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Longitudinal prospective study of matrix metalloproteinase-9 as a serum marker in gliomas

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Abstract

The objective of this study was to evaluate if longitudinal measurements of serum matrix metalloproteinase-9 (MMP-9) correlated with disease status or survival in adults with gliomas. Serum samples were collected prospectively and concurrently with MRI scans at multiple time points during the course of the disease. MMP-9 levels were determined by ELISA and correlated with radiographic disease status and survival. Forty-one patients with low-grade gliomas, 105 with anaplastic gliomas, and 197 with glioblastoma enrolled in this study from August 2002 to September 2008. A total of 1,684 serum samples (97.1% of all MMP-9 samples) had a matching MRI scan. No statistically significant association was observed between levels of serum MMP-9 and radiographic disease status in low-grade gliomas ($P = 0.98$), anaplastic gliomas ($P = 0.39$) or glioblastomas ($P = 0.33$). Among patients with glioblastoma, longitudinal increases in MMP-9 had a weak association with shorter survival (HR = 1.1 per each doubling in MMP-9 levels, 95% CI, 1.0–1.3, $P = 0.04$) but they were not independently associated with survival when adjusted for age, extent of resection, and performance status. Changes in serum MMP-9 were not associated with survival in the anaplastic glioma cohort. Serum MMP-9 showed no utility in determining glioma disease status and was not a clinically relevant prognostic marker of survival.

Keywords

Glioma; Glioblastoma; Serum marker; Matrix metalloproteinase-9

Introduction

Neuroimaging using MRI scans is the standard method to evaluate disease status in patients with glioma but the frequency of pseudo-progression and pseudo-response after treatment are well-known limitations [1]. Molecular prognostic markers such as 1p and 19q chromosome co-deletion in oligodendroglial tumors [2, 3] and MGMT promoter methylation in glioblastomas (GBMs) [4], require adequate tumor tissue that is often not readily accessible. Easily available biomarkers to assess disease status, prognosis or both could improve glioma drug development and patient care. Desirable features of a potential serum biomarker for glioma should include ease of performance and it should reflect the dynamic changes that occur in gliomas over the course of the patient's illness.

One of the main features of WHO grade II–IV gliomas is their infiltrative nature into surrounding brain making surgery inherently palliative rather than curative. One of the mechanisms involved in glioma cell invasion and infiltration is degradation of extracellular matrix proteins by matrix metalloproteinase-9 (MMP-9, previously called 92-kDa type collagenase or gelatinase B) [5, 6]. MMP-9 is overexpressed in gliomas, especially in anaplastic glioma and GBM, compared to normal brain tissue [6]. In addition to tumor invasion and infiltration, MMP-9 participates in the angiogenic switch required for tumor neovascularization and growth [7]. MMP-9, once secreted into the bloodstream, can be easily measured by ELISA. Our preliminary results suggested that serum MMP-9 levels may correlate with glioma disease status and hence may be a potential biomarker [8]. We report an expanded cohort of consecutive adults with WHO grade II–IV gliomas followed lowed for a longer period to ascertain whether prospective longitudinal serum MMP-9 measurements correlated with disease status or survival.

Patients and methods

Eligibility

Patients with glioma confirmed histologically at our institution were eligible any time during their disease course. Patients with brain tumor identified by imaging, who had not yet undergone resection, could be enrolled before their initial surgical procedure but continued on study only if glioma was confirmed histologically. Additional eligibility criteria included age ≥ 18 years and KPS C ≥ 40. Concurrent active systemic malignancy, infection, HIV, rheumatoid arthritis and severe osteoarthritis were exclusion criteria because those conditions can elevate MMP-9. Post surgical samples were obtained at least 2 weeks from resection or biopsy because serum MMP-9 increases in the immediate postoperative period [8]. Patients were considered to have a newly diagnosed glioma if their first serum MMP-9 measurement was obtained within 3 months of the pathological diagnosis date; this included 58 newly diagnosed GBM patients who enrolled in a Memorial Sloan-Kettering Cancer Center (MSKCC) randomized phase II trial of chemoradiation with temozolomide [9]. This study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board and all patients signed a written informed consent.

