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Letter to the Editor

Improved survival among females and association with lymphopenia in patients with newly diagnosed glioblastoma

Recent work suggests possible differences in clinical outcomes between male and female glioblastoma (GBM) patients.[1,2] We used a clinically and molecularly annotated database to identify sex-specific features that could be associated with outcomes in patients with GBM.

Methods

We reviewed 665 newly diagnosed, isocitrate dehydrogenase (IDH) wild type GBM patients with Karnofsky Performance Status (KPS) ≥60 treated at Dana-Farber/Brigham and Women's Cancer Center from January 1, 2010 to May 30, 2019, including 585 patients with targeted exome sequencing of 447 cancer associated genes. Deleterious mutations were defined as homozygous deletions or loss of function mutations of known tumor suppressors (as reported in TCGA, ≥3 times in the Catalogue of Somatic Mutational Signatures [COSMIC], or predicted as "damaging" in the Sorting Intolerant from Tolerant (SIFT) and/or "probably damaging" in the Polyphen 2 prediction tools), or known oncogenic mutations in proto-oncogenes (as reported in TCGA or ≥3 times in COSMIC).

Results

There were 384 (57.7%) males and 281 (42.3%) females in our cohort. There were no significant differences in clinical factors based on sex (Table 1).

Median overall survival (OS) was 22.5 months for females and 19.3 months for males (hazard ratio [HR] 0.80, 95% CI 0.67–0.96, $P = .02$). On multivariable analysis adjusted for age, KPS, extent of resection, and MGMT methylation status, female sex was associated with improved OS (adjusted hazard ratio [AHR] 0.78, 95% CI [0.64–0.95], $P = .015$, Table 1). Presence of lymphopenia within 6 weeks of completing chemoradiation approached statistical significance as a predictor of reduced OS (HR 0.84, 95% CI [0.70–1.02, $P = .081$]). On multivariable analysis adjusted for the above factors and lymphopenia, sex was no longer a significant predictor of OS (AHR 0.83, 95% CI [0.69–1.01], $P = .065$). Among non-lymphopenic patients ($N = 216$), the association between female sex and improved OS was more pronounced (AHR 0.59, 95% CI 0.411–0.85, $P = .005$) compared to the overall cohort. Among lymphopenic patients ($N = 383$), female sex was not associated with a benefit in OS (AHR 0.99, 95% CI [0.76–1.33], $P = .95$). Superior OS in females versus males was observed in MGMT unmethylated (HR 0.69, 95% CI [0.54–0.90], $P = .005$) but not in MGMT methylated (HR 0.85, 95% CI [0.64–1.14], $P = .28$) patients. Biologic sex was not associated with progression-free survival among all patients (AHR 0.94, 95% CI [0.78–1.12], $P = .49$), lymphopenic patients (AHR 0.92, 95% CI [0.72–1.18], $P = .53$), or non-lymphopenic patients (AHR 0.98, 95% CI [0.71–1.35], $P = .90$). There were no differences in rates of pseudoprogression, seizures, or venous thromboembolism between males and females, but more female patients developed lymphopenia (82.6% vs 74.0%, $P = .03$).

Thirteen genes were deleteriously altered in ≥ 5% of patients and did not differ in frequency between males and females (Table 1).

Discussion

Female sex was associated with improved survival in GBM patients after adjustment of known clinical covariates. We did not identify sex-based differences in deleterious tumor genomic alterations, though our sequencing panel may not capture all relevant mutations, and we note our data are from a single institution.

Our results suggest a possible interplay between sex and lymphopenia. Among glioma patients, female sex has been associated with lymphopenia, a predictor of worse survival.[3,4] Our results are consistent with reports of higher myelosuppressive toxicities among female patients with gliomas[3,4] and non-glioma cancers.[5] While the underlying cause is unknown, this could be due to differences in cerebral perfusion in males versus females,[6] or differential pharmacodynamics of drug clearance.

Improved female survival was seen among patients who did not develop lymphopenia, suggesting that this subgroup could be driving sex-based survival differences. Further study is necessary to understand the mechanism for sex-based differences in outcome given implications for therapy development and clinical trial design.

Table 1 Patient and Tumor Characteristics, Cox Proportional Hazards Regression Model on Overall Survival

Baseline Characteristics ($N = 665$)			
	Males (384, 57.7%)	Females (281, 42.3%)	*P*-value*
Median age	60.6 y	60.0 y	.16
KPS ≥ 90	46.1%	43.4%	.53
Extent of resection			
GTR	44.8%	47.7%	.48
STR/biopsy	55.2%	52.3%	
MGMT			
Methylated	37.8%	43.4%	.11
Unmethylated	62.2%	56.6%	
Received temozolomide	95.1%	95.7%	.71
Radiation dose			
≥59.4 Gy	85.2%	87.5%	.43
<59.4 Gy	14.8%	12.5%	
Clinical trial enrollment	24.7%	21.0%	.27
Tumor Mutational Characteristics ($N = 585$)			
Gene	Males (340, 58.1%)	Females (245, 41.9%)	*P*-value*
CDKN2A	45.6%	45.7%	.93
CDKN2B	41.8%	43.3%	.74
EGFR	34.7%	40.0%	.19
PTEN	28.2%	29.8%	.71
TP53	28.2%	30.2%	.64
MTAP	18.2%	18.8%	.91
NF1	11.5%	9.4%	.50
CDK4	12.1%	7.8%	.18
RB1	5.6%	6.5%	.72
MDM4	6.2%	5.7%	.86
ATM	5.9%	3.7%	.25
MDM2	7.4%	4.1%	.11
PIK3R1	6.2%	4.1%	.19
Pseudoprogression and Toxicity			
	Males	Females	*P*-value*
Pseudoprogression			
Yes	86 (32.0%)	69 (36.9%)	.27
No	183 (68.0%)	118 (63.1%)	
Seizures			
Yes	127 (43.3%)	75 (36.9%)	.15
No	166 (55.9%)	128 (63.1%)	
VTE			
Yes	49 (16.7%)	23 (11.5%)	.11
No	245 (83.3%)	177 (88.5%)	
Lymphopenia			
Yes	199 (74.0%)	161 (82.6%)	.029
No	70 (26.0%)	34 (17.4%)	

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Table 1 Continued

Cox proportional hazards regression model on overall survival				
	Univariate AHR (95% CI)	*P*-value	Multivariate AHR (95% CI)	*P*-value
Age	1.03 (1.03–1.04)	<.001	1.04 (1.03–1.05)	<.001
KPS ≥ 90	0.68 (0.57–0.82)	<.001	0.73 (0.60–0.89)	.002
Extent of resection (GTR vs STR/biopsy)	0.81 (0.68–0.97)	.02	1.12 (0.92–1.37)	.28
MGMT methylated	0.49 (0.40–0.59)	<.001	0.38 (0.31–0.47)	<.001
Biologic sex (female vs male)	0.81 (0.68–0.97)	.02	0.78 (0.64–0.96)	.016

GTR, gross total resection; KPS, Karnofsky performance status; MGMT, O^6-methylguanine-DNA methyltransferase; STR, subtotal resection; VTE, Venous thromboembolism.
*Unpaired *t*-tests and Fisher's exact tests were used for analyses as appropriate.

Author Contributions

Data collection: D.D.S., G.C.Y., M.J.L.-F. Method development: D.D.S., A.H.N., K.L.L., R.R. Project conception: P.Y.W., R.R.

Conflict of interest statement. None declared.

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