Next generation sequencing can reveal personalized treatment options and impact survival in glioma patients

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Abstract

Background: Gliomas are driven by various genetic mutations, but are largely treated the same. Next Generation Sequencing (NGS) using STRATA Oncology and Foundation Medicine provide the oncologist with important characteristics of the tumor, and may reveal a targetable mutation. The goal of this study is to quantify the impact of NGS on patients with gliomas.

Methods: The medical records of patients with a diagnosis of glioma who received either a craniotomy for resection or biopsy at our institution from 2015-2018 were retrospectively reviewed. The records were filtered for patients that had NGS, and the impact the sequencing reports had on treatment was determined from the physician’s notes.

Results: There were 225 patients in our cohort, and 98 of those patients had their tumor sequenced. Of the 98 patients, 9 (9.2%) had their treatment changed as a result of a mutation found on the sequencing report. The group that received NGS had an overall survival of 1.89 years, compared to 0.97 years in the group that did not receive NGS (p-value=0.067).

Conclusion: NGS of gliomas provides the physician with the characteristics specific to the tumor, making it possible to personalize treatments based on the mutation status.

Introduction

• Despite understanding the genetic and histologic differences of gliomas, they are mostly treated the same.
• Stupp protocol (2005) suggested a survival advantage when temozolomide (TMZ) was added to radiation therapy versus radiation alone in high grade glioma.1
• Other cancers are routinely sequenced to find targetable mutations, this is not routinely done for brain tumor patients.2,3
• Next Generation Sequencing (NGS) is an umbrella term describing laboratory techniques that allow us to identify DNA and RNA alterations of tissue.
• NGS may allow us to treat a tumor based on its genetic profile, as opposed to its histologic characteristics.5
• In 2016, UNC began routinely sequencing glioma patients.
• The aim of this study is to determine if sequencing a patient’s tumor impacted their care.

Table 1. Patient demographic and clinical characteristics
<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>225</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>58 (16)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female (40.8) Male (59.2)</td>
</tr>
<tr>
<td>Insurance</td>
<td>No Insurance 28 (12.4) Private Insurance 77 (44.2)</td>
</tr>
<tr>
<td>Pathology</td>
<td>Glioblastoma (Grade IV) 153 (80.0) Anaplastic astrocytoma (Grade III) 15 (8.1) Gliosarcoma (Grade III) 10 (4.4) Oligodendroglioma (Grade II) 16 (7.8) Anaplastic oligodendroglioma (Grade III) 10 (4.4) Diffuse astrocytoma (Grade II) 23 (9.5) Anaplastic oligoastrocytoma (Grade II) 1 (0.8) Oligoependymoma (Grade IV) 0 (0.0)</td>
</tr>
<tr>
<td>Next Generation Sequencing</td>
<td>STRATA Oncology 1 (0.0) Foundation Medicine 21 (9.3) STRATA Oncology and Foundation Medicine 3 (0.9)</td>
</tr>
<tr>
<td>Drug targeting mutation</td>
<td>1 (11.1)</td>
</tr>
</tbody>
</table>

Table 2. The changes in treatment due to STRATA and Foundation testing, and the ways treatment was changed
| Patient | Sequencing | Treatment Changed | N (%)
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>98 (100)</td>
<td>No</td>
</tr>
<tr>
<td>STRATA</td>
<td>84 (85.7)</td>
<td>79 (94.0)</td>
</tr>
<tr>
<td>Foundation</td>
<td>13 (13.3)</td>
<td>9 (69.2)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (1.0)</td>
<td>3 (100.0)</td>
</tr>
</tbody>
</table>

How was treatment changed?

| Clinical Trial | 1 (11.1) |
| Drug targeting mutation | 8 (88.9) |

Median Progression Free Survival (PFS) in Years (CI)*

<table>
<thead>
<tr>
<th>Sequencing</th>
<th>No Sequencing</th>
<th>p = 0.16</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRATA</td>
<td>0.48 (0.31, 0.70)</td>
<td>1.07 (0.67, 1.56)</td>
</tr>
<tr>
<td>Foundation</td>
<td>0.97 (0.76, 1.18)</td>
<td>0.97 (0.76, 1.18)</td>
</tr>
<tr>
<td>Both</td>
<td>1.89 (1.50, 2.76)</td>
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</table>

* Survival times only include high grade glioma patients (grade III and IV)

CASE REPORT:

This is a 72-year-old female with left temporal GBM (MGMT hypermethylation and IDH WT). She underwent tumor resection followed by concurrent chemoRT, which was complicated by severe pancytopenia. Due to her NGS profile, she started crizotinib (c-MET inhibitor), in conjunction with alternating electric treating fields (Opptune®). She had a partial response on initial MRI, but showed progression two months later. Crizotinib was discontinued. She started on low dose daily temozolomide with vigilant attention to her hematologic parameters. However, a subsequent MRI revealed progression and she showed clinical decline. She was started on cabozantinib (c-Met and VEGFR2) at 60 mg daily. She tolerated cabozantinib for 22 days but was forced to stop treatment due to low platelets. MRI showed a complete response and treatment was held until platelets recovered. The following MRI showed progression, the patient was restarted on cabozantinib 40 mg daily and MRI one month later showed partial response.

Methods

Data Collection

• Retrospectively reviewed records of all patients who received a craniotomy or biopsy at UNC from 2015-2018.
• Variables collected included age, sex, glioma grade, insurance provider, medications used, and NGS sequencing reports.
• The primary outcomes measured were change in treatment (yes or no), overall survival (OS), and progression free survival (PFS).

Next Generation Sequencing

• Tissue biopsy is collected and sent for sequencing.
• The two platforms used were Foundation Medicine® and STRATA Oncology®.
• STRATA was the preferred sequencing platform due to its current clinical collaboration with UNC.
• The laboratory would respond with a report in 2-3 weeks.
• The treating physician would determine if there was appropriate to alter treatment based on the NGS report.

Data Analysis

• Patients were grouped into having genetic sequencing or not.
• Fisher’s exact test was used for characteristics that can be categorized into discrete groups.
• Wilcoxon rank sum test was used for continuous characteristics.
• For OS and PFS, Kaplan Meier method was used to estimate survival times, the Log-Rank test was used to compare survival between the sequencing groups.

Summary

• The treatment regimen for gliomas has remained the same since 2005.1
• Using NGS to find a more personalized treatment option for patients can improve PFS and OS.
• Although the data was not statistically significant, we believe that improving OS from 0.97 years to 1.89 years is clinically significant.
• Molecular defined “Basket Trials” assessing whether targeted treatments approved in other cancers can be effective in brain tumors with a similar genetic profile may open the door to many treatment options for glioma patients.
References


