Journal of BUON **16:** 138-141, 2011

ORIGINAL ARTICLE

Serum granulocyte colony-stimulating factor levels in gliomas

R. Yildiz[1], U. Coskun[1], S. Buyukberber[1], B. Sancak[2], A.O. Kaya[1], O. Gulbahar[2], M. Benekli[1]

Department of [1]Medical Oncology and [2]Biochemistry, Gazi University, School of Medicine, Ankara, Turkey

Summary

Purpose: *Apart from its known effects on granulopoiesis, granulocyte-colony stimulating factor (G-CSF) is also involved in growth and progression of malignant cells. In this study we report the serum G-CSF levels and their relationship with survival in patients with glial cell tumors.*

Methods: *Serum G-CSF levels of 17 patients (10 male, 7 female, median age 55 years, range 19-75), with histologically proven glial cell tumors and of 17 sex- and age-matched healthy controls were assayed by enzyme-linked immunosorbent assay (ELISA).*

Results: *All patients were treated with radiotherapy and concomitant temozolomide, followed by temozolomide alone. Eight patients were treated with carboplatin plus cyclophosphamide combination as second-line chemotherapy. The median follow-up was 21 months (4-42). The median OS was 36 months (95% CI, 15.7-56.4). Serum G-CSF levels in glioma patients and healthy controls were 44.14 ± 18.89 pg/ml and 28.84±15.65 pg/ml, respectively (p=0.027). There was no significant correlation between survival time and serum G-CSF levels (r=0.384; p=0.217).*

Conclusion: *Serum G-CSF levels were high in glioma patients compared with healthy controls and they may be involved in tumor progression, but the G-CSF role in prognosis was not clarified. Further studies with larger numbers of patients must be conducted to elucidate the role of G-CSF in glial cell tumors.*

Key words: disease progression, glial cell tumors, granulocyte colony-stimulating factor, prognosis

Introduction

Gliomas are the most common primary malignant tumors of the brain in adults and children. The median survival is 12-15 months for patients with glioblastomas and 2-5 years for patients with anaplastic gliomas. Prognosis, however, remains poor despite extensive research and advances in treatment, including surgical resection, radiotherapy and chemotherapy [1]. Better understanding of the biology and molecular mechanisms of glioma development and progression may contribute to the improvement of the current therapeutic modalities.

G-CSF is a cytokine mainly synthesized by macrophages, monocytes and endothelial cells. It is usually produced at an infection site, its role being to stimulate bone marrow neutrophil progenitor cells to replace consumed neutrophils. The primary source of serum G-CSF in G-CSF-producing tumors is the tumor itself and secondary causes are other cytokines that induce G-CSF production by endothelial cells, macrophages and monocytes [2,3]. G-CSF has a role in controlling the proliferation, maturation and functional activity of these cells [4].

G-CSF production by non-hematopoietic malignancies, including carcinomas of head and neck, thyroid, lung, stomach, liver, gallbladder, pancreas, rectum, kidney, urinary bladder, prostate and uterine cervix has been frequently reported [3,5-17]. It has also been reported that G-CSF-producing tumors bear a poor prognosis [18]. Expression of G-CSF in glioma cells was reported but serum G-CSF levels in this tumor type has not been reported yet. In this study we present the serum G-CSF levels and their relationship with survival in patients with glial cell tumors.

Correspondence to: Ugur Coskun, MD. Gazi University, School of Medicine, Department of Medical Oncology, Besevler, Ankara, 06500, Turkey.
Tel: +90 312 2025831, Fax: +90 312 2158710, E-mail: ugur.coskun@gazi.edu.tr

Received 10-05-2010; Accepted 04-06-2010

Methods

Patients

Serum samples were obtained from 17 (10 male, 7 female) patients with glial cell tumor, with median age 55 years (range 19-75; study group), and from 17 (10 male, 7 female) healthy individuals with median age 54 years (range 29-71; control group). Patients had a histologically confirmed diagnosis of glioblastoma multiforme (n=11) and astrocytoma (n=6) with partially resected or recurrent disease. Blood samples from patients were taken at Gazi University, Medical School Hospital from January 2005 to September 2007. None of the patients had received chemo- or radiotherapy before blood sample collection. Blood samples were allowed to coagulate at room temperature, centrifuged at 10,000 rpm for 10 min, and were then frozen at 84° C until assayed. Informed consent was taken from patients and healthy controls before sample collection.

