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

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Background
Recent reports have shown that bevacizumab (B) and irinotecan (I) induces significant responses in recurrent GBM. Primary GBM is a very often associated with amplification of EGFR (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 in vivo. The use of the combination of C and I has shown a significantly higher response rate compared to Irinotecan 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 approximate 15% response rate and a progression free survival of 3-6 months. Given the synergy between Irinotecan and bevacizumab in colorectal cancer, and the high-level expression of vascular endothelial growth factor in malignant gliomas, one would expect synergy between bevacizumab and irinotecan against gliomas. In addition, 40-50% of GBMs have EGFR amplification/mutation making the EGFR an additional target. By combining cetuximab, with irinotecan and bevacizumab, one would expect further responses, than Irinotecan and bevacizumab alone. In addition, recurrent gliomas have an extremely poor prognosis, so innovative therapies are needed. The study was approved by DIKA 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 (EGFR, p-EGFR, EGFRvIII, VEGF, PTEN, ALK, p-ALK, p21)

Treatments schedule

Cetuximab 400 mg/m² as starting dose, followed by weekly cetuximab 250 mg/m², bevacizumab 10 mg/kg every second week, Temozolomide 125 mg/m² (No enzyme Inducing antiepileptic drugs (EIADES) every other week. Response evaluation every 6 week (McDonald criteria).

Toxicity evaluation every 2 weeks according to CTCAE 3.0

Patient characteristics

Recruited or progressed 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

Minimum 6 weeks from major surgery

No proteinuria

No pregnancy or breastfeeding

Prescribed medication was we

Maximum dose of corticosteroids was 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, seizures, hyperglycemia, etc.) OR a greater than 25% increase in the bi-dimensional measurement on CT/MRI OR increased dose of corticosteroids (>25% increase above study entry dose) required to maintain stable neurologic status or imaging.

Progressive disease (No enzyme inducing antiepileptic drugs (EIADES) every other week. Response evaluation every 6 week (McDonald criteria).

Toxicity evaluation every 2 weeks according to CTCAE 3.0

Response (McDonald) Number Percent

Complete remission 1 35%

Partial remission 14 42%

Stable disease 13 39%

Progressive disease 5 15%

Main outcome measures

Overall response rate (OR + PR) was 48%. 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%, 45% and 41%).

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 20-78 weeks.

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 B 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:

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