AT/RT is rare, fatal, primary and malignant in the CNS that have a high degree of recurrence and dissemination. The diagnosis is made through anatomopathological examination and the loss of INI-1 expression constitutes an important finding for its conclusion. Treatment is multimodal and may combine surgery, chemotherapy and radiotherapy.

ATRT-26. THE PI3K INHIBITOR PAXALISIB COMBINES WITH THE NOVEL HDAC1/3 INHIBITOR RG2833 TO IMPROVE SURVIVAL IN MICE BEARING ORTHOTOPIC XENOGRAFTS OF ATYPICAL TERATOID/RHABDOID TUMORS

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We previously identified high activation of mTORC1 and mTORC2 in AT/RT by immunohistochemistry of 18 primary tumors expanding over each molecular subgroup of AT/RT. Paxalisib is a highly brain-penetrant PI3k inhibitor acting upstream of mTORC1/2 to fully inhibit the activation of both complexes. Ongoing pediatric clinical trials have reported Paxalisib as safe and well-tolerated. We find that Paxalisib leads to minimal toxicities in mice bearing AT/RT orthotopic xenografts, slows tumor growth (as determined by bioluminescent imaging), and significantly extends survival (CHLA-06: 40 to 54 days, p=0.0011; BT12: 21 to 35 days, p=0.02). However, due to limited durability of single agent therapy, we conducted pilot studies to identify rational combination therapies to further enhance these survival benefits. RG2833 is a novel, highly brain penetrant, histone deacetylase 1/3 (HDAC1/3) inhibitor. HDAC inhibitors have previously been identified as synergistic partners with PI3k/mTOR inhibitors through complementary activation of FOXO signaling pathways. We hypothesized that RG2833 would synergize with Paxalisib, minimize toxicities compared with pan-HDAC inhibitors, and maximize therapeutic benefits due to superior CNS penetration. We demonstrate that Paxalisib and RG2833 combine synergistically to decrease AT/RT cell growth (SynergyFinder ZIP score 11.1; CellTiter-Blue Cell Viability Assay, p<0.0001), and increase apoptosis (Western blot cPARP, MUSE Annexin V Assay, ANOVA p<0.001) compared to each agent alone and DMSO control. Our pilot combination study in orthotopic xenograft models of AT/RT demonstrate that combination therapy is well tolerated and slows tumor growth more significantly than each agent alone and vehicle control (IVIS bioluminescent imaging). This novel combination therapy could readily translate into a new clinical trial aimed at improving survival in this deadly pediatric brain tumor.

CRANIOPHARYNGIOMA AND RARE TUMORS

RARE-01. CEREBRAL INFARCTION IN CHILDHOOD-ONSET CRANIOPHARYNGIOMA PATIENTS: RESULTS OF KRANIOPHARYNGEOM 2007

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BACKGROUND: Cerebral infarction (CI) is a known vascular complication following treatment of suprasellar tumors. Risk factors for CI, incidence rate, and long-term prognosis are unknown for patients with childhood-onset craniopharyngioma (CP). METHODS: MRI of 244 CP patients, recruited between 2007 and 2019 in KRANIOPHA-RYNGEOM 2007, were reviewed for CI. Risk factors for CI and outcome after CI were analyzed. RESULTS: Twenty-eight of 244 patients (11%) presented with CI based on reference assessment of MRI. One CI occurred before initial surgery and one case of CI occurred after release of intracystic pressure by a cyst catheter. 26 of 28 CI were detected after surgical tumor resection at a median postoperative interval of one day (range: 0.5 - 53 days). Vascular lesions during surgical procedures were documented in 7 cases with CI. No relevant differences with regard to surgical approaches were found. In all 12 irradiated patients, CI occurred before irradiation. Multivariable analyses showed that hydrocephalus and gross-total resection at the time of primary diagnosis / surgery both were risk factors for CI. After CI, quality of life (PEDQOL) and functional capacity (FMH) were impaired. CONCLUSIONS: CI occurs in 11% of surgically-treated CP cases. Degree of resection and increased intracranial pressure are risk factors, which should be considered in the planning of surgical procedures for prevention of CI.

