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Background: Germ cell tumours (GCTs) are cancers of the testis, ovary and extragonadal sites that occur in infants, children, adolescents and adults. Post-pubertal (type II) malignant GCTs may present as seminoma, non-seminoma or mixed histologies. In contrast, pre-pubertal (type I) GCTs are limited to (benign) teratoma and (malignant) yolk sac tumour (YST). Epidemiological and molecular data have shown that pre- and post-pubertal GCTs arise by distinct mechanisms. Dedicated studies of the genomic landscape of type I and II GCT in children and adolescents are lacking.
Material and methods: We performed whole-exome sequencing, panel-based deep sequencing, copy-number analysis, RNASeq and methylations analysis on a clinically annotated cohort of GCTs from patients aged 0–24 years. We complemented the genomic analysis with functional studies in human cells and zebrafish models.
Results: Activation of the WNT pathway by somatic mutation, copy-number alteration, and differential promoter methylation is a prominent feature of GCTs in children and adolescents, and is associated with poor clinical outcomes. Significantly, we find that small molecule WNT inhibitors can suppress GCT cells both *in vitro* and *in vivo* in zebrafish models. These results highlight the distinctive mechanisms underlying the development of childhood and adolescent GCTs and provide a foundation for future efforts to develop targeted therapies for these cancers.

GCT-25 The avian embryo as a new patient-derived xenograft model to explore germ cell tumour aetiology, heterogeneity and therapeutic screening

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Background: Gonadal and extragonadal germ-cell-tumours (GCTs) arise from pluripotent primordial-germ-cells (PGCs). The aetiology of extragonadal GCT and metastasis is still debated, mainly because of lack of suitable models recapitulating GCT pathogenesis, including i*n vivo* patient-driven analyses of tumour migration/chemosensitivity. Our main objective was to develop an avian Patient-Derived Xenograft (PDX) system, to reproduce GCT heterogeneity/clinical features.
Methods: Based on previous experiments on neuroblastoma, we conceived an avian model of GCTs in which tumorigenesis is driven in HH25 chick embryos either in gonadal site by grafting GCTs in the migration path of PGCs, or in extragonadal brain site. We set up the technique with NCC-IT and Tera2 GCT cell lines with extension to 3 GCT patient samples, harvested from fresh surgical resections and preserved in DMSO freezing medium: one mediastinal yolk-sac tumour in a 6-year-old patient and two metastatic testicular mixed GCT (in 16- and 15-year-old patients).
Results: Cell lines grafted in the PGC migration path formed visible tumours in avian primitive gonads 5 days after engraftment while grafts in the developing brain permitted the replication of secondary foci in 2 days. Similar graft experiments on GCT patient samples confirmed a rapid and highly reproducible tumour intake in the embryo for both paradigms. Intravenous injection of 5.1 mg/kg cisplatin into embryos grafted with patient samples reduced tumour volume of these avian replicas of cisplatin-responding patients within 48 h. Our GCT avian model opens exciting possibilities ranging from the study of GCT aetiology to the evaluation of novel drug/combination efficacy on patient-derived material.

Ovarian GCTs Including Teratoma

GCT-26 Survival outcomes and long-term follow-up in children treated for ovarian nonseminomatous germ cell tumours in the French TGM-95 study

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Background: To analyze characteristics and outcomes with actualized very-long-term follow-up data from patients treated for ovarian non seminomatous germ-cell-tumours (NS-GCT).
Methods: Children (≤18 years) treated for ovarian NS-GCT in 1995–2005 in France and Belgium were included in TGM-95. Patients with localized, completely-resected tumours (FIGO-stage IA) had no adjuvant treatment (low-risk, LR). Patients with advanced-stage (FIGO-stage ≥IC) received 3–5 VBP cycles (vinblastin-bleomycin-cisplatinum) in intermediate-risk disease (IR: FIGO-stage IC-II-III and AFP<15,000 ng/ml) or 4–6 VIP (etoposide-ifosfamide-cisplatinum) in high-risk (HiR: metastatic and/or AFP ≥ 15,000 ng/ml).
Results: Seventy-seven patients were included (median age = 12 years, 43 pure yolk-sac tumour; 34 mixed NS-GCT). Primary surgery was performed in 55/77 cases. Fourteen patients were LR (12 stage IA, 2 retrospectively stage IC), 26 IR (12 stage IC, 12 stage II-III, 2 not-available) and 37 HiR (8 metastatic, 29 loco-regionally advanced). After a median follow-up of 13 years, 9 events (including 5 relapses/bilateralizations and 2 secondary acute-myeloid-leukemias) and 6 deaths occurred. All relapses/bilateralizations occurred in LR (n = 4, including the 2 retrospectively-stage-IC) and IR groups (n = 1), within 2 years post-diagnosis. Five-year EFS and OS were 89% (95%CI = 80–95%)

and 95% (95%CI = 87–98%). Bilateral gonadectomy was performed in 6/77 patients. At a median age (at last update) of 26 years, 28 pregnancies were reported in 19 patients (25 natural, 3 medically-assisted), leading to 23 healthy-born children. Three patients treated with ifosfamide/platinum-based chemotherapy suffered from chronic-kidney-disease. Seven Brock grade-1 and 1 grade-2 ototoxicities were described in patients treated with cisplatinum. Ovarian NS-GCT have an excellent prognosis even in advanced cases with conservative surgery and platinum-based chemotherapy, with few long-term complications.

