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The consequences of *SMARCB1* loss in Atypical Teratoid Rhabdoid Tumors (ATRTs) have been extensively characterized at the epigenetic/transcriptomic level. In this study we detail the functional effect of *SMARCB1* mutation on the MRT proteome, its relationship with RNA deregulation or lack thereof. We performed unlabeled discovery proteomics using MS-SWATH on MRT cells in which SMARCB1 was forcibly re-expressed (5 cell lines, +/-SMARCB1); analyzing changes in protein abundance within 3 fractions (total, membrane, nuclear). We generated a custom spectral library, covering >8,000 proteins, for analysis of the ATRT proteome using a pH fractionated pool of each cellular subfraction. This SMARCB1-dependent ATRT spectral library constitutes a powerful tool for profiling proteins of potentially therapeutic relevance in both model systems and primary ATRT samples. We show that whilst gene expression and protein abundance are significantly related there are many instances whereby expression changes do not reliably predict protein abundances. Several hundred proteins show significantly increased abundance ($p<0.01$) with no concomitant change by RNA-seq. *SMARCB1* mutation is able to invoke critical changes in post-transcriptional/translational regulation as well as sub-cellular localization. By integration with whole-genome CRISPR/cas9 screening we describe functionally essential SMARCB1 dependent pathway/membrane biomarkers, evident at the protein but not the RNA level. We describe several which are druggable and suggest certain therapeutic modalities e.g. specific combinations of RTKs, RNA-binding proteins/splicing factors (SpliceosomeA, U4:U5:U6 tri-snRNP complexes). Our analysis links, for the first time in ATRT, genome-wide transcriptomic and proteome aberrations and reveals broad mechanisms underlying the effect of *SMARCB1* mutation.

ATRT-26. META-ANALYSIS OF TREATMENT MODALITIES IN METASTATIC ATYPICAL TERATOID/RHABDOID TUMORS IN CHILDREN

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BACKGROUND: Metastatic atypical teratoid/rhabdoid tumors (AT/RT) are aggressive central nervous system tumors that present during infancy and are associated with dismal outcomes. Patients receive multimodal treatment including surgical resection, systemic chemotherapy and one or more of intrathecal chemotherapy (IT), marrow-ablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) and radiation therapy (XRT). While data regarding treatment modalities for AT/RT patients exist, no comprehensive data have been published regarding the metastatic patient population. METHODS: We performed a meta-analysis of 1,578 articles published through September 2018, including 44 studies with a total of 123 subjects. Additionally, seven patients were incorporated through chart review of patients treated at Nationwide Children's Hospital. RESULTS: Analysis of 130 patients revealed a 3-year overall survival (OS) of 25%. Age at diagnosis had a significant impact on survival ($p=0.0355$); 3-year OS for infants < 18 months was 21%; 18–36 months was 26%; and > 36 months was 36%. Location of the primary tumor, metastatic stage and extent of surgical resection did not have significant impact on OS. On univariate analysis, XRT ($p<0.0001$), IT ($p=0.01$) and AuHCR ($p<0.0001$) were found to significantly improve survival. The most substantial effect was noted in patients who received AuHCR (3-year OS of 60% *versus* 9% in those who did not). On multivariable analysis XRT ($p=0.0006$), IT ($p=0.0124$) and AuHCR ($p<0.0001$) were independently associated with reduced risk of death.

