MODL-31. NOVEL IN VIVO MODELS OF POST-RADIATION RECURRENT PEDIATRIC HIGH-GRADE GLIOMA SHOW INCREASED SUSCEPTIBILITY TO MAPK INHIBITION

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BACKGROUND: Pediatric high-grade glioma (pHGG) is the most common cause of childhood cancer mortality, with median survival of less than one year. The standard of care for pHGG includes radiation therapy (RT), but almost all patients who respond initially relapse with aggressive, radiation-resistant disease. Matched primary/recurrent models and effective therapies for recurrent pHGG have not been adequately developed. METHODS: Orthotopic patient derived xenograft (PDX) models of radiation-resistant pHGG were developed by implanting BT245 (H3K27M) and HSJD-GBM-001 (GBM1, H3-wt) cells into mice. Resultant tumors were irradiated at 8Gy (4Gy x 2d) and allowed to regrow. Recurrent, radiation-resistant tumors (BT245MR and GBM1MR) and initial tumors (BT245M and GBM1M) were collected for bulk RNA-Seq analysis and ex vivo cell culture. Dose-response experiments were conducted in explant cells to identify drugs with increased effectiveness against recurrent (MR) cell lines versus wild-type cell lines. RESULTS: In both BT245 and GBM1 explant cells, geneset enrichment analysis (GSEA) showed upregulated mesenchymal (BT245MR: NES=3.4, FDR=0; GBM1MR: NES=2.4, FDR<0.002) and hypoxia-related (BT245MR: NES=3.6, FDR=0; GBM1MR: NES=3.4, FDR=0) pathways. GBM1MR tumors also showed enrichment in MAPK signaling (NES=4.7, FDR=0). RNA processing (NES=-6.5, FDR=0) and translation (NES=-5.8, FDR=0) pathways were depleted in BT245MR cells, and DNA repair pathways (NES=-5.8, FDR=0) were depleted in GBM1MR cells. The MAPK inhibitor trametinib demonstrated increased effectiveness in BT245MR and GBM1MR cell lines versus wild-type controls (BT245 IC50 158.7nM (wt) vs. 56.0 (MR), p<0.05; GBM1 IC50 150.7 (wt) vs. 53.4 (MR), p<0.05). BT245MR and GBM1MR cells reliably form PDX tumors after injection into mice. CONCLUSION: BT245MR and GBM1MR represent novel in vivo models of radiation-resistant pHGG, with gene expression alterations consistent with an irradiated phenotype. GSEA and in vitro dose-response data suggest MAPK inhibition may be effective in radiation-resistant pHGG. We are currently conducting in vivo experiments to validate increased trametinib sensitivity in these models.

RADIATION ONCOLOGY

RONC-01. A 10 YEAR, SINGLE INSTITUTION EXPERIENCE OF RE-IRRADIATION FOR PAEDIATRIC INTRACRANIAL TUMOURS

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INTRODUCTION: Re-irradiation has become integral in the management of relapsed and recurrent intracranial tumours in children. It is used as salvage therapy for a number of tumours including; diffuse intrinsic pontine glioma (DIPG), high grade glioma (HGG), ependymoma and medulloblastoma. We report the patient demographics, dose, outcomes and toxicity for patients treated with re-irradiation at our institute. METHODS: 33 patients with a diagnosis of DIPG (n=11, 33%), ependymoma (n=11, 33%), HGG (n=4, 12%) or medulloblastoma/sPNET (n=7, 21%), treated with intracranial re-irradiation since 2012 were analysed in this retrospective study. Statistical survival analysis was performed. RESULTS: The median follow-up was 19 months (range 0–216 months). The median age at re-irradiation was 10 years (2-20 years). The median time from first radiation to re-radiation was 34 months (range 3–113 months). Re-irradiation techniques included; photons (n=26), protons (n=2) and stereotactic radiotherapy (n=6). The median re-irradiation dose was 36.37Gy EQD2 (range 20-95.05Gy), given in dose per fraction between 1.8Gy–2Gy. The median overall survival (OS) and progression free survival (PFS) for the cohort was 15.68 months and 7 months respectively. For DIPG, the median OS and PFS were 6.12 months and 4 months respectively. At 2 years, the OS and PFS rates for the cohort were 34.37% and 32.45% respectively. For the non-DIPG cohort, the 2 year OS and PFS rates were 55.37% and 48.13% respectively. In the DIPG cohort, 88% (n=7) had a reported symptomatic benefit from re-irradiation. A stable or improved radiological response was reported in majority of patients (78%, n=18). No acute or late toxicities ≥ grade 3 were reported within the cohort, specifically, there were no reports of brainstem necrosis. CONCLUSION: Re-irradiation for paediatric intracranial tumours is safe and offers a benefit to patients. Further work is ongoing to evaluate cumulative brainstem doses and predictive variables.

