Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com

Letter to the Editors-in-Chief

In primary glioblastoma fewer tumor copy number segments of the F13A1 gene are associated with poorer survival

Steven Lehrer[a,*], Francine R. Dembitzer[b], Peter H. Rheinstein[c], Kenneth E. Rosenzweig[a]

[a] Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, United States
[b] Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, United States
[c] Severn Health Solutions, Severna Park, MD, United States

ARTICLE INFO

Keywords:
Glioblastoma
Survival
Factor XIII
The Cancer Genome Atlas

Glioblastoma multiforme (GBM), the most common primary tumor of the central nervous system, is associated with hypercoagulability and venous thromboembolism. The circulating substance inducing the hypercoagulability is uncertain. Anticoagulants are frequently administered to GBM patients, although these agents increase the risk of intracerebral hemorrhage [1].

An inhibitor of the colony stimulating factor-1 receptor (CSF-1R) alters macrophages and blocks glioma progression. The CSF-1R inhibitor targets tumor-associated macrophages and microglia (TAMs) in a mouse proneural GBM model, dramatically increasing survival and causing regression of established tumors. Clotting factor F13A1 is part of a five gene signature associated with response [2]. Moreover, F13A1 is one element of a 9-microRNA prognostic signature which stratified patients into risk groups strongly associated with survival in all glioblastoma subtypes except the non-G-CIMP (Glioma CpG Island Methylator Phenotype) proneural group [3].

Coagulation factor XIII A chain is a protein that in humans is encoded by the F13A1 gene [4]. The macrophages that contain factor XIII reportedly facilitate the deposition of crosslinked fibrin or fibrinogen in some patients with breast cancer and Hodgkin's disease [5].

In this analysis, we examined the role of F13A1 in human glioblastoma survival.

In newly diagnosed GBM, we assessed the association between F13A1 and glioblastoma overall survival using the GBM cohort (dataset IDTCGA.GBM.sampleMap/SNP6_nocnv_genomicSegment) in TCGA (The Cancer Genome Atlas) database (TCGA-GBM). To access and analyze the data we used the UCSC Xena browser (https://xenabrowser.net). Survival data of the GBM subgroup were extracted for analysis and generation of Kaplan–Meier curves for overall survival. The optimal cutoff was identified by methods described in the R2 web-based application (http://r2.amc.nl). Further details have been published [6].

Data from 571 patients was analyzed. The mean age at diagnosis was 57.8 ± 14.5 (mean ± SD). The longest tumor dimension was 1.1 ± 0.43 cm; shortest dimension 0.44 ± 0.24 cm. Karnofsky performance score was 77.2 ± 15.8. The patients were 38.8% women and 60.2% men; in 1% of cases gender was not specified. 64% of patients received chemotherapy; 81.6% received radiation therapy. 11.6% received hormonal treatment (glucocorticoids).

Patient overall survival (days) by tumor F13A1 copy number segments (log2tumor/normal), after removal of common germ-line copy-number variants (CNVs), is shown in Fig. 1. The common CNVs and method of removal are described on the xena browser site [7]. Note that copy number segments ≤ 0.02270 are associated with significantly poorer survival ($p = 0.028$). 282 patients with copy number segments ≤ 0.02270 had median survival 337 days; 289 patients with copy number segments ≥ 0.02270 had median survival 407 days. Survival was identical for optimal or median cutoff. F13A1 copy number segments did not significantly differ for treated and untreated patients.

O-6-methylguanine-DNA methyltransferase (MGMT) copy number segments did not correlate with F13A1 copy number segments ($r = -0.057$, $p = 0.495$). Among molecular markers, the methylation status of the O-6-methylguanine-DNA methyltransferase (MGMT) gene

* Corresponding author at: Box 1236, Radiation Oncology, Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York 10029, United States.
Email address: steven.lehrer@mssm.edu (S. Lehrer)