ATRT-27. COST-EFFECTIVE ASSAYS TO SUBGROUP ATRT IN THE DAILY ROUTINE

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Three atypical teratoid rhabdoid tumors (ATRT) molecular subgroups with different bio-clinical characteristics have been reported (TYR, SHH and MYC). Molecular subgrouping relies on either methylation profiling (reference methods), or expression profiling. However, the cost-effectiveness of such pangenomic screening is questionable. This work aims to study the reliability of alternative techniques for subgroup classification in the daily routine. Illumina EPIC-arrays were performed on 46 samples. Among those cases, expression profiling were analysed by RNAseq (n=30). We designed a 26-gene panel to assess expression profiling using the Nanostring technology; this was applied to 35 tumors. Immunohistochemistry (IHC) was used for 20 samples; it relied on the expression of MITF, TYR, OTX2 and MYC. We first assessed the concordance between DNA methylation and RNAseq based profilings; then, between RNAseq and Nanostring and, finally, between methylation profiling and Nanostring or IHC, the two rapidest and cheapest tools. The concordance between the two expression-based profiling was 19/21. EPIC-arrays and RNAseq or Nanostring were concordant in 26/30 and 30/35 samples, respectively. The concordance was perfect for methylation-defined MYC subtype. Finally, 17/20 tumor samples were classified in the same subgroup by EPIC-arrays and IHC; the 3/20 misclassified tumors were SHH by methylation but consistently MYC by IHC, Nanostring and RNAseq. There was 90–100% of concordance for TYR subgroup (all techniques). We have designed a gene panel-based expression signature that shows promising concordance with RNAseq and methylation profiling. Nanostring assay and IHC well predict ATRT subgroup classification for MYC and TYR subclass, but less so for methylation-defined SHH ones.

ATRT-28. SINGLE NUCLEI SEQUENCING REVEALS THE DIFFERENT PHENOTYPIC COMPOSITION OF THE ATRT SUBGROUPS

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Atypical teratoid/rhabdoid tumors (ATRT) represents a genomically homogeneous disease characterized by loss of SMARCB1 protein in the vast majority of cases. In recent years, it has become clear that these tumors display a high degree of intertumoral heterogeneity with three molecularly distinct subgroups. However, the degree of intratumoral heterogeneity and the information on cellular subpopulations currently remains largely an uncharted territory. To explore the transcriptomic composition of ATRTs, we performed single nuclei RNA sequencing for 16 ATRTs representing all three molecular subgroups (5 ATRT-TYR, 7 ATRT-SHH, 4 ATRT-MYC). By performing tSNE cluster analyses of all the single cell data (~50.000 cells have been sequenced), we were able to gain unprecedented insights into the phenotypic composition of ATRTs and unravelled substantial differences between the three subgroups. Integrating transcriptomic information from non-neoplastic brain cells and the data derived from single nuclei sequencing, we found an OPC like gene signature in ATRT-SHH. In contrast, ATRT-TYR subpopulations overexpressed more markers of neuronal stem cells suggesting a larger fraction of undifferentiated cells in this subgroup. We also identified a subpopulation of cells with a clear overexpression of cell cycle associated genes (CDK4, CDKN3), predominantly present in ATRT-MYC samples, a finding which may harbour important consequences for a targeted therapy with e.g. CDK inhibitors. In summary, our analyses reveal different cellular compartments in ATRT and provide important insights into the cellular differentiation of the three ATRT-subgroups. Further analyses to achieve a specific mapping of ATRT to its physiological cell of origin are currently being pursued.

ATRT-30. RETROSPECTIVE ANALYSIS OF CHILDREN WITH ATYPICAL TERATOID RHABDOID TUMOR TREATED ACCORDING TO ACNS0333

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Atypical teratoid rhabdoid tumor (ATRT) is a central nervous system tumor with poor outcome. ACNS0333, a Children's Oncology Group phase 3 trial, enrolled 65 evaluable patients who received two cycles of induction chemotherapy, three cycles of consolidative high-dose chemotherapy (HDCT), and focal radiation therapy (RT) pre- or post-consolidation. Craniospinal irradiation (CSI) was left to clinician discretion. We retrospectively analyzed medical records of 27 children treated at our institutions according to ACNS0333. Median age at diagnosis was 14 months (range 4–165); 13 (48%) were male. M-stage was M0, M2, and M3 for 18 (66%), 5 (19%), and 4 (15%), respectively. Tumor location was supratentorial (n=14, 52%), infratentorial (n=12, 44%), or both (n=1, 4%). Complete resection was achieved for 17 (63%). All but one completed induction. Of 13 (51%)

with residual disease at diagnosis, 5 (36%) and 7 (50%), respectively, exhibited complete and partial response to induction. Three patients progressed on therapy, and six progressed after completion of therapy at a median of 9.7 months. In all, 18 patients completed RT (16 focal/4 CSI and 6 pre-/12 post-consolidation). Three died of therapy-related toxicity (two in primary therapy and one in relapse therapy), and 8 died of disease. Sixteen patients (59%) are alive at a median follow up of 53 months (range 9–114). Of 17 with germline testing, eight (47%) had rhabdoid predisposition syndrome of whom three are alive. At the time of presentation, data for approximately 50 patients is expected, and we will compare outcomes to soon-to-be published data from ACNS0333.

