Radiation Oncology/CNS/High grade glioma/Overview

Glioblastoma and High Grade Gliomas Overview

Pathology

  - Glioma mouse model. p75 neurotrophin receptor (p75\textsubscript{NTR}) identified as critical regulator of glioma invasion. This invasion is neurotrophin dependent, resulting in cytoskeletal changes

Prognosis

- **EORTC Online Nomogram** (http://www.eortc.be/tools/gbmcalculator/)
- **EORTC 26981 / NCIC**
  - For trial details please see the adjuvant therapy page
  - **RTOG RPA Validation; 2006** PMID 16735709 -- Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. (Mirimanoff RO, J Clin Oncol. 2006 Jun 1;24(16):2563-9.)
  - Evaluation of predictive power of RPA in the trial. RPA adapted to EORTC as below
  - Conclusion: RPA retains its prognostic significance overall, as well as in treatment arms

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Median OS</th>
<th>2-year OS</th>
<th>p-value vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Age &lt;50, PS 0</td>
<td>21 vs. 15 mo</td>
<td>43% vs. 20%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>IV</td>
<td>Age &lt;50, PS 1-2</td>
<td>16 vs. 13 mo</td>
<td>28% vs. 11%</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>V</td>
<td>Age &gt;=50 and either Biopsy only or MMSE &lt;27</td>
<td>10 vs. 9 mo</td>
<td>17% vs. 6%</td>
<td>p=0.05</td>
</tr>
</tbody>
</table>
- Subanalysis. 573 patients. Modeling done on 1) intent-to-treat (n=573), 2) RT + TMZ group (n=287), and 3) RT + TMZ group with MGMT status s/p resection (n=103)
- Nomograms: Developed to predict median and 2-year OS. Available at EORTC GBM Calculator (http://www.eortc.be/tools/gbmcalculator) web page
- Conclusion: MGMT promoter methylation status, age, performance status, extent of resection, and MMSE are suggested as eligibility or stratification factors for future trials
- Comment (editorial): More accurate than RTOG RPA class. For patients with MGMT status, age was not statistically significant in multivariate setting, only MGMT status, PS, and MMSE. Still considered an exploratory analysis

- Analysis of RTOG 74-01 / ECOG 1374, RTOG 79-18, and RTOG 83-02. 1578 pts included.
- Age <50 or >=50 was most significant determinant of survival.

RTOG RPA Stages For GBM WHO Grade IV (No TMZ)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Median Survival (mo)</th>
<th>1-year OS</th>
<th>2-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Age &lt;50, KPS 90-100</td>
<td>18</td>
<td>70%</td>
<td>35%</td>
</tr>
<tr>
<td>IV</td>
<td>Age &lt;50, KPS &lt;90 or Age &gt;=50, surgical resection, good neurologic function</td>
<td>11</td>
<td>45%</td>
<td>15%</td>
</tr>
<tr>
<td>V</td>
<td>Age &gt;=50, KPS &gt;=70, surgical resection, unable to work or Age &gt;= 50, KPS &gt;= 70, biopsy only and RT dose &gt; 54.4 or Age &gt;=50, KPS &lt;70 and normal MS</td>
<td>9</td>
<td>30%</td>
<td>6%</td>
</tr>
<tr>
<td>VI</td>
<td>Age &gt;=50, KPS &gt;=70, biopsy only and RT dose &lt;=54.4 Gy or Age &gt;=50, KPS &lt;70, abnormal MS</td>
<td>5</td>
<td>20%</td>
<td>4%</td>
</tr>
</tbody>
</table>

- Abstract update of this study combined groups 5&6 into a single risk group.

- Validation of RPA classification using new dataset (RTOG 90-06)
- Outcome: Median OS and 2-year OS within 95% confidence interval; all classes but Class II statistically distinct (p<0.0001)
- Conclusion: Validation of RPA classes, useful as historical controls for future Phase II trials

Biologic markers for prognosis

- EGFR gene amplification
- EGFR gene mutations (most common is EGFRvIII, a constitutively active mutated form)
- Loss of PTEN tumor suppressor
- Overexpression of PDGFR α
- Mutated p53
- Loss of heterozygosity for chromosomes 1p and 19q, first identified in anaplastic oligodendrogliomas.
- MGMT repair gene

MGMT

- O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme depleted by daily treatment with temozolomide.
- The MGMT gene on chromosome 10q26. The gene product removes alkyl groups from the O6 position of guanine, an important site of DNA methylation by DNA alkylation agents. *High levels of MGMT in tumors create resistance to this type of chemotherapy.
- Low levels of MGMT in tumor is associated with longer survival in patients with GBM receiving nitrosourea-based chemotherapy.
- Silencing of the MGMT gene by methylation of its promoter is associated with better survival.