https://doi.org/10.1016/j.thromres.2018.05.001
Available online xxx
0049-3848/

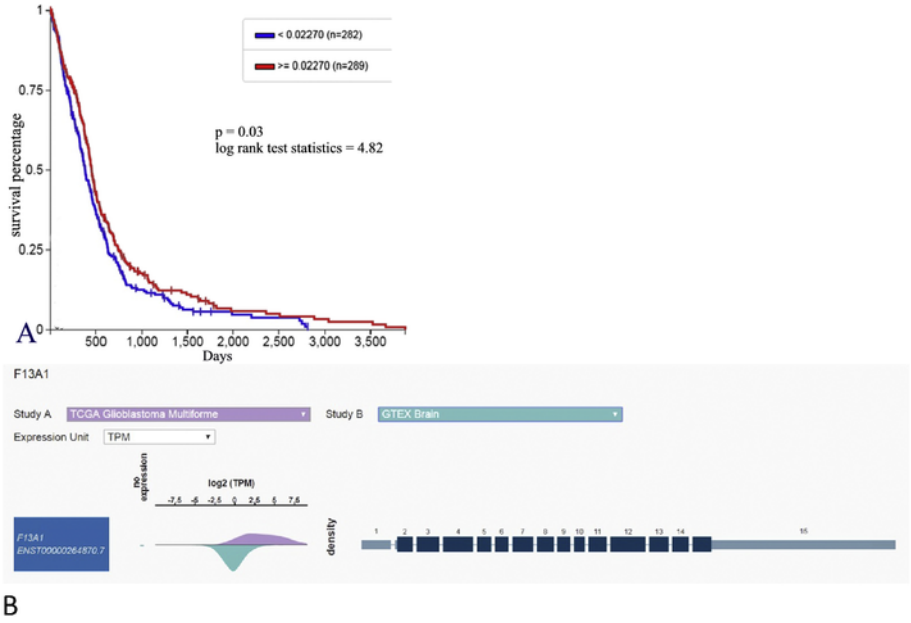

Fig. 1. (A). Patient survival (days) by copy number segments (log2tumor/normal) after removal of common germ-line copy-number variants (CNVs). Removing the common germline copy-number variants can make it easier to focus on the copy variation that is just in the tumor. Note that that copy number segments ≥ 0.02270 (red line) are associated with significantly better survival, while copy number segments ≤ 0.02270 (blue line) are associated with significantly poorer survival.(B). F13A1 Transcript-specific expression for "tumor" TCGA data and "normal" GTEX data (transcripts per million). All RNAseq data was generated by the Toil pipeline recompute done by the UCSC Computational Core using the RSEM package. All transcripts are from Gencode V23 comprehensive annotation. Regions that are intronic in all transcripts are removed. The remaining exonic regions are numbered 1.0.15. Note the variation of expression of the F13A1 ENST00000264870.7 transcript in tumor (lavender) versus normal (blue-green) tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

has shown a significant association with survival in patients with GBM [8].

TCGA studies have identified four subtypes of GBM. These subtypes are defined by genomic characteristics, survival length, patient age and treatment response. The four groups were named Proneural, Neural, Classical and Mesenchymal [9]. The proneural subtype has the best survival. There is no significant variation in F13A1 copy number segments among the 4 subtypes.

Armand Trousseau first reported the relationship of malignant tumors and coagulation in 1865. Trousseau diagnosed the syndrome in himself two years later, dying soon afterward of gastric cancer. Recent findings suggest that genetic pathways within tumor cells might trigger some thrombotic phenomena [10]. One common factor XIII Variant, Val34Leu, is protective against venous thromboembolism [11] and might be partly responsible for the increased survival of GBM patients with tumors having multiple copy number segments of F13A1.

D-dimer plasma level, a marker of coagulation activation, is elevated in patients with active malignant disease. Moreover, elevated d-dimer levels are significantly associated with mortality compared to normal values in GBM [12]. Combined measurement of factor XIII and D-dimer is helpful for differential diagnosis in patients with suspected pulmonary embolism, suggesting that the two substances may interact [13].

The increased median overall survival associated with increased F13A1 copy number segments (2.3 months, hazard ratio 0.812, 95% confidence interval 0.72 to 0.91; P = 0.028 by the log-rank test Fig. 1A) is comparable to the increased median overall survival after treatment with temozolomide (2.6 months) [14]. Stupp et al. found that the unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95% confidence interval, 0.52 to 0.75; P < 0.001 by the log-rank test). The hazard ratio difference (0.812 versus 0.63) implies that the survival increase seen with the F13A1 copy number segments difference was not as great as that seen with temozolomide, though the confidence intervals overlap slightly.

Fig. 1B shows F13A1 Transcript-specific expression for "tumor" TCGA data and "normal" GTEX data (transcripts per million). Note the variation of expression of the F13A1 ENST00000264870.7 transcript in tumor (lavender) versus normal (blue-green) tissue.

Although molecular markers for GBM are limited, some epigenetic markers, copy number variants, and mutation genotypes predict survival, for example IDH status, PTEN and EGFRvIII [15]. Other coagulation markers also relate to survival, for example von Willebrand Factor (vWF) [16].

Multiple copy number segments and transcript-specific expression of F13A1 may represent another molecular marker. Further studies would be worthwhile.

Compliance with ethical standards

Disclosure of potential conflicts of interest: none. Drs. Lehrer, Dembitzer, Rheinstein, and Rosenzweig declare that they have absolutely no financial or other interest.

Research involving human participants and/or animals: not applicable. We used data entirely from a public database, The Cancer Genome Atlas (https://cancergenome.nih.gov/).

Informed consent: not applicable.

Compliance with ethical standards: We are entirely in compliance.

Funding

None.

Conflicts of interest

None.