Study design

This study collected serum samples and obtained MRI scans at baseline and every 2–3 months. One hundred and forty-three patients reported in our preliminary study [8] were included in the current analysis. MMP-9 levels were determined by ELISA (Quantikine R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. A subset of patients had both serum and plasma MMP-9 levels measured because MMP-9 is released by leukocytes and platelets during clotting, which can affect serum MMP-9 results. Radiographic disease status was assessed by MRI, and tumor size was determined by measuring contrast-enhancing lesions using standard Macdonald criteria [10]. Non-enhancing gliomas were measured by cross-sectional evaluation of areas of FLAIR hyperintensity. To ensure uniformity, all MRI scans were reviewed by at least two of three authors (A.F.H., S.K. and F.M.I.) who were blinded to the MMP-9 levels and patients' outcomes. MRI scans and MMP-9 levels were considered matched if they were performed within 30 days of each other. Patients with complete response were considered as having no evidence of radiographic disease while patients with partial response, stable disease, and progressive disease were classified as having evidence of radiographic disease.

Statistical analyses

MMP-9 values were log transformed before all statistical testing because the distribution of MMP-9 values was skewed. We tested the association between MMP-9 and radiographic disease status by incorporating all measurements in a logit model with generalized estimating equations that corrected for within-patient correlations [11]. Survival was measured from study registration to date of death or last follow-up and estimated by Kaplan–Meier methodology. The effect of MMP-9 (on the log-scale) on survival was analyzed as a time-dependent covariate in a Cox proportional hazards model [12]. Correlations between tumor size and serum MMP-9 levels and between MMP-9 measurements in plasma and serum were assessed by Pearson's correlation coefficient.

Results

Patient characteristics

A total of 343 eligible patients with gliomas (59% men) enrolled in this study from August 2002 to September 2008. Follow-up extended through December 2009. There were 41 patients with low-grade gliomas, 105 with anaplastic gliomas, and 197 with GBM. Forty percent of anaplastic glioma and 72% of GBM patients were enrolled within the first 3 months of diagnosis. At time of analysis, 24% of low-grade glioma, 48% of anaplastic glioma, and 81% of GBM patients had died. Median follow-up for survivors was 52 months for low-grade glioma patients, 44 months for anaplastic glioma patients, and 29 months for GBM patients.

Correlation of serum and plasma MMP-9 levels

There were 714 samples from 24 patients with low-grade gliomas, 60 patients with anaplastic gliomas, and 111 with GBMs that were evaluated for MMP-9 levels in both serum and plasma. There were strong correlations between serum and plasma MMP-9 levels in

low-grade gliomas ($r = 0.52$, $P < 0.0001$), anaplastic gliomas ($r = 0.58$, $P < 0.0001$), and GBMs ($r = 0.61$, $P < 0.0001$). Based on these results, all subsequent analyses were performed with serum levels.

Serum MMP-9 level and radiographic disease status

A total of 1,734 serial serum samples were collected, including 266 samples from patients with low-grade gliomas, 634 from anaplastic gliomas, and 834 from GBM. A total of 1,684 (97.1%) serum samples had a matched MRI scan, including 263 low-grade glioma, 622 anaplastic glioma, and 799 GBM samples. Fifty (2.9%) serum samples had no matching MRI and were excluded. MMP-9 was obtained within 1 week of the MRI in 77% of samples; 56% of samples were obtained on the same day of the MRI scan. Levels of serum MMP-9 were not significantly different according to radiographic disease status in low-grade gliomas ($P = 0.98$), anaplastic gliomas ($P = 0.39$) or GBM ($P = 0.33$). In addition, there was no correlation between either unidimensional (length) or bidimensional (area) tumor size and serum MMP-9 levels in patients with a low-grade glioma, anaplastic glioma, or GBM. Correlation coefficient values ranged from −0.05 to 0.12.

MMP-9 and survival

Twenty-seven patients with (68%) low-grade glioma, 78 (73%) with anaplastic glioma, and 118 (60%) with GBM had at least a doubling in serum MMP-9 level during this longitudinal study. Increases in serum MMP-9 were not associated with changes in survival in the anaplastic gliomas (hazard ratio (HR) = 1.1 per each doubling in MMP-9 levels, 95% CI: 0.8–1.3, $P = 0.62$) or even when the anaplastic astrocytoma (HR = 1.2 per each doubling in MMP-9 levels, 95% CI: 0.9–1.6, $P = 0.22$) cohort was examined separately. Among patients with GBM, longitudinal increases in MMP-9 had a weak correlation with shorter survival (HR = 1.1 per each doubling in MMP-9 levels, 95% CI, 1.0–1.3, $P = 0.04$) (Table 1). On a multivariate analysis, longitudinal MMP-9 increases were not an independent prognostic marker after adjusting for age, extent of resection, and performance status (Table 2). No MMP-9 effect on survival was seen in the subgroups of patients with newly diagnosed anaplastic glioma and GBM or 58 GBM enrolled in an upfront phase II trial of chemoradiation with temozolomide [9]. Survival analysis for the low-grade glioma cohort was not performed due to the small number of deaths in that group ($n = 10$).

MMP-9 and chemoradiotherapy

Among 58 patients with newly-diagnosed GBM enrolled in our chemoradiation trial, 53 had baseline values prior to radiation and temozolomide. The median MMP-9 values were similar before (492 ng/ml, interquartile range: 312 and 717) and after (445, interquartile range: 282 and 744) chemoradiotherapy.

Discussion

This prospective longitudinal study failed to show any clinical relevance of serum MMP-9 as a marker for disease status or survival in a large cohort of patients with glioma. Although our prior study showed that serum MMP-9 could be potentially useful as a biomarker of disease status in anaplastic gliomas [8], this significantly larger cohort did not confirm that

finding. Our preliminary results showing that, in patients with anaplastic gliomas, there was a moderated correlation between serum MMP-9 and radiographic disease status was based on the analysis of 112 MRI scans [8]. The current study, encompassing 622 MRI scans matched with serum MMP-9 levels in anaplastic gliomas, clearly refuted that association. Due to the small sample size in our previous work, no multivariate analysis was performed [8]. The current study reports that although longitudinal MMP-9 increase was weakly associated with increased risk of death in glioblastoma patients on a univariate Cox analysis, it was not an independent factor after correction for other clinical prognostic factors. This lack of correlation occurred despite reports of MMP-9 expression in glioma detected by immunohistochemistry in up to 81% of tissue samples, tumor overexpression of MMP-9 mRNA in 91% of gliomas [13], and MMP-9 secretion by tumor cells in the bloodstream. Several studies in other solid tumors showed that MMP-9 in serum or plasma is elevated in patients with cancer compared to normal controls [14, 15]. Most of these studies did not collect MMP-9 longitudinally and the association between MMP-9 and prognosis or disease status has not been well characterized [16–19]. A small study in primary brain tumors showed that urinary MMP had very good sensitivity and specificity to differentiate individuals with primary brain tumors (n = 28) from healthy controls (n = 23) [20]. A very small longitudinal study of five patients with primary brain tumors showed clearance of urinary MMP after gross total resection of the tumor [20]. A serum marker to evaluate disease status in conjunction with standard imaging methods or to predict prognosis over time, would be most helpful but its identification remains elusive.

Several issues could have accounted for our negative MMP-9 results. It is possible that the inclusion solely of patients whose glioma overexpressed MMP-9 would strengthen the correlation with disease status or survival. For example, a recent study showed that MMP-9 overexpression was more common in primary than in secondary GBM, and in those overexpressing EGFR or expressing an activated mutant EGFR, EGFRvIII [21]. Unfortunately, tumor tissue was not available to evaluate the association between serum MMP-9 and tumor EGFRvIII status. Technical differences could also have influenced the results. Some studies report that MMP-9 measurements in serum can be contaminated by metalloproteinases released by leukocytes and platelets during the clotting process [16]. Prior studies have suggested that MMP-9 measurements in serum do not reliably reflect circulating MMP-9 levels and may be artificially high compared to results obtained from plasma samples [22–24]. We showed, however, that serum and plasma MMP-9 samples were highly correlated in our large sample size, so serum samples could be used appropriately. Another limitation is that MMP-9 is unstable even when stored at −80 C and its detection drops by 65% at 2 years [25]. Our samples, however, were processed after collection so this should not have influenced the results. It is possible that determination of MMP-9 activity through zymography would more reliably predict disease status and survival. However, a study of MMP-9 in the cerebrospinal fluid showed that MMP-9 concentration was more sensitive and specific to detect CNS malignancies than MMP-9 activity [26]. Finally, the treatment in the overall cohort of patients was not standardized. Nonetheless, MMP-9 was not a significant marker of disease status in the subgroup of patients with newly diagnosed GBM who were treated uniformly in a chemoradiation clinical trial in our institution [9].

In conclusion, we showed that longitudinal evaluation of serum MMP-9 is not associated with survival or radiographic disease status in molecularly unselected patients with grade II–IV glioma. Serum or plasma MMP-9 could still prove useful in prospective clinical trials using inhibitors of MMP-9 [27] or in patients selected according to MMP-9 tumor expression.

