KS05.7.A. CHARACTERIZATION OF THE IMMUNE COMPOSITION OF EXTREME LONG-TERM SURVIVORS WITH MALIGNANT GLIOMA AT SINGLE-CELL LEVEL.

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BACKGROUND: Glioblastoma Multiforme (GBM) remains the most common malignant primary brain tumor with a dismal prognosis that rarely exceeds beyond two years despite extensive therapy, which consists of maximal safe surgical resection, radiotherapy and/or chemotherapy. Recently, it has become clear that GBM is not one homogeneous entity and that both intra-and intertumoral heterogeneity contribute significantly to differences in tumor behavior which may consequently be responsible for differences in survival. Strikingly and in spite of its dismal prognosis, small fractions of GBM patients seem to display extended survival compared to the large majority of patients. The underlying mechanisms for this peculiarity remain largely unknown however, even though emerging data suggest that both cancer cell-autonomous and microenvironmental factors and their interplay probably play an important role. MATERIAL AND METHODS: We used high-dimensional, multiplexed immunohistochemistry to spatially and cytometry by time-of-flight to quantitatively characterize the cell constitution and interactions within the tumor microenvironment (TME) in 21 extreme long-term survivors (living over ten years since primary diagnosis or five years after recurrence) and 42 deeply matched short-term controls (living under 1.5 year) on a single cell level. For all tumors (epi-)genetic data was also collected. RESULTS: We identified a high level of both inter- and intrapatient heterogeneity defined by several distinct tumor niches, as well as described interactions within these niches and with the surrounding infiltrating immune cells of the TME. By linking patient characteristics with the heterogeneous immune composition we are building an immune stratification that can be linked to patient survival in GBM. CONCLUSION: Generating an immune map for GBM will allow us to identify tumor components that may serve as a potential target for personalized treatment strategies. Therefore, this study is also an essential initial step towards such clinical trials which alter the TME in a favorable way with a personalized modulatory strategy.

JS03.5.A. PEDIATRIC NEUROFIBROMATOSIS TYPE 1-ASSOCIATED MALIGNANT PERIPHERAL NERVE SHEATH TUMORS: A NATIONAL EXPERIENCE


BACKGROUND: Malignant peripheral nerve sheath tumors (MPNST) are rare soft tissue sarcomas and although less than 10% occur in the pediatric age, they are the most feared complication in the follow-up of Neurofibromatosis Type 1 (NF1) patients. NF1-children tend to have larger tumors and worse prognosis than non-NF1 patients. There is a lack of data regarding MPNST in pediatric populations with NF1, and the present work aims to characterize a Portuguese population of pediatric NF1 patients that developed a MPNST. MATERIAL AND METHODS: Retrospective analysis of all NF1-pediatric patients diagnosed with MPNST between 2000 to 2021, from three centers in Portugal. Patient characteristics, treatment modalities and clinical outcomes were reviewed. RESULTS: 12 patients (6 males and 6 females) met the inclusion criteria. 7 had no family history of NF1. Median age at diagnosis was 14.1 years (range 10-18). 5 had been diagnosed previously with Plexiform Neurofibromas and were treated with selumetinib (2) and partial surgical (2). MPNSTs were mostly located in the retroperitoneum (7) and in the proximal lower limbs (2). Only 1 patient had a resectable tumor at diagnosis and 3 patients had metastatic disease. In the FDG-PET scan of evaluated patients (7), the mean maximum standardized uptake value of the main lesion was 6 (range 3.6-9.7). Neoadjuvant ifosfamide plus doxorubicin chemotherapy was used in 4 patients. The median overall survival in this population was 10.3 months (95% CI 0.1-20.6). 2 patients remain alive. CONCLUSION: The prognosis of MPNSTs in NF1 pediatric patients is very poor. In a subset of patients, MPNSTs develop from known Plexiform Neurofibromas. Current surveillance and treatment protocols need to be improved.

JS04. Diffuse midline gliomas and other pediatric tumours

JS04.4.A. BEYOND B-CATENIN: GENETIC ALTERATIONS OF TP53 AND CTNX2 AND OLDER AGE INDICATE INCREASED RISK OF RELAPSE IN WNT MEDULLOBLASTOMAS

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BACKGROUND: The most common CNS tumors in children are WNT-mediated Medulloblastomas (WBMs), which are typically diagnosed before six years of age and are characterized by the activating mutation of the WNT-signaling component B-Catenin (CTNNB1). Both the age of diagnosis (≥6 years) and TP53-mutations are currently utilized as negative independent prognostic markers. In order to identify further genetic alterations with an impact on the patient outcome, we performed a comprehensive analysis of the TP53-genome in a cohort of 124 untreated WBMs. MATERIAL AND METHODS: We firstly performed array comparative genomic hybridization (aCGH, Agilent 4x180K) and identified 160 significantly differentially genetted regions (377 genes with at least a 2-fold change in copy number), which were then validated in an independent cohort of 48 WBMs using high-resolution single nucleotide polymorphism (SNP) arrays ( Illumina) in parallel to sequencing the known cancer genes TP53, CTNNB1, ARID1B, IDH1, IDH2, and TET1. RESULTS: TP53-mutations were present in 9.7% of patients (n=12). The most frequent alterations were deletions and translocations of TP53 and CTNNB1. Genetically intact WBMs were observed in 16% of patients whereas there were 82% and 2% of patients with TP53 and CTNNB1 somatic mutations, respectively. CONCLUSION: TP53-mutations and age ≥6 years are predictive for a poor outcome of WBMs. These data indicate that TP53 is a potential therapeutic target in TP53-mutated WBMs and that further studies are necessary to investigate the role of TP53 in WBMs.
JS04.5.A. ENHANCING THE ACTIVITY OF ANTI-CD47 THERAPY WITH RADIODERMORTHERAPY IN PRECLINICAL MODELS OF MEDULLOBLASTOMA
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BACKGROUND: Brain cancers are the most common solid cancer in children and the leading cause of cancer-related deaths in children. Medulloblastoma is the most common paediatric brain tumour. A major challenge in medulloblastoma involves surgery, craniospinal irradiation (CSI) and chemotherapy. These therapies are extremely damaging to the developing brain and have not changed in decades, resulting in stagnation in the survival outcomes for children with medulloblastoma, and poor quality of life for children who survive their treatment. Immunotherapy has become a focus of novel treatments development. While there are multiple clinical trials aiming to increase the activity of existing or new therapies, these therapies are extremely damaging to the developing brain and do not take into account age-related differences in glioma-associated immune cell compartments.

MATERIAL AND METHODS: Using a small animal radiotherapy platform, we have developed a preclinical CSI protocol which mimics clinical radiotherapy. Using an orthotopic xenograft model of medulloblastoma, mice were treated with either anti-CD47 antibody therapy, CSI, or the combination of both anti-CD47 and CSI. RESULTS: CSI was found to deplete adaptive immune cells in the brain, while myeloid cells remained the dominant populations. Anti-CD47 antibody therapy was ineffective as a single agent against a patient derived xenograft (PDx) model of Group 3 medulloblastoma, and CSI as a monotherapy resulted in temporary tumour regression. We found that the combination of anti-CD47 with CSI resulted in marked and persistent tumour regression. CONCLUSIONS: This work has shown promising efficacy of anti-CD47 in combination with CSI, which we are currently testing in additional models. Our work is currently employing a range of techniques such as high dimensional flow cytometry and single cell sequencing to elucidate the mechanisms by which radiotherapy enhances the anti-tumour activity of myeloid cells. This work will enable the rational design and translation of optimal combination therapies for medulloblastoma clinical trials.

JS06 EURACAN AND RARE BRAIN CANCERS
JS06.4.A. INTRACRANIAL EPENDYMOMAS OF THE ADULT: OUTCOME AND RESPONSE TO TREATMENTS ACROSS MOLECULAR SUBTYPES
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BACKGROUND: The 2021 WHO Classification lists two molecularly defined types of supratentorial ependymomas (STE), i.e., ZFTA and YAP1 fusions, and posterior fossa ependymomas (PFE) at the most posterior cranial fossa (PCF). Based on retrospective data, the presence of the ZFTA fusion (for STEs) and the PFA subtype (for PFEs) seem to correlate with a poorer outcome. However, prospective data on large cohorts of adult patients is lacking, and the role of treatments is uncertain. The objective of our study is to investigate the clinical characteristics, response to treatment, and outcome of a cohort of adult patients with supratentorial and posterior fossa ependymomas across different molecular subtypes. PATIENTS AND METHODS: Clinical data of patients ≥18 years with STEs and PFEs were retrospectively collected from 2 Italian Centres (Turin, Treviso). ZFTA and YAP1 fusions were detected by FISH, while PFA and PFB subtypes were defined by anti-H3K27me3 immunohistochemistry. RESULTS: We collected 42 adult patients with STEs (11, 26.2%) and PFEs (31, 73.8%) diagnosed between 1984 and 2021. Median age was 45 years. ZFTA and YAP1 fusions were found in 5 (45.5%) and 1 (9.1%) case of STEs. PFA and PFB subtypes accounted for 9 (29.0%) and 22 (71.0%) cases of PFEs. Extent of resection (EOR) was gross-total (GTR) in 11 (54.5%) STEs, in 8 (28.6%) PFA subtypes, and in 9/31 (29.0%) PFB subtypes received adjuvant radiotherapy (RT). Median progression-free survival (mPFS) and overall survival (mOS) were 172 and 61.6 months for STEs patients, and not reached (NR) and 332 months for PFEs patients. For patients with STEs, only one of our patients died due to therapy-related complications. For patients with PFEs, PFA and PFB subtypes did not significantly affect survival of STEs patients.

For patients with PFEs, PFA and PFB subtypes did not significantly differ in terms of mPFS (NR vs 137.0 months, p = 0.513) and mOS (NR vs NR, p = 0.132). Conversely, GTR was associated with a significantly longer mPFS (NR vs 63.0 months, p = 0.007) and with a trend for longer mOS (NR vs 332 months, p = 0.146). In multivariable analysis, GTR was associated with a significantly lower risk of disease progression, both in the entire cohort of PFE patients (p = 0.016), and within the PFA subtype (p = 0.013). Similarly, GTR was associated with a trend for better PFS within the PFB