ATRT-31. SUCCESSFUL MULTIMODALITY MANAGEMENT OF ATRT OF THE LOWER DORSAL SPINE WITH SPINAL DROP METASTASIS

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A 6 year old boy presented with low backache for the last 5 months. MRI of the spine showed a 1.5x1.5x4.7cm intradural mass extending from D10-D12, causing compression of the conus medullaris. With a preoperative diagnosis of intradural ependymoma, a gross total resection (GTR) of tumour was performed. Post-operative histopathology showed a markedly cellular, malignant tumour with frequent mitotic figures. Cells were round to polygonal with vesicular nuclei, prominent nucleoli and were immunopositive for CK,EMA,p53 and immunonegative for MIC2,desmin,SMA,GFAP,INI-1(MIB1 labeling index-35–40%). The overall impression was spinal atypical teratoid rhabdoid tumour(ATRT). Post-operative neuraxis MRI revealed post-operative changes(D10-D12) with a 9 mm enhancing lesion at L5-S1 junction suggesting drop metastasis. There was no brain lesion. CSF cytology did not show any malignant cell. The metastatic work-up was normal. He was started on chemotherapy with ICE regimen (Ifosfamide-2g/m^2IVD1–D3,Carboplatin-500mg/m^2IVD3,Etoposide-100mg/m^2IVD1–D3q3weeks). Subsequently he received craniospinal irradiation (CSI)-36Gray/20fractions/4weeks→ focal boost to primary tumour bed and spinal drop metastasis-14.4Gray/8fractions/1.5 weeks. Thereafter he received 3 more cycles of ICE regimen. End-of-treatment MRI spine showed post-op changes(D10-D12) and 38.9%reduction of the L5-S1 lesion suggesting partial response. Six monthly spinal MRI showed serial reduction of the metastatic lesion leading to complete response (CR) 1 year after completion of treatment. On last follow-up (30 months from initial diagnosis), he was neurologically intact and in CR. Multimodality management comprising GTR,CSI followed by focal boost and multiagent chemotherapy(ICE) can lead to successful outcome in patients with this rare and aggressive spinal tumour.

ATRT-32. GENOME-WIDE CRISPR AND SMALL-MOLECULE SCREENS UNCOVER TARGETABLE DEPENDENCIES IN AT/RTS

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Brain tumors are the leading cause of cancer-related deaths in children and adolescents. Embryonal brain tumors are a group of high-grade neoplasms which primarily affect young patients, and atypical teratoid rhabdoid tumors (AT/RTs) are the second most common type of tumor within this group. In spite of intensive research efforts and the knowledge of molecular mechanisms driving subgroup-specific heterogeneity within ATRTs, survival estimates stay relatively low as compared to other tumor entities with a median survival of around 17 months. More efficacious and durable therapies are urgently needed to improve the situation of patients. We here used a combination of genome-wide CRISPR dependency screens and small-molecule drug assays to identify genetic vulnerabilities and novel therapeutic targets for this tumor entity. Here, we successfully generated a chemical library that shows preferential activity in AT/RT cell lines, thereby validating our CRISPR approach to identify tumor-specific vulnerabilities. Of note, none of the identified dependencies seemed to be subgroup-specific, suggesting that targets identified here can be used as pan-AT/RT therapeutic avenues. Among others, these include inhibition of EGF signaling and CDK4/6. Our data provide a comprehensive map of dependencies for AT/RTs which will serve as a starting point in the development of targeted therapies for this tumor entity.

