Randomized phase II study of neoadjuvant bevacizumab and irinotecan versus bevacizumab and temozolomide followed by concomitant chemoradiotherapy in newly diagnosed primary glioblastoma multiforme

SN0 November 2011

Kenneth F. Hoff1,1, Steinbrihn Hansen2, Morten P. Sørensen1, Henrik P. Schultz2, Alida Muhic1, Sille Engelholm1, Anders Ask1, Charlotte Kristiansen2, Carsten Thomsen1, Hans Skovgaard Poulsen1, Ulrik Lassen1,1, Rigshospitalet, Copenhagen University Hospital, Odense University Hospital, Århus University Hospital, Denmark.

Supported by F. Hoffmann-La Roche

Background

Concomitant temozolomide (T) and radiotherapy (RT) is standard of care in patients with newly diagnosed glioblastoma multiforme (GBM) and good performance status (PS). Bevacizumab (B) and irinotecan (I) has shown activity in patients with recurrent disease with a significant number of responders. The response rate of temozolomide is around 10%, and increased response rates may indicate survival benefit. We tested bevacizumab combined with either temozolomide or irinotecan and concomitant radiotherapy as 1. line therapy in patients with newly diagnosed GBM. The aim of the study was to investigate if the combination of bevacizumab and irinotecan was sufficiently active to warrant a head-to-head comparison to Stupp’s regimen combined with bevacizumab in a future randomized phase III trial.

Endpoints:
The primary endpoint was response at 8 weeks. Secondary endpoints were 6- and 12-months PFS, overall survival (OS), safety and feasibility. Response was assessed every 8 weeks. Toxicity was assessed every 2 weeks.

Methods:

Pts with newly diagnosed GBM (previously untreated except for primary surgery/biopsy), were randomized to bevacizumab and irinotecan on days 1 and 14 (BI regimen) or to bevacizumab on days 1 and 14 and temozolomide on days 1-5 in a 28-day cycle (BT regimen) for 8 weeks, followed by radiotherapy (60 Gy/30 fractions/5 fractions per week) and concomitant BI or BT. Post-radiotherapy, chemotherapy was continued for 8 weeks.

Protocol procedure: A "two-stage" design was employed. A true response rate of 30% was considered worthy of further study, while a response rate of 10% would not. If ≤1 response was observed among the first 10 pts, inclusion to that specific experimental arm should be terminated. If ≥2 responses were observed, the inclusion was to be continued.

Inclusion criteria: 1) Signed informed consent, 2) Primary GBM, 3) No prior therapy except primary surgical resection or biopsy, 4) PS 0-2, 5) Age ≥18 years, 6) Expected OS >3 months, 7) Adequate organ function. 8) No sign of cerebral bleeding on cerebral MRI-scanning at baseline.

Chemotherapy: Bevacizumab was dosed 10 mg/kg every 14 days, intravenously. Irinotecan was dosed every 14 days. The dose was dependent on use of enzyme-inducing anti-epileptic drugs (EIAED) so the patients not on EIAED were dosed with irinotecan 125 mg/m2 and patients on EIAED were dosed with 340 mg/m2. Temozolomide was administered differentially during the study. For the patients on and the patients not on bevacizumab and irinotecan, temozolomide 200 mg/m2 was given daily for 5 days followed by 23 days off (The dose in the first cycle was 150 mg/m2 though). During radiotherapy, temozolomide 75 mg/m2 was given daily.

Radiotherapy: Target was determined from fusion of CTC and baseline MRI. If PD after neo-adjunct part, the largest target (baseline or 8-week MRI) was used for radiotherapy planning. Planning is with Eclipse-system (Varian Medical Systems). GTV was the enhancing tumor on the post-contrast T1 image and/or the non-enhancing area on the T2 image on the baseline MRI scan. CTV : GTV − 2 cm margin, except for bony structures. Meningeal structures were considered anatomic barriers to tumor spread when appropriate. If present, operation cavity were included in the tumor volume. ITT: ITV=CTV. PET : CTV + 0.5 cm margin for patient setup inconsistencies. Tolerance doses for organs at risk were as by Emami et al, JROBP 1991, 21:109-122. Radiotherapy was performed using a linear accelerator.

Response evaluation: Response evaluation was according to the MacDonald criteria, modified as described below. Complete response (CR): A complete disappearance of all measurable and non-measurable disease sustained for at least 4 weeks with no new lesions. Patient should be off corticosteroids with stable or improved clinical status. Partial response (PR): A ≥50% decrease in the sum of products of perpendicular diameters of all measurable enhancing lesions compared with baseline with no new lesions, on stable or reduced corticosteroid dose and with stable or improved clinical status. Minor response (MR): A ≥25% or more of the product of perpendicular diameters of all measurable enhancing lesions compared to baseline but less than 50%, thus not qualifying for a full PR. As with CR and PR, there could be no new lesions and corticosteroids and neurological status should be stable. Progressive disease (PD): An increase of ≥25% in the sum of products of perpendicular diameters of enhancing lesions, the appearance of new enhancing lesions or signs of critical deterioration. Stable disease (SD): was declared if the patient did not qualify for complete response, partial response or progressive disease and was stable clinically. Because of the neo-adjunct study design, it was not mandatory that PR or MR could be confirmed at subsequent evaluations.

