Article

Molecular Characterization of Ovarian Yolk Sac Tumor (OYST)

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Simple Summary: Ovarian yolk sac tumors (OYSTs) are rare and specific therapeutic strategies are needed after failure of platinum-based first-line and salvage regimens. In this retrospective study of ten OYST patients (including relapsed and disease free patients), a subset of three patients (33.3% of all patients) harbored a potentially targetable (KRAS, KIT and ARID1A) oncogenic mutations. We also identified that all relapsed patients with molecular analysis had a clinically relevant molecular alterations. Future research with dedicated trials and multicenter collaborations are needed to demonstrate if specific therapeutic strategies are effective after failure of platinum-based first-line and salvage regimens.

Abstract: Most malignant ovarian germ cell tumors (MOGTCs) have a very good prognosis and can be cured by chemotherapy, with yolk sac tumors (OYSTs) having the worse prognosis among MOGCTs. These tumors are rare and can benefit in the next future from specific therapeutic strategies after failure of platinum-based first-line and salvage regimens. In collaboration with EORTC SPECTA, we have developed a project to explore the molecular characteristics of OYST. The pilot part of the project was performed using retrospective samples and ten OYST patients including relapsed and disease free patients. The molecular analysis was performed using FoundationOne CDx. For each patient, the following variables are described in the molecular report provided by FMI (Fondation Medicine Incorporation): alteration type (SNV, deletion), actionable gene alteration, therapies approved in EU (patient's tumor type and other tumor types), tumor mutational burden (TMB) and microsatellite instability (MSI) status. A total of 10 patients with OYST diagnosed between 2007 and 2017 were analyzed. Four patients (40%) had a molecular alteration, according to the FMI test. A subset of three patients (33.3% of all patient) harbored targetable (KRAS, KIT, ARID1A) oncogenic mutations. Two patients at relapse harbored a targetable mutation. In this retrospective study, we were able to identify clinically relevant molecular alterations for all relapsed patients with molecular analysis. Dedicated studies are needed to demonstrate if they could benefit from specific therapeutic strategies after failure of platinum-based first-line and salvage regimens and if the presence of a molecular alteration could be linked to patients' outcome.

Keywords: OYST; molecular characteristics; targetable mutation, patients' outcome

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1. Introduction

Malignant germ cell tumors (MGCTs) represent 5% of all ovarian cancers and 80% of the pre-adolescent malignant ovarian tumors. Most patients with ovarian germ cell tumors will be cured with first-line therapy, with 5-year overall survival rates of 95.6% and 73.2% in stage I and advanced stages, respectively [1].

The Malignant Ovarian GCTs (mOGCTs) are believed to be derived from primordial germ cells (PGCs) [2]. PGCs are progenitors of the germ cell lineage that derived from the embryonic stem cells. PGCs can be identified in human embryos at 5-6 weeks of gestational age. Orchestrated by the KIT ligand (KITLG, also known as the stem cell factor, SCF) and its receptor KIT as well as the chemokine SDF1 (CXCL12) and its receptor CXCR4, PGCs migrate from the proximal epiblast (yolk sac) through the hindgut and mesentery to the genital ridge and become gonocytes [3][4]. Both the timing and level of expression of the genes controlling these processes are crucial. The alterations in critical factors may either be inherited or somatically acquired in the PGCs and/or gonadal cells and initiate GCT.

The primitive GCTs are subdivided into dysgerminoma (DG), the ovarian counterpart of the male testicular seminoma, and non-DGs. The development of non-DGs is characterized by differentiation of these cells into histologies that mimic embryonic tissues (embryonal carcinoma (EC), teratoma) and extraembryonic tissues (yolk sac tumor (YST), also known as endodermal sinus tumor or non-gestational choriocarcinoma (CC)) (figure 1) [5].

Ovarian yolk sac tumors (OYSTs), have the worst prognosis among MOGCTs [6]. These tumors are rare and could benefit in the next future from specific therapeutic strategies after failure of platinum-based first-line and salvage regimens. Risk factors for recurrence are stage (greater than I), age (older than 45 years) and management of treatment in non-referral center [7].

Comprehensive knowledge of the molecular biology might help to better understand the pathogenesis, the risk of relapse and the development of potential innovative therapies [8]. However, only few dedicated molecular investigation concern mOGCT.

Most of the therapeutic progress emerged from the experience acquired in the treatment of testicular NSGCTs. However, a certain degree of gender-specific molecular characteristics may also be expected, due to gender-specific differences in the normal development of PGC to spermatogonia or oogonia and then oocytes. In testicular GCTs molecular structures amenable to targeted treatment approaches have been identified, and many of the available targeting agents have shown promising activity in vitro [9]. However, until today, results of pre-clinical models have rarely been translated into a benefit in clinical practice [10].

Since 2011, a national network activity for the rare ovarian tumors has been supported by the French National Cancer Institute (INCa). The network provides diagnostic expertise and aims to improve the care of patients with these rare tumors with a referral multidisciplinary tumor boards. It also facilitate recruitment for trials dedicated to only rare cancers with international effort [11][12][13].

In this context, in collaboration with EURACAN and EORTC SPECTA, we developed a project to understand better the molecular landscape of rare cancers. Here we focus on OYSTS sequenced during the pilot phase of this project (retrospective samples) including relapsed and disease free patients.

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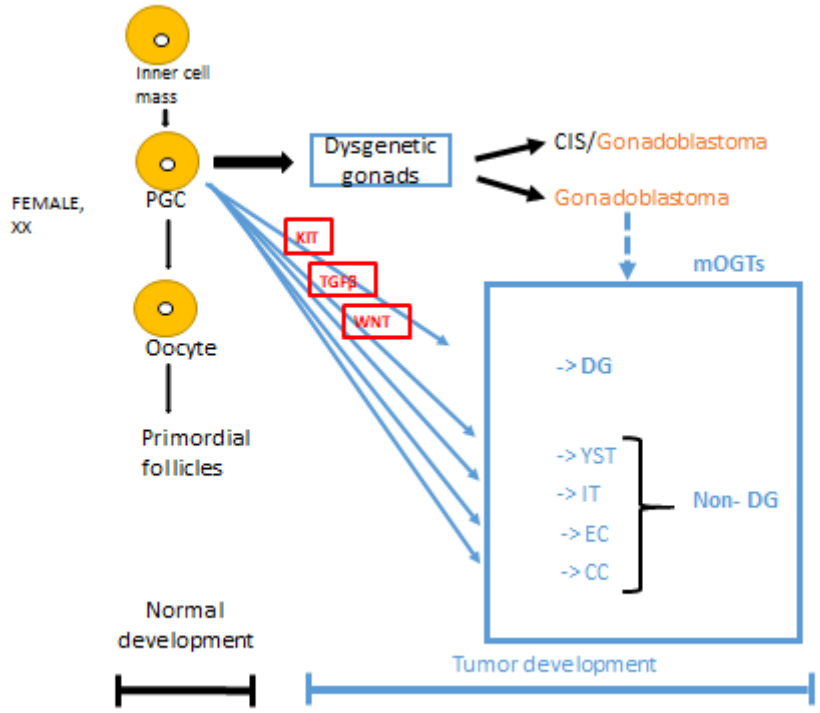

Figure 1: Illustrating the development of GCT
CC: choriocarcinoma; CIS: carcinoma in situ; DG: dysgerminoma; EC: embryonal carcinoma; IT immature teratoma; mOGCT malignant ovarian GCT; PGC: Primordial Germ cell; YST: yolk sac tumor

2. Materials and Methods

- Eligibility criteria and data collection:

In collaboration with EURACAN and EORTC SPECTA, data and samples were collected as per hospital policy. Patients signed a specific hospital consent to allow the use of their samples for future research, including genomic analysis, according to The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and applicable national laws. Two hospitals participated in the pilot phase of the Arcagen project: patients were seen at Centre Léon Berard (CLB), Lyon, France and Institut Bergonie, Bordeaux, France. We retrospectively identified a series of 10 patients with a yolk sac tumor in our database and reviewed their clinical, radiological, histological, and molecular characteristics

- Pathology review:

The ESMO guidelines were used as a standard for diagnosis, in order to ensure consistency. All cases were examined by an expert pathologist in the diagnosis of Yolk sac tumor as per ESMO guidelines through the national network activity for the rare ovarian tumors.

- Sample workflow and molecular analyses :

Samples were sent to the Foundation Medicine lab (Penzberg, Germany). The molecular analysis was performed using FoundationOne CDx. A single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage

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>100X). For each patient, the following variables are described in the molecular report provided by FMI: alteration type (SNV, deletion), alteration name, actionable gene alteration, therapies approved in EU (patient's tumor type and other tumor types), tumor mutational burden (TMB) and microsatellite instability (MSI) status.
Actionability was defined as a molecular alteration for which there is clinical or preclinical evidence of a predictive benefit from a specific therapy (in any cancer type).

- Regulatory aspects

Patient signed a specific hospital consent to allow the use of their samples for future research, including genomic analysis according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and applicable national laws. Data collections were in accordance with Act n°78-17 of 6 January 1978 on Data Processing, Data Files and Individual Liberties.

3. Results

2.1. Population

A total of 10 patients with a yolk sac tumor diagnosed between 2007 and 2017 were selected. Five patients (50%) were FIGO stage Ia, two (20%) stage IIIc and three (30%) were stage IV. Median age at diagnosis was 28 years (range17-52). Nine patients had an oophorectomy and one patient had a radical surgery (bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and lymphadenectomy) because she was first misdiagnosed as having an ovarian high grade serous carcinoma and received a first cycle with Carboplatin and paclitaxel. 9 of 10 received adjuvant BEP based chemotherapy. 57% of patients who were planned to have four cycle of chemotherapy had their last cycle without Bleomycin. Three patients relapsed, one of them was cured with first line salvage regimen, one died 2 years after diagnosis after many lines of chemotherapy and one showed progression after first line treatment and died (table 2 and 3).

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Table 1. Patient characteristics

Patient number	Age at diagnosis (year)	Medical history	Histology	Stage FIGO at diagnosis
1	37y	None	YST	Ia
2	37y	None	YST	IVb
3	25y	None	YST	IIIc
4	27y	None	YST	IIIc
5	52y	None	YST, first misdiagnosed as ovarian high grade serous carcinoma	IVb
6	29y	None	YST	Ia
7	20 y	None	YST	IVa
8	35y	Polycystic ovary syndrome	YST + mucinous cystadenoma	Ia
9	17y	None	YST	Ia
10	26y	Pure gonadal dysgenesis XY	YST + gonadoblastoma	Ia

Description of patient characteristics at diagnosis with FIGO stage and initial localization
YST : Yolk sac tumor

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Table 2. Patient initial treatment

Patient number	Surgery (oophorectomy (A) vs radical surgery (B))	Adjuvant chemotherapy	Response to first line treatment	Relapse
1	A	4 cycles of BEP	Complete response	No
2	A	4 BEP	Complete response	No
3	A	3 BEP, 1 EP	Complete response	No
4	A	3 BEP, 1 EP	Complete response	No
5	B	1 cycle of Carboplatin paclitaxel then 3 cure of BEP	Progression	Died 1 month after the end of chemotherapy
6	A	3 BEP	Complete response	No
7	A	4 BEP	Complete response	No
8	A	3 BEP, 1 EP	Complete response	No
9	A	3 BEP 1 EP	Complete response	Relapsed after 5 year : aFP elevation and abdominal pain (one peritoneal node).
10	Bilateral oophorectomy	No	Complete response	Elevation of aFP 6 months after first surgery. Lesion of the upper bowel and iliac lymph node. Died 2 year after diagnosis

Description of initial treatment including type of surgery, chemotherapy and initial response to treatment

BEP : Bleomycin, Etoposide, Cisplatin

EP : Etoposide, Cisplatin

Radical surgery (B) involves bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and lymphadenectomy

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Table 3. Treatment at relapse

Patient number	Treatment after first relapse	Response to treatment	Other treatment	Last news
9	2 ICE with autologous stem cell injection	Complete response	No	Complete response (12/2019)
10	3 BEP, 1 EP	Progression with peritoneal carcinosis and spleen metastasis before surgery of residual active mass	*3 VeIP * Docetaxel/Gemcitabine (4 cycles) *Adriamycin/Cyclophosphamid/Avastin (2 cycles) *Carboplatin/ Paclitaxel (1 cycle) *Endoxan/Affinitor (1 cycle)	Died 2 year after diagnosis

