Multidisciplinary treatment for glioblastoma

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Epidemiology of glioblastoma

- Most common primary brain tumour of adults
- Incidence: 4-5/100,000/year
- Twice as common in European descendants as compared to African American or Asian descendants
- Median age at diagnosis
  - Primary glioblastoma: 64 years
  - Secondary glioblastoma: 45 years
- Male to female ratio = 1.3:1
Relative frequencies of gliomas

Roman numerals denote World Health Organisation (WHO) tumour grades.

Risk factors of glioblastoma

- Cranial irradiation
- Hereditary tumour syndromes (<5% of glioblastomas)
  - Li Fraumeni syndrome (TP53 mutations)
  - Turcot syndrome (APC, MLH1, MSH2, MSH6, MPS2 mutations)
  - Neurofibromatosis 1 (Neurofibromin mutations)
  - Neurofibromatosis 2 (Merlin mutations)
- No clear evidence for occupational factors or cell phone as risk factor
Clinical presentation

- Most cases (>90%) develop *de novo* with short clinical history of days to few months (primary glioblastoma)
- Few cases (<10%) develop from lower grade gliomas (secondary glioblastomas), typically clinical history of years
- Clinical presentation is highly variable, depends on tumour localisation and size
  - Focal neurological signs (aphasia, paraesthesia, hemiparesis, visual disturbances, etc.)
  - Mood and personality changes
  - Seizures
  - Symptoms of increased intracranial pressure (nausea, vomiting, headache)
Magnetic resonance imaging (MRI)

Axial postcontrast T1-weighted MRI

Axial T2-weighted MRI

Pseudoprogression

Before surgery

After radio-chemotherapy

After re-surgery, which showed only necrotic tissue without tumour

After surgery
Pseudoresponse

Before Vascular Endothelial Growth Factor (VEGF) inhibitor

One day after VEGF inhibitor

Histopathology: Diagnostic features

Prognostic factors

- Patient age
  - Young age favourable

- Karnofsky performance status
  - High Karnofsky index favourable

- Extent of resection
  - Gross total resection more favourable than partial resection or biopsy

- Molecular information, especially O6-methylguanine-methyltransferase gene (MGMT) promoter methylation status and isocitrate dehydrogenase gene (IDH) mutation status
  - MGMT promoter hypermethylation favourable
  - Presence of IDH mutation favourable
Maximal safe resection is the initial therapy of choice. It may rapidly improve symptoms. Due to infiltrative growth, residual tumour cells persist even after macroscopically complete resection. Tumour localisation in sensible CNS parts (e.g., eloquent cortex) may allow only partial debulking or biopsy. Modern neurosurgery involves multimodal planning of the procedure by advanced neuroimaging.
Fluorescence-guided neurosurgery

Reprinted from The Lancet Oncol, 7.5, Stummer W et al., Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial, 392–401, Copyright (2006), with permission from Elsevier
Combined radiochemotherapy

Treatment schedule

Abbreviations: AED anti-epileptic drugs, PcP pneumocystis carinii, TMZ, temozolomide, RT radiotherapy, LMWH low molecular weight heparin

Radiotherapy

(A) Target delineation showing a glioblastoma in the left parietal lobe with the gross target volume outlined in blue, the clinical target volume covering a 2cm margin of possible microscopic spread in green, and the planning target volume (PTV) with a 0.5cm margin to account for day to day setup variability in red. (B) Radiotherapy plan showing the same patient’s plan using 3 fields, with the high dose in orange conforming to the shape of the PTV. The blue color represents the volume of brain receiving 50% of the prescribed dose.

## Selected randomised phase III trials for newly diagnosed glioblastoma

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Trial arms</th>
<th>Trial results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 26981</td>
<td>Temozolomide-radiation vs. radiation</td>
<td>Temozolomide-radiation with improved OS, PFS and 2-years survival rate</td>
</tr>
<tr>
<td>RTOG 0525</td>
<td>Dose dense vs. standard temozolomide</td>
<td>No improvement in OS or PFS with dose dense temozolomide</td>
</tr>
<tr>
<td>RTOG 0825</td>
<td>Standard chemoradiation + bevacizumab vs. standard chemoradiation</td>
<td>No improvement in OS, PFS prolonged, but insignificantly increased; symptom burden, worse quality of life, and a decline in neurocognitive function were more frequent in the bevacizumab group</td>
</tr>
<tr>
<td>AvaGLIO</td>
<td>Standard chemoradiation + bevacizumab vs. standard chemoradiation</td>
<td>No improvement in OS, PFS prolonged; QoL maintained longer with bevacizumab</td>
</tr>
<tr>
<td>CENTRIC</td>
<td>Standard chemoradiation + cilengitide vs. standard chemoradiation</td>
<td>No improvement in OS or PFS</td>
</tr>
</tbody>
</table>

Newly diagnosed glioblastoma in elderly patients (>65 years)

Reprinted from The Lancet Oncol, 13.7, Wick W et al., Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial, 707-715, Copyright (2012), with permission from Elsevier
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class of evidence</th>
<th>Level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of care for glioblastoma (age &lt;65–70 years) includes resection as</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>feasible or biopsy, followed by involved-field radiotherapy and concomitant and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjuvant temozolomide chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly patients who are not candidates for combined radiochemotherapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>should be treated with radiotherapy alone or temozolomide alone based on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGMT promoter methylation status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Weller M et al., Lancet Oncol. 2014;15(9):e395-403
Treatment options for recurrent glioblastoma