Serum G-CSF estimation

Levels of G-CSF in serum samples were quantified by a commercially available ELISA kit (Biosource, USA). The G-CSF was assayed according to the manufacturer's protocol and expressed as pg/ml.

Statistical analyses

Statistical analyses were performed using SPSS version 11.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The variation of distribution was assessed by the one-sample Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation or median and range, as appropriate. The statistical significance of the differences observed between patients and healthy controls was evaluated by the Mann-Whitney U test. Correlations between variables were tested by two-tailed Sperman's test. Overall survival (OS) was defined as the period from the diagnosis of disease until the date of last follow up or death. The probability of OS was estimated using the Kaplan-Meier method. A p-value less than 0.05 was considered statistically significant.

Results

The characteristics and serum G-CSF levels of the patients and healthy controls are summarized in Table 1. All patients were treated with radiotherapy and concomitant temozolomide, followed by temozolomide alone. Eight patients were treated with carboplatin and cyclophosphamide combination therapy as second-line chemotherapy. The median follow-up was 21 months (range 4-42). The median OS was 36 months (95% CI, 15.7-56.4) (Figure 1). Serum G-CSF levels in glioma patients and healthy controls were 44.14 ± 18.89 pg/ml and 28.84±15.65 pg/ml, respectively (p=0.027; Figure 2). There was no significant correlation between survival time and serum G-CSF levels for glioma patients (r=0.384; p=0.217). Serum G-CSF levels of patients according to tumor grade were 49.34±14.49 pg/ml for astrocytoma and 42.61±17.14 pg/ml for glioblastoma (p= 0.383).

Table 1. Therapy, disease characteristics and serum G-CSF levels of glioma patients and healthy controls

Characteristics	*Patients (n=17) n (%)*	*Healthy controls (n=17) n (%)*
Median age, years (range)	55 (19-75)	54 (29-71)
Sex		
Male	10	10
Female	7	7
Tumor grade		
Glioblastoma multiforme	11 (64.7)	
Astrocytoma	6 (35.3)	
Chemotherapy		
Temozolomide	17 (100)	
Carboplatin+cyclophosphamide	8 (47.1)	
Radiotherapy	17 (100)	
Serum G-CSF (pg/ml)	44.14 ± 18.89*	28.84 ± 15.65*

G-CSF: granulocyte colony-stimulating factor, *: significant difference between serum G-CSF levels of patients and healthy controls (p= 0.027)

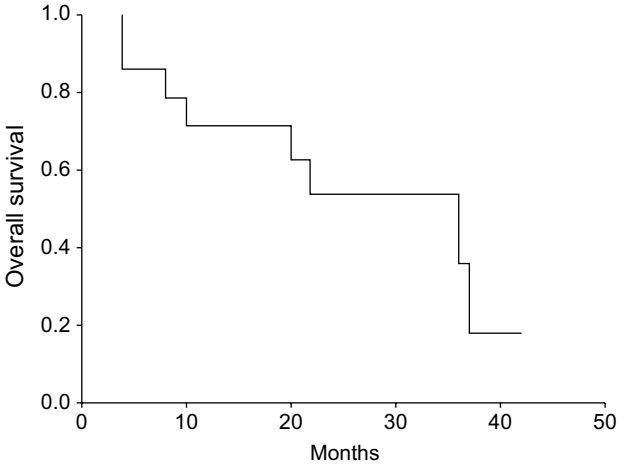

Figure 1. Overall survival. Median survival was 36 months (95% CI, 15.7-56.4).

