Pathol. Oncol. Res. (2008) 14:79–83
DOI 10.1007/s12253-008-9002-7

ORIGINAL PAPER

The Diagnostic Value of Macrophage Migration Inhibitory Factor (MIF) in Gastric Cancer

Hakan Camlica · Derya Duranyildiz · Hilal Oguz · Ethem Nezih Oral · Vildan Yasasever

Received: 15 January 2007 / Accepted: 26 July 2007 / Published online: 18 March 2008

Abstract The present study was conducted to investigate the sensitivity, specificity, predictive values and accuracy of serum MIF, CEA, CA 19-9 levels and their various combinations in patients with gastric cancer. Study group consists of pathologically verified, gastric cancer (n=63) and apparently healthy controls (n=50). Serum MIF concentrations were determined by enzyme-linked immunosorbent assay (ELISA). Serum values of patients were significantly higher than the controls (p=0.011). Diagnostic sensitivity and specificity, predictive values and accuracies were calculated for each marker and their various combinations. The best results were achieved with the marker combination of MIF–CEA–CA 19-9 and MIF–CEA combination. In our opinion, the combination of the markers MIF–CEA is a valuable diagnostic tool for gastric cancer.

Keywords MIF · CEA · CA 19-9 · Tumor markers · Gastric cancer · Accuracy

H. Camlica (✉)
Preventive Oncology, Biostatistics and Epidemiology,
Institute of Oncology, University of Istanbul,
Capa, 34390 Istanbul, Turkey
e-mail: hcamlica@istanbul.edu.tr

D. Duranyildiz · H. Oguz · V. Yasasever
Basic Oncology, Institute of Oncology,
University of Istanbul,
Istanbul, Turkey

E. N. Oral
Radiation Oncology, Institute of Oncology,
University of Istanbul,
Istanbul, Turkey

Introduction

Despite its decline in incidence, gastric carcinoma (GC) remains the second most frequent cancer in the world [1]. The prognosis of GC is dismal because the majority of cases are found to have advanced disease at the time of diagnosis. To improve the diagnosis and management of GC, a better understanding of the pathogenesis and tumor biology is mandatory [2].

Tumor markers are useful tests in the management and follow-up of patients with cancer [3, 4]. Generally, tumor markers are not useful for diagnosis because of their low specificity and sensitivity. Moreover, several authors propose that tumor markers as a prognostic parameters in different tumors [5–7]. MIF was first identified as a T-cell-derived lymphokine [8, 9]. In addition to its original ability to inhibit the migration of macrophages, MIF exhibits a broad range of immunostimulatory and proinflammatory activities [10]. In the context of tumorigenesis, overexpression of MIF has been observed in prostate [11, 12], lung [13, 14], skin [15], pituitary [16], brain [17], breast [18], liver [19], and colon tumors [20]. Carcinoembryonic antigen (CEA) is an oncofetal glycoprotein with a molecular weight of about 186 kDa [21] and has been one of the most popular and most frequently used tumor markers in clinical practice. Elevations of CEA have been observed in colorectal, breast, pancreatic, lung, thyroid and cervical cancers and it is suggested that CEA should only be recommended to monitor the response to treatment [22]. Persistently high or increasing CEA values are likely to indicate poor response to treatment and progressive disease [23]. Carbohydrate antigen 19.9 (CA 19.9) is a tumor marker described by molecular hybridization techniques [24]. This tumor marker is still used for the follow-up colorectal carcinoma patients.

Table 1 Descriptive characteristics of the groups

Gastric cancer (n=63)	Values
Surgery (gastrectomy)	37 (58.73%) (%95 CI: 45.62–70.99)
Biopsy	26 (41.27%) (% 95CI: 29.01–54.38)
Family history	
Yes	10 (15.87%) (% 95CI: 7.88–27.26)
No	53 (84.13%) (% 95CI: 72.74–92.12)

The aim of this prospective study was to evaluate the sensitivity, specificity, predictive values and accuracy of MIF, CEA and CA 19.9 in patients with gastric cancer. The diagnostic value, sensitivity, specificity, predictive values and accuracy values were calculated for each marker and their combinations.

