Multiplatform tumor-profiling of 50 malignant Sertoli-Leydig cell tumors of the ovary reveals therapeutic opportunities

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Abstract

Objectives: Sertoli-Leydig cell tumors (SLCTs) of the ovary are a rare subtype of sex cord-stromal tumor accounting for less than 0.5% of ovarian malignancies. Their management largely relies on surgery followed by adjuvant chemotherapy for high grade and advanced stage tumors; however the drugs of choice for treatment of initial and recurrent disease remain unknown. We aim to systematically evaluate biomarkers from a relatively large cohort of SLCTs to explore therapeutic opportunities for this rare subtype of ovarian tumor.

Methods: SLCTs profiled between 2009 and 2015 with multiple platforms including IHC and sequencing were included.

Results: 50 SLCTs were identified: 17 were sampled from the ovary and 33 from metastatic sites. The average age of patients was 36.3 yrs. Hormone receptors ER, PR and AR were overexpressed in 27% (13 of 49), 55% (27/49) and 31% (9/29) of tumors, respectively, suggesting the potential use of hormonal therapies. Overexpression of EGFR, TOPO2A, TOPO1 and TLE3 were seen in 88% (7 / 8), 66% (27/41) and 35% (15 /43) and 2% (1/41) of tumors, suggesting possible benefit from EGFR-targeted agents, anthracyclines, topotecan and taxanes, respectively. cMET overexpression was rare, seen in 2% (1/41) tumors studied. Low expression of ERCC1, MGMT, RRM1, PTEN and TS were seen in 88% (28/32), 62% (29/47), 66% (27/41), 37% (18/49) and 32% (8/25) tumors, suggesting benefit from platinums, temozolomide, gemcitabine, mTOR inhibitors and fluoropyrimidines, respectively. High Pgp was seen in 10% (4/41), showing potential resistance to agents including etoposide. Tumor expression of PD-L1 was not seen (0/12); PD-1 expression on tumor-infiltrating lymphocyte was seen in 1 of 10 tumors evaluated. NextGen sequencing on 19 tumors showed one mutation in KRAS (G12C), AKT1 (E17K), TP53 (C277F) and BRCA2 (S3366frameshift), respectively, revealing opportunities for targeted therapies. Variants of unknown significance were seen on ALK, STK11, MPL, MLH1, JAK3 and GNA11 in one case each. In addition, Sanger sequencing on KRAS and BRAF on 7 tumors revealed two KRAS mutations (Q61H and G12V) and BRAF G466V (exon 11) mutation.

Conclusion: Molecular profiling of 50 rare SLCTs suggested therapeutic opportunities including commonly used agents including platinums/taxane, as well as additional cytotoxic, targeted and biological agents that would not be otherwise considered.

Background:

SLCTs are a rare subtype of sex-cord stromal tumors occurring most frequently in the 2nd and third decades. The cancer is characterized by the presence of testicular structures that produce androgens and clinical virilization is frequent. SLCTs are more frequently low-grade malignancies while the most important prognostic factors are clinical stage and degree of differentiation. Most of these tumors are treated with conservative surgery and adjuvant chemotherapy is considered for patients with poor prognostic factors. We aim to systematically evaluate biomarkers from a relatively large cohort of SLCTs that include about 45% of poorly differentiated/high grade tumors to explore therapeutic opportunities for this rare subtype of ovarian tumor.

Method:

Sertoli-Leydig tumors were tested at Caris Life Sciences between 2009 and 2015 by immunohistochemistry, fluorescent/chromogenic in-situ hybridization and sequencing. De-identified biomarker data were analyzed.

Results:

Figure 1: Patient Age distribution: As expected, age group of 21-30 has the highest patient number, followed by age group of 11-20 and 51-60. Total tumors analyzed: N=50

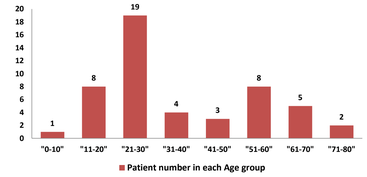


Figure 2: Tumor characteristics

Grade		N
Well-to-moderately differentiated tumors	low grade/ well-differentiated	2
	intermediate grade/differentiation	8
	Moderately differentiated	2
Poorly-differentiated / high grade		22
Unclear/not annotated		16

Specimen Site	N
Ovary	17
Abdomen, NOS	12
Pelvis, NOS	7
Retroperitoneum & Peritoneum	8
Connective & Soft Tissue	2
Rectum	1
Small Intestine	1
Vagina & Labia	1
Lung	1

Results:

Figure 3: Overexpression (IHC) or amplification (ISH) in all Sertoli-Leydig Ovarian Tumors Shown on the Y-axis are biomarkers tested; the platforms used (mmunohistochemistry/IHC or *in-situ* hybridization/ISH). Numbers in the parentheses are the N numbers. Selected associated therapies are shown in the boxes on the right.

