LGG-28. NOVEL BRAF INTRAGENIC DELETION IN A GLIOMA: A CASE REPORT OF A PEDIATRIC PATIENT

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BACKGROUND: Numerous variant BRAF genetic alterations have been associated with malignancies. BRAF activating fusions/mutations are frequently present in low grade gliomas. BRAF intragenic deletions have been reported in melanoma, but have not previously been reported in gliomas. OBJECTIVE: To report a BRAF intragenic deletion in a pediatric patient with recurrent low-grade glioma. RESULTS: A 3-year-old female underwent a complete resection of a posterior fossa pilocytic astrocytoma. She had recurrences at age 4, and then at age 9; pathology was consistent with pilocytic astrocytoma. Microarray analysis on sample from the first recurrence showed one region of loss encompassing 86 Kbp within the BRAF gene. The deletion breakpoints are within intron 1 and 9, resulting in loss of exons 2 through 9, inclusive. This has been previously described melanoma, but appears to be a novel finding in glioma. It is hypothesized that, since the loss retains the kinase and ATP binding pocket domains but deletes the N-terminal conserved region 1 and 2 (CR1, CR2) of the BRAF gene, it is likely functionally similar to the loss and activation resulting from the more usually described KIAA1549 and BRAF gene fusion. CONCLUSION: This is the first BRAF intragenic deletion involving exons 2–9 reported in a glioma. Although 86kbp is small using whole genome microarray technology, it is large using sequencing strategies, and a targeted sequencing approach to investigate the BRAF gene would not readily identify this deletion. It is speculated that the deletion may be under ascertained in the pediatric population.

LGG-29. TREATMENT FOR RECURRENT OPTIC PATHWAY PILOCYTIC ASTROCYTOMA

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Chemotherapy after biopsy or partial resection of the tumor is widely accepted as first-line therapy for optic pathway pilocytic astrocytoma. However, there is no standard of care for recurred tumors. We investigated our cases which showed recurrence after initial therapy. Retrospective analysis of four recurrent optic pathway pilocytic astrocytoma cases was performed. All patients underwent partial resection or biopsy of the tumor, and all received carboplatin and etoposide- based chemotherapy as initial treatment. Mean age at first therapy was 2.3 years old, and mean time from initial therapy to recurrence of the tumor was 5.6 years. Two patients were totally blind at the time of recurrence, and other two had partial visual field losses. One patient underwent total resection of the tumor, and other three patients underwent partial resection followed by chemotherapy. Visual function in patients with visual acuity did not deteriorate after removal of the recurrent tumor. There was no recurrence of the tumor who underwent total resection. All of the three patients who had partial resection followed by chemotherapy recurred. Mean time from first recurrence to second recurrence was 1.8 years. After second recurrence, all patients underwent radiation therapy. One patient died due to malignant transformation of the tumor. For recurrent optic pathway pilocytic astrocytoma, prognosis may be better if total resection of the tumor without deteriorating the vision is possible.

LGG-30. TRAMETINIB-ASSOCIATED HYPONATREMIA IN A CHILD WITH LOW GRADE GLIOMA IS NOT SEEN FOLLOWING TREATMENT WITH ALTERNATIVE MEK INHIBITOR

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Molecularly targeted therapy with MEK inhibitors is increasingly being incorporated into the treatment of pediatric low-grade gliomas (LGGs). Trametinib is an orally available MEK1/2 inhibitor that has demonstrated tumor control in LGGs with BRAF alterations. Safe expansion of MEK inhibitor therapy within the pediatric patient population demands adequate understanding of and surveillance for potential MEK-inhibitor specific toxicities, especially among young children. Hyponatremia has been reported in adult patients receiving BRAF/MEK inhibitor combination treatment as well as in two pediatric patients with known diabetes insipidus treated with trametinib monotherapy. To our knowledge, single-agent trametinib has not previously been reported to be associated with hyponatremia in children in the absence of an underlying endocrinopathy. We present a case of hyponatremia associated with trametinib use in an infant with progressive LGG without known endocrine dysfunction, which recurred after significant dose reduction. Therapy with an alternative MEK1/2 inhibitor, binimetinib, provided excellent tumor response without hyponatremia. Hyponatremia is a rare but serious side effect of trametinib, even without underlying pituitary dysfunction. Infants and patients lacking the ability to quickly regulate fluid intake in response to osmolality changes are at particular risk of suffering severe consequences from hyponatremia and should be monitored closely with initiation of trametinib. Switching to a different drug within the same class may offer an alternative to significant dose reduction or discontinuation due to this toxicity.

