Bevacizumab, a monoclonal antibody to the Vascular Endothelial Growth Factor (VEGF) and Irinotecan for treatment of recurrent primary malignant brain tumors in adults

B. Hasselbalch[1], U. Lassen[2] K. Grunnet[1], M. Kosteljanetz[3], H. Laursen[4], H. S. Poulsen[1,2].

[1]Department of Radiation Biology, Section 6321, Finsen Center, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark.
[2]Department of Oncology, Finsen Center, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark.
[3]Department of Neurosurgery , Copenhagen University Hospital, DK-2100 Copenhagen, Denmark.
[4]Department of Neuropathology, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark.

email:benedikte.hasselbalch@rh.regionh.dk
www.radiationbiology.dk

Background

- The prognosis of recurrent malignant brain tumors/gliomas is poor, and no efficacious therapy exist in patients previously treated with radiotherapy and standard chemotherapy
- Angiogenesis is a requirement for growth of malignant brain tumors
- Vascular endothelial growth factor (VEGF) is abundantly produced in gliomas and is a prognostic factor with more VEGF expression correlating with a poor prognosis
- Bevacizumab is a monoclonal antibody which binds to VEGF, thereby inhibiting activation of the VEGF receptor (VEGFR)
- Irinotecan is a topoisomerase inhibitor, with limited effect when used as monotherapy for gliomas
- Promising results from Duke Comprehensive Cancer Center, NC, with bevacizumab and Irinotecan for patients with recurrent gliomas, induced similar treatment regimen of recurrent brain tumor patients at Copenhagen University Hospital (Rigshospitalet), Denmark, (Duke results published Clin. Cancer Res., 2007 Feb 15;13(4) and J. Clin. Oncol. 2007 Oct 20; 25(30)

Aim

To investigate the effect of bevacizumab (Avastin®) and Irinotecan in recurrent malignant brain tumors

Conclusions

- Bevacizumab and Irinotecan induces a substantial number of Complete Responses (CR)
- The therapy is reasonably safe and induces clinically relevant and durable responses in heavily pretreated patients
- Our results confirm the promising results from Duke
- Bevacizumab and Irinotecan should be tested as a part of a primary setting

Methods

- **Selection of patients:**
  - Referred by The Danish Board of Health
- **Inclusion criteria:**
  - No standard treatment accessible
  - Biopsy verified primary brain tumor
  - Progressive disease according to MacDonald criteria and verified by CT/MRI scan
  - Performance status 0-2
  - No hypercholesterolemia
  - No hypertriglyceridemia
  - Blood pressure < 150/100 mmHg
  - No anticoagulation therapy
- **Treatment administration:**
  - Treatment once every 2 weeks of a 4 weeks cycle
  - Bevacizumab, 10 mg/kg on day 1 and 15
  - Irinotecan 340 mg/m^2 (patients treated with enzyme inducing anti-epileptic drugs) or 125 mg/m^2 (patients without treatment with enzyme inducing anti-epileptic drugs) on day 1 and 15
- **Evaluation:**
  - Every second month according to MacDonald criteria
- **End Points**:
  - Best Response
  - Progression Free Survival at 6 months (PFS-6)

Results

Patients Characteristics

Sex
- 17 female & 33 male

Age
- Median 46 years (26 – 67)

Performance status (WHO)
- PS 0: 20
- PS 1: 19
- PS 2: 11

Time from primary diagnosis until enrollment:
- Median: 36,7 months (5 – 183)

Number of interventions before enrollment
- 2 (2 patients)
- 3 (16 patients)
- 4 (16 patients)
- >5 (16 patients)

Tumor Types

- 25 Glioblastoma Multiforme
- 13 Grade III Astrocytoma
- 5 Grade III Oligodendroglioma

= 43 patients

- 1 Malignant Ependymoma
- 1 Malignant Prolactinoma
- 3 Brainstem Glioma
- 1 Anaplastic Medulloblastoma

= 50 patients

Until now, 42 of 50 patients are evaluable

Response

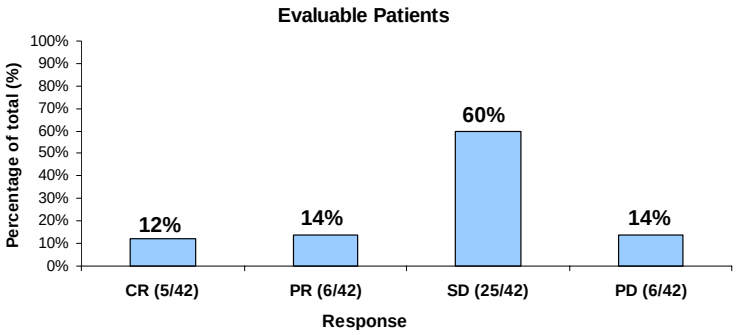

Figure 1: Number of Complete Responses (CR), Partial Responses (PR), Stable Disease (SD) and Progressive Disease (PD) according to MacDonald criteria with bi-dimensional measurement at MRI/CT scan

Tumor	CR	PR	SD	PD	Number of patients
Glioblastoma Multiforme	4	2	10	2	18
Grade III Astrocytoma	-	2	8	2	12
Grade III Oligodendroglioma	1	-	3	1	5
Others	-	2	4	1	7
Total	5	6	25	6	42

Table 1: Distribution of responses according to tumor type

PFS at 6 months

Tumor	Number of patients	PFS-6	PFS-6 %
Glioblastoma Multiforme	15	6	40.0 %
Grade III Gliomas	17	6	35.6%
Others	4	-	-
Total	36	12	33.3%

Table 2: Progression Free Survival at 6 months (PFS-6)

Toxicity

Overall Toxicity	
Grade I - II	4 - 56 %
Grade III	2 - 6 %
Grade V	2%

Table 3: Overall Toxicity (WHO)

Manageable side effects
- 1 patient with trombosis
- 3 patients with hypertension

Unmanageable side effects
(further treatment cancelled)

- 1 patient with diarrhea (Grade V)
- 1 patient with cerebral hemorrhage
- 1 patient with cardiac arrhytmia
  Recived cardiac bypass 2 years prior to therapy
- 1 patient with gastrointerstinal perforation
  Location of perforation was a 20 year old anastomosis originate from a intestine resection