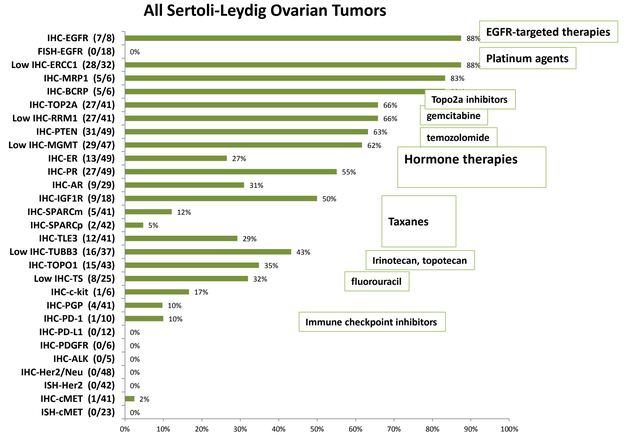
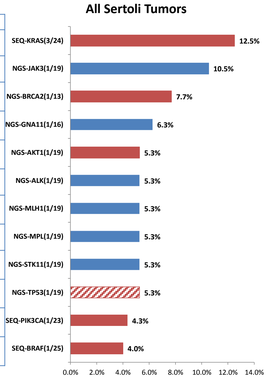


Figure 4: Gene mutations in Sertoli-Leidig Tumors

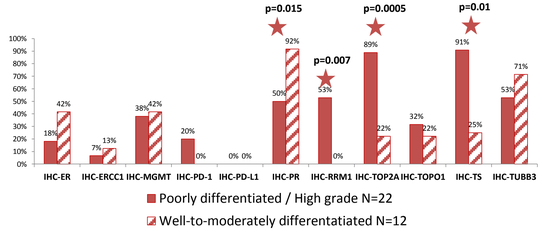
A subgroup of tumors have sequencing results available. Specific mutations found and the frequencies are shown below. VUS: variant of unknown signficance. Solid red: pathogenic mutations; shaded red: presumed pathogenic mutations; blue, variant of unknown significance

Gene	Mutation	Interpretation
SEQ-KRAS	G12C, G12V, Q61H	Pathogenic
NGS-JAK3	V722I	VUS
NGS-BRCA2	S3366fs	Pathogenic
NGS-GNA11	I259V	VUS
NGS-AKT1	E17K	Pathogenic
NGS-ALK	P271R	VUS
NGS-MLH1	V384D	VUS
NGS-MPL	A486T	VUS
NGS-STK11	F354L	VUS
NGS-TP53	C277F	Presumed pathogenic
SEQ-PIK3CA	E542K	Pathogenic
SEQ-BRAF	G466V	Pathogenic



Results:

Figure 5: Biomarker differences observed in poorly-differentiated/high grade and well-to-moderately differentiated Sertoli ovarian tumors .



- Hormone receptors ER and PR are more frequently overexpressed in well-moderately differentiated tumors, with the difference of PR reaching statistical significance.
- Protein markers indicative of high DNA replication and synthesis activities including RRM1, TOP2A and TS are all significantly more prevalently expressed in poorly-differentiated/high grade tumors, with RRM1 expression seen exclusively in the high grade group.
- In addition to markers shown above, one deleterious BRCA2 mutation (refer to fig. 4) are seen in the one well-to-moderately differentiated tumor with NextGen SEQ data (1/1, 100%), in contrast to no BRCA2 mutation seen in the poorly differentiated group (0/6, 0%, p=0.008)

Conclusions

- Molecular profiling of 50 rare SLCTs suggested therapeutic opportunities including commonly used agents including platinums/taxane, as well as additional cytotoxic, targeted and biological agents that would not be otherwise considered.
- Interesting biomarker differences revealed by IHC, ISH and SEQ were observed when tumors of different pathological grades were compared, suggesting different treatment approaches.
- Of particular interest, the significantly elevated expression of TOP2A in the poorly differentiated/high grade tumors may suggest increased benefit of using TOP2A inhibitors in treating the most aggressive subgroup of SLCT.
- These findings warrant further investigation in clinical trials.

References

- *Colombo, N., A. Insinga, et. al (2007), "Management of ovarian stromal cell tumors" J Clin Oncol 25:2944-2951*
- *Tandon R., RP Punia, et. al (2007), "A rare ovarian tumor - Sertoli-Leydig cell tumor with heterologous element. " MedGenMed 9(4):44*