Materials and Methods

Sixty-three male patients with metastatic gastric cancer pathologically verified, consecutively admitted to the Istanbul University, Oncology Institute were investigated. Serum samples were obtained on first admission before any type of chemotherapeutic treatment was given. Staging was performed on a pathological basis according to AJCC classification.

Blood samples were obtained from male patients with gastric cancer and from apparently healthy male controls who were blood donors undergoing regular physical and laboratory examinations (n=50) by venipuncture and clotted at the room temperature. The sera were collected following centrifugation and frozen immediately at −20°C until analysis. The protocol was consistent with the Declaration of Helsinki (1989). Informed consent was obtained from all patients.

Human MIF ELISA (Raybiotech, Inc. GA, USA) levels were measured by solid-phase enzyme immunoassay. The amount of MIF was quantitated by an automated ELISA reader (SLT Labinstruments, Austria). The results were expressed as picograms per milliliter (pg/mL). CA 19.9 (U/mL) and CEA (ng/mL) levels were measured by microparticle enzyme immunoassay (Abbott Laboratories, Chicago, IL, USA).

Data analysis was performed by using SPSS 7.5 software (SPSS, Chicago, IL, USA). The report design was adopted from the standards for reporting diagnostic accuracy (STARD) group [25]. Cut-off values were calculated using receiver operating characteristic (ROC) curves, which plots the ROC curve corresponding to the overall accuracy of the test.

Normality of the distribution of biomarker values (MIF, CEA, CA 19-9) were tested using Kolmogorov–Smirnov test. Mann Whitney-U test was used for statistical significance between the gastric cancer and the apparently healthy group. Student's t-test was used to compare age differences between patients and apparently healthy control group [26]. The sensitivity, specificity, (+) predictive value, (−) predictive value, and accuracy were calculated for each of the three markers and their various combinations [27]. Reported p values are two sided and p values <0.05 were considered to be significant. Survival analysis was performed using Kaplan–Meier methods, implications of marker levels on survival were tested with log-rank tests.

Results

All patients were admitted to the surgical clinic for pathologic diagnosis. Of the 63 patients 26 (41.27%) underwent only biopsy and 37 (58.73%) had gastrectomy surgery. There was family history (relatives with gastric carcinoma) in ten (15.87%) patients with gastric carcinoma (Table 1). Descriptive statistics and the values of age, serum CEA, CA 19-9 and MIF levels between gastric cancer patients and apparently healthy controls are shown in Table 2.

Before starting to calculate values for age and tests, the groups were checked for distribution with Kolmogorov–Smirnov test for normality. The results showed that there was normal distribution for age (Z=0.52; p=0.95). There is

Table 2 Group characteristics and statistical analyses (SD: standard deviation)

	Patients (n=63)	Control (n=50)	Statistical probability
	Mean±SD median (min–max)	Mean±SD median (min–max)	
Age	54.24±12.4; 54 (28–85)	51.8±11.0; 35 (35–71)	t=1.09, df=111.0, p=0.28
MIF (pg/mL)	682.74±1336.66; 61.69 (0.69–5990.30)	22.04±28.22; 7.76 (5.53–100.4)	U=360.5, Z=−3.95, p<0.001
CEA (ng/mL)	72.4±208.95; 3.0 (0.4–1236)	0.94±0.53; 0.9 (0.4–2.3)	U=219.5, Z=−4.21, p<0.001
CA 19-9 (U/mL)	198.56±670.81; 13.8 (0.00–4163.0)	7.27±7.36; 4.25 (0.00–22.4)	U=323.0, Z=−2.9, p=0.003

