Abstract #4306

A Prognostic Model for Clinical Response to Bevacizumab in Recurrent Glioblastoma

Thomas Urup[1,2], Kirsten Grunnet[1,2], Ib Jarle Christensen[3], Signe Regner Michaelsen[1,2], Anders Toft[1,2], Vibeke Andrée Larsen[4], Helle Broholm[5], Michael Kosteljanetz[6], Hans Skovgaard Poulsen[1,2], Ulrik Lassen[1,2,7]

[1]Department of Radiation Biology, [2]Department of Oncology, Rigshospitalet, Copenhagen, Denmark; [3]Department of Gastroenterology, Hvidovre Hospital; [4]Department of Radiology, [5]Department of Neuropathology, [6]Department of Neurosurgery, [7]Phase I Unit; Rigshospitalet, Copenhagen, Denmark

www.radiationbiology.dk
Email: thomas.urup@regionh.dk

BACKGROUND

- Glioblastoma (GBM) are characterized by aberrant angiogenesis which has been linked to the overexpression of Vascular Endothelial Growth Factor A (VEGF).
- Bevacizumab, an antibody targeting VEGF, has shown high response rates in recurrent GBM patients.
- Objective response to bevacizumab in recurrent GBM patients is associated with increased overall survival.
- No validated predictive factors associated with clinical durable bevacizumab response have been identified.

OBJECTIVES

1° OBJECTIVE

Identify predictive factors associated with objective response to bevacizumab

2° OBJECTIVES

Identify prognostic factors and evaluate response as a bevacizumab efficacy endpoint

METHODS

Patients: Recurrent GBM patients treated with bevacizumab in combination with irinotecan in the period from May 2005 to December 2013 according to a previous published clinical protocol.[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.[1]

Response evaluation: The MacDonald and RANO criteria.

Statistical analysis: Tests of location were done using the Mann-Whitney method and tests for independence between categorical variables were performed by the χ^2 test. Changes in immunohistochemistry (IHC) expression was analyzed by Wilcoxon's Signed Rank test. Factors were screened by univariate analysis using logistic regression and Cox regression modelling response and survival endpoints. Screened factors with a *P*-value of <10% were considered for multivariate analysis. The association between objective response and survival at 9 weeks was evaluated using the landmark method. A prognostic index for OS was developed based on the final multivariate analysis.

RESULTS

Table 1. Patient characteristics

	Population (n=219)
Gender, n (%)	
Female	73 (33.3)
Male	146 (66.7)
Age, years (range)	
Median	56 (21-79)
WHO PS, 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 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)
Prior anti-angiogenic therapy, n (%)	
Yes	13 (5.9)
No	206 (94.1)
Best response to previous therapy, n (%)	
Response (CR+PR)	28 (12.8)
Non-response (SD+PD)	174 (79.4)
Missing	17 (7.8)
Relapse surgery prior to BEV + IRI, n (%)	
Yes	111 (50.7)
No	108 (49.3)
Multifocal disease, n (%)	
Yes	72 (32.9)
No	142 (64.8)
Missing	5 (2.3)
Frontal location, n (%)	
Yes	52 (23.7)
No	167 (76.3)
Tumor size, mm² (range)[a]	
Median	1264 (90-8291)
Use of corticosteroids, n (%)[b]	
Yes	155 (70.8)
No	59 (26.9)
Missing	5 (2.3)
Corticosteroid dose, mg (range)	
Median	37.5 (0-160)
EIAED, n (%)	
Yes	37 (16.9)
No	182 (83.1)
Objective neurological deficit in general, n (%)	
Yes	144 (65.8)
No	75 (34.2)
Neurocognitive deficit, n (%)	
Yes	116 (53.0)
No	103 (47.0)
Aphasia, n (%)	
Yes	76 (34.7)
No	143 (65.3)
Hemianopsia, n (%)	
Yes	50 (22.8)
No	169 (77.2)
Hemiparesis, n (%)	
Yes	79 (36.1)
No	140 (63.9)
Ataxia, n (%)	
Yes	50 (22.8)
No	163 (74.4)
Missing	6 (2.7)
Time since initial GBM diagnosis, 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: WHO PS, WHO performance status; EIAED, enzyme inducing anti-epileptic drug; RT, radiotherapy; TMZ, temozolomide.
[a]Sum of products of perpendicular diameters of all measurable enhancing lesions.
[b]Prednisolone >10mg

Table 2. Patient characteristics by best response

	Responders (CR+PR) (n = 66)	Non-responders (SD+PD) (n = 131)	*P*-value
Gender, n (%)			
Female	21 (33.9)	41 (66.1)	0.94
Male	45 (33.3)	89 (66.7)	
Age, n (%)			
≤65 years	63 (37.7)	104 (62.3)	< 0.01
>65 years	3 (10.0)	27 (90.0)	
Age, years			
Median	55.5	57.0	0.13
WHO PS, n (%)			
0	28 (36.8)	48 (63.2)	0.13
1	33 (36.3)	58 (63.7)	
2	5 (17.2)	24 (82.8)	
Tumor size, mm²			
Median	1100	1398	0.07
Multifocal disease, n (%)			
No	47 (36.4)	82 (63.6)	0.28
Yes	18 (28.6)	45 (71.4)	
Use of corticosteroids, n (%)			
No	27 (46.6)	31 (53.4)	0.01
Yes	38 (27.9)	98 (72.1)	
Corticosteroid dose, mg			
Median	25	50	< 0.01
Neurocognitive deficit, n (%)			
No	34 (35.8)	61 (64.2)	0.51
Yes	32 (31.4)	70 (68.6)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

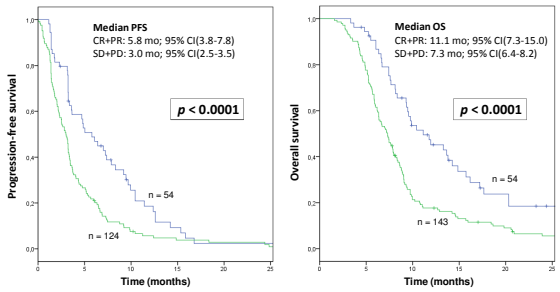
Immunohistochemistry

- IHC markers EGFR (n=158), P53 (n=158), MGMT (n=138) and IDH1 (n=72) was not associated with response, PFS and OS (*P*>0.10).
- In paired biopsies MGMT-expression increased significantly from initial GBM diagnosis to time of first relapse (n=52, *P*=0.0001). No significant changes in expression patterns were observed for EGFR (n=70), P53 (n=68) and IDH1 (n=27).

Table 3. Multivariate analysis of 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*=0.70	1.18 (0.59-2.35) *P*=0.63	1.01 (0.73-1.41) *P*=0.95	1.16 (0.82-1.63) *P*=0.40
WHO PS, 2 vs. 0	0.41 (0.10-1.65) *P*=0.21	0.52 (0.16-1.70) *P*=0.28	1.14 (0.73-1.78) *P*=0.58	1.29 (0.82-2.03) *P*=0.27
Cognitive deficit, yes vs. no	0.94 (0.48-1.85) *P*=0.86	1.00 (0.53-1.90) *P*=0.99	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*=0.20	0.67 (0.34-1.31) *P*=0.24	1.56 (1.15-2.11) ***P*=0.004**	1.87 (1.37-2.56) ***P*<0.0001**
Cortico-steroids, yes vs. no	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	0.66	0.63	0.63	0.64

Figure 1. Kaplan-Meier plot of PFS and OS by response at landmark week 9



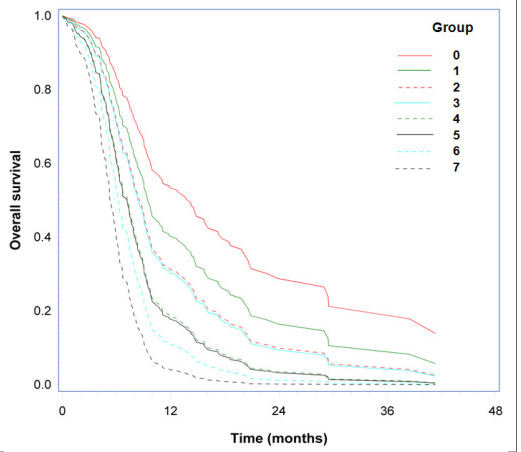
When adjusted for prognostic factors by multivariate analysis, response at first evaluation could significantly predict PFS (HR=1.45; 95% CI: 1.01-2.07; *P*=0.043) and OS (HR=1.55; 95% CI: 1.06-2.26; *P*=0.0232) at landmark week 9.

Table 4. Changes in clinical status according to best response

	CR+PR (n=66)	SD (n=108)	PD (n=23)	*P*-value
Corticosteroid 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 PS; 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 and statistics).

Figure 2. Prognostic index (n=219)



Group	Cognitive deficit	Cortico-steroid	Multifocal disease	OS6 (%) 95% CI	OS12 (%) 95% CI
0				84 (78-90)	53 (43-67)
1	x			77 (70-85)	40 (29-55)
2		x		72 (64-80)	31 (22-44)
3			x	71 (61-82)	30 (19-49)
4	x	x		62 (53-71)	19 (12-29)
5	x		x	61 (50-75)	18 (9-35)
6		x	x	53 (43-66)	11 (5-22)
7	x	x	x	40 (30-53)	4 (2-11)

Survival of risk groups: X indicates the presence of a prognostic factor.
Abbreviations: OS6, 6 month overall survival; OS12, 12 month overall survival.

CONCLUSION

- **Use of corticosteroid predicts objective response (Table 3)**
- **Neurocognitive deficit, multifocal disease and corticosteroid use are prognostic factors for poor PFS and OS (Table 3)**
- **Objective response is an early efficacy endpoint for bevacizumab treatment (Figure 1 and Table 4)**
- **Prognostic indexes, when validated, can be used in clinical practice in order to individualize and optimize relapse treatment (Figure 2)**

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