MULTIDISCIPLINARY TREATMENT OF GLIOBLASTOMA

Univ.-Prof. Dr. Matthias Preusser
Division of Oncology, Medical University of Vienna, Austria
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 use as risk factor
Most cases (>90%) develop de novo with a short clinical history of days to a few months (primary glioblastoma).

Few cases (<10%) develop from lower grade gliomas (secondary glioblastomas), typically with a 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 post contrast T1-weighted MRI

Axial T2-weighted MRI
Neuropathology of glioblastoma

(A) Histopathology of a typical case of glioblastoma showing cellular glial tumour tissue with central necrosis (x) with perinecrotic nuclear pseudopalisading and microvascular proliferates (arrows; hematoxylin and eosin staining; original magnification, 3100)

(B) Immunostaining for the astroglial marker glial fibrillary acidic protein shows strong labeling of the tumour cells (brown signal; original magnification, 3400)

(C) Immunostaining for the endothelial marker CD34 shows glomeruloid microvascular proliferates (original magnification, 3200)

(D) Immunostaining for the cell-cycle–related antigen Ki67 shows that many tumour cells undergo mitosis (brown signal; original magnification, 3400)
Histology

- Astrocytoma
- Oligoastrocytoma
- Oligodendroglioma
- Glioblastoma

IDH status

- IDH mutant
- IDH wild-type

1p/19q and other genetic parameters

- ATRX loss
- TP53 mutation
- 1p/19q codeletion

Diffuse astrocytoma, IDH mutant

Oligodendroglioma, IDH mutant and 1p/19q codeleted

After exclusion of other entities:
Diffuse astrocytoma, IDH wild-type
Oligodendroglioma, NOS

Glioblastoma, IDH mutant

Glioblastoma, IDH wild-type

Genetic testing not done or inconclusive

Diffuse astrocytoma, NOS
Oligodendroglioma, NOS
Oligoastrocytoma, NOS

*Characteristic but not required for diagnosis.

TOP 20 MUTATED GENES IN GLIOBLASTOMA BASED ON 712 SAMPLES OF ASTROCYTOMA GRADE IV

<table>
<thead>
<tr>
<th>Gene name (frequency)</th>
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<tbody>
<tr>
<td>TP53 (22%)</td>
<td></td>
</tr>
<tr>
<td>EGFR (14%)</td>
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<tr>
<td>PTEN (12%)</td>
<td></td>
</tr>
<tr>
<td>CHEK2 (10%)</td>
<td></td>
</tr>
<tr>
<td>H3F3A (6%)</td>
<td></td>
</tr>
<tr>
<td>PIK3CA (6%)</td>
<td></td>
</tr>
<tr>
<td>RB1 (6%)</td>
<td></td>
</tr>
<tr>
<td>NF1 (5%)</td>
<td></td>
</tr>
<tr>
<td>PIK3R1 (4%)</td>
<td></td>
</tr>
<tr>
<td>HIF1A (4%)</td>
<td></td>
</tr>
<tr>
<td>ATRX (4%)</td>
<td></td>
</tr>
<tr>
<td>IDH1 (4%)</td>
<td></td>
</tr>
<tr>
<td>PDGFRA (3%)</td>
<td></td>
</tr>
<tr>
<td>KMT2C (3%)</td>
<td></td>
</tr>
<tr>
<td>BCOR (2%)</td>
<td></td>
</tr>
<tr>
<td>BRCA1 (2%)</td>
<td></td>
</tr>
<tr>
<td>ACVR1 (2%)</td>
<td></td>
</tr>
<tr>
<td>BRAF (2%)</td>
<td></td>
</tr>
<tr>
<td>STAG2 (2%)</td>
<td></td>
</tr>
<tr>
<td>ROS1 (2%)</td>
<td></td>
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</table>

Nørøxe DS, et al. ESMO Open 2016;1:e000144. Copyright © European Society for Medical Oncology. All rights reserved.
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
NEWLY DIAGNOSED GLIOBLASTOMA

Therapy
Maximal safe resection is the initial therapy of choice

May rapidly improve symptoms

Due to infiltrative growth residual tumour cells persist even after macroscopically complete resection

Tumour localisation in functionally important CNS regions (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

INTRAOP VISUALISATION OF GBM WITH 5-ALA FLUORESCENCE

Courtesy of Prof. Georg Widhalm, Department of Neurosurgery, Medical University of Vienna
INTRAOP VISUALISATION OF GBM WITH 5-ALA FLUORESCENCE

PreOP MRI
GBM temporal

Fluorescence-guided resection with 5-ALA

PostOP MRI
Complete resection

Courtesy of Prof. Georg Widhalm, Department of Neurosurgery, Medical University of Vienna
COMBINED CHEMORADIATION

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 2 cm margin of possible microscopic spread in green, and the planning target volume (PTV) with a 0.5 cm 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 colour represents the volume of brain receiving 50% of the prescribed dose.
TREATMENT SCHEDULE FOR PATIENTS WITH FAVOURABLE PROGNOSTIC FACTORS

Age <70 years, KPS >70: “Stupp protocol”

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

LOMUSTINE-TEMOZOLOMIDE COMBINED WITH 60GY/30 FRACTION RADIATION THERAPY

In patients with newly diagnosed glioblastoma with methylated MGMT promoter

Caveat: non-definitive data due to limited statistical power

TUMOUR-TREATING FIELDS (TTF) THERAPY IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA


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Overall survival

Median survival from randomization:

- **20.9 months** for TTF plus temozolomide (n=466) vs. **16.0 months** for temozolomide-alone (n=229) (HR, 0.63; 95% CI: 0.53, 0.76; p<0.001)

- Median follow-up: 44 months (range 25–91 months) in both groups.

Caveat: role of TTF in standard treatment unclear due to controversies around trial design and interpretation

TTF device is applied after completion of concomitant chemo-radiation
REDUCED CHEMORADIATION REGIMEN
In elderly patients (age >65) with newly diagnosed glioblastoma

Overall survival

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy + temozolomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy + temozolomide</td>
<td>281</td>
<td>217</td>
<td>129</td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>281</td>
<td>196</td>
<td>100</td>
</tr>
</tbody>
</table>

Median Overall Survival

- Radiotherapy + Temozolomide: 9.3 (8.3–10.3)
- Radiotherapy Alone: 7.6 (7.0–8.4)

Hazard ratio for death:
- 0.67 (95% CI, 0.56–0.80)
- P<0.001

RADIOTherapy VersUS CHEMOTHERAPy
STRATIFICATION BY MGMT STATUS

In elderly patients (age >60) with newly diagnosed glioblastoma

TREATMENT SCHEDULE FOR PATIENTS WITH FAVOURABLE PROGNOSTIC FACTORS
Age <70 years, KPS >70

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

Before surgery

After surgery

After radio-chemotherapy

After re-surgery, which showed only necrotic tissue without tumour
TREATMENT OPTIONS FOR RECURRENT GLIOBLASTOMA

Neurosurgery

Radiotherapy

Systemic therapy
  - Nitrosoureas
  - Temozolomide
  - Bevacizumab (according to approval status per country)
  - Other

Clinical trial
Before Vascular Endothelial Growth Factor (VEGF) inhibitor

One day after VEGF inhibitor

TREATMENT
Supportive care
ANTI-OEDEMA THERAPY

Results from leakage of plasma into the tissue through disrupted BBB
Detectable on 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>EIAED</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>Non-EIAED</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>
OUTLOOK: SELECTED ONGOING TRIALS

Proteasome-inhibitor marizomib

CDK-inhibitor TG02

Targeted treatment based on molecular profiling (e.g. tumour mutational burden, BRAF mutations, NTRK fusions, FGFR fusions, MET amplifications/fusions)
**THERAPEUTIC APPROACH TO GLIOBLASTOMA**

*Additional treatment with tumour-treating fields (TTFs) may be offered to eligible patients. Depending on availability and approval status.*

GTR, gross total resection; IDH, isocitrate dehydrogenase; KPS, Karnofsky performance score; MGMT, O6-methylguanine DNA methyltransferase; RT, radiation therapy; TMZ, temozolomide.

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TREATMENT SCHEDULE FOR PATIENTS WITH FAVOURABLE PROGNOSTIC FACTORS
Age <70 years, KPS ≥70

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

Glioblastoma is the most common primary brain tumour of adults

High morbidity and mortality

Standard first line therapy: maximal safe resection and combined chemoradiation with temozolomide

To be considered in elderly patients: reduced chemoradiation or stratification by MGMT promoter methylation status into radiotherapy (MGMT unmethylated or unknown) versus temozolomide (MGMT methylated)

Recurrent glioblastoma commonly treated with CCNU (lomustine)

Supportive therapy with anti-oedema and anticonvulsive therapy of importance in most patients

Trials for newly diagnosed and recurrent glioblastoma ongoing
THANK YOU!