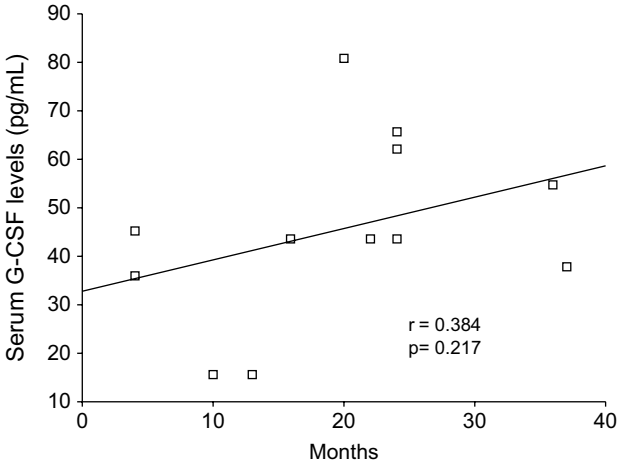

Figure 2. Correlation between survival time and serum G-CSF levels.

Discussion

Serum G-CSF levels were significantly higher in patients compared with healthy controls, but no significant correlation between survival and serum G-CSF levels was found in the present study. Elevated serum G-CSF levels have been reported in most types of malignancies [5-17]. These reports were commonly case studies. Stan et al. reported G-CSF expression in recurrent glial cell tumors and also high G-CSF levels were demonstrated in a case report of glioblastoma by Hintzen et al. [19,20]. To the best of our knowledge, this is the first study to compare serum levels of G-CSF in glioma patients with patient OS.

Kaminska et al. reported that increased serum G-CSF concentrations are related to clinicopathological features of the tumor, thus suggesting that their determination may have a prognostic value [21]. Expression of G-CSF receptors on tumor cells was correlated with poor prognosis [18]. Binding of tumor-secreted G-CSF to its receptors enhances tumor cell proliferation, invasion, and migration by an autocrine mechanism [3]. In addition, G-CSF induces proliferation and migration of endothelial cells and promotes angiogenesis which is considered to be a regulating factor of vascular development and growth in malignant gliomas [22-25]. Significantly higher levels of serum G-CSF in glioma patients compared with healthy controls may support the role of this cytokine in tumor progression. However, in the present study there was no significant correlation between serum G-CSF levels and OS, a fact that does not support the prognostic importance of G-CSF in patients with glial cell tumors. The small number of patients may, however, decrease the value of the results taken.

The serum G-CSF levels of patients according to tumor grade (astrocytoma vs. glioblastoma) were not significantly different.

In conclusion, serum G-CSF levels were high in glioma patients and this cytokine may be involved in tumor progression. No prognostic role of G-CSF concerning both tumor grade and OS in patients with glial cell tumors was identified. Studies with larger numbers of patients are warranted to elucidate whether G-CSF has any impact on glioma cells' biology.

References

1. Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med 2008; 359: 492-507.
2. Ikeda T, Ohgaki K, Miura M, Aishima S, Shimizu T, Maehara Y. Granulocyte-colony stimulating factor-producing gallbladder cancer without recurrence more than 2 years after resection: report of a case. Surg Today 2005; 35: 590-593.
3. Toyoda M, Chikamatsu K, Sakakura K et al. A case of squamous cell carcinoma of the head and neck producing granulocyte-colony stimulating factor with marked leukocytosis. Auris Nasus Larynx 2007; 34: 267-271.
4. Metcalf D. The granulocyte-macrophage colony-stimulating factors. Science 1985; 229: 16-22.
5. Saito K, Kuratomi Y, Yamamoto K et al. Primary squamous cell carcinoma of the thyroid associated with marked leukocytosis and hypercalcemia. Cancer 1981; 48: 2080-2083.
6. Furihata M, Sonobe H, Iwata J et al. Lung squamous cell carcinoma producing both parathyroid hormone-related peptide and granulocyte colony stimulating factor. Pathol Int 1996; 46: 376-379.
7. Obara T, Ito Y, Kodama T et al. A case of gastric carcinoma associated with excessive granulocytosis. Production of a colony-stimulating factor by the tumor. Cancer 1985; 56: 782-788.
8. Araki K, Kishihara F, Takahashi K et al. Hepatocellular carcinoma producing granulocyte colony-stimulating factor: report of a resected case with a literature review. Liver Int 2007; 27: 716-721.

