Glioblastoma: Adjuvant Treatment

Abdulrazag Ajlan, MD, MSc, FRCSC, UCNS(D)

*Neurosurgery Consultant, King Saud University, Riyadh, KSA

*Adjunct Teaching Faculty, Neurosurgery, Stanford School Of Medicine, Palo Alto CA, USA
88 years ago

→Surgical inspection, Dandy could not find all the neoplasm to be "extirpated"
Infiltration of high-grade astrocytoma into adjacent brain tissue
Preoperative situation

Infiltration of high-grade astrocytoma [adapted from Wilson 1990];.
<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrocytic tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subependymal giant cell</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>astrocytoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilomyxoid astrocytoma</td>
<td></td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell glioblastoma</td>
<td></td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Gliosarcoma</td>
<td></td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oligodendroglial tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oligoastrocytic tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**NCCN Guidelines Version 1.2015**

**Anaplastic Gliomas\(^a\)/Glioblastoma**

---

**GLIOBLASTOMA PATHOLOGY**

- **Age \(\leq 70\) y**
  - Good performance status (KPS \(\geq 60\))
  - Poor performance status (KPS <60)

  *Glioblastoma\(^i\) ± carmustine (BCNU) wafer\(^m\)*

- **Age >70 y**
  - Good performance status (KPS \(\geq 60\))

  - Poor performance status (KPS <60)

**ADJUVANT TREATMENT**

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good performance status (KPS (\geq 60))</td>
<td>Standard or hypofractionated focal brain RT(^i) or Temozolomide(^p) or Palliative/Best supportive care</td>
</tr>
<tr>
<td>Poor performance status (KPS &lt;60)</td>
<td>Hypofractionated focal brain RT alone(^i) (category 1) or Standard focal brain RT(^i) + concurrent and adjuvant temozolomide or Hypofractionated focal brain RT(^i) + concurrent and adjuvant temozolomide or Temozolomide(^p)</td>
</tr>
</tbody>
</table>

**FOLLOW-UP**

- MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently

**See Recurrence (GLIO-4)**
Anaplastic Gliomas®/Glioblastoma

**RECURRENCE**

- **Diffuse or multiple**
  - Recurrent disease for:
    - Anaplastic oligodendroglioma
    - Anaplastic oligoastrocytoma
    - Anaplastic astrocytoma
    - Anaplastic gliomas
    - Glioblastoma

- **Local**
  - Resectable
    - Resection + carmustine (BCNU) wafer
    - Resection without carmustine (BCNU) wafer
  - Unresectable

**TREATMENT**

- Palliative/Best supportive care if poor performance status
- Systemic chemotherapy
- Surgery for symptomatic, large lesion
- Consider alternating electric field therapy for glioblastoma (category 2B)

- Palliative/Best supportive care if poor performance status
- Systemic chemotherapy
- Consider reirradiation (category 2B)
- Consider alternating electric field therapy for glioblastoma (category 2B)

See NCCN Guidelines For Palliative Care
Radiation Improves Survival!

• 1978 (AA)

Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

A cooperative clinical trial


The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland

➔ Median OS improved from 14 weeks to 35 weeks with radiation

OS was 13.9 months for the BCNU wafer group and 11.6 months for the placebo wafer group.
FDA: Wafer is indicated for the treatment of patients with:
- newly-diagnosed high-grade malignant glioma as an adjunct to surgery and radiation
- recurrent glioblastoma multiforme as an adjunct to surgery
2005: STUPP is the new Standard of Care

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma


Table 3. Overall and Progression-free Survival According to Treatment Group.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiotherapy (N=286)</th>
<th>Radiotherapy plus Temozolomide (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>value (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Median overall survival (mo)</td>
<td>12.1 (11.2–13.0)</td>
<td>14.6 (13.2–16.8)</td>
</tr>
<tr>
<td>Overall survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>84.2 (80.0–88.5)</td>
<td>86.3 (82.3–90.3)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>50.6 (44.7–56.4)</td>
<td>61.1 (55.4–66.7)</td>
</tr>
<tr>
<td>At 18 months</td>
<td>20.9 (16.2–26.6)</td>
<td>39.4 (33.8–45.1)</td>
</tr>
<tr>
<td>At 24 months</td>
<td>10.4 (6.8–14.1)</td>
<td>26.5 (21.2–31.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Deaths/patients</th>
<th>Median (months; 95% CI)</th>
<th>2 years (%)</th>
<th>5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>278/286</td>
<td>12.1 (11.2–13.0)</td>
<td>10.9 (7.6–14.8)</td>
<td>1.9 (0.6–4.4)</td>
</tr>
<tr>
<td>Combined</td>
<td>254/287</td>
<td>14.6 (13.2–16.8)</td>
<td>27.2 (22.2–32.5)</td>
<td>9.8 (6.4–14.0)</td>
</tr>
</tbody>
</table>

Once a diagnosis of high grade glioma is made, the treatment is the same regardless of the surgical intervention.

- Concomitant TMZ/RT
- Adjuvant TMZ

Weeks

- TMZ 75 mg/m² orally once a day for 6 weeks, then 150 to 200 mg/m², day 1 to 5 every 28 days for 6 cycles
- Focal RT daily, 30 cycles (2 Gy/cycle)
- Total dose 60 Gy

RT, radiotherapy
TMZ, Tamadol
Temozolomide

- Readily crosses the BBB with relatively high concentrations.
- Is nearly 100% bioavailable after oral dosing.
- Does not require hepatic metabolism for activation.
- Exhibits dose-linear pharmacokinetics with little variability.
- Is associated with generally mild and predictable toxicity.
Bevacizumab

- **Bevacizumab (Avastin)** → angiogenesis inhibitor

Recombinant humanized monoclonal antibody vascular endothelial growth factor (VEGF)

On May 5, 2009, the FDA granted accelerated approval to bevacizumab injection as a single agent for patients with glioblastoma, with progressive disease. The approval was based on demonstration of durable objective response rates observed in two single-arm trials.

http://www.avastin-hcp.com/about-avastin/proposed-moa
OS was 15.7 months in the bevacizumab group and 16.1 months in the placebo group (P=0.21)

OS was 16.8 months in the bevacizumab group and 16.7 months in the placebo group (P=0.10)
http://www.zdnet.com/article/novocures-electric-cap-for-brain-cancer-now-fda-approved/
Tumor Treating Fields, or TTFields, are low intensity, alternating electric fields within the intermediate frequency range.

→ TTFields disrupt cell division
A large, multinational, open-label, randomized Phase 3 trial comparing Optune in combination with temozolomide to temozolomide alone in 700 patients with newly diagnosed GBM

Median progression-free survival in the intent-to-treat population was 7.1 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide alone group (P = .001)

Median overall survival in the per-protocol population was 20.5 months in the TTFields plus temozolomide group and 15.6 months in the temozolomide alone (P = .004)
Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population

A Progression-free survival

HR, 0.62 (98.7% CI, 0.43–0.89); log-rank P = .001

B Overall survival

HR, 0.74 (95% CI, 0.56–0.98); log-rank P = .03

No. at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTFFields plus temozolomide</td>
<td>210</td>
<td>195</td>
<td>147</td>
<td>94</td>
<td>65</td>
<td>43</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide alone</td>
<td>105</td>
<td>86</td>
<td>68</td>
<td>42</td>
<td>23</td>
<td>14</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Survival analyses on time from date of randomization until tumor progression, death, or last follow-up (censored patients) according to the Kaplan-Meier method. The small vertical ticks on the curves indicate censored patients. HR indicates hazard ratio; TTFFields, tumor-treating fields.
Indications for Use Optune:

- For the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy

- Indicated following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy

- Optune is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy
NCCN Guidelines Version 1.2015
Anaplastic Gliomas\(^a\)/Glioblastoma

**GLIOBLASTOMA PATHOLOGY**

- **Age ≤70 y**
  - Good performance status (KPS ≥60)
    - Hypofractionated focal brain RT\(^i\)
      + concurrent and adjuvant temozolomide (category 1)\(^i,\text{n,}\text{o}\)
      - Standard or hypofractionated focal brain RT\(^i\)
      - Temozolomide\(^d\)
      - Palliative/Best supportive care
  - Poor performance status (KPS <60)
    - Hypofractionated focal brain RT alone\(^i\) (category 1)
      - Standard focal brain RT\(^i\) + concurrent and adjuvant temozolomide
      - Hypofractionated focal brain RT\(^i\)
      + concurrent and adjuvant temozolomide
      - Temozolomide\(^d\)

- **Glioblastoma\(^i\) ± carmustine (BCNU) wafer\(^m\)**
  - Good performance status (KPS ≥60)
  - Poor performance status (KPS <60)

- **Age >70 y**
  - Hypofractionated focal brain RT\(^i\)
    - Temozolomide\(^d\)
    - Palliative/Best supportive care

**FOLLOW-UP\(^b\)**

- MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently
- See Recurrence (GLIO-4)
Glioblastoma

• Adjuvant Treatment:
  ‣ Concurrent (with RT) temozolomide\(^{13}\) 75 mg/m\(^2\) daily
  ‣ Post RT temozolomide\(^{13}\) 150–200 mg/m\(^2\) 5/28 schedule
  ‣ Temozolomide\(^{13,31}\) 150–200 mg/m\(^2\) 5/28 schedule

• Recurrence Therapy
  ‣ Bevacizumab\(^{†, 32-35}\)
  ‣ Bevacizumab + chemotherapy\(^{††}\)
    (irinotecan,\(^{33-35}\) carmustine/lomustine,\(^{22}\) temozolomide, carboplatin
    [category 2B for carboplatin]\(^{23,24}\))
  ‣ Temozolomide\(^{5,13,36}\)
  ‣ Lomustine or carmustine\(^{16}\)
  ‣ Combination PCV
  ‣ Cyclophosphamide (category 2B)\(^{27}\)
  ‣ Platinum-based regimens\(^{α}\)
2016

Vaccines
Immunotherapy
Antiviral treatment
Gene therapy
Ketogenic Diet
Traditional medicine
Alternative medicine
Cannabinoid
Spiritual Medicine

MGMT

*p15, ATRX, P53*

The TCGA study (pathways)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td><strong>Phase I Study of a Dendritic Cell Vaccine for Patients With Either Newly Diagnosed or Recurrent Glioblastoma</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Conditions:</strong> Glioblastoma; Glioblastoma Multiforme; Glioma; Astrocytoma; Brain Tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Interventions:</strong> Biological: Dendritic cell vaccination, in addition to standard temozolomide chemotherapy and involved field radiation therapy; Biological: Dendritic cell vaccination, with optional bevacizumab treatment for patients previously treated with bevacizumab</td>
</tr>
</tbody>
</table>
Conclusion
Thank you!