Molecular profile of uterine papillary serous carcinoma compared to ovarian serous carcinoma: Is it the same disease at different sites?

Haider. Mahdi[1], Joanne Xiu[2], Sandeep. K. Reddy[2] and R. DeBernardo[1]
[1]*The Cleveland Clinic, Cleveland, OH,* [2]*Caris Life Sciences, Phoenix, AZ*

Abstract

Objective: To compare the molecular profile of a large cohort of uterine papillary serous carcinoma (UPSC) and ovarian serous carcinoma (EOC-S).

Methods: 240 UPSC and 1587 EOC-S tumors were evaluated using a commercial multiplatform profiling service (CARIS Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH).

Results: TP53 was the most commonly mutated gene in both UPSC and EOC-S (76% vs. 69%, p=0.03). UPSC were more likely to have mutation in PIK3CA (29% vs. 2%, p<0.001), FBXW7 (12% vs. 1%, p<0.001), KRAS (9% vs. 5%, p<0.001) PTEN (7% vs. 1%, p<0.001), and CTNNB1 (2% vs. 0%, p<0.001) compared to EOC-S. On the other hand, EOC-S were more likely to harbor mutation in BRCA1 (20% vs. 9%) and BRCA2 (18% vs. 6%), however this difference was not statistically significant (p=0.12 and 0.08 respectively). No difference in the rate of mutation of APC, (3% v. 3%) ATM (3% vs. 2%), BRAF (1% vs. 1%) and AKT1 (1% vs. 0.2%) was identified (p<0.05 for all). IHC MRP-1 (88% vs. 83%, p=0.07), PD-1 (68% vs. 68%, p=0.9), PTEN (56% vs. 58%, p=0.22), TOPO1 (36% vs. 40%, p=0.06) and PR (32% vs. 30%, p=0.39), were overexpressed in both USC and EOC-S. MGMT (80% vs. 53%, p<0.001) was more expressed in EOC-S than UPSC. Whereas, IHC TOP2A (89% vs. 69%, p<0.001), ER (60% vs. 53%, p=0.0008), RRM1 (35% vs. 27%, p<0.001), HER2 ISH (17% vs. 4%, p<0.001) and Her2/neu (10% vs. 2%, p<0.001) were more expressed in UPSC than EOC-S respectively.

Conclusion: UPSC have a distinct mutation profile indicating higher activity of PI3K/PTEN/MTOR pathway but no difference in alteration of homologous recombination pathway compared to EOC-S. Over-expression of TOPO2A and other markers needs to be correlated with outcome and response to chemotherapy.

Background

- Uterine papillary serous carcinoma (UPSC) is a clinically aggressive subtype of endometrial carcinoma accounting for 10% of endometrial cancer diagnoses and represents up to 40% of endometrial cancer-associated deaths.
- Comprehensive surgical staging or debulking surgery similar to epithelial ovarian cancer is recommended for patients diagnosed with UPSC. Following surgery, adjuvant chemotherapy has become the standard treatment for UPSC.
- UPSC is histologically indistinguishable from high-grade serous ovarian carcinoma.
- Prior studies showed similarities in response to platinum-based chemotherapy and applicability of platinum-free interval between recurrent UPSC and serous ovarian carcinoma.
- Given the resemblances in histologic and clinical behavior between UPSC and serous ovarian carcinoma, one would assume these two cancers share a similar molecular profile.
- This is an important question as it may elucidate the molecular basis for this aggressive behavior and may have implications on the development of targeted treatment modalities.
- In a prior study using The Cancer Genome Atlas (TCGA) data, the molecular profile of 66 patients with UPSC was compared to that of serous ovarian carcinoma and basal-like breast cancer. The authors reported some similarities between the three cancer types.
- The objective of this study was to compare the molecular profile of a large cohort of patients with UPSC to that of serous ovarian carcinoma using a commercial multiplatform profiling service (Caris Life Sciences, Phoenix, AZ).

Methods

- Retrospective data analysis was done on uterine papillary serous tumors and ovarian serous carcinomas that were submitted to a commercial referral diagnostic laboratory (Caris Life Sciences, Phoenix, AZ) for molecular profiling aimed to provide therapeutic information based on tumor biomarkers.
- A multiplatform approach was taken that included sequencing, immunohistochemistry (IHC) and FISH/CISH. Association studies were performed by two-tailed chi-square or Fisher Exact tests.

Results

Patient Characteristics:

EOC-S		UPSC	
Case Total N	5335	Case Total N	628
Cases with NGS	1600	Cases with NGS	241
Average Age (Range)	62(11-97)	Average Age (Range)	68(44-94)
Specimen site EOC-S	**N**	**Specimen site UPSC**	**N**
Ovary	1655	Corpus Uteri	384
Peritoneum	1779	Peritoneum	105
Colon & Rectum	316	Lymph Nodes	28
Pelvis	278	Ovary	22
Connective & Soft Tissue	249	Abdomen	13
Lymph nodes	234	Pelvis	13
Abdomen	190	Vagina & Labia	13
Fallopian tube	108	Connective & Soft Tissue	9
Small Intestine	94	Colon	9
Liver	80	Liver	6
Other	352	Other	26

Results

Figure 1: Select IHC and ISH marker comparisons between UPSC and EOC. Bars indicate distribution frequencies (%). Numbers indicate Relative Risk of the comparison (95% Confidence Intervals). * and bold indicate p values <0.05

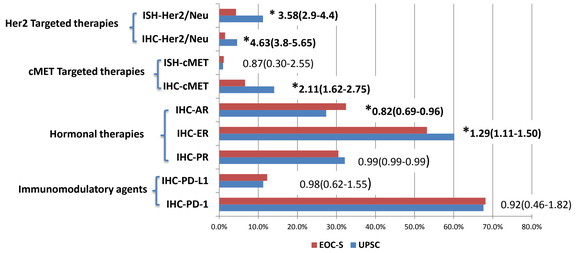

Figure 2: Additional IHC and ISH (*in situ* hybridization) biomarkers comparisons between UPSC and EOC-S along with associated therapies. (* and bold indicate p<0.05)

		UPSC		EOC-S	
Associated therapies	**Biomarkers**	**N/Total N**	**Frequency**	**N/Total N**	**Frequency**
Fluoropyrimidines	Low IHC-TS	223/545	41%	1244/2809	44%
mTor inhibitors	Low IHC-PTEN	275/622	44%	2192/5259	42%
Topotecan, irinotecan	IHC-TOPO1	194/542	36%	1923/4804	40%
platinum agents	Low IHC-ERCC1	245/301	81%	2792/3594	78%
Taxanes	IHC-SPARC	85/616	14%	776/4936	16%
	IHC-TLE3	48/389	12%	474/4544	10%
	Low IHC-TUBB3 *	**216/275**	**79%**	**3615/3989**	**91%**
EGFR targeted therapies	FISH-EGFR	16/193	8%	10/95	11%
multidrug resistance	IHC-PGP	39/504	8%	431/4623	9%
Anthracyclines	FISH-TOP2A	4/59	7%	14/330	4%
	IHC-TOPO2A*	**435/488**	**89%**	**2989/4315**	**69%**
Temozolomide	**Low IHC-MGMT***	**286/615**	**47%**	**989/5069**	**20%**
Gemcitabine	**Low IHC-RRM1***	**358/548**	**65%**	**3548/4849**	**73%**

Figure 3: Gene mutation comparisons between UPSC and EOC. Shown are genes with significantly different mutation rates between UPSC and EOC-S. Bars indicate distribution frequencies (%). Numbers indicate Relative Risk of the comparison (95% Confidence Intervals). * indicates p values <0.05