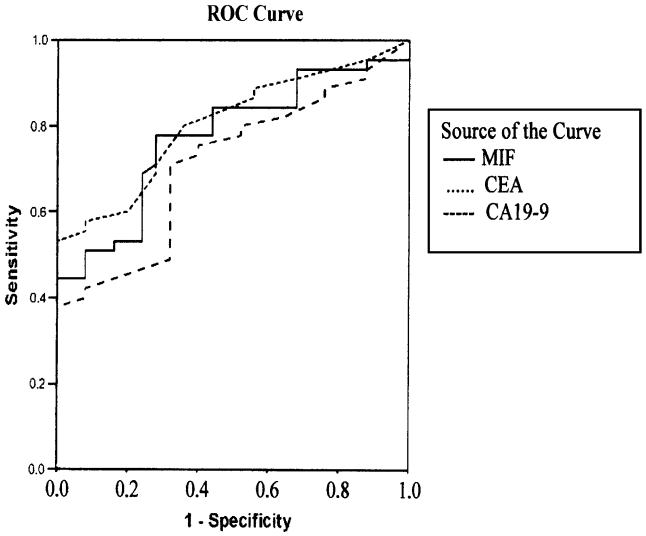

Fig. 1 Receiver operating characteristics (ROC) curves for each individual analyte and a combination of all three analytes (area under the curve for MIF; CA 19-9; CEA is 77.6%; 71.5%; 80.7%, respectively

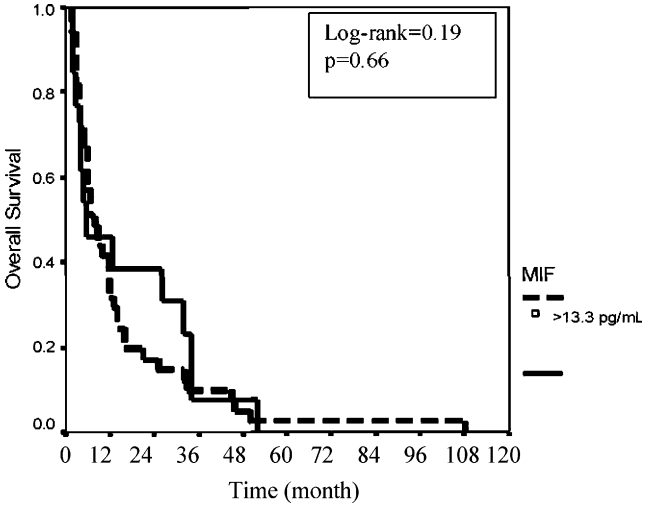

Fig. 2 Kaplan–Meier survival curve according to MIF levels

no normal distribution for the markers MIF (Z=2.84, p<0.001), CA 19-9 (Z=2.82, p<0.001) and CEA (Z=2.37, p<0.001). There was no difference between the age of patients and control group by using Student's t-test (t=1.09, p=0.28). The serum MIF, CEA and CA 19-9 levels were significantly higher in patients with gastric cancer than in the control group by using Mann Whitney-U test (MIF: U=360.5, p=0.001; CEA: U=219.5, p=0.00l; CA 19-9: U=323, p=0.003).

We used receiver operating characteristic (ROC) curves to determine cut-off values and the sensitivity, specificity, positive and negative predictive values and accuracy of MIF, CEA and CA 19-9 in gastric cancer patients. The cut-off levels were MIF=13.3 pg/mL, CEA=2.05 ng/mL and CA 19-9=27.58 U/mL, respectively (Fig. 1). Using these cut-off values the areas under the curve were 0.776 (95% CI: 0.667–0.884) for MIF; 0.807 (95% CI: 0.708–0.906) for CEA and 0.715 (95% CI: 0.595–0.835) for CA 19-9, respectively. To determine the most accurate test or combination to detect gastric cancer patients, we evaluated sensitivity, specificity, positive and negative predictive values and accuracy with the calculated cut-off values (Table 3). MIF–CEA–CA 19-9 and MIF–CEA combinations were the most accurate and best diagnostic tests in gastric cancer patients.

CEA and CA 19-9 have a close positive correlation with serum concentrations in the patient groups (R=0.38; p=0.01). There is no significant correlation between MIF and other tumor marker values. That is why MIF can be considered as an independent parameter (R=0.468; p=0.018). Survival analyses according to high and normal MIF levels (cut-off=13.3 pg/mL) in the whole patient group, revealed no significant correlations between tumor marker levels and survival (log rank=0, 19; df=1; p=0.66; Fig. 2). In the cases with short survival (less than 1 year), no significant correlation with survival and high MIF expression was observed.