Description of treatment at relapse and outcomes
BEP : Bleomycin, Etoposide, Cisplatin
ICE : Ifosfamide, Carboplatin, Etoposide
VeIP : Vinblastine, Ifosfamide, Cisplatin

2.2. Molecular Characteristics and abnormalities

All clinically significant alterations identified are shown in table 4. One sample failed molecular analysis (patient 5). A gene alteration was identified in four out of nine patient' tumors achieving profiling. A subset of three (33.3% of all patient) patients harbored a potentially targetable (KRAS, KIT and ARID1A) activating mutations. Patient 4 had seven concomitant mutations (KRAS G12V amplification, CCND2 amplification, FGF23 amplification, FGF6 amplification, KDM5A amplification, KIT D816A, ARID1A Q538). All patients tested were MSI stable/low and had a low TMB. Patient number 7 had a CRKL amplification. Patient 10 has a KRAS D33E mutation.

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Table 4. Molecular Characteristics

Patient ID	Alteration type	Alteration: Gene	MSI status	TMB Status	TMB Muts/ MB	Actionable Alteration+	Potential therapies*	Potential therapies°
1	None	None	Stable	Low	3	None	None	
2	None	None	Stable	Low	3	None	None	
3	None	None	Stable	Low	0	None	None	
4	SNV +amplification	KRAS G12V amplification	Stable	Low	0	KRAS G12V amplification	Binimetinib, CobimetinibTrametinib	
	amplification	CCND2 amplification				None	None	
	amplification	FGF23 amplification				None	None	
	amplification	FGF6 amplification				None	None	
	amplification	KDM5A amplification				None	None	
	SNV	KIT D816A				KIT D816A	Dasatinib, Imatinib, Nilotinib, Ponatinib, Sorafenib, Sunitinib, Binimetinib, CobimetinibTrametinib	Ripretinib, Avapritinib
	SNV	ARID1A Q538*				ARIDA1	None	Olaparib
5	Failed	Failed	Failed	Failed	Failed	Failed	Failed	
6	None	None	stable	Low	5	None	None	
7	amplification	CRKL amplification	stable	Low	4	None	None	
8	None		Stable	Low	4	None	None	

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9	rearrangement	ARID1A rearrangement exon 19	stable	Low	0	ARID1A	None	Olaparib
10	SNV	KRAS D33E	Stable	Low	4	KRAS D33E	Binimetinib, CobimetinibTrametinib	

Description of clinically significant variants for each patient based on FMI report

TMB : tumor mutational burden

* Specific therapies that can be used for the molecular alteration in other cancer type

+ molecular alteration for which there is clinical or preclinical evidence of a predictive benefit from a specific therapy (in any cancer type) from FMI report

° Potential therapy not included in FMI report [14] [15]

4. Discussion

In the present retrospective study, a total of 10 patients with a yolk sac tumor diagnosed between 2007 and 2017 were analyzed. 90% had a complete response after a first line treatment, but three patients relapsed (30%), one reported a complete response after HDCT (10%), one patient (10%) died 2 year after diagnosis and one died one month after first line treatment.

Germ cell tumors are remarkably chemo sensitive, and despite the high cure rates with initial and salvage chemotherapy, there remains a cohort of germ cell tumor patients who will eventually succumb to their progressive malignancy. New therapeutic agents are still needed for this patient population.

Here we describe the molecular characteristics of our 10 patients YST cohort. A subset of three patients (33.3% of all patients) harbored a potentially targetable (KRAS, KIT and ARID1A) oncogenic mutations. Actionability is defined as a molecular alteration for which there is clinical or preclinical evidence of a predictive benefit from a specific therapy (in any cancer type). Interestingly, we were able to identify clinically relevant molecular alterations for all relapsed patients (patient 9 and 10) with molecular analysis. Dedicated studies are needed to prove if they could benefit from specific therapeutic strategies after failure of platinum-based first-line and salvage regimens and if the presence of a molecular alteration could be linked to patients' outcome.

