Biomedicine & Pharmacotherapy 77 (2016) 86–91

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Original article

Serum activated leukocyte cell adhesion molecule and intercellular adhesion molecule-1 in patients with gastric cancer: Can they be used as biomarkers?

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ARTICLE INFO

Article history:
Received 9 August 2015
Received in revised form 26 November 2015
Accepted 11 December 2015

Keywords:
Serum activated leukocyte cell adhesion molecule
Intercellular adhesion molecule-1
Gastric cancer

ABSTRACT

Cellular adhesion molecules might be used as markers in diagnosis and prognosis in some types of malignant tumors. The purpose of this study was to determine the clinical significance of the serum levels of activated leukocyte cell adhesion molecule-1 (ALCAM) and intercellular adhesion molecule-1 (ICAM-1) in gastric cancer (GC) patients. Fifty-eight GC patients and 20 age- and sex-matched healthy controls were enrolled into this study. Pretreatment serum markers were determined by the solid-phase sandwich enzyme-linked immunosorbent assay (ELISA). The median age at diagnosis was 59.5 years (range 32–82 years). Tumor localizations of the majority of the patients were antrum ($n = 42$, 72.4%) and tumor histopathologies of the majority of the patients were diffuse ($n = 43$, 74.1%). The majority of the patients had stage IV disease ($n = 41$, 70.7%). Thirty six (62.1%) patients had lymph node involvement. The median follow-up time was 66 months (range 1–97.2 months). At the end of the observation period, 26 patients (44.8%) were dead. The median survival for all patients was 21.4 ± 5 months (%95 CI, 11.5–31.3). The 1-year survival rates were 66.2%.

The baseline serum ALCAM levels of the patients were significantly higher than those of the controls ($p = 0.001$). There was no significant difference in the serum levels of ICAM-1 between the patients and controls ($p = 0.232$). No significant correlation was detected between the levels of the serum markers and other clinical parameters ($p > 0.05$). Tumor localization ($p = 0.03$), histopathology ($p = 0.05$), and response to chemotherapy ($p = 0.003$) had prognostic factors on survival. Neither serum ALCAM levels nor serum ICAM-1 levels were identified to have a prognostic role on overall survival (ICAM-1 $p = 0.6$, ALCAM $p = 0.25$). In conclusion, serum levels of ALCAM were found to have diagnostic value in GC patients.

1. Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third common cause of cancer death worldwide [1]. Activated leukocyte cell adhesion molecule (ALCAM) (or CD166) is a 110 kDa multidomain transmembrane type 1 glycoprotein of the immunoglobulin superfamily that acts as a mediator in the homotypic and heterotypic interactions between cells [2,3]. It has also been found to be overexpressed in various types of epithelial cancers, thus considered as a prognostic marker of disease progression and poor survival in such cancers [4–6]. Extracellular domain of ALCAM (soluble ALCAM or s-ALCAM) is shed by metalloproteases, such as ADAM 17, and then can be detected in the serum. Increased levels of s-ALCAM were observed in cancer patients compared to healthy controls [7–11].

Intercellular adhesion molecule-1 (ICAM-1) (or CD54) belongs to the immunoglobulin superfamily that functions as the ligand for the β2 integrins lymphocyte function-associated antigen-1 (LFA-1) and CD11b/CD18. ICAM-1 is expressed on a number of hematopoietic and nonhematopoietic cells, including B and T cells, dendritic cells, macrophages, fibroblasts, endothelial cells, keratinocytes, and some epithelial tissues [12]. Once it binds to LFA-1 on the surface of T lymphocytes it enhances the susceptibility of such tumor cells to lymphocyte-mediated tumor cytotoxicity [13].

ICAM-1 has been found to augment the metastatic potential of malignant tumor cells [14]. Increased levels of sICAM-1 have been reported in patients with various types of tumors [15–19] and it is also associated with tumor progression and metastasis [20–22] in

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http://dx.doi.org/10.1016/j.biopha.2015.12.006
0753-3322/

cancers, such as malignant melanoma [23], lung cancer [24], colorectal cancer [25], breast cancer [26], and hepatocellular cancer [27].

We aimed to assess the association of serum levels of ALCAM and ICAM-1 with diagnosis, treatment response and survival in GC patients and also we analyzed the relationships of these biomarkers with clinicopathological parameters in GC patients and we discussed the potential use of these new biomarkers in GC.

2. Material and methods

2.1. Patients characteristics

Fifty eight patients, who were admitted to the Institute of Oncology, Istanbul University and all of who had histologically confirmed gastric cancer were enrolled in the study. None of them had received chemotherapy or chemoradiation during the previous 6 months. Their diseases were staged by the AJCC (American Joint Committee on Cancer) and UICC (International Union against Cancer) staging systems. Detailed clinical history and physical examination along with a series of biochemistry tests were completed before the onset of the treatment. The patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and appropriate blood chemistry tests had received chemotherapy in the outpatient clinic. The treatment protocols were comprised of various combinations of fluorouracil, folinic acid, capecitabine, docetaxel, cisplatin, epirubicine, with or without radiotherapy according to the stage of the disease. The follow ups of the patients were done with clinical, laboratory, and radiological evaluations every 8th week while they were receiving chemotherapy and every 12 weeks after they had completed chemotherapy. Treatment responses were graded according to the revised RECIST criteria version 1.1. Twenty age and sex-matched healthy controls participated in the study. Informed consent was obtained from all of the patients and healthy control group and the study was reviewed and approved by our local ethical committee.

Table 1
Patient and disease characteristics.

Variables	*n*
No. of patients	58
Age, years median (range) 59.5 (32–82)	
≥60	29
<60	29
Gender	
Male	36
Female	22
Tumor localization	
Cardia	13
Antrum	42
Undetermined	3
Histopatology	
Diffuse	43
Intestinal	9
Undetermined	6
Tumor (T) stage	
1–3	13
4	41
Unknown	4
Lymph node involvement	
No	19
Yes	36
Unknown	3
Stage of disease	
Nonmetastatic	30
Metastatic	28
Response to chemotherapy	
Responsive	19
Non-responsive	27
Unknown	12

Table 2
The values of serum ALCAM and ICAM-1 levels in gastric cancer patients and healthy controls.

	Patients ($n=58$)		Controls ($n=20$)		
Marker	Median	Range	Median	Range	*p*
ALCAM (ng/mL)	0.13	0.07–0.16	0.11	0.08–0.14	0.001
ICAM-1 (ng/mL)	18939.8	182–78029.9	5067.8	203.1–77029.9	0.232

2.2. Measurement of serum ICAM-1 and ALCAM levels

Before the onset of the treatment serum samples were collected from patients with gastric cancer and healthy controls by venipuncture and were let clot at room temperature. The sera were then centrifuged and frozen immediately at −20 °C.

Serum sICAM-1 (Diaclone, France) and serum ALCAM (Wuhan Eiaab, China) levels were measured by the solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) method that used double-antibody sandwich ELISA. Then, serum samples and standards were added to the wells which were pre-coated with human sICAM-1 and ALCAM monoclonal antibodies. Then, biotin-conjugated anti-human SICAM-1 and anti-human ALCAM antibodies and Streptavidin-HRP were added in order for biotin-conjugated anti-human antibodies to bind to human antibodies and Streptavidin-HRP was allowed to bind to the biