A phase II trial with cetuximab, bevacizumab and irinotecan for patients with primary glioblastomas and progression after radiation therapy and temozolamid

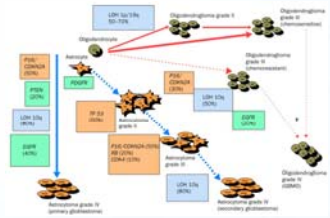
U. Lassen[1], B. Hasselbalch[1], M. Sørensen[1], M. Holmberg[2], S. Hansen[3], M. Kosteljanetz[1], H. Laursen[1], H. S. Poulsen[1]

[1]Rigshospitalet, Copenhagen, [2]Aalborg and [3]Odense University Hospitals, Denmark

Background

Recent data has shown that bevacizumab (B) and irinotecan (I) induces significant responses in recurrent GBM. Primary GBM is very often associated with amplification of EFGR (40-50%) and alterations in the EGFR gene. In vivo experiments have shown that cetuximab (C) increases apoptosis, decreases cell proliferation and decrease vascular endothelial growth factor expression in EGFR-amplified GBM cells in vitro. The use of the combination of C and I has shown a significantly higher response rate compared to irinotecan as monotherapy in colorectal cancer. In addition, adverse events (AE) have been acceptable and the BOND-2 study has shown the feasibility of combining C, B and I. In this phase II study we examine the safety and efficacy of CBI in recurrent de novo GBM.

Genetic alterations in Gliomas



Study Rationale

Irinotecan has demonstrated activity in malignant gliomas in multiple phase II studies. The activity is limited, with an approximately 15 % response rate and a progression-free survival of 3-5 months. Given the synergy between irinotecan and bevacizumab in colorectal cancer, and the high-level expression of vascular endothelial growth factor on malignant gliomas, one would expect synergy between bevacizumab and irinotecan against gliomas. In addition, 40-50 % of GBM have EGFR amplification/mutation making the EGFR an additional target. By combing cetuximab, with irinotecan and bevacizumab, one would expect further response, than irinotecan and bevacizumab alone. In addition, recurrent gliomas have an extremely poor prognosis, so innovative therapies are needed.
The study was approved by DKMA and ethics committee.

Primary Objective

Determine the disease control rate (progression free survival (PFS), response rate (RR) of the combination of cetuximab, bevacizumab and irinotecan (CBI) in patients with recurrent GBM).

Secondary Objective

Determine safety, tolerability and toxicity in patients with recurrent or progressive GBM.
Determine overall survival (OS).
Correlate tumor response with the expression of tumor markers (EFGR, p-EGFR, EGFRvIII, VEGF, PTEN, Akt, p-Akt, p53)

Treatment schedule

Cetuximab 400 mg/m^2 as starting dose, followed by weekly cetuximab 250 mg/m^2
Bevacizumab 10 mg/kg every second week
Irinotecan 125 mg/m^2 (No enzyme inducing antiepileptic drugs (EIAEDs) or 340 mg/m^2 (EIAEDs) every other week.
Response evaluation every 8 week (McDonald criteria).
Treatment cycles of 4 weeks until progression.
Toxicity evaluation every 2 weeks according to CTCAE 3.0

Patient characteristics

Recurrent or progressive primary GBM certified with MRI scan and clinically (MacDonald criteria)

Main inclusion criteria:

Recurrent glioblastoma with progression < 6 months from temozolomide
PS 0-2
Minimum 6 weeks from major surgery
No concurrent severe cardiac, renal or hepatic disease
No hypercholesterolaemia
No thrombo-embolic event within last 6 months
No uncontrolled hypertension
No proteinuria
No pregnancy or breastfeeding
Signed informed consent

Pretreatment characteristics N=42	
Median Age (range)	57 (23-70 years)
Gender Male/female	26/16
Performance status 0 1 2	 11 26 5
Site: Rigshospitalet Ålborg Univ. Hospital Odense Univ Hospital	 32 7 3

MacDonald Response Evaluation

Complete Response: Complete disappearance on CT/MRI of all enhancing tumor and mass effect, off all corticosteroids (or receiving only adrenal replacement doses), accompanied by a stable or improving neurologic examination, and maintained for at least 4 weeks.

Partial Response: Greater than or equal to 50% reduction in tumor size on CT/MRI by bi-dimensional measurement on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination, and maintained for at least 4 weeks.

Stable Disease: Neurologic exam is at least stable and maintenance corticosteroid dose not increased, and CT/MRI imaging meets neither the criteria for PR or the criteria for Progressive Disease. If this category is to be reported as of possible clinical benefit, Stable Disease status must be maintained for a clinically appropriate interval (e.g. 8 weeks for recurrent high grade gliomas).

Progressive Disease: Progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, etc.) OR a greater than 25% increase in the bi-dimensional measurement on CT/MRI OR increased dose of corticosteroids (>100% dose increment above study entry dose) required to maintain stable neurologic status or imaging.

Patients

A total of 42 pts were included between August 2006 and January 2008.
After a safety analysis of the first 10 pts bevacizumab was increased from 5 to 10 mg/kg and this regimen was well tolerated.
All patients were evaluable for toxicity, and 33 patients were evaluable for response.

Safety

Four pts had grade 3-4 thromboembolic complications, including 1 lacunar infarction, , 2 pulmonary embolisms, 1 myocardial infarction. These patients went off-study according to study protocol. Two patients had 2 deep vein thromboses and continued on-study after LMWH was initiated.
One patient had a severe GI-bleeding after LMWH was initiated for pulmonary embolism.
No patient went off-study due to unmanageable hypertension.
Hematologic toxicity was mild and no grade 3 or 4 haematological events were observed.
Non-hematological toxicity included transient elevation of transaminases due to irinotecan, grade I-II diarrea, grade I-II proteinuria, and hyperglycemia due to corticosteroids.

Cetuximab specific toxicity.

3 pts experienced grade III-IV allergic reaction during first cetuximab administration despite pre-medication.
EGFR-antagonist related skin toxicity was frequent, but manageable with normal guidelines for most patients.
1 pt. with developed severe dyspnoea during second cycle and CT showed diffuse pulmonary changes which were characterised as interstitial pneunomitis, with normalisation after discontinuation of cetuximab.
In addition, 3 patients developed severe ulcerations of the skin or mucosa. These were considered as cetuximab induced rash with wound healing complications due to bevacizumab.
The changes healed in 2 patients after discontinuation of cetuximab, but the 3rd. patient developed severe deep ulcerations of the tibia, which needed plastic surgery.
Therefore, also bevacizumab was discontinued. Skin biopsy showed vasculitis-like lesions.
It is likely that high-dose glucocortico-steroid also has a major role in the development of these lesions, as such ulcerations have not been reported in other studies with combinations of cetuximab and bevacizumab (CAIRO-2 and BOND-2).
However, in these studies bevacizumab was administered at a lower dose (5 mg/kg).

Response (McDonald)	Number	Percent
Complete remission	1	3%
Partial remission	14	42%
Stable disease	13	39%
Progressive disease	5	15%

Main outcome measures

Overall response rate (CR + PR) was 45%.
In addition, stable disease was 39%, and the disease control rate was 84%
Among patients with stable disease, minor response (25-50% regression) was observed in 4 patients (35%, 46%, 48% and 48%).

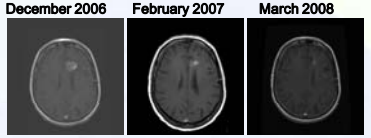
Time to progression

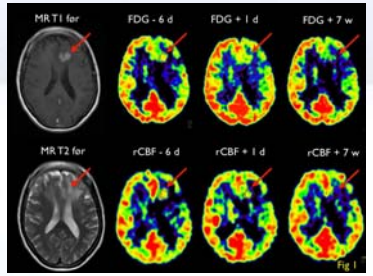
Median time to progression was 25.5 weeks (95% CI 16-35 weeks)

Median survival

Median survival time was 27 weeks (95% CI 19-24 weeks)
25 patients have died and 17 patients are still alive with follow-up from 20-76 weeks.

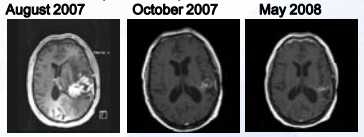
Serial MRI of a patient with partial remission
December 2006 February 2007 March 2008





In order to identify early responders serial dynamic PET scans with FDG and O^{15} water were performed prior to treatment, during first week and at 8 weeks from start

Serial MRI of a patient with partial remission
August 2007 October 2007 May 2008



Conclusion

The CBI regimen was well tolerated, with encouraging response rates, including 1 CR. However, the efficacy of the combination seems to be similar to BI alone , therefore is further evaluation of this regimen not planned.
Bevacizumab based regimens are now investigated in first line setting was radiotherapy and as salvage treatment with other targeted therapies

Aknowledgement:
This study was supported by the Danish Board of Health