LGG-31. CHARACTERIZING TEMPORAL GENOMIC HETEROGENEITY IN PEDIATRIC LOW GRADE GLIOMAS: ANALYSIS OF AN EXPANDED MULTI-INSTITUTIONAL COHORT WITH 101 PAIRED TUMOR SAMPLES

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INTRODUCTION: Recent discoveries have provided valuable insight into the genomic landscape of pediatric low grade gliomas (LGGs) at diagnosis, facilitating molecularly targeted treatment. However, little is known about their temporal and therapy-related genomic heterogeneity. An adequate understanding of the evolution of pediatric LGGs' genomic profiles over time is critically important in guiding decisions about targeted therapeutics and diagnostic biopsy at recurrence. METHODS: Fluorescence in situ hybridization, mutation-specific immunohistochemistry, and exome analyses were performed on paired tumor samples from primary diagnostic and subsequent surgeries. RESULTS: 101 tumor samples from 48 patients (43 with 2 specimens, 5 with 3 specimens) from 3 institutions underwent testing. *BRAF* fusion and $BRAF^{V600E}$ status were conserved in 100% and 97% of paired specimens, respectively. No loss or gain of *IDH1* mutations or *FGFR1*, *NTRK2*, *MYB*, or *MYBL1* rearrangements were detected over time. Histologic diagnosis remained the same in all tumors, with no acquired H3K27M mutations or malignant transformation. *CDKN2A* deletions were acquired in 7 patients (including 3 who received chemotherapy [2 with temozolomide] and 1 who received radiation), and were associated with a trend toward shorter time to progression (median: 5.5 vs. 13.0 months [p=0.08]). CONCLUSIONS: Most targetable genetic alterations in pediatric LGGs, including *BRAF* alterations, are conserved at recurrence and following chemotherapy or radiation. However, *CDKN2A* deletion acquisition was demonstrated and may define a higher risk group. Given potential for targeted therapies for tumors acquiring *CDKN2A* deletions, performing a biopsy at recurrence may be indicated in certain patients, especially those with rapid progression.

LGG-32. CLINICAL OUTCOME OF PEDIATRIC GLIOMAS IN SINGLE INSTITUTION

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Gliomas in children are rarer than in adult, then treatment strategies might vary from facility to facility. We report clinical features and outcome of pediatric glioma in our institution. Twenty-nine patients diagnosed with glioma, exclude ependymoma, 14 boys and 15 girls, among 98 pediatric brain tumor patients treated at Kagoshima University Hospital since 2006 were reviewed histopathology, extent of resection, adjuvant therapy and outcome, etc. Mean age at surgery was 10.4 (S.D. 5.6) years. Median follow-up period was 19.1 months. Histopathological diagnosis comprised 8 pilocytic astrocytoma, 3 ganglioglioma, 2 subependymal giant cell astrocytoma, 5 WHO grade II astrocytoma, 8 glioblastoma, and desmoplastic infantile astrocytoma, anaplastic astrocytoma and astroblastoma were one case each. Tumor resection was performed in 24 cases, and 5 cases underwent biopsy. Chemotherapy was performed in 15 cases and irradiation was performed in 9 cases. Out of 5 WHO grade II astrocytoma cases, 2 cases underwent biopsy following chemotherapy, 1 case underwent biopsy only and other 1 case underwent total resection. The four cases show long survival ranged from 71 to 136 months without irradiation. All of eight glioblastoma cases show poor prognosis ranged from 8.6 to 26.7 months regardless of chemoradiotherapy. In management for pediatric brain tumor patients, irradiation is often laid over until recurrence. In WHO grade II astrocytoma, the treatment strategy might be reasonable using appropriate chemotherapy even though biopsy cases.