Concurrent Chemoradiotherapy in CNS tumors – Guidelines and Evidence

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Distribution of primary CNS Tumors by Histology

- Glioblastoma 20.3%
- Meningioma 30.1%
- Pituitary 6.3%
- Embryonal, including medulloblastoma 1.7%
- Ependymomas 2.3%
- Oligodendrogliomas 3.7%
- Astrocytomas 9.8%
- Craniopharyngioma 0.7%
- Nerve sheath 8.0%
- Lymphoma 3.1%
- All others 13.9%

Prognostic Classification

- WHO classification system
  - Released in 1993; updated in 2007
  - Tumors classified by cell origin and level of aggression (grades 1-4)\(^{[1,2]}\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histology</th>
<th>Median Survival, Yrs(^{[2]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pilocytic astrocytoma</td>
<td>&gt;10</td>
</tr>
<tr>
<td>2</td>
<td>Well-differentiated astrocytoma</td>
<td>&gt;5</td>
</tr>
<tr>
<td>3</td>
<td>Anaplastic astrocytoma</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Glioblastoma multiforme</td>
<td>1</td>
</tr>
</tbody>
</table>

Treatment Modalities

- Surgery
- Radiotherapy
- Chemotherapy
Challenges to treatment

- Biologically aggressive
- Drug delivery
  - Blood brain barrier
- Toxicity to normal brain
- Infiltration of malignant cells into brain parenchyma
A bit of history..

- Surgery and radiation mainstays of treatment (and still are)
- Chemotherapy options
  - PCV standard of care for many years
    - Procarbazine
    - Carmustine (BCNU)
    - Vincristine
      - Significant side effects
  - Single agent nitrosurea (lomustine/carmustine) equivalent
Types of Surgery

- Complete Resection
- Near Total Resection
- Subtotal Resection
- Debulking
- Biopsy only
- No Biopsy
Radiotherapy:

- Curative (PORT): Low grade, High grade Gliomas, Ependymomas
- Paediatric tumors: Medulloblastoma
- SRT & SRS
- Intracranial Brachytherapy
- Palliative Radiotherapy
Conventional orthogonal plain film planning
Conformal Radiotherapy

Excellent conformation
Stereotactic Radiation

- Radiosurgery
- SRT
- Stereotactic IMRT
Proton Beam Therapy: The ultimate in conformal therapy (St Clair, IJROBP '04)

Conventional Bilateral Photons

Dose to Cochlea, Pituitary Hypoth. axis etc significantly less with Protons

IMRT Photons

3 Field PROTONS
Boron Neutron Capture Theory

The Boron Neutron Capture Therapy (BNCT) consists of the injection of boron compounds into the human body, collecting them in tumor cells and then irradiating them with thermal neutrons in order to destroy these cells.
Timing of chemotherapy

- **Adjuvant**
  - After surgery or radiation
  - Defined number of cycles
  - Aim
    - prolong time to recurrence

- **Recurrence**
  - Number of cycles limited by side effects
  - Aim
    - improve symptoms, quality of life and slow progression
Temozolomide (TMZ)

- Oral administration
- Excellent concentration in CNS
- Encouraging antitumour activity
- Favourable toxicity profile
- Synergism with radiotherapy and other agents
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D.,
Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D.,
Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D.,
Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D.,
Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D.,
Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D.,
and René O. Mirimanoff, M.D., for the European Organisation for Research
and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National
Cancer Institute of Canada Clinical Trials Group*
Stupp Treatment Schema

Concomitant → Adjuvant TMZ

**TMZ/RT***

- Temozolomide 75 mg/m² po qd for 6 weeks,
  then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles
- **Focal RT** daily — 30 x 200 cGy
  Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.
Significant improvement in survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>RT</th>
<th>RT + TMZ</th>
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</thead>
<tbody>
<tr>
<td>Median, mos</td>
<td>12.1</td>
<td>14.6</td>
</tr>
<tr>
<td>2 yr, %</td>
<td>10.9</td>
<td>27.2</td>
</tr>
<tr>
<td>3 yr, %</td>
<td>4.4</td>
<td>16.0</td>
</tr>
<tr>
<td>4 yr, %</td>
<td>3.0</td>
<td>12.1%</td>
</tr>
<tr>
<td>5 yr, %</td>
<td>1.9</td>
<td>9.8</td>
</tr>
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Stupp et al. Lancet Oncology 2009
Temozolomide + RT in newly diagnosed GBM

NEW STANDARD OF CARE

Throughout the world
Food and Drug Administration Drug approval summary: temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme.
MGMT gene silencing and benefit from temozolomide in glioblastoma.