9. Yamamoto S, Takashima S, Ogawa H et al. Granulocyte-colony-stimulating-factor-producing hepatocellular carcinoma. J Gastroenterol 1999; 34: 640-644.
10. Furihata M, Sonobe H, Ohtsuki Y, Enzan H, Tokuoka H, Nakanuma Y. An immunohistochemical study on a case of granulocyte-colony stimulating factor-producing gall-bladder carcinoma. Pathol Int 1999; 49: 1010-1013.
11. Groblewska M, Mroczko B, Wereszczyńska-Siemiatkowska U, Myśliwiec P, Kedra B, Szmitkowski M. Serum levels of granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) in pancreatic cancer patients. Clin Chem Lab Med 2007; 45: 30-34.
12. Takahashi H, Yasuda A, Ochi N et al. Granulocyte-colony stimulating factor producing rectal cancer. World J Surg Oncol 2008; 6: 70.
13. Wang YC, Yang S, Tzen CY, Lin CC, Lin J. Renal cell carcinoma producing granulocyte colony-stimulating factor. J Formos Med Assoc 2006; 105: 414-417.
14. Yoshino T, Yoneda K. Urinary bladder cancer producing granulocyte-colony stimulating factor: a case report and review of the literature. Hinyokika Kiyo 2008; 54: 775-778.
15. Matsuoka Y, Arai G, Okada Y, Aida J. Prostate cancer producing granulocyte colony-stimulating factor. Urol Int 2009; 82: 113-115.
16. Watanabe A, Wachi T, Omi H et al. Granulocyte colony-stimulating factor-producing small-cell carcinoma of the uterine cervix: report of a case. Diagn Cytopathol 2000; 23: 269-274.
17. Kyo S, Kanaya T, Takakura M, Inoue M. A case of cervical cancer with aggressive tumor growth: possible autocrine growth stimulation by G-CSF and Il-6. Gynecol Oncol 2000; 78: 383-387.
18. Tsuzuki H, Fujieda S, Sunaga H, Noda I, Saito H. Expression of granulocyte colony-stimulating factor receptor correlates with prognosis in oral and mesopharyngeal carcinoma. Cancer Res 1998; 58: 794-800.
19. Stan AC, Walter GF, Welte K, Schneider B, Bona CA, Pietsch T. Expression of granulocyte colony-stimulating factor in recurrent glial tumors is inversely correlated with tumor progression. J Neuroimmunol 1999; 94: 66-73.
20. Hintzen RQ, Voormolen J, Sonneveld P, van Duinen SG. Glioblastoma causing granulocytosis by secretion of granulocyte-colony-stimulating factor. Neurology 2000; 54: 259-261.
21. Kaminska J, Nowacki MP, Kowalska M et al. Clinical significance of serum cytokine measurements in untreated colorectal cancer patients: soluble tumor necrosis factor receptor type I-an independent prognostic factor. Tumour Biol 2005; 26: 186-194.
22. Bussolino F, Colotta F, Bocchietto E, Guglielmetti A, Mantovani A. Recent developments in the cell biology of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor: activities on endothelial cells. Int J Clin Lab Res 1993; 23: 8-12.
23. Bikfalvi A, Han ZC. Angiogenic factors are hematopoietic growth factors and vice versa. Leukemia 1994; 8: 523-529.
24. Argyriou AA, Giannopoulou E, Kalofonos HP. Angiogenesis and anti-angiogenic molecularly targeted therapies in malignant gliomas. Oncology 2009; 77: 1-11.
25. Obermueller E, Vosseler S, Fusenig NE, Mueller MM. Cooperative autocrine and paracrine functions of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in the progression of skin carcinoma cells. Cancer Res 2004; 64: 7801-7812.