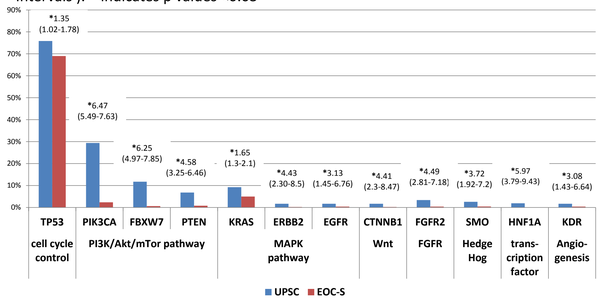

Figure 4: Gene mutations that are NOT significantly different between UPSC and EOC-S (all p>0.05)

		UPSC		EOC-S	
Pathway	**Biomarkers**	**N/Total N**	**Frequency**	**N/Total N**	**Frequency**
DNA Repair	BRCA1	3/33	9.10%	72/360	20.00%
	BRCA2	2/32	6.30%	65/356	18.30%
	ATM	7/240	2.90%	30/1581	1.90%
	MLH1	0/241	0	4/1597	0.30%
Wnt	APC	7/241	2.90%	49/1595	3.10%
HGF/cMET	cMET	6/240	2.50%	48/1595	3.00%
MAPK	NRAS	3/305	1.00%	16/1907	0.80%
	ERBB4	2/240	0.80%	5/1592	0.30%
	GNAQ	0/123	0	1/790	0.10%
	BRAF	2/365	0.50%	28/2182	1.30%
	PTPN11	0/241	0	3/1596	0.20%
	GNA11	0/179	0	3/1254	0.20%
SCF/cKIT	PDGFRA	1/239	0.40%	2/1584	0.10%
	cKIT	3/307	1.00%	11/1922	0.60%
	FLT3	2/241	0.80%	4/1590	0.30%
PI3K/Akt/mTor	AKT1	2/238	0.80%	4/1591	0.30%
	STK11	3/224	1.30%	20/1478	1.40%
JAK/STAT	JAK3	5/241	2.10%	35/1594	2.20%
Others	RB1	4/240	1.70%	9/1580	0.57%
	ABL1	4/229	1.70%	11/1530	0.70%
	VHL	1/212	0.50%	6/1460	0.40%
	SMAD4	1/240	0.40%	8/1589	0.50%
	FGFR1	1/240	0.40%	0/1597	0
	NOTCH1	0/236	0	4/1551	0.30%
	RET	0/239	0	4/1583	0.30%
	CSF1R	0/239	0	3/1590	0.20%
	CDH1	0/241	0	2/1595	0.10%
	SMARCB1	0/240	0.00%	1/1586	0.10%

Conclusions

- Both uterine and ovarian serous carcinoma had high rates of TP53 mutation.
- Our study shows significantly higher activation of PI3K/Akt/mTor pathway in UPSC as manifested by more frequent PIK3CA, FBXW7 and PTEN mutations.
- Patients with UPSC were more likely to show Her2/neu overexpression /amplification as well as cMET overexpression compared to EOC.
- In addition, multiple targetable cancer pathways including FGFR, hedgehog and angiogenesis pathways are more activated in endometrial cancer than ovarian cancer.
- While both cancers show significant hormone receptor expression, ovarian cancers have higher androgen receptor expression and endometrial cancers have higher estrogen receptor expression.
- Ovarian serous carcinoma had a higher rate of alterations in the homologous recon. pathway than UPSC.
- These data suggest a potential benefit of targeted therapy directed towards multiple cancer pathways including PI3K/AKT/mTOR pathway, Her2 and cMET in patients with UPSC.
- Clinical trials are needed to assess the efficacy of therapies targeted these pathways on clinical outcomes

References

1. Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73.
2. Janku F, et al. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol Cancer Ther. 2011 Mar;10(3):558-65.
3. Janku F, et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol. 2012 Mar 10;30(8):777-82.