CONCLUSIONS:
Patients with glioblastoma containing a methylated MGMT promoter benefited from temozolomide, whereas those who did not have a methylated MGMT promoter did not have such a benefit.
MGMT (Methylguanine DNA methyltransferase) and TMZ Resistance

- 573 specimens
- 307 Methylation specific PCR.
- 206/307 paraffin blocks could be studied adequately.
- Studied in two groups as original design of EORTC and NCIC study (Stuup et al)

Hegi et al NEJM, 2005
✓ **Dose-dense regimen** of temozolomide given **every other week** in patients with **recurrent central nervous system tumors**
RECOMMENDED DOSE:

- On days 1–3 and 14–16 every 28 days (ONE CYCLE).

- The starting daily dose was 200 mg/m2 with subsequent increments of 50 mg/m2 until unacceptable toxicity was reached.

CONCLUSION:

- TMZ can be given safely using a dose-dense regimen of 300 mg/m2/day for 3 consecutive days every 2 weeks in patients with recurrent brain tumors.
Phase II study of two-weekly temozolomide in patients with high-grade gliomas

✓ Overall, two-weekly temozolomide is an active & well tolerated schedule, but does not appear to improve on the activity of temozolomide using the standard 5-day schedule.
Alternative schedules of adjuvant temozolomide in glioblastoma multiforme: A 6-year experience.

Conclusions:

Continuous daily dose of 75 mg/m2 was more advantageous than a standard monthly or a biweekly regimen, as it resulted in the highest OS with the lowest hematologic toxicity.
Efficacy and Tolerability of Temozolomide in an Alternating Weekly Regimen in Patients With Recurrent Glioma

Purpose: Evaluation of toxicity and efficacy of an alternating weekly regimen of temozolomide administered 1 week on and 1 week off in patients with recurrent glioma.
Conclusion:

- Feasible
- Safe
- Effective
- Less toxic
- Also active in patients lacking MGMT gene promoter methylation.
Temozolomide *three weeks on and one week off* as first line therapy for patients with recurrent or progressive low grade gliomas.
Conclusion:

The prolonged temozolomide schedule considered in the present study is followed by a high response rate; toxicity is acceptable.

Further randomized trials should therefore be conducted to confirm the efficacy of this regimen as first-line therapy in patients with progressive low grade glioma.
Multi-Institutional Trial of BID Regimen of Temozolomide for Recurrent Malignant Gliomas

Conclusions:

✓ BID regimen of Temozolomide is tolerated will by most patients. Response rates are promising.
MGMT Promoter Methylation Status Can Predict the Incidence and Outcome of “Pseudoprogression” After Concomitant Radiochemotherapy in Newly Diagnosed Glioblastoma Patients
GRADE II/III Tumors

✓ Anaplastic Tumors
Cancer Invest. 2007

GRADE II/III GLIOMAS

- Newly launched and planned phase III trials - overall survival in grade II/III as well as the prognostic and predictive value of 1p/19q analyses and MGMT promoter methylation status.
Role of chemotherapy

- Temozolamide in **progressive** LGG
- n= 41 (16 = 35% astrocytomas)
- newly diagnosed or previously Rx (52% resected, 22% prior chemo, 15% prior RT)
- 200mg/m²/day x 5days q28 days x 12 cs
- **70% ENHANCING** on CT / MR
- MR every 8 weeks, Macdonald’s criteria

Overall Median PFS 22 months, 12 mo PFS 73% for astrocytoma
Overall CR = 24% (31% for astrocytoma)
Overall PR = 37% (38% for astrocytoma)
Overall CR + PR = 61% (69% for astrocytoma)
Cancer Invest. 2007

- Temozolomide and radiation in low-grade and anaplastic gliomas: “TEMORADIATION”
Treatment options at recurrence

- Surgery
  - Re-resection
  - BCNU (Carmustine) wafer
- Repeat radiation
- Chemotherapy
  - Temozolomide rechallenge
  - Nitrosoureas (CCNU, BCNU)
  - Bevacizumab
  - Clinical trial
Gliadel Wafers

- Gliadel wafers at time of surgery (carmustine soaked) in completely resected high grade glioma (3 or 4)
Gliasite: MRI and Treatment Plan

Target area receives at least 100% of the prescribed dose. Typically 40-60 Gy.

Rapid dose drop-off outside the target volume due to low energy photons of I-125.