Mutations in KIT among mOGCTs, have been previously described exclusively in dysgerminoma (DG) at frequencies of 27% (6 of 22) and 24% (4 of 17), whereas no mutations have been reported in tumors of patients with pure or mixed histologies of IT and YST[16][17]. The success of KIT-targeting imatinib mesylate in the treatment of GIST [18] and chronic myelogenous leukemia [19] may be relevant for DG treatment, given their high frequency of KIT expression. There are case reports describing a complete remission of chemoresistant and/or disseminated TGCT after treatment with imatinib mesylate [20]. However, a small trial administering imatinib mesylate to patients with KIT-positive metastatic TGCT (n = 6) did not result in remission for any of them but [21]. Or in this phase II study, KIT positivity was defined by IHC as >10% cells staining for KIT and the type of mutation was not defined. All KIT mutations reported in DG, also in case reports, were located in exon 17 (D816V, D816H, and D816Y). Mutations of KIT within the activation loop (A-loop), including amino acids D816, have been reported to confer preclinical and clinical resistance to imatinib and sunitinib in GIST[22] [23]. KIT exon 17 mutations, including at D816, were reported to be sensitive to avapritinib [14].

In our cohort, patient number four harbored a KIT D816A mutation, but also a KRAS G12V hotspot mutation with amplification, CCND2 amplification, FGF23 amplification, FGF6

amplification, KDM5A amplification, and ARID1A Q538* truncated mutation. Three of them are actionable gene alterations (KIT D816A, KRAS G12V and ARID1A Q538*) and targeted therapies are available. KRAS encodes a member of the RAS family of small GTPases and activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation [24]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib and cobimetinib tested in colorectal cancer [25].

The ARID1A gene provides instructions for making a protein that forms a subunit of several different SWI/SNF protein complexes. SWI/SNF complexes regulate gene activity by a process known as chromatin remodeling. ARID1A is also recruited to DNA double-strand breaks (DSB) via its interaction with the upstream DNA damage checkpoint kinase ATR [26]. Tumors harboring this mutation may exhibit therapeutic vulnerability to PARP inhibitors according to preclinical results [15].

The other alterations are involved in cell growth with no targeted therapies that directly address these genomic alterations. FGF6 and FGF23 encodes a member of the fibroblast growth factor protein family with role in muscle tissue regeneration and in phosphate homeostasis respectively. The CCND2 gene provides instructions for making a Cyclin D2 protein which helps to regulate the G1-S transition in cell cycle. KDM5A encodes a lysine-specific histone demethylase that potentiates the expression of genes involved in cellular proliferation, senescence, angiogenesis, and migration.

All patients analyzed are microsatellite stable (MSS) and have a low tumor mutational burden (TMB). The role of immune check-point inhibitors should be analyzed in these rare tumors. However, preliminary results from two studies of pembrolizumab and avelumab in male GCTs did not show significant results [27][28]. The immune infiltrate is associated with patients' outcome in TGCT and study of tumor microenvironment may help for the development of immunotherapeutic strategies [29][30][31].

Molecular markers for YST are limited. The YSTs often display complex and varied histological appearance, making correct differential diagnosis difficult, in particular between YST and endometroid or clear-cell carcinoma of the ovary. In our cohort, one patient was first misdiagnosed as high grade serous carcinoma. A central pathology review confirmed the diagnosis of YST. Diagnosis of rare cancer can be challenging to achieve and expert pathological review is recommended [12][13].

5. Conclusions

This study is the 1st part of new research program (prospective SPECTA,), where rare gynecological tumors will be tested for molecular alterations and for potential therapies. Other program as Petale trial (support by ENGOT) with dedicated clinical trials to rare tumors molecular driven.

Future research on both constitutional and somatic alterations in YST patients are needed to fully understand their pathogenesis. This includes evaluation of the contributions of epigenetic, genetic, and (micro) environmental alterations. Due to the low incidence of mOGCT, there is a need for multicenter collaborations for the molecular, clinical and epidemiologic studies to reach critical sample sizes.

Conflicts of Interest: The authors declare no conflict of interest.

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