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References

1. van den Bent MJ, Vogelbaum MA, Wen PY, Macdonald DR, Chang SM (2009) End point assessment in gliomas: novel treatments limit usefulness of classical Macdonald's Criteria. J Clin Oncol 27:2905–2908. 10.1200/JCO.2009.22.4998 [PubMed: 19451418]
2. Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Laperierre N, Mehta M, Curran W (2006) Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 24:2707–2714. 10.1200/JCO.2005.04.3414 [PubMed: 16782910]
3. van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, Haaxma-Reiche H, Kros JM, van Kouwenhoven MC, Vecht CJ, Allgeier A, Lacombe D, Gorlia T (2006) Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 24:2715–2722. 10.1200/JCO.2005.04.6078 [PubMed: 16782911]
4. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997–1003. 10.1056/NEJMoa043331 [PubMed: 15758010]
5. Lakka SS, Rajan M, Gondi C, Yanamandra N, Chandrasekar N, Jasti SL, Adachi Y, Siddique K, Gujrati M, Olivero W, Dinh DH, Kouraklis G, Kyritsis AP, Rao JS (2002) Adenovirus-mediated expression of antisense MMP-9 in glioma cells inhibits tumor growth and invasion. Oncogene 21:8011–8019. 10.1038/sj.onc.1205894 [PubMed: 12439751]
6. Rao JS, Yamamoto M, Mohaman S, Gokaslan ZL, Fuller GN, Stetler-Stevenson WG, Rao VH, Liotta LA, Nicolson GL, Sawaya RE (1996) Expression and localization of 92 kDa type IV collagenase/gelatinase B (MMP-9) in human gliomas. Clin Exp Metastasis 14:12–18 [PubMed: 8521611]
7. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, Tanzawa K, Thorpe P, Itohara S, Werb Z, Hanahan D (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744. 10.1038/35036374 [PubMed: 11025665]
8. Hormigo A, Gu B, Karimi S, Riedel E, Panageas KS, Edgar MA, Tanwar MK, Rao JS, Fleisher M, DeAngelis LM, Holland EC (2006) YKL-40 and matrix metalloproteinase-9 as potential serum biomarkers for patients with high-grade gliomas. Clin Cancer Res 12:5698–5704. 10.1158/1078-0432.CCR-060181 [PubMed: 17020973]
9. Clarke JL, Iwamoto FM, Sul J, Panageas K, Lassman AB, DeAngelis LM, Hormigo A, Nolan CP, Gavrilovic I, Karimi S, Abrey LE (2009) Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma. J Clin Oncol 27:3861–3867. 10.1200/JCO.2008.20.7944 [PubMed: 19506159]
10. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277–1280 [PubMed: 2358840]
11. Zeger SL, Liang KY (1992) An overview of methods for the analysis of longitudinal data. Stat Med 11:1825–1839 [PubMed: 1480876]