1. Dosimetry issues, clinical data not encouraging
Bevacizumab (Avastin)

- VEGF inhibitor
- Targets angiogenesis
Bevacizumab (Avastin)

- To date mainly investigated in Phase II trials
- Usually in combination with irinotecan chemotherapy
- TGA approved for use in relapsed glioma
- Not approved on PBS
  - Requires co-payment (~$20,000)
- No trials have demonstrated a survival benefit
Bevacizumab ± Irinotecan in Recurrent GBM

- Phase II study in 167 patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response %</th>
<th>6-mo PFS %</th>
<th>Survival (months)</th>
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<tbody>
<tr>
<td>Bevacizumab (n = 85)</td>
<td>28.2</td>
<td>42.6</td>
<td>9.2</td>
</tr>
<tr>
<td>Bevacizumab + Irinotecan (n = 82)</td>
<td>37.8</td>
<td>50.3</td>
<td>8.7</td>
</tr>
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Friedman HS, et al. JCO 2009
Bevacizumab adverse events

- Side effects include
  - Hypertension (9%)
  - Delayed wound healing (2%)
  - Bowel perforation (2%)
  - Intracranial haemorrhage (2%)
  - Venous and arterial clots (4%)
**Phase III Trials of Bevacizumab in newly diagnosed GBM**

### AvaGlio[1]

- Newly diagnosed GBM (planned N = 920)

- **Placebo** q2w + standard RT (60 Gy D1-5) x 6 wks + TMZ 75 mg/m² PO/day for 6 wks then 150-200 mg/m² Days 1-5 of each 6 x 4-wk cycle until progression

- **Bevacizumab** 10 mg/kg q2w + standard RT (60 Gy D1-5) x 6 wks + TMZ 75 mg/m² PO/day for 6 wks then 150-200 mg/m² Days 1-5 of each 6 x 4-wk cycle until progression

### RTOG 0825[2]

- Newly Diagnosed GBM ≥ 18 years; KPS 70% to 100%
- Standard RT + concurrent TMZ (Planned N = 942)

- **Wk 4 of chemoRT:** Bevacizumab q2w, continuing until completion of adjuvant TMZ

- **4 wks after chemoRT:** Adjuvant TMZ 200 mg/m² D1-5 Q28D for up to 12 courses + placebo

Genetic Targets in Glioblastoma

- EGFR, mutated/amplified in 45%
- HER2 mutated in 8%
- PDGFRα, amplified in 13%
- MET, amplified in 4%
- SRC
- NF1, mutated/deleted in 18%
- RAS, mutated in 2%
- PI3K, mutated in 15%
- PTEN, mutated/deleted in 36%
- AKT, amplified in 2%
- FOXO, mutated in 1%
- Proliferation, survival, translation

Primary CNS Lymphoma

< 2 - 13 (ALL)>

R

P
Primary Cerebral Lymphoma

- Primary cerebral lymphoma – HIV related
- Steroids
- Chemo (methotrexate based)+/- XRT
- Cognitive impairment
- Poor outcomes
Medulloblastoma -Chemotherapy
when & What?

- A range of alkylator and platinum based regimens available
- Adjuvant VCP=Adjuvant VLP
- Other effective regimens: VLCP, VC, VJPE, MICE
Standard-Risk: New Standard

- GTR
- Reduced dose CSI (23.4Gy)
- Adjuvant chemotherapy
High-Risk: Standard of care

- GTR
- CSI (36Gy)+PF boost 19.8Gy
- Adjuvant chemotherapy
- Chemotherapy improves survival by 15-20% c/t RT alone historical cohorts
Recurrent brain stem gliomas

- Individualise, symptomatic care/steriods
- Re-irradiation rarely ever possible/helpful
- Chemo largely ineffective
- Temozolomide, Tamoxifen, interferons, Iressa, etc – several small phase II studies - investigational

Large study material – learnt what does not work
Something very original/innovative needed
Chemotherapy

- Role unknown
- Randomised trial of RT Vs RT + adj V, CCNU & P – no benefit (*MPO* 1996;27:8-14)
- CCG trial – V, CCNU, P Vs 8-in-1 chemo: no difference (*JNS* 1999;88:695-03)
- Could consider for children < 5 years with 40% not requiring RT for 2 years (*JCO* 2001)
- Role needs to be crystallised
Radiochemotherapy for Brain Metastasis: How to Define a Role for Temozolomide

Michael Weller

Department of General Neurology, Center for Neurology, University of Tübingen Medical School, Germany
Brain Metastasis

- Lung Tumors
- Breast Tumors

- Malignant Melanoma
CONCLUSION: Temozolomide was well tolerated and demonstrated activity in the treatment of brain metastases from MM. Further evaluation of temozolomide combination therapy is warranted.
Conclusion

■ Current standard of care
  – TMZ + RT followed by 6 months of TMZ

■ Recurrence
  – Treatment options unsatisfactory
  – TMZ / nitrosurea / bevacizumab

■ Involvement in clinical trials encouraged

■ Multiple new therapies under development