Discussion

Primary aim of the present study was to evaluate the serum MIF, CEA and CA 19-9 concentrations and their diagnostic

Table 3 Sensitivity, specificity, positive and negative predictive values and accuracy for CEA, CA 19-9, MIF and their various combinations

Cut-off values	Sensitivity (%)	Specificity (%)	(+) Pred. value (%)	(−) Pred. value (%)	Accuracy (%)
MIF (13.3 pg/mL)	77.8	72.0	87.5	56.25	76.14
CEA (2.05 ng/mL)	33.33	92.0	92.59	53.49	68.57
CA 19-9 (27.58 U/mL)	55.56	100.0	100.0	45.45	57.14
MIF–CEA	91.1	72.0	85.42	81.81	84.29
MIF–CA 19-9	84.44	72.0	84.44	72.0	80.0
CEA–CA 19-9	60.0	92.0	93.1	43.9	71.43
MIF–CEA–CA 19-9	91.1	72.0	85.42	81.82	84.29

value in patients with gastric cancer. There are some studies with MIF–CEA, MIF, CEA and CA 19-9 in colorectal cancers. Elevated levels of MIF, CEA and CA 19-9 predicts the presence of extensive disease in colorectal carcinoma with high specificity and high positive predictive value [21, 22, 24, 27]. We could not find any trial which was conducted using the combinations these three tumor markers (CEA–CA 19-9–MIF) to achieve a higher diagnostic value for gastric cancer in the literature. The most striking feature of this study was the demonstration that serum MIF, CEA and CA 19-9 levels were significantly higher in patients with metastatic gastric cancer than in the apparently healthy controls.

Shkolnik et al. have suggested in their study that MIF may be useful as a clinical marker for colorectal cancer, and warrants further technical refinement and study of specific patient populations [28, 29]. In the patient group, we achieved similar findings and also suggest that MIF could be an useful marker for diagnosis (U=360.5; p<0.001), but we could not find any evidence supporting the prognostic value of MIF (log-rank=0.19; p=0.66).

In this study, we tried to improve the predictive power of tumor markers for gastric cancer by making various combinations. In the current study, serum MIF levels showed a diagnostic value with a sensitivity and specificity of 77.8% and 72.0%, respectively. The high sensitivity and specificity using combinations of MIF–CEA and MIF–CEA–CA 19-9 were 91.1% and 72.0%, respectively. These results describe better diagnostic values than the results with MIF alone.

There was a positive correlation between CEA and CA 19-9 in the patient group (r=0.382; p=0.01). MIF and CA 19-9 showed a positive correlation in the control group (r=0.468; p=0.018).

Serum MIF, CEA and CA 19-9 concentrations were significantly higher in gastric cancer patients. He et al. suggested in their study that MIF expression is involved in gastric carcinogenesis [30]. In this study gastric cancer patients had also highly significant elevated serum MIF levels than the apparently healthy control. All patients had metastases and nearly all serum MIF levels were increased. In our patients, we could not show any other features of presence of MIF, based on various parameters such as prognosis, clinical benefit etc. (data not shown). In our study group, we could not confirm these results with Kaplan–Meier analyses. In the cases with short survival (less than 1 year), no significant correlation between survival and high MIF expression was achieved.

In conclusion, CA 19-9 still fulfills the need of diagnosis of gastric carcinoma. Many large-scale studies for MIF and its combinations are needed in this field and exciting new knowledge will ultimately emerge for its diagnostic and prognostic values.