RONC-02. CLINICAL OUTCOME AFTER CRANIOSPINAL IRRADIATION WITH PENCIL BEAM SCANNING PROTON THERAPY FOR CHILDREN AND YOUNG ADULTS/ADOLESCENTS WITH BRAIN TUMORS

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BACKGROUND: Craniospinal irradiation (CSI) is an essential treatment component to achieve cure for some brain tumors in children and young adults/adolescents (C-AYAs). Multimodal treatment approaches are however associated with treatment-related late toxicities in these developing patients. Pencil beam scanning proton therapy (PBSPT) allows for a minimization of dose delivered to organs at risk and the brain integral dose and, thus, potentially also a reduction of radiation-induced adverse events. We report the clinical outcome and toxicity rates after CSI for C-AYAs treated with PBSPT. METHODS: We reviewed 71 C-AYAs with a median age of 7.4 years (1.7 – 21.3) who received CSI with PBSPT. Medullobastoma (n=42, 59%) and ependymoma (n=8, 11%) were the most common histologies. Thirty-four (48%) patients presented with metastatic disease at diagnosis. Sixteen (23%) patients were treated for tumor recurrence/progression and 9 (13%) patients underwent re-irradiation. Median prescribed total dose was 54 GyRBE (18 – 60.4) and median craniospinal dose 24 GyRBE (18 – 36.8). Toxicities were recorded according to CTCAE v5.0. RESULTS: With a median follow-up time of 24 months (2 – 195), 12 (17%) patients died due to progressive disease. Eight (11%) patients experienced local failure and 15 (21%) distant failure after PBSPT. Estimated 2-year OS, LC and DC was 86.9%, 86.0% and 80.4%, respectively. Grade 3 acute toxicity (thrombocytopenia, neutropenia, nausea) was observed in 5 (7%) patients. Late grade 3 toxicities (stroke, cataract and CNS necrosis) were observed in 3 (4%) patients, 8, 9 and 16 months after PBSPT, respectively. One (1%) patient developed grade 4 CNS necrosis 8 months after CSI. Late grade ≥3 toxicity free rate was 92.3% at 2 years. No radiation-induced secondary cancer was observed. CONCLUSION: Excellent tumor and brain/spinal distant control and a low late grade ≥3 toxicity rate after CSI were observed in our cohort of C-AYAs treated with PBSPT.

RONC-03. SECONDARY NEOPLASMS IN CHILDREN WITH CENTRAL NERVOUS SYSTEM (CNS) TUMORS FOLLOWING RADIOTHERAPY IN THE MODERN ERA

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PURPOSE: To assess reduction of secondary radiation-induced neoplasms over the past two decades, focusing on children with CNS tumors who received intensity modulated radiotherapy (IMRT) or proton therapy (PT). METHODS: A total of 1044 children received radiotherapy for a primary CNS tumor at 2 institutions between 1999 and 2020, including 99 treated with IMRT and 945 treated with PT. Median age was 8.7 years old. Median follow-up was 6.0 years and included 83 and 510 patients with >5 years follow-up in the IMRT and proton cohorts, respectively. Cumulative incidence method provided estimates of secondary neoplasms encompassing benign and malignant solid tumors as well as leukemia. Multiple variables were assessed using proportional hazard regression for competing risks. RESULTS: Ten-year overall survival was 87.4%. Patients treated with IMRT were significantly older, with a median age of 10.4 vs 8.4 years old (p <0.001), but were more likely to receive craniospinal irradiation (31.3% vs 14.2%, p <0.001) or alkylating chemotherapy (50.5% vs 29.7%, p <0.001). The 5- and 10-year cumulative incidence of second neoplasm was 0.7% and 2.3%, respectively. On multivariate analysis, age <5 (4.9% vs 0.7% at 10 years) and tumor predisposition syndrome (34.3% vs 1.5% at 10 years) were significantly associated with a second neoplasm (p < 0.01 for each). On both univariate and multivariate analyses, PT was not associated with a lower incidence of second neoplasm. Following IMRT, 1/2 second solid tumors occurred outside the target volume, compared to 2/11 after PT. CONCLUSION: Following modern radiotherapy, approximately 2% of children with a CNS tumor will develop a second neoplasm within 10 years of treatment. Compared to IMRT, PT was not associated with an overall reduction in second neoplasms. More events and follow-up beyond 10 years are needed to determine if proton therapy reduces the incidence of second solid tumors occurring specifically in the low dose region.