GCT-27 Pure paediatric ovarian immature teratomas: the French experience

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Background: To describe characteristics and outcome of paediatric ovarian immature teratomas (IT), to better define the place of chemotherapy.
Methods: Children with ovarian IT enrolled in TGM-95 and TGM-2013 studies were analysed. Norris grading and FIGO (International Federation of Gynecology and Obstetrics) staging system were used. Gliomatosis peritonei (GP) and mature teratoma peritoneal implants did not result in upstaging, whereas IT peritoneal implants did.
Results: Thirty-seven cases were identified (median age = 11 years): 36/37 stage I (17 stage IA, 14 stage IC and 5 stage IX), including 7 patients with GP, and 1 stage IIIB (IT peritoneal implants). All patients had surgery first: 22 underwent unilateral oophorectomy, 14 unilateral adnexectomy and 1 bilateral cystectomy. No extensive GP surgery was performed. Seven patients received adjuvant VBP (vinblastine-bleomycin-cisplatinum), for tumour rupture (n = 6, 2 had GP) and stage III (n = 1). After a median follow-up of 27 months, 2 events occurred: 1 bilateralization (initial stage IX, grade I) and 1 TI peritoneal relapse (initial stage IA, grade II), 10 and 11 months after diagnosis. Both were successfully treated with platinum-based chemotherapy and delayed surgery. No stage-IC-patients treated without adjuvant chemotherapy relapsed (4 grade I and 3 grade III). None of the 7 GP-patients suffered from progressive disease. Two-year EFS and OS were 94% (95%CI = 80–98%) and 100%. No significant impact of grading on EFS was observed (p = 0.73). The current series confirms the excellent prognosis of paediatric ovarian IT, even with GP or rupture, pleading for conservative surgical approach in GP and against systematic adjuvant chemotherapy, even in ruptured tumours.

GCT-28 Genetic profiling and clonal evolution in ovarian yolk-sac tumours

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Background: Yolk-sac tumour (YST) is the most common histological subtype of germ-cell-tumour (GCT). The molecular basis associated with chemo-resistance and genomic evolution under selective pressure from chemotherapy are incompletely characterized.
Methods: We performed whole-exome sequencing on 43 tumour and germline DNA samples from 30 patients with ovarian YST, which were categorized as chemo-sensitive or chemo-resistant group. Among chemo-resistant samples, eight paired sets of primary and relapsed tumours were under clonality analysis.
Results: Mutation rate was low in ovarian YST compared with other solid tumours. Total mutational burden increased with patient age. Primary untreated tumours in chemo-resistant group had higher microsatellite instability than those in chemo-sensitive group, while total mutational burden was not significantly different between two groups. *MUC4* and *BCLAF1* were recurrent mutated in both groups, while *TP53* and *KRAS* alterations were present exclusively in chemo-resistant group and shared both in primary and relapsed samples of two patients. Relapsed tumour samples had significantly increased mutational burden and were characterized by intratumoral heterogeneity. Clonality analysis revealed relapsed ovarian YST evolved either from one of the subclones of primary tumours at a very early timepoint or new clones emerged after initial treatment. This is first whole exome sequencing data of pure ovarian YST. Our data provide genetic-level evidence that patient age is an independent predictor of mortality. We confirmed chemotherapy resistance was associated with *TP53* alterations (previously reported in testicular GCTs). Two different clonal evolution patterns found in relapsed ovarian YST might indicate different multi-step chemo-resistance mechanisms.

GCT-29 Behaviour and outcome of paediatric immature teratomas at children cancer hospital in Egypt. What did we learn over 10 years?

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Background: Teratomas are derived of more than one germ layer [1]. Based on quantity of immature neuroepithelium they are graded as mature G0 or immature (G1, G2, G3). Teratomas are tumours with variable behaviour depending on age, site, size and pathological grade.
Methods: Records of all new cases with immature teratomas equal or below 18 years of age, treated at Children Cancer Hospital in Egypt over a 10-year period from July 2007 to December 2017, were revised for epidemiology, primary site, stage, pathological grading, management and outcome (OS, EFS).
Results: Teratomas constitute 45% (134/300) of all germ cell tumours, with female predominance (60%), more commonly at extragonadal sites (60%) predominantly sacrococcygeal and retroperitoneal. Ovarian teratomas exceed testicular (66%). Grade 0, 1, 2 and 3 constitutes (63%, 7%, 6% and 24%) respectively with 5 y overall (OS) and event-free survival (EFS) ranged from 100% in grade 1 to 86.2% in grade 3. 10 y OS of high grade immature teratomas was 85.8% in patients <11 years compared with 75% in older age. In conclusion, immature teratoma of high grade carries less favourable outcome. Extensive surgical resection±more aggressive treatment are essential to improve outcome.

Reference

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