Doxorubicin Response to Temozolomide-resistant Brain Cancer Glioblastoma Cells

Amy Hui 1, Om Prakash 2
Washington and Lee University, Lexington, VA 1, Stanley S. Scott Cancer Center, LSUHSC, New Orleans, LA 2

Background & Significance

- Glioblastoma Multiforme (GBM) is the most aggressive primary neoplasm of the CNS, accounting for approximately 60% of all primary brain tumors with 12,500 newly diagnosed cases in the US annually.
- Standard of care includes surgery, radiotherapy, and temozolomide (TMZ) chemotherapy.
- Drug resistance against TMZ occurs because of the unmethylation of MGMT, a DNA repair enzyme.
- Methylation of the MGMT promoter region of the DNA repair enzyme by TMZ inactivates the enzyme resulting in survival benefit of GBM patients (Fig. 1).

Rationale

- Doxorubicin is a highly effective therapeutic agent for the treatment of many malignant tumors.
- Several different formulations of doxorubicin have been developed, but lack of penetration through the blood brain barrier (BBB) limits their use in the treatment of brain tumors.
- Dr. Prakash and his colleagues have shown potent anti-GBM activity of a novel drug – aldoxorubicin, which is an albumin binding doxorubicin (Neoplasia 2014; 16:874).
- This provided strong rationale for evaluating this drug as a treatment for patients with GBM.

Hypothesis

TMZ and doxorubicin induce DNA damage by different mechanisms. Thus, it is our hypothesis that TMZ-resistant GBM cells will remain sensitive to the cytotoxic effects of doxorubicin.

Results

Table 1: Genetic characteristics of different cell lines

<table>
<thead>
<tr>
<th>Xenograft or cell line</th>
<th>U87*</th>
<th>T98*</th>
<th>GBM12-Arg**</th>
<th>GBM12TMZ**</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMZ resistant</td>
<td>MGMT methylated</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>TMZ sensitive</td>
<td>MGMT unmethylated</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Mouse survival (days)*

<table>
<thead>
<tr>
<th>Xenograft or cell line</th>
<th>U87*</th>
<th>T98*</th>
<th>GBM12-Arg**</th>
<th>GBM12TMZ**</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMZ resistant</td>
<td>68</td>
<td>43</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>TMZ sensitive</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>


Conclusions & Translational Relevance

Our preliminary study suggests that doxorubicin can be an effective cytotoxic agent in TMZ resistant GBM cells and provides a strong rationale for evaluating the efficacy of aldoxorubicin, the albumin-binding doxorubicin (Fig. 2) in preclinical TMZ-resistant GBM tumor cells and in clinical studies in patients with recurrent GBM.

Acknowledgements

We thank Adriana Zapata, Matthew Dean, and Drs. Adam Lassak and Krzysztof Reiss for their guidance and assistance in laboratory procedures. We also thank Dr. John Estrada, Director of the Short Term Research Experiences in Cancer.