ATRT-33. ENABLING RAPID CLASSIFICATION OF ATRT WITH NANOSTRING NCOUNTER PLATFORM

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In recent years, using gene expression and methylation array platform, multiple research groups have reported the presence of at least three major Atypical Teratoid Rhabdoid Tumor (ATRT) subtypes that exhibit distinct epigenetic, transcriptomic and clinical features. Yet, utilizing ATRT subtypes in a clinical setting remains challenging due to a lack of suitable biological markers, limited sample quantities and relatively high cost of current assays. To address this gap between research and clinical practice, we have designed an assay that utilizes a custom 35 signature genes panel for the NanoString nCounter System and have created a flexible machine learning classifier package for ATRT tumour subtyping. We have analyzed 71 ATRT primary tumours with matching gene expression data using the 35 genes panel. 60% of the data was used for models training (10 repeats of 10-fold cross validation with subgroup balanced sample splitting) resulting in overall 94.6% training accuracy. The remaining 40% of the samples were used for model validation and the assay was able to achieve 92–100% accuracy with no subgroup bias. To demonstrate the flexibility of the workflow, we have tested it against other transcriptome-based methods such as gene expression array and RNASeq. We have also demonstrated its use in samples that were not classifiable by methylation-based method. We are presenting here a rapid and accurate ATRT subtyping assay for clinical usage that is compatible with archived ATRT tissues.

COVID-19 AND PEDIATRIC NEURO-ONCOLOGY

COVD-01. VINBLASTINE MONOTHERAPY INDUCTION FOR LOCALISED CNS GERMINOMA DURING THE COVID-19 PANDEMIC

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INTRODUCTION: Patients with localised CNS-germinoma have excellent survival. More recently, intensive inpatient chemotherapy (carboPEI=carboplatin/etoposide/ifosfamide in Europe) has been effectively employed to reduce radiotherapy fields and/or dose. Current research priorities focus on reducing treatment burden and long-term sequelae. Of note, outpatient-based single-agent carboplatin chemotherapy is associated with excellent outcomes in metastatic testicular seminoma (an identical pathology) [Alifrangis,*EJC*,2020]. Recently, successful vinblastine monotherapy was reported in localised CNS-germinoma [Murray,*Neurooncol-Adv*,2020]. METHODS: Due to the COVID-19 pandemic, adapted UK guidelines for germ-cell-tumour management were distributed, including potential non-standard treatment options that would reduce hospital visits/admissions. A 30-year-old patient presented with a 32mmx30mmx35mm diameter solid+multi-cystic localised pineal CNS lesion, consistent radiologically with a germ-cell-tumour with prominent teratoma component. Investigation revealed negative AFP/HCG markers and biopsy-proven pure germinoma. After appropriate consent, the patient commenced 12-week induction with weekly vinblastine monotherapy (low-grade-glioma dosing [Lassaletta,*JCO*,2016]), with wk6&12 MRI re-assessment prior to definitive radiotherapy. RESULTS: Vinblastine was well-tolerated. After initial 4mg/m2 test-dosing (wk1), standard 6mg/m2 was delivered for wk2, but resulted in asymptomatic neutropenia (nadir 0.3x10^9/l) and missed dosing at wk3. Subsequent doses were 4mg/m2, with no further neutropenia. As expected, MRI showed moderate 40% tumour volume reduction by wk12. Surgical resection of the residual presumed teratoma component was undertaken prior to radiotherapy. CONCLUSION: Patients with CNS-germinoma have excellent outcomes and reduction of treatment-effects remains a priority. The exquisite chemosensitivity of germinoma, excellent results from monotherapy for metastatic testicular disease, and early promise of vinblastine monotherapy lend itself to further exploration for CNS-germinoma.

COVD-02. COVID-19 AND CHILDHOOD CANCER CARE - THEMATIC ANALYSIS OF PUBLISHED SCIENTIFIC AND CLINICAL LITERATURE

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INTRODUCTION: The SARS-CoV-2 pandemic has affected modern medicine and healthcare provision profoundly. National and regional ex-