References

[1] A.D. Norden, J. Bartolomeo, S. Tanaka, J. Drappatz, A.S. Ciampa, L.M. Doherty, D.C. Lafrankie, S. Ruland, E.C. Quant, R. Beroukhim, P.Y. Wen, Safety of concur-

rent bevacizumab therapy and anticoagulation in glioma patients, J. Neuro-Oncol. 106 (1) (2012) 121–125.
[2] S.M. Pyonteck, L. Akkari, A.J. Schuhmacher, R.L. Bowman, L. Sevenich, D.F. Quail, O.C. Olson, M.L. Quick, J.T. Huse, V. Teijeiro, M. Setty, C.S. Leslie, Y. Oei, A. Pedraza, J. Zhang, C.W. Brennan, J.C. Sutton, E.C. Holland, D. Daniel, J.A. Joyce, CSF-1R inhibition alters macrophage polarization and blocks glioma progression, Nat. Med. 19 (10) (2013) 1264–1272.
[3] J. Hayes, H. Thygesen, C. Tumilson, A. Droop, M. Boissinot, T.A. Hughes, D. Westhead, J.E. Alder, L. Shaw, S.C. Short, S.E. Lawler, Prediction of clinical outcome in glioblastoma using a biologically relevant nine-microRNA signature, Mol. Oncol. 9 (3) (2015) 704–714.
[4] V. Ivaskevicius, A. Biswas, M.L. Garly, J. Oldenburg, Comparison of F13A1 gene mutations in 73 patients treated with recombinant FXIII-A2, Haemophilia 23 (3) (2017), e194-e203.
[5] V.C. Yee, L.C. Pedersen, T.I. Le, P.D. Bishop, R.E. Stenkamp, D.C. Teller, Three-dimensional structure of a transglutaminase: human blood coagulation factor XIII, Proc. Natl. Acad. Sci. U. S. A. 91 (15) (1994) 7296–7300.
[6] R2 Support Team, Chapter 8: Working with Kaplan Meier. R2 tutorials. Release 3.1.2, 201773–82.
[7] dataset Copy Number Segments - After Remove Germline Cnv, in: https://xenabrowsernet/datapages/?dataset=TCGAGBMsampleMap%2FSNP6_nocnv_genomicSegment&host=https%3A%2F%2Ftcgaxenahubs.net, 2018, (retrieved 3/13/2018).
[8] S. Kreth, N. Thon, S. Eigenbrod, J. Lutz, C. Ledderose, R. Egensperger, J.C. Tonn, H.A. Kretzschmar, L.C. Hinske, F.W. Kreth, O-methylguanine-DNA methyltransferase (MGMT) mRNA expression predicts outcome in malignant glioma independent of MGMT promoter methylation, PLoS One 6 (2) (2011), e17156.
[9] R.G.W. Verhaak, K.A. Hoadley, E. Purdom, V. Wang, Y. Qi, M.D. Wilkerson, C.R. Miller, L. Ding, T. Golub, J.P. Mesirov, G. Alexe, M. Lawrence, M. O'Kelly, P. Tamayo, B.A. Weir, S. Gabriel, W. Winckler, S. Gupta, L. Jakkula, H.S. Feiler, J.G. Hodgson, C.D. James, J.N. Sarkaria, C. Brennan, A. Kahn, P.T. Spellman, R.K. Wilson, T.P. Speed, J.W. Gray, M. Meyerson, G. Getz, C.M. Perou, D.N. Hayes, Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1, Cancer Cell 17 (1) (2010) 98–110.
[10] A. Varki, Trousseau's syndrome: multiple definitions and multiple mechanisms, Blood 110 (6) (2007) 1723–1729.
[11] P.S. Wells, J.L. Anderson, D.K. Scarvelis, S.P. Doucette, F. Gagnon, Factor XIII Val34Leu variant is protective against venous thromboembolism: a HuGE review and meta-analysis, Am. J. Epidemiol. 164 (2) (2006) 101–109.
[12] M. Hoke, K. Dieckmann, R. Koppensteiner, M. Schillinger, C. Marosi, W. Mlekusch, Prognostic value of plasma d-dimer levels in patients with glioblastoma multiforme - results from a pilot study, Wien. Klin. Wochenschr. 123 (7–8) (2011) 199–203.
[13] N. Tang, Z. Sun, D. Li, J. Yang, S. Yin, Q. Guan, Combined measurement of factor XIII and D-dimer is helpful for differential diagnosis in patients with suspected pulmonary embolism, Clin. Chem. Lab. Med. 55 (12) (2017) 1948–1953.
[14] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S.K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R.O. Mirimanoff, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N. Engl. J. Med. 352 (10) (2005) 987–996.
[15] J. Lu, M.C. Cowperthwaite, M.G. Burnett, M. Shpak, Molecular predictors of long-term survival in glioblastoma Multiforme patients, PLoS One 11 (4) (2016), e0154313.
[16] G. Marfia, S.E. Navone, C. Fanizzi, S. Tabano, C. Pesenti, H.L. Abdel, A. Franzini, M. Caroli, M. Miozzo, L. Riboni, P. Rampini, R. Campanella, Prognostic value of preoperative von Willebrand factor plasma levels in patients with glioblastoma, Cancer Med. 5 (8) (2016) 1783–1790.