BLM*, *CHEK2*, *MUTYH*, *BAP1*, and MMR genes.

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Results

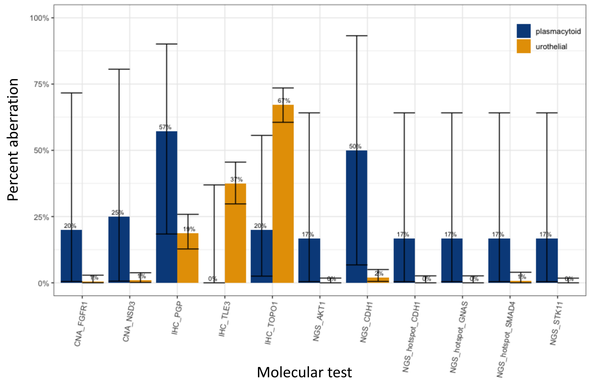

Figure 1. Comparison of select profiling differences between plasmacytoid and urothelial carcinoma

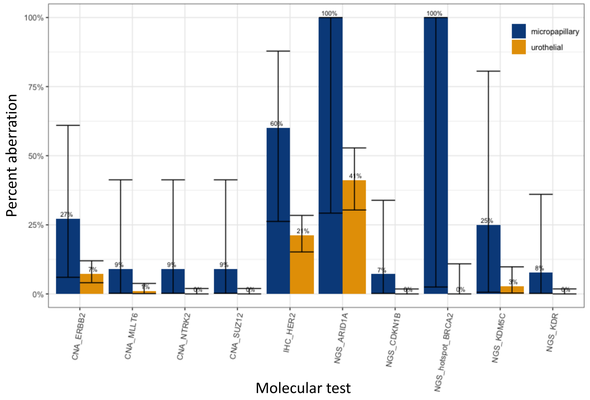

Figure 2. Comparison of select profiling differences between micropapillary and urothelial carcinoma

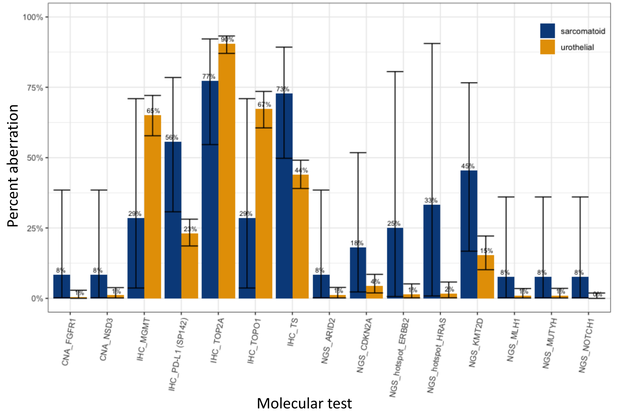

Figure 3. Comparison of select profiling differences between sarcomatoid and urothelial carcinoma

Table 1. Percentages of select molecular aberrations according to histologic subtype

	MP (n=23)	P (n=16)	S (n=23)	N (n=7)	CC (n=6)	GC (n=2)	UC (n=435)
PTEN/PI3K/ mTOR/AKT	9.5	41.7	17.6	0	33.3	0	19.9
DDR Genes	0	0	28.9	0	0	0	20.8
ERBB2	4.8	8.3	5.9	0	0	0	5.5
HER2 (CISH)	27.3	0	0	20	33	0	10.4
TP53	61.9	50	58.8	33.3	33.3	100	57.1
RB1	15.8	27.3	18.8	0	0	100	10.6
FGFR3	0	0	0	33	0	0	12.1
RAS/RAF	0	8.3	12.1	0	0	50	8.4
PD-L1 (IHC)	11.8	0	55.6	0	0	50	23.1
TMB-high	14.3	0	16.7	0	0	50	18.4

DDR, DNA damage repair; UC, urothelial carcinoma; MP, micropapillary; P, plasmacytoid; S, sarcomatoid; N, nested; C, clear cell; GC, giant cell; TMB, tumor mutational burden

Result Highlights

- The rates of DNA damage repair (DDR) mutations was low in MP, P, N, CC, and GC compared with UC. However, the rate of DDR mutations in sarcomatoid vUC was comparable to UC.
- CISH HER2 amplification was seen in 27.3% MP compared with only 10.4% UC (p=0.005).
- Compared to UC, PD-L1 IHC was positive in a higher proportion of S (55.6% v. 23.1%, p=0.002). However, PD-L1 IHC was positive in lower rates among other vUC
- Tumor mutational burden was high in a lower proportion of most vUC compared to UC: 18.4% UC vs. 14.3% MP (p=0.7), 0% P (p=0.25), 16.7% S (p=0.88). In the limited GC samples, TMB was high in 50%.
- There were more *ARID1A* mutations detected in MP than UC (100% [3 specimens] v. 41.3%, p=0.044), and more *CDH1* mutations in P than UC (50% [4 specimens] v. 2%, p<0.001).

Conclusions

- Aggressive variant histology UCs have a differential profile of molecular aberrations compared to UC
- Several of these differences are in molecular targets that are under active investigation in the treatment of UC, such as DNA damage repair, *HER2*, and *FGFR*.
- Other differences are in biomarkers associated with response to checkpoint inhibitors, such as PD-L1 expression and TMB.
- Further studies are needed to confirm these findings, and may support therapy development for these rare, aggressive UC subtypes.

References

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