Medulloblastoma: candidate pathways for novel treatment strategies

Tiffany R. Hodges1, Nader San1,2, Joanne Xiu3, Lyndon Kim3, Shouhao Zhou3, Santosh Kesari2, Marta Penas-Prado1, Amy Heimberger1
1Departments of Neurosurgery, Biostatistics, and Neuroepidemiology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030; 2Division of Neurosurgical Oncology, Barrow Neurological Institute, Phoenix, AZ 85024; 3Life Sciences, Phoenix, AZ; 4Department of Neurosurgical Oncology and Medical Oncology, Thomas Jefferson University Hospital, Philadelphia, PA; 5Department of Translational Neuro-Oncology and Neurotherapeutics, Pacific Neuroscience Institute and John Wayne Cancer Institute at Providence Saint John’s Health Center, Santa Monica, CA

Abstract

BACKGROUND: Medulloblastoma, an aggressive but potentially curable CNS disease, remains a treatment challenge due to the biological heterogeneity of the disease. Analysis of actionable targets can provide opportunities in the development of curative therapies. To identify potential candidate genes, we investigated alterations in a cohort of medulloblastoma patients.

METHODS: Tumors from 36 medulloblastoma patients were profiled using immunohistochemistry, next generation sequencing, pyrosequencing, fluorescence in situ hybridization, and fragment analysis at Caris Life Sciences.

RESULTS: Primary tumor location included the posterior fossa (n = 18) and other (n = 18). There were 18 adults (9 male, 9 female, median age: 30, range: 18-47 years) and 18 pediatric patients (14 male, 4 female, median age: 7, range: 2-14 years). Medulloblastomas showed the highest expression of MRPI (88.9%, 8/9 tumors), TUBB3 (85.7%, 18/21 tumors), PTEN (94.1%, 16/17 tumors, 61.5%, 8/13 tumors), TUBB3 (85.7%, 18/21 tumors), PIK3CA (84.8%, 28/33 tumors), and PTEN (84.8%, 28/33 tumors). Among them, TS expression was higher in male, 4 female, median age: 7, range: 2-14 years) and 18 pediatric patients (14 male, 4 female, median age: 30, range: 18-47 years) and 18 pediatric patients; C: comparison of tumors taken from male patients with female patients; D: comparison of tumors taken from posterior fossa with other tumor locations. (An asterisk indicates statistical significance by Fisher-Exact test).

Background

Medulloblastoma is the most common malignant CNS pediatric tumor and is less frequent in adults. Current treatment paradigms are based on standard or high-risk criteria, as multimodal therapeutic approaches include surgical resection, crani-spinal radiation followed by a boost to the tumor bed with concurrent and adjuvant chemotherapy. However, patients < 3 years of age are usually treated postsurgically with high-dose chemotherapy, instead of irradiation, due to the risk of neurocognitive and neuroendocrine dysfunction. Current treatment strategies have shown an improvement in 5-year overall survival to 85% for children with standard-risk disease and ~60% for those with high-risk disease1. However, identifying novel targeted therapies may help improve disease outcome. Profiling medulloblastoma for potential candidate genes and molecular biomarkers may provide insights into optimal, targeted therapeutic strategies.

Results

Table 1: Molecular alterations in medulloblastoma

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Posterior Fossa</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female: N=11</td>
<td>N=6</td>
<td>N=17</td>
</tr>
<tr>
<td>Tumor</td>
<td>N=12</td>
<td>N=6</td>
<td>N=18</td>
</tr>
</tbody>
</table>

Figure 2: Protein expression frequencies in the medulloblastoma cohorts. A: all cases studied (n=19); B: comparison of expression in tumors taken from adults with patients with pediatric patients; C: comparison of tumors taken from male patients with female patients; D: comparison of tumors taken from posterior fossa with other tumor locations. (An asterisk indicates statistical significance by Fisher-Exact test).

Figure 3: A Mutation frequencies seen in the cohort (n=19). Figure 3: A: NGS-CTNNB1 (1/19); IHC-TUBB3 (18/21); IHC-RRM1 (15/21); TOPO1 (13/19); IHC-PTEN (28/33); IHC-PD-L1 (1/27); IHC-PD-1 (1/25); IHC-EGFR (4/13); IHC-MRP1 (8/9); IHC-TLE3 (3/19); NGS-ARID1A (1/2); NGS-PTCH1 (1/7); NGS-SMO (1/12); CISH-cMET (N=16); CISH-Her2 (N=16).

Figure 4: Oncoprint of 19 tumors that went through NextGen sequencing. Pathogenic/putative pathogenic mutations are marked red with protein changes shown; wild type/benign variants are shown in blue. Blank indicates data not available.

Conclusions

1. Using a combination of different test technologies on 36 medulloblastoma tumor samples, we found biomarkers expressed at various frequencies, which could be linked to responsiveness to chemotherapies used in medulloblastoma treatments.

2. Distinct molecular features in adult and pediatric medulloblastomas identified candidate pathways for further investigation. A significantly higher expression of drug efflux pump Pgp in pediatric tumors indicates potential increased chance of drug resistance to its substrate, including topotecan.

3. Higher expression of TOP2A seen in non-posterior fossa medulloblastomas may indicate an aggressive clinical behavior and may suggest the use of TOP2A inhibitors.

4. Targetable gene mutations including BRCA2, PIK3CA, ARID1A, SMO, PTCH were seen in our cohort, suggesting potential opportunities for targeted therapies.

References