RARE-02. CRANIOPHARYNGIOMAS DIAGNOSED AS INCIDENTALOMAS - RESULTS OF KRANIOPHARYNGEOM 2007

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PURPOSE: Childhood-onset craniopharyngiomas (CP) are diagnosed due to clinical symptoms (symCP) or incidentally (incCP). We investigated clinical manifestations and outcome in incCPs and symCPs. METHODS: IncCP were discovered in 4 (3m / 1f) and symCP in 214 (101m / 113f) CP recruited 2007–2014 in KRANIOPHARYNGEOM 2007. Age, sex, height, body mass index (BMI), tumor volume, degree of resection, pre- and postsurgical hypothalamic involvement/lesions, pituitary function and outcome were compared between both subgroups. RESULTS: Reasons for imaging in incCP were cerebral palsy, head trauma, nasal obstruction, and tethered-cord syndrome, whereas headache (44%), visual impairment (25%), and growth retardation (17%) lead to imaging in symCP. Tumor volume at diagnosis was smaller in incCP (median 2.39 cm^3; range: 0.14 – 4.10 cm3) when compared with symCP (15.86 cm^3; 0.002 – 286.34 cm^3). Age, gender, BMI, height, hydrocephalus, tumor location, and hypothalamic involvement at diagnosis of incCP were within the range of these parameters in symCP. Complete resections were achieved more frequently (3/4 patients) in incCP when compared with symCP (20%). Surgical hypothalamic lesions were distributed similar in incCP and symCP. Irradiation was performed only in symCP (33%). No noticeable differences were observed concerning survival rates, endocrine deficiencies, BMI, height, functional capacity and quality of life of the 4 incCP cases when compared with the symCP cohort. CONCLUSIONS: IncCP are rare (1.8%) and characterized by lack of endocrine deficiencies, resulting in normal height and BMI, no hydrocephalus, and smaller tumor volume at diagnosis when compared with symCPs. Outcome of the observed incCP is similar with symCP.

RARE-03. VISION-RELATED QUALITY OF LIFE IN PATIENTS WITH CHILDHOOD-ONSET CRANIOPHARYNGIOMA – RESULTS OF KRANIOPHARYNGEOM 2000 / 2007

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BACKGROUND: Quality of life (QoL) has become a critical component of therapeutic outcomes in the survivors of childhood-onset adamantinomatous craniopharyngioma (CP) patients. Visual deficiency adversely affects daily functioning and QoL. This study aimed to report the vision-related QoL and associated factors in CP patients. PATIENTS AND METHODS: 120 CP patients recruited between 2001 and 2019 in KRANIOPHARYNGEOM 2000/2007 were included in this study. Mean age at CP diagnosis was 10 years (range: 1.3-16.8 years); age at study was 18 years (range: 6-33 years). The primary outcome measures were QoL assessed by PEDQOL, functional capacity measured by Fertigkeitenskala Münster-Heidelberg ability scale and risk factors associated with decreased QoL during 3 years follow-up in CP patients with and without visual impairment (VI). RESULTS: The most common presenting symptoms were headache (42%), VI (20%), and growth retardation (12%). After diagnosis, VI defined as visual acuity less than 20/40, was found in 87 (70%) patients. Ophthalmologic examination and PEDQOL score were evaluated at three months, one year, and 3 years after CP diagnosis. A difference in the parental assessment of CP patient social functioning within the family was found between patients with and without VI in the first year (48 vs. 39, p=0.017) and third year (43 vs. 37, p=0.011). For the PEDQOL domain autonomy, a difference in self- (51 vs. 45, p=0.029) and parental (47 vs. 42, p=0.048) assessment was observed 3 years after diagnosis. In terms of risk factors, tumor volume more than 21 mm3, incomplete tumor resection and optic atrophy at initial presentation were associated with VI during follow-up. CONCLUSIONS: VI has an impact on QoL after CP. Accordingly, early detection of VI, together with the assessment of the patient's QoL and the provision of adequate support during follow-up plays an important role in minimizing adverse late effects after CP.

RARE-04. HYPOTHALAMIC SYNDROME – SEVERE SEQUELAE DUE TO DIFFERENT SELLAR AND PARASELLAR MASSES

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Hypothalamic syndrome is a rare disorder caused by disease- and/or treatment-related injury to the hypothalamus, most commonly associated with rare, noncancerous parasellar masses such as craniopharyngioma, germ cell tumours, gliomas, cysts of Rathke's pouch and Langerhans cell histiocytosis as well as gen-