References

1. Correa P (1992) Human gastric carcinogenesis: a multistep and multifactorial process. Cancer Res 52:6735–6470
2. Tahara E, Semba S, Tahara H (1996) Molecular biological observations in gastric cancer. Semin Oncol 23:307–315
3. Waldman TA, Heberman RH (1982) Tumor markers in diagnosis and in monitoring therapy. In: Holland JF, Frei E (eds) Cancer Medicine. Lea & Febiger, Philadelphia, pp 1068–1089
4. Klavins JV (1985) Tumor markers: clinical and laboratory studies. Alan R. Liss, New York
5. Babaian RJ, Orlando RP (1986) Elevated prostatic acid phosphatase: a prognostic factor for stage C adeno carcinoma of prostate. J Urol 136:1035–1037
6. Wanebo HJ, Rao B, Pinsky CM et al (1978) Preoperative carcinoembryonic antigen level as a prognostic indicator in colorectal cancer. N Eng J Med 299:448–451
7. Molina R, Filella X, Mengual P et al (1990) MCA in patients with breast cancer: correlation with CEA and CA 15.3. Int J Biol Markers 5:14–21
8. David JR (1996) Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. Proc Natl AcadSci USA 56:72–77
9. Bloom BR, Bennett B (1996) Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. Science 153:80–82
10. Nishihira J (2000) Macrophage migration inhibitory factor (MIF): its essential role in the immune system and cell growth. Interferon Cytokine Res 20:751–762
11. Meyer-Siegler K, Hudon PB (1996) Enhanced expression of macrophage migration inhibitory factor in prostatic adenocarcinoma metastases. Urology 48:448–452
12. Del Vecchio MT, Tripodi SA, Arcuri F et al (2000) Macrophage migration inhibitory factor in prostatic adenocarcinoma: correlation with tumor grading and combination endocrine treatment related changes. Prostate 45:51–57
13. Kamimura A, Kamachi M, Nishihira J et al (2000) Intracellular distribution of macrophage migration inhibitory factor predicts the prognosis of patients with adenocarcinoma of the lung. Cancer 89:334–341
14. Tomiyasu M, Yoshino I, Suemitsu R et al (2002) Quantification of macrophage inhibitory factor mRNA expression in non-small cell lung cancer tissues and its clinical significance. Clin Cancer Res 8:3755–3760
15. Shimizu T, Abe R, Nakamura H et al (1999) High expression of macrophage migration inhibitory factor in human melanoma cells and its role in tumor cell growth and angiogenesis. Biochem Biophys Res Commun 264:751–758
16. Pyle ME, Korbonits M, Gueorguiev M et al (2003) Macrophage migration inhibitory factor expression is increased in pituitary adenoma cell nuclei. Endocrinol 176:103–110
17. Munaut C, Boniver J, Foidart JM et al (2002) Macrophage migration inhibitory factor (MIF) expression inhuman glioblastomas correlates with vascular endothelial growth (VEGF) expression. Neurophathol Appl Neurobiol 28:452–460
18. Bando H, Matsumoto G, Bando M et al (2002) Expression of macrophage migration inhibitory factor in human breast cancer: association with nodal spread. Jpn J Cancer Res 93:389–396
19. Akbar SM, Abe M, Murakami H et al (2001) Macrophage migration inhibitory factor in hepatocellular carcinoma and liver cirrhosis: relevance to pathogenesis. Cancer Lett 171:125–132
20. Legendre H, Decaestecker C, Nagy N et al (2003) Prognostic values of galectin-3 and the macrophage migration inhibitory factor (MIF) in human colorectal cancers. Mod Pathol 16:491–504

21. Gold P, Freedman SO (1965) Specific carcinoembryonic antigens of the human digestive system. J Exp Med 122:467–481
22. Yasasever V, Camlica H, Oral EN et al (1999) Utility of CEA in the Diagnosis of Patients with Cancer. J Tumor Marker Oncol 14 (1):33–38
23. Duffy MJ (2006) Serum tumor markers in breast cancer: are they of clinical value? Clin Chem 52:345–351
24. Koprowski H, Steplewski Z, Mitchell K et al (1979) Colorectal carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genet 5:957–972
25. Bossuyt PM, Reitsma JB, Bruns DE et al (2004) Towards complete and accurate Reporting of studies of diagnostic accuracy: the STARD initiative. Fam Pract 21:4–10
26. Campbell MJ (1999) Medical statistics: a commonsense approach. John Wiley & Sons Inc, Chichester
27. Solberg HE (1986) Textbook of clinical chemistry. W.B. Saunders Company, Lexington, pp 356–409
28. Shkolnik T, Livni E, Reshef R et al (1987) Comparison of two lymphokines (macrophage migration inhibition, leukocyte adherence inhibition factors) and carcinoembryonic antigen, in colorectal cancer and colonic premalignant lesions. Am J Gastroenterol 82:1275–1278
29. Shkolnik T, Livni E, Reshef R et al (1987) The macrophage migration inhibition (MIF) assay as a marker of colorectal cancer. Studies in patients with colorectal cancer, noncolonic neoplasms, and conditions predisposing to colorectal cancer. Dis Colon Rectum 30:101–105
30. He XX, Yang J, Ding YW et al (2006) Increased epithelial and serum expression of migration inhibitory factor (MIF) in gastric cancer: potential role of MIF in gastric carcinogenesis. Gut 55:797–802