First-line therapy with Bevacizumab and Irinotecan versus Bevacizumab and Temozolomide and Delayed Concomitant Radiotherapy in Newly Diagnosed Primary Glioblastoma Multiforme: Early Results From a Randomized Phase II Study
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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 proven efficacious in patients with recurrent disease with a significant number of complete responders. We tested the use of Bevacizumab in combination with Temozolomide or Irinotecan with concomitant radiotherapy as first-line therapy in patients with newly diagnosed GBM.

Methods

Patients 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) and concomitant BI or BT. Post-radiotherapy, chemotherapy was continued for 8 weeks. **See table "treatment outline"**

Endpoints and Safety

Toxicity was assessed every 2 weeks. Response was assessed every 8 weeks. Study endpoints are safety, response and 6- and 12-months progression free survival.

Here we report on a pre-planned safety and feasibility analysis of the initial 12 patients, 6 patients on each experimental arm.

We employed a "two-stage" design and a true response rate of 30% was considered worthy of further study, while a response rate of 10% would not be. Thus in the first stage, if for each group 0-1 response is observed among the first 10 patients, the regimen is thought to be ineffective. However, if 2 or more responses are observed, then 20 more patients are included.

Inclusion criteria

Signed informed consent
Primary glioblastoma multiforme
No prior therapy except primary surgical resection or biopsy
PS 0-2; Age > 18 years
Expected survival > 3 months
Adequate liver, renal and bone-marrow function: Standard criteria
Use of proper anti-conception if relevant
No sign of cerebral bleeding on cerebral MR-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 (EIAID) so the patients not on EIAED were dosed with irinotecan 125 mg/m^2 and patients on EIAED were dosed with 340 mg/m^2.
Temozolomide was administered differentially during the study: During the neo-adjuvant and the adjuvant part, temozolomide 200 mg/m^2 was given daily for 5 days followed by 23 days off (The dose in the first cycle was 150 mg/m^2 though). During radiotherapy, temozolomide 75 mg/m^2 was given daily.

Radiotherapy

Target was determined from fusion of CTC and baseline MRC. If PD after neo-adjuvant part, the largest target (baseline or 8-week MRC was used for radiotherapy planning. Planning is with Eclipse-system (Varian Medical Systems).

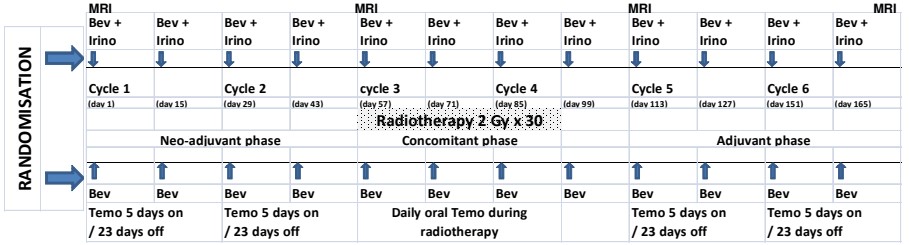
Volumes of interest were defined in agreement with ICRU, Report 50 and 62:

- **GTV** : The enhancing tumor volume on the post-contrast T1 image and/or the none-enhancing area on the T2 image on the baseline MR-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.
- **ITV** : ITV=CTV. No variations in size, shape or position of CTV in relation to anatomical reference structures were considered.
- **PTV** : CTV + 0.5 cm margin for patient setup inconsistencies.

Tolerance doses for organs at risk (including normal brain, optic chiasm, bilateral optic nerves, bilateral lenses, and brainstem) were as given in Emami et al, IJROBP 1991, 21; 109-122.

Radiotherapy was performed using a linear accelerator, and the dose prescribed was 60 Gy in 30 fractions to PTV, 5 fractions per week. The PTV was encompassed by the 95% isodose line.

Treatment outline



Demographics: Initial cohort of 6 + 6 patients

	Bevacizumab-Temozolomide	Bevacizumab-Irinotecan
No. of patients (Male/Female)	6 (5M / 1F)	6 (1F / 5M)
Median age (Range)	63.5 (41 - 71)	64 (50 - 69)
Surgery	6	6
Biopsy only	0	0
ECOG Performance status		
0	3	4
1	3	2
2	0	0

Among the initial cohort of 6 + 6 patients, 1 patient on each experimental arm experienced early progressive diasease (PD) prior to radiotherapy. Both went off-study and were replaced, according to protocol . Both patients were PS 2 and both had biopsy only.

Non-hematological toxicity: Initial safety analysis of 6+6 patients

	Bevacizumab - Temozolomide					Bevacizumab - Irinotecan			
	I	II	III	IV		I	II	III	IV
Nausea	5					3			
Emesis	2					1			
Constipation	2		1			2			
Diarrhoea	0					3	1		
Hypertension	1	1	1			1	2		
Fatique	2	3				2	1	1	
Alopecia	1					3	2		
Speaking/Language/Cognition	1					1	1		
Convulsions		1							
Bleeding				1		2			
Confusion			1						

Toxicity was graded according to the CTCAE vers 3.0. The most severe grade of toxicity that was recorded for each patient is shown. Note: One patient on the Bevacizumab-Temozolomide arm experienced a grade IV gastric bleeding that required surgery and an episode of grade III confusion after having completed 10 treatments. Other toxicities were: Sleeplessness grade I (once on BT-regimens), tremor manum and allergy grade I on BI-regimen, infection and headache grade I (once on both regimens), skin toxicity and stomatitis grade II (both once on BI-regimen, infection grade III on BI-regimen (cystitis treated with oral antibiotics),

Safety of Neo-adjuvant Approach

Bi-dimensional tumor measures of contrast-enhancing lesions after neo-adjuvant treatment expressed as percent of baseline measures (baseline is 100%)

Bevacizumab-Temozolomide		Bevacizumab-Irinotecan	
#1	42%	#1	52%
#2	64%	#2	37%
#3	79%	#3	46%
#4	72%	#4	66%
#5	69%	#5	54%
#6	19%	#6	68%

Changes in bi-dimensional (BD) measures were calculated as: (BD tumor-measures on pre-radiotherapy MRI – BD tumor-measures on baseline MRI) divided by (BD tumor-measures on baseline MRI) x 100%.
Note: MRI were blinded prior to expert neuroradiological review. There were 2 cases of clinical PD (1 patient on each arm) after only 1 and 3 treatments, respectively. Both patients were PS 2 and had only biopsy. These two patients went off-study and were replaced.

Results

Early safety analysis

Here we report our pre-planned safety analysis. Patients had to complete the neo-adjuvant regimen and to start the concomitant part to be eligible for toxicity analysis. In addition, patients were evaluated with MRI prior to concomitant radiotherapy in order to rule out that delay of radiotherapy had detrimental consequences.

Early progressive disease:

Two patients in our study, 1 from each regimen, progressed rapidly and recieved only 1 and 3 treatments, respectively. Thus, these 2 patients are not included in the toxicity analysis; however, they are reported here, because it is of safety concerns if patients progress during the neo-adjuvant part.
As it is, both patients had poor prognostic factors in terms of PS 2 and biopsy only.

Demographics:

At the time of presentation, all patients will have passed 24 weeks since treatment start, except for 2 patients that have just completed the concomitant part; thus, toxicity analysis is not complete.
The median age and performance status were well balanced; however, there were more men in the BT group and more women in the BI group. **See table "Patient characteristics".**

Toxicity:

Toxicity has been unsurprising and mostly mild (CTC grade I-II) with a few cases of more severe toxicity (grade III and IV); there is so far no indication of any unexpected adverse interaction with the chemotherapy and cerebral radiotherapy. It is well known to be difficult in this patient population to distinguish between adverse effects and tumor-related symptoms. **See table "Non-hematological toxicity: Initial safety analysis"**

Safety of the neo-adjuvant approach:

Blinded MRI review of the effect after the first 8 weeks of neo-adjuvant chemotherapy confirmed 2 partiel responses in both groups wherefore inclusion continues until 30 evaluable patients have been included in both groups. **See "Safety of neo-adjuvant Approach".**

Discussion

This neo-adjuvant and concomitant approach as first-line therapy for patients with newly diagnosed GBM seems safe and feasible.
Toxicity has been predictable and mostly mild, except for an episode of acute gastric bleeding. It is to early to speculate about efficacy.
Accrual is actively ongoing.