Targetable gene fusions and other alterations in central nervous system tumors assessed by RNA and DNA-based next-generation sequencing

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Background

- Central nervous system (CNS) tumors may have an underlying genetic mechanism, where oncogenic fusion proteins play an important role in tumorigenesis. This provides an opportunity to develop specific and effective therapies.
- Here, we used RNA and DNA-based next-generation sequencing (NGS) to identify actionable or potentially actionable oncogenic fusions and other molecular alterations in patients with CNS tumors.

Methods

- Pediatric and adult patients with CNS tumors treated in our hospital between 2018 and 2022 undergoing surgery were enrolled.
- Fusion transcript detection and mutation analysis in FFPE tumor samples were assessed by both DNA-based next-generation sequencing (NGS) assay (520-gene panel) and RNA-based NGS assay (115 fusion-related-gene panel) to identify molecular alterations.

Results

- DNA-based NGS detected 50 tissue samples from 50 enrolled patients. RNA-based NGS successfully detected 49 samples, excluding 1 RNA degraded sample.
- Oncogenic fusions were identified in 63.2% (31/49) of patients by RNA-based NGS. At least 2 kinds of fusion transcripts were detected in 7 patients.
- Actionable fusions were KIAA1549::BRAF in 13 patients with pilocytic astrocytoma, FGFR1::TACC1 fusion in 2 patients with pilocytic astrocytoma and PTPRZ1::MET fusion in a patient with high-grade glioma.
- ZFTA::RELA fusions were found in 13 patients with ependymoma.
- A total of 31 patients (62.0%) were identified with at least an actionable or potentially actionable alteration by RNA- or DNA-based NGS.
- Besides targetable fusions, actionable alterations were most often located in SETD2 mutation (n=8), CDKN2A deletion (n=4) and CDKN2B deletion (n=4).

Table: Patients with druggable or potential druggable fusion detected by RNA-based NGS for genetically matched therapies

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Gene fusion</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>13</td>
<td>KIAA1549::BRAF</td>
<td>Pilocytic astrocytoma</td>
</tr>
<tr>
<td>2</td>
<td>FGFR1::TACC</td>
<td>Pilocytic astrocytoma</td>
</tr>
<tr>
<td>1</td>
<td>PTPRZ1::MET</td>
<td>High-grade glioma</td>
</tr>
</tbody>
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Take home message

➢ The combination of RNA- and DNA-based NGS provides information about molecular alterations for the management of patients with CNS tumors.