  - Analyzed MGMT methylation in pts from the EORTC / NCI Canada trial. 206 pts could be analyzed. 44% had detectable MGMT promoter methylation by PCR. There is a 55% decrease (HR 0.45) in death in the methylated group. Median survival 18.2 months vs 12.2 months. There was a benefit to RT+Temodar vs RT alone for the methylated group (HR=0.51) but there was only a trend for the unmethylated group. 2-year OS for methylated was 46% (RT+Temodar), 23% (RT alone); for non-methylated 13.8% and 2%. Median survival for methylated was 21.7 m (RT+Temodar), ? (RT); for non-methylated, 12.7 m (RT+T), 11.8 m (RT).
  - For methylated, (RT+Temodar) 2-year OS 46% , 23% (RT alone)
  - Conclusion: Most of the benefit of Temodar is in the subgroup of patients with a methylated MGMT promoter.

Cancer biology

**Radiobiology:**

  - Median tumor a/b 9.3; median cellular doubling time 39.5 days
  - Temozolomide: median equivalent BED 11 Gy (9.1 Gy in 2 Gy/fx)

**Radioresistance:**

Vaccine:

  - A phase II, multicenter trial was undertaken to assess the immunogenicity of an EGFRvIII-targeted peptide vaccine and to estimate the progression-free survival (PFS) and overall survival (OS) of vaccinated patients with newly diagnosed EGFRvIII-expressing GBM with minimal residual disease.
  - The 6-month PFS after vaccination = 67% (95% CI, 40% to 83%) and after diagnosis = 94% (95% CI, 67% to 99%; n = 18).
  - The median OS = 26.0 months (95% CI, 21.0 to 47.7 months).
  - After adjustment for age and Karnofsky performance status, the OS of vaccinated patients > that observed in a control group matched for eligibility criteria, prognostic factors, and temozolomide treatment (hazard ratio, 5.3; P = .0013; n = 17).
  - OS effected by: 1. development of specific antibody (P = .025), 2. delayed-type hypersensitivity (P = .03)
  - 82% patients lost EGFRvIII expression at recurrence
  - CONCLUSION: "EGFRvIII-targeted vaccination in patients with GBM warrants investigation in a phase III, randomized trial."

Treatment overview

- Surgery is the primary treatment modality. Patients who are not surgical candidates and have only diagnostic biopsy have extremely poor outcomes
- Post-op EBRT is standard therapy
  - Dose to 60 Gy in 30 fractions (dose intensification via escalation and fractionation not successful so far)
  - For patients >60, RT 40/15 appears comparable to 60/30
  - For patients >70 and KPS >=70, RT 50/28 GY provides modest survival benefit (median 29 weeks vs. 17 weeks) without reducing QOL or cognition over supportive care only
  - For patients >70 and poor KPS, supportive care alone may be reasonable
- Addition of temozolomide to post-op RT is now effectively the standard of care

Surgery

**Review**


Response Assessment Criteria

  - Problem: Contrast enhancement on CT (as required by the Macdonald Criteria) or MRI is nonspecific for tumor response
  - Complete response: Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or
improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.

- **Partial response:** Requires all of the following: >=50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.

- **Stable disease:** Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

- **Progression:** Defined by any of the following: >=25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

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**Macdonald Criteria; 1990** PMID 2358840 -- "Response criteria for phase II studies of supratentorial malignant glioma." (Macdonald DR, J Clin Oncol. 1990 Jul;8(7):1277-80.)

- **Complete response:** Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically.

- **Partial response:** Requires all of the following: >= 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically.

- **Stable disease:** Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically.

- **Progression:** Defined by any of the following: >=25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration.