Clinical Variables Serve as Predictive Factors in a Model for Clinical Response to Bevacizumab in Recurrent Glioblastoma Multiforme

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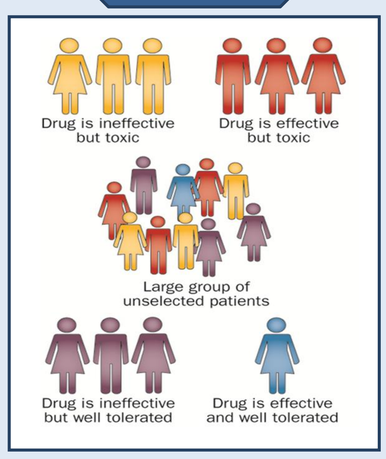
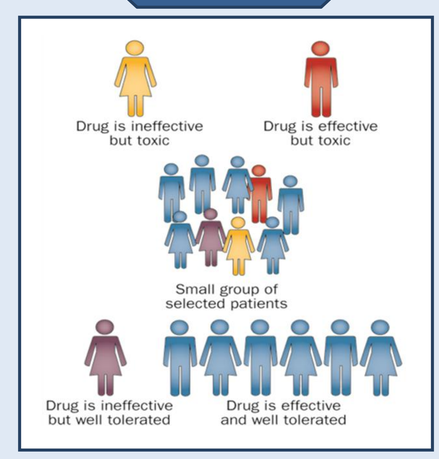
BACKGROUND

- Glioblastoma Multiforme (GBM) is the most common and aggressive malignant primary brain tumor in adults.
- GBM tumors are characterized by excessive and aberrant angiogenesis, which is thought to be linked to the expression of the angiogenic promoter – the Vascular Endothelial Growth Factor A (VEGF).
- Bevacizumab, an antibody targeting VEGF, has shown high response rates in recurrent GBM patients.
- Recurrent GBM patients treated with bevacizumab who achieve an objective response live longer and have an improved quality of life.
- Few studies have identified prognostic factors in recurrent GBM patients treated with bevacizumab and no validated predictive factors associated with clinical durable bevacizumab response have been identified.

Old Model



New Model



Objectives

The primary objective was to identify predictive and prognostic clinical factors associated with objective response to bevacizumab.
The secondary objectives were to identify prognostic factors for progression-free survival (PFS) and overall survival (OS) in recurrent GBM and to evaluate quality of life according to response.

PATIENTS AND METHODS

Patients: 219 non-selected recurrent GBM patients were treated at our institution with bevacizumab in combination with irinotecan in the period from May 2005 to December 2013 according to a previous published clinical protocol.[1] Patient characteristics are summarized in Table 1.

Inclusion criteria: Histologically confirmed grade IV glioma; measurable progressive disease by contrast-enhanced MRI after standard therapy; WHO performance status (PS) 0-2; > 4 weeks from chemotherapy; >3 months from completion of radiation therapy. Detailed inclusion and exclusion criteria have been described previously.[1]

Treatment: Bevacizumab (10mg/kg) and irinotecan were administered every 2 weeks and each cycle of treatment was defined as two treatment administrations.[1]

Evaluation: Response and disease progression were evaluated every two cycles using the MacDonald criteria.

Statistical analysis: Factors were screened by univariate analysis of response, PFS and OS. Screened factors with a *P*-value of <10% were considered for multivariate analysis.

Table 1. Patient characteristics

Characteristics	Population, n = 219
Gender, n (%)	
Female	73 (33.3)
Male	146 (66.7)
Age, years (range)	
Median	56 (21-79)
WHO Performance Status, n (%)	
0	78 (35.6)
1	98 (44.7)
2	40 (18.3)
Missing	3 (1.4)
GBM diagnosis, n (%)	
Glioblastoma	184 (84.0)
Secondary glioblastoma*	35 (16.0)
Prior GBM surgical resections; n (%)	
1	103 (47.0)
≥2	116 (53.0)
Relapse surgery prior BI treatment, n (%)	
Yes	111 (50.7)
No	108 (49.3)
Multifocal at time of BI treatment, n (%)	
Yes	72 (32.9)
No	142 (64.8)
Missing	5 (2.3)
Prior chemotherapy lines, n (%)	
1	188 (85.8)
≥2	31 (14.2)
Prior first line therapy, n (%)	
RT + concomitant and adjuvant TMZ	184 (84.0)
Other	35 (16.0)
Steroid** (>10mg) at initiation of BI, n (%)	
Yes	155 (70.8)
No	59 (26.9)
Missing	5 (2.3)
Steroid** dose at initiation of BI, mg (range)	
Median	37.5 (0-160)
EIAED, n (%)	
Yes	37 (16.9)
No	182 (83.1)
Tumor size, mm^2 (range)***	
Median	1264 (90-8291)
Frontal location, n (%)	
Yes	52 (23.7)
No	167 (76.3)
Objective neurological deficit in general, n (%)	
No	75 (34.2)
Yes	144 (65.8)
Neurocognitive deficit, n (%)	
No	103 (47.0)
Yes	116 (53.0)
Aphasia, n (%)	
No	143 (65.3)
Yes	76 (34.7)
Hemianopsia, n (%)	
No	169 (77.2)
Yes	50 (22.8)
Hemiparesis, n (%)	
No	140 (63.9)
Yes	79 (36.1)
Ataxia, n (%)	
No	163 (74.4)
Yes	50 (22.8)
Missing	6 (2.7)
Time from GBM diagnosis to start of BI treatment, months (range)	
Median	10 (1-107)
Time since last RT or TMZ, months (range)	
Median	3 (1-104)
Time since last surgery, months (range)	
Median	3 (1-48)

Abbreviations: BI, bevacizumab plus irinotecan; EIAED, enzyme inducing anti-epileptic drug; RT, radiotherapy; TMZ, temozolomide.
Prior anaplastic astrocytoma or other histology progressing to grade IV glioma.
****Prednisolone***
***** Sum of products of perpendicular diameters of all measurable enhancing lesions.***

RESULTS

Table 2. Multivariate analysis of response at first evaluation, best response, PFS and OS.

	Response at first evaluation OR (95% CI)	Best response OR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
WHO PS, 1 vs. 0	1.15 (0.56-2.38) *P* = 0.700	1.18 (0.59-2.35) *P* = 0.634	1.01 (0.73-1.41) *P* = 0.951	1.16 (0.82-1.63) *P* = 0.403
WHO PS, 2 vs. 0	0.41 (0.10-1.65) *P* = 0.207	0.52 (0.16-1.70) *P* = 0.280	1.14 (0.73-1.78) *P* = 0.579	1.29 (0.82-2.03) *P* = 0.270
Neurocognitive deficit, yes vs. no	0.94 (0.48-1.85) *P* = 0.857	1.00 (0.53-1.90) *P* = 0.994	1.33 (1.00-1.77) ***P* = 0.049**	1.40 (1.04-1.89) ***P* = 0.029**
Multifocal disease, yes vs. no	0.62 (0.30-1.29) *P* = 0.201	0.67 (0.34-1.31) *P* = 0.239	1.56 (1.15-2.11) ***P* = 0.004**	1.87 (1.37-2.56) ***P* < 0.0001**
Steroid dose, > 10mg vs. ≤ 10mg	0.45 (0.22-0.93) ***P* = 0.030**	0.51 (0.26-1.02) *P* = 0.056	1.42 (1.00-2.00) ***P* = 0.049**	1.70 (1.18-2.45) ***P* = 0.004**
C-index	0.662	0.625	0.625	0.644

Logistic regression analysis was used modelling the probability of response; Cox proportional hazards model was used in PFS and OS analysis.

Fig. 1. Kaplan-Meier curves of residual PFS by response at landmark week 9

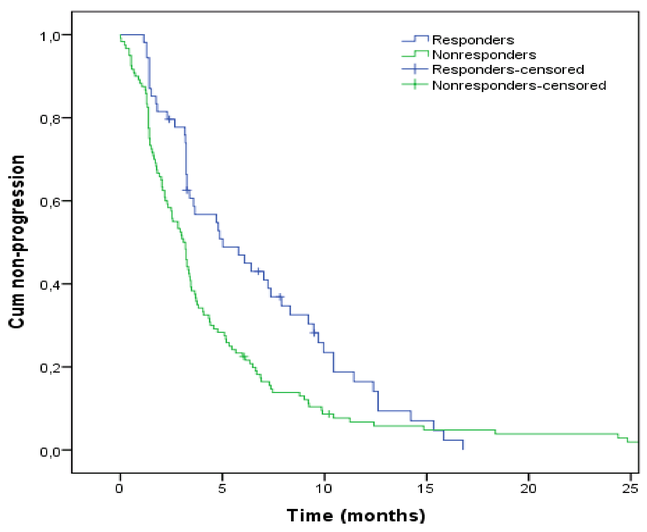


Fig. 2. Kaplan-Meier curves of residual OS by response at landmark week 9

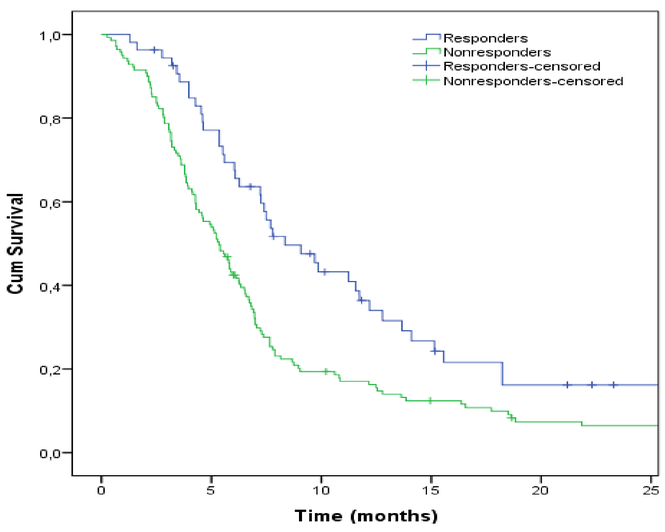


Table 3. Multivariate analysis of residual PFS and residual OS at landmark week 9

	Residual PFS HR (95 % CI)	Residual OS HR (95 % CI)
WHO PS at landmark, 1 vs. 0	1.37 (0.94-2.00) *P* = 0.105	1.37 (0.93-2.01) *P* = 0.110
WHO PS at landmark, ≥ 2 vs. 0	1.76 (1.06-2.91) ***P* = 0.029**	1.91 (1.19-3.07) ***P* = 0.008**
Neurocogntive deficit at baseline, yes vs. no	1.11 (0.81-1.52) *P* = 0.534	1.23 (0.89-1.69) *P* = 0.210
Multifocal at baseline, yes vs. no	1.85 (1.31-2.62) ***P* = 0.001**	2.00 (1.42-2.81) ***P* < 0.0001**
Steroid dose at landmark, > 10 mg vs. ≤ 10 mg	1.03 (0.71-1.48) *P* = 0.874	1.45 (1.00-2.10) *P* = 0.051
Response at landmark, SD + PD vs. objective response	1.45 (1.01-2.07) ***P* = 0.043**	1.55 (1.06-2.26) ***P* = 0.023**
C-index	0.675	0.695

Cox proportional hazards model was used in PFS and OS analysis.

Table 4. Change in steroid dose, WHO PS and neurological status according to best response in evaluable patients

	CR+PR (*n* = 66)	SD (*n* = 108)	PD (*n* = 23)	*P*-value
Steroid dose; n (%)				
Decreased	28 (43)	45 (43)	4 (19)	<0.0001
Unchanged	34 (52)	46 (43)	7 (33)	
Increased	3 (5)	15 (14)	10 (48)	
NR[a]	1	2	2	
WHO performance status; n (%)				
Improved	10 (15)	10 (9)	1 (5)	<0.0001
Unchanged	55 (83)	79 (75)	11 (50)	
Worsened	1 (2)	17 (16)	10 (45)	
NR[a]	0	2	1	
Neurological status; n (%)				
Improved	12 (19)	12 (12)	0 (0)	<0.0001
Unchanged	49 (78)	74 (72)	11 (48)	
Worsened	2 (3)	17 (16)	12 (52)	
NR[a]	3	5	0	

[a] Data not recorded (not included in percent determination).

CONCLUSION

- Steroid dose can predict objective response to bevacizumab.
- Neurocognitive deficit, multifocal disease and steroid dose are prognostic factors for PFS and OS.
- Response at first evaluation is a predictor of residual PFS and OS.
- Quality of life was improved in responders.

[1]Poulsen HS, Grunnet K, Sorensen M et al. Bevacizumab plus irinotecan in the treatment patients with progressive recurrent malignant brain tumours. *Acta Oncol* 2009;48(1):52-58