Contrast enhancing (CE) lesions <10 mm in diameter at baseline were not measurable but were evaluable. When such lesions increased in size to ≥10 mm they were included as measurable. CE lesions that were ≥10 mm in diameter at baseline were measurable and followed as measurable, even if they decreased in diameter to <10 mm during therapy. Immediately following the chemo-radiotherapy, an aggravation of neurological symptoms necessitating dose-escalation of corticosteroids may be seen; however, this should not in itself be considered evidence of PD. In case of radiological progression on MRI within 2 months following the chemo-radiotherapy, PD was declared if this was confirmed on subsequent MRI or if the clinical condition deteriorated. If PD on MRI could not be confirmed, the increase in size of the lesion following chemo-radiotherapy was defined as progressive disease (PSPD), and the status of the patient was SD. All MRI were reviewed by an expert neuroradiologist, blinded to treatment.

In some cases the blinded MRI review diagnosed radiological progression at time of PD, but the patient was clinically evaluable as progression disease, and progression disease was defined as disease progression (PD) and the status of the patient was SD. All MRI were reviewed by an expert neuroradiologist, blinded to treatment.

In some cases, the blinded MRI review diagnosed radiological progression at time of PD, but the patient was clinically evaluable as progression disease, and progression disease was defined as disease progression (PD) and the status of the patient was SD. All MRI were reviewed by an expert neuroradiologist, blinded to treatment.

In some cases, the blinded MRI review diagnosed radiological progression at time of PD, but the patient was clinically evaluable as progression disease, and progression disease was defined as disease progression (PD) and the status of the patient was SD. All MRI were reviewed by an expert neuroradiologist, blinded to treatment.

Results

Two pts on the BI arm were not included in the analysis: One was claustrophobic and refused the MRI, and the other had a bleeding on the baseline MRI. Both were excluded from the study and were not included in the ITT population.

Non-hematological toxicity from neoadjuvant therapy

Bevacizumab - Temozolomide - Irinotecan

Toxicity graded according to CTCAE criteria version 3.0:
I  II  III (IV)  I  II  III (IV)

- Neutropenia
- Diarrhea
- Constipation
- Alopecia

Response after 8 weeks of neoadjuvant therapy

Bevacizumab - Temozolomide - Irinotecan

Complete response 10  6
Partial response 11  7
Stable disease 6  7
Progressive disease 4  6
Not evaluable  1  6

Patients randomized (n=60)

ITT arm (n=33)

Bevacizumab vs Temozolomide (GBM)

Bevacizumab and Temozolomide, a dose of 25 mg was used in the current study and a dose of 30 mg was used in the historical control arm with a median survival of 445 days on the BI arm vs. 337 days on the BT arm in a phase III trial.

The most severe toxicity for each patient during the first 2 cycles of neoadjuvant therapy is shown. The more common chemotherapy-induced toxicities are shown, as well as the toxicities of toxicity that resulted in grade III or worse toxicity, are shown here. There were no wound healing complications.

The side-effects were manageable and there were no apparent increased toxicity from the combined chemotherapy, bevacizumab and radiotherapy.

Assessment of disease at time of PD: Surveillance imaging was performed every 3 months, with a minimum of 10 months of surveillance imaging after PD. The number of pts was relatively small and the distribution of performance status was imbalanced, favouring the BI-arm and the observed survival benefit should be interpreted cautiously. When survival was stratified for PS (0 vs. 1-2), the improved survival from BI was still observed, most clearly in the good PS group. All pts were allowed to cross-over to the alternative regimen at time of PS.

Conclusion

The response rate at 8 weeks seemed to favor the combination of bevacizumab and temozolomide compared to bevacizumab and irinotecan: If true PR and "minor response" were combined for the analysis, the increased response rate on the BT-arm was borderline statistically significant. However, it should be remembered that no formal statistical comparison of efficacy data were pre-planned, due to the relatively small sample sizes.

PFS at 6- and 12 months were similar between the two arms. Survival was significantly prolonged on the BI arm with a median survival of 445 days on the BI-arm vs. 337 days on the BT arm (p-value = 0.014 (Log-rank)). The median follow-up was 405 days (SD: 181). The number of pts were relatively small and the distribution of performance status was imbalanced, favouring the BI-arm and the observed survival benefit should be interpreted cautiously. When survival was stratified for PS (0 vs. 1-2), the improved survival from BI was still observed, most clearly in the good PS group. All pts were allowed to cross-over to the alternative regimen at time of PS. The use of blinded critical review of all MRI possibly deflated our response rates as well as the 6- and 12 months PFS. The discussion of the validity of radiological evaluation of response/relapse in GBM is ongoing; however, in this study, it ensured unbiased and similar evaluations of all patients.