Rigshospitalet
Department of Oncology

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Prognostic and predictive biomarkers in recurrent WHO grade 3 glioma patients treated with bevacizumab and irinotecan

Toft A[1], Urup T[1,2], Grunnet K[1,2], Christensen IJ[3], Michaelsen SR[1], Broholm H[4], Larsen VA[5], Kosteljanetz M[6], Lassen U[1,2,7], Poulsen HS[1,2]

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

anders.toft.02@regionh.dk
www.Radiationbiology.dk

Results

- Malignant gliomas (WHO grade 3 and 4) are the most common and aggressive primary brain tumors in adults
- These cancers are characterized by aberrant angiogenesis, which has been linked to the overexpression of Vascular Endothelial Growth Factor (VEGF)
- Bevacizumab, an antibody targeting VEGF, has shown high response rates in recurrent grade 3 gliomas
- Objective response to bevacizumab is associated with increased overall survival in malignant gliomas
- No validated predictive factors associated with clinical durable response to bevacizumab have been identified

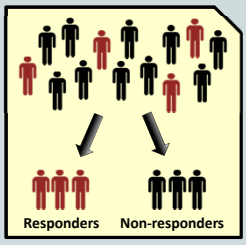
Objectives

1st Objective

To identify predictive factors associated with objective response to bevacizumab

2nd Objective

To identify prognostic factors and evaluate response as a bevacizumab efficacy endpoint



Patients and Methods

Variables	Population (n = 62)
Gender, n (%)	
Female	31 (50.0)
Male	31 (50.0)
Age, years (range)	
Median	46 (17-80)
WHO Performance Status, n (%)	
0	24 (38.7)
1	27 (43.5)
2	11 (17.8)
Grade 3 diagnosis, n (%)	
AA	22 (35.5)
AO	19 (30.6)
AOA	21 (33.9)
Primary grade 3 glioma, n (%)	
Yes	34 (54.8)
No	28 (45.2)
Frontal location, n (%)	
Yes	22 (35.5)
No	40 (64.5)
Baseline tumor size*, mm² (range)	
Median	795 (93-6314)
First line treatment, n(%)	
RT + Temozolomide	58 (93.5)
RT + Other CTX	4 (6.5)
Lines of CTX prior to baseline, n (%)	
1	52 (83.9)
2	10 (16.1)
Response to previous CTX, n (%)	
Yes	14 (22.6)
No	48 (77.4)
Relapse surgery prior to baseline	
Yes	8 (12.9)
No	54 (87.1)
Time from diagnosis to baseline, months (range)	
Median	20.4 (2.0-175.1)
Corticosteroid use at baseline, n (%)	
Yes	38 (61.3)
No	24 (38.7)
Corticosteroid dose at baseline, mg (range)	
Median	37.5 (0-125)
EIAED	
Yes	22 (35.5)
No	40 (64.5)
Multifocal disease, n (%)	
Yes	23 (37.1)
No	39 (62.9)
IDH-1†, n (%)	
Positive	33 (53.2)
Negative	19 (30.6)
Missing	10 (6.2)
ATRX†, n (%)	
Retained	28 (45.1)
Loss	24 (38.7)
Missing	10 (6.2)
p53†, n (%)	
Positive	27 (43.5)
Negative	25 (40.3)
Missing	10 (6.2)
Ki-67†, % (range)	
Median	7 (0-65)
Missing (n)	7
Microvascular proliferation†, n (%)	
Present	28 (45.2)
Absent	31 (50.0)
Missing	3 (4.8)
Necrosis†, n (%)	
Present	20 (32.3)
Absent	40 (64.5)
Missing	2 (3.2)
Cognitive deficit, *n* (%)	
None	36 (58.1)
Moderate/Major	26 (41.9)

Patients

62 recurrent grade 3 glioma patients treated with bevacizumab and irinotecan between December 2005 and November 2014 according to a previously published clinical protocol.[1]

Inclusion criteria

Histologically confirmed grade 3 glioma; measurable progressive disease by contrast-enhanced MRI after standard therapy; WHO performance status (PS) of 0-2; more than 4 weeks from chemo-therapy; more than 3 months from completion of radiation therapy.[1]

Response evaluation

RANO criteria.

Immunohistochemistry

Extent of staining was semiquantitatively evaluated. Cut-points were prespecified according to published litterature.

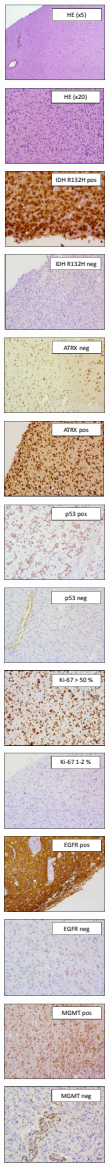
Statistical analysis

Comparison of group medians were performed using the Mann-Whitney U method and tests for independence between categorical variables were done by Fisher's exact test. Factors were screened by univariate analysis using logistic regression and Cox regression modelling response and survival endpoints. Screened factors with a *p*-value < 5 % were considered for multivariate analysis. The association between objective response and survival at 9 weeks was evaluated using the landmark method.

[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

Results

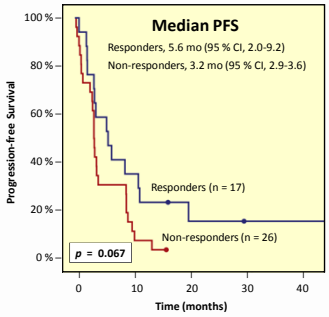
IHC

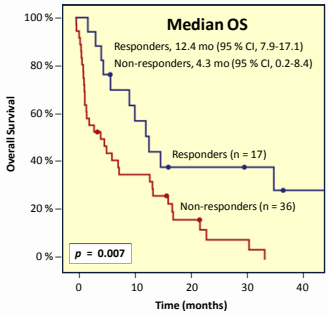


Cut points

- IDHR132H (pos/neg)
- ATRX (pos/neg)
- p53 (5 %)
- Ki-67 (quantitative)
- EGFR (pos/neg)
- MGMT (10 %)

Residual survival form landmark (week 9)





Multivariate analysis of response data

	Best response OR (95 % CI)
PS 1 vs 0	**0.44** (0.11-1.45) *p* = 0.311
PS 2 vs 0	**0.03** (0.001-0.61) *p* = 0.041
Necrosis present	**0.19** (0.05-0.79) *p* = 0.023
C-index	0.82

Multivariate analysis of survival data

	PFS HR (95 % CI)		OS HR (95 % CI)
PS 1 vs 0	**0.95** (0.53-1.70) *p* = 0.863	PS 1 vs 0	**0.79** (0.79-3.51) *p* = 0.181
PS 2 vs 0	**4.17** (1.94-8.96) *p* = 0.0003	PS 2 vs 0	**7.38** (2.94-18.53) *p* < 0.0001
Responder to previous CTX	**1.89** (1.01-3.57) *p* = 0.045	p53 positive	**2.63** (1.31-5.29) *p* = 0.007

Conclusions

- Poor PS and necrosis were negatively associated with response
- Poor PS and response to prior CTX were prognostic of reduced PFS
- Poor PS and high p53 expression were prognostic of reduced OS
- Objective response is an early efficacy endpoint for bevacizumab