12. Cox D, Oakes D (1990) Analysis of survival data. Chapman & Hill, New York
13. Komatsu K, Nakanishi Y, Nemoto N, Hori T, Sawada T, Kobayashi M (2004) Expression and quantitative analysis of matrix metalloproteinase-2 and −9 in human gliomas. Brain Tumor Pathol 21:105–112 [PubMed: 15696970]
14. Tutton MG, George ML, Eccles SA, Burton S, Swift RI, Abulafi AM (2003) Use of plasma MMP-2 and MMP-9 levels as a surrogate for tumour expression in colorectal cancer patients. Int J Cancer 107:541–550. 10.1002/ijc.11436 [PubMed: 14520690]
15. Ranuncolo SM, Matos E, Loria D, Vilensky M, Rojo R, Bal de Kier Joffe E, Ines Puricelli L (2002) Circulating 92-kilodalton matrix metalloproteinase (MMP-9) activity is enhanced in the euglobulin plasma fraction of head and neck squamous cell carcinoma. Cancer 94:1483–1491. 10.1002/cncr.10356 [PubMed: 11920505]
16. Zucker S, Cao J (2005) Measurement of matrix metalloproteinases in serum of patients with melanoma: snarled in technical pitfalls. Clin Cancer Res 11:5069–5070. 10.1158/1078-0432.CCR-05-0774 [PubMed: 16033818]
17. Nikkola J, Vihinen P, Vuoristo MS, Kellokumpu-Lehtinen P, Kahari VM, Pyrhonen S (2005) High serum levels of matrix metalloproteinase-9 and matrix metalloproteinase-1 are associated with rapid progression in patients with metastatic melanoma. Clin Cancer Res 11:5158–5166. 10.1158/1078-0432.CCR-04-2478 [PubMed: 16033831]
18. Ranuncolo SM, Armanasco E, Cresta C, Bal De Kier Joffe E, Puricelli L (2003) Plasma MMP-9 (92 kDa-MMP) activity is useful in the follow-up and in the assessment of prognosis in breast cancer patients. Int J Cancer 106:745–751. 10.1002/ijc.11288 [PubMed: 12866035]
19. Roy R, Yang J, Moses MA (2009) Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. J Clin Oncol 27:5287–5297. 10.1200/JCO.2009.23.5556 [PubMed: 19738110]
20. Smith ER, Zurakowski D, Saad A, Scott RM, Moses MA (2008) Urinary biomarkers predict brain tumor presence and response to therapy. Clin Cancer Res 14:2378–2386. 10.1158/1078-0432.CCR-07-1253 [PubMed: 18413828]
21. Choe G, Park JK, Jouben-Steele L, Kremen TJ, Liau LM, Vinters HV, Cloughesy TF, Mischel PS (2002) Active matrix metalloproteinase 9 expression is associated with primary glioblastoma subtype. Clin Cancer Res 8:2894–2901 [PubMed: 12231534]
22. Gerlach RF, Uzuelli JA, Souza-Tarla CD, Tanus-Santos JE (2005) Effect of anticoagulants on the determination of plasma matrix metalloproteinase (MMP)-2 and MMP-9 activities. Anal Biochem 344:147–149. 10.1016/j.ab.2005.04.038 [PubMed: 15950912]
23. Jung K, Lein M, Laube C, Lichtinghagen R (2001) Blood specimen collection methods influence the concentration and the diagnostic validity of matrix metalloproteinase 9 in blood. Clin Chim Acta 314:241–244. [PubMed: 11718702]
24. Souza-Tarla CD, Uzuelli JA, Machado AA, Gerlach RF, Tanus-Santos JE (2005) Methodological issues affecting the determination of plasma matrix metalloproteinase (MMP)-2 and MMP-9 activities. Clin Biochem 38:410–414. 10.1016/j.clinbiochem.2005.02.010 [PubMed: 15820769]
25. Rouy D, Ernens I, Jeanty C, Wagner DR (2005) Plasma storage at −80 degrees C does not protect matrix metalloproteinase-9 from degradation. Anal Biochem 338:294–298. 10.1016/j.ab.2004.10.052 [PubMed: 15745750]
26. Friedberg MH, Glantz MJ, Klempner MS, Cole BF, Perides G (1998) Specific matrix metalloproteinase profiles in the cerebrospinal fluid correlated with the presence of malignant astrocytomas, brain metastases, and carcinomatous meningitis. Cancer 82:923–930 [PubMed: 9486583]
27. Groves MD, Puduvalli VK, Hess KR, Jaeckle KA, Peterson P, Yung WK, Levin VA (2002) Phase II trial of temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme. J Clin Oncol 20:1383–1388 [PubMed: 11870183]

Table 1

Univariate analyses of the effect of longitudinal increases in serum MMP-9 on survival

Cohort	*n*	*n* events (death)	Each doubling in MMP-9 value	
			HR (95% CI)	*P*
Anaplastic gliomas[a]	107	52	1.1 (0.8–1.3)	0.62
Newly diagnosed anaplastic gliomas	42	23	1.1 (0.8–1.6)	0.57
Anaplastic astrocytomas	65	36	1.2 (0.9–1.6)	0.22
Glioblastoma	196	161	1.1 (1.0–1.3)	0.04
Newly diagnosed glioblastoma	139	117	1.1 (0.9–1.2)	0.29

n number, *HR* hazard ratio, *CI* confidence interval

[a]Includes two patients who progressed from low-grade to anaplastic glioma

Table 2

Multivariate analysis including standard prognostic factors and the effect of any longitudinal increase in serum MMP-9 in glioblastoma patients

Variable	Glioblastoma (*n* = 164, 140 deaths)	
	HR (95% CI)	***P***
Each doubling in MMP-9 value	1.1 (0.9–1.2)	0.11
Age (per 10-year increase)	1.3 (1.1–1.5)	0.003
Extent of resection		
Gross total resection	1	0.02
Partial resection	1.0 (0.7–1.5)	
Biopsy	1.8 (1.2–2.8)	
Karnofsky performance scale		
<70	1	0.91
≥70	0.9 (0.4–2.1)	