- Neurosurgery
- Radiotherapy
- Systemic therapy
  - Nitrosoureas
  - Temozolomide
  - Bevacizumab
  - Other
- Tumour treating fields (Novo TTF device)
- Clinical trial
## Targeted therapies for recurrent glioblastoma

### Single-agent targeted therapies for recurrent glioblastoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Trial phase</th>
<th>Number of patients</th>
<th>6-month PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (50)</td>
<td>PDGFR, c-kit, and c-ABL</td>
<td>II</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td>Gefitinib (51,52)</td>
<td>EGFR</td>
<td>II</td>
<td>53 and 28</td>
<td>13 and 14</td>
</tr>
<tr>
<td>Erlotinib (53, 54)</td>
<td>EGFR</td>
<td>II</td>
<td>110 and 38</td>
<td>11 and 3</td>
</tr>
<tr>
<td>Pazopanib (55)</td>
<td>VEGFR and PDGFR</td>
<td>II</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Tipifarnib (56)</td>
<td>Farnesyltransferase</td>
<td>II</td>
<td>67</td>
<td>12</td>
</tr>
<tr>
<td>Temsirolimus (57)</td>
<td>mTOR</td>
<td>II</td>
<td>65 and 41</td>
<td>8 and 3</td>
</tr>
<tr>
<td>Cediranib (58,59)</td>
<td>VEGFR</td>
<td>II and III</td>
<td>31 and 131</td>
<td>26 and 16</td>
</tr>
<tr>
<td>Bevacizumab (60,61)</td>
<td>VEGF-A</td>
<td>II</td>
<td>85 and 48</td>
<td>36 and 29</td>
</tr>
<tr>
<td>Aflibercept (62)</td>
<td>VEGF-A</td>
<td>II</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Cilengitide (63,64)</td>
<td>αβ3,αβ5 integrins</td>
<td>II</td>
<td>81 and 26</td>
<td>15 and 12</td>
</tr>
<tr>
<td>Vorinostat (65)</td>
<td>HDAC</td>
<td>II</td>
<td>66</td>
<td>15</td>
</tr>
<tr>
<td>Enzastaurin (66,67)</td>
<td>PKC</td>
<td>II and III</td>
<td>72 and 174</td>
<td>7 and 11</td>
</tr>
<tr>
<td>Cabozantinib (68)</td>
<td>EGFR AND C-MET</td>
<td>II</td>
<td>124</td>
<td>21</td>
</tr>
</tbody>
</table>

Anti-oedema therapy

- Results from leakage of plasma into the tissue through disrupted BBB
- Detectable of T2-weighted and FLAIR MRI images
- Increased intracranial pressure with headache, vertigo, nausea/vomiting
- May lead to life-threatening brainstem compression and herniation
- Drug of choice: Dexamethasone
  - Initial daily dose usually 12-16 mg
  - Steroid dose should be rapidly reduced and tapered to individual need ("as much as needed, as little as possible")
- Dexamethasone may be combined with osmotic agents such as mannitol or glycerol
- Obstructive hydrocephalus may be treated with CSF shunt
- Bevacizumab may reduce brain oedema and is associated with decreased corticosteroid need
# Anticonvulsive therapy

## Overview of antiepileptic drugs commonly used in glioblastoma patients

<table>
<thead>
<tr>
<th>EIAED/Non-EIAED</th>
<th>Drug</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EIAED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>Sedation, rash, impaired cognitive function</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Gingival hypertrophy, hirsutism, hepatotoxicity, rash, lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Drowsiness, dizziness, diplopia, rash, leukopaenia, hyponatraemia, hepatotoxicity, nausea/vomiting, cardiac arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Oxacarbazepine</td>
<td>Drowsiness, dizziness, diplopia, rash, hyponatraemia, hepatotoxicity, nausea/vomiting</td>
</tr>
<tr>
<td><strong>Non-EIAED</strong></td>
<td>Valproic acid</td>
<td>Weight gain, nausea/vomiting, hair loss, thrombocytopenia, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>Somnolence, dizziness, agitation/anxiety, ataxia</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td>Somnolence, dizziness, rash, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
<td>Drowsiness, fatigue, agitation/anxiety, headache</td>
</tr>
<tr>
<td></td>
<td>Pregabalin</td>
<td>Somnolence, dizziness, weight gain, ataxia</td>
</tr>
</tbody>
</table>

EIAED = enzyme-inducing antiepileptic drug
Outlook: Selected ongoing trials

- Newly diagnosed glioblastoma
  - Tumour treating fields (EF-21 trial)
  - EGFRvIII vaccine rindopepimut (ACT-IV trial)

- Recurrent glioblastoma
  - Bevacizumab (EORTC 26101 trial)
  - Immune-checkpoint inhibitors, e.g. nivolumab/ipilimumab (Checkmate 143 trial)
Summary

- Glioblastoma is the most common primary brain tumour of adults
- High morbidity and mortality, median OS 14-17 months
- Standard first line therapy: maximal safe resection and combined radiochemotherapy with temozolomide
- In elderly patients not qualifying for combined treatment stratification by MGMT promoter methylation status into radiotherapy (MGMT unmethylated or unknown) versus temozolomide (MGMT methylated)
- No accepted treatment standard for recurrent glioblastoma
- Supportive therapy with anti-oedema and anticonvulsive therapy of importance in most patients
- Ongoing trials evaluating tumour-treating fields and vaccination strategies for newly diagnosed glioblastoma and bevacizumab and immune checkpoint inhibitors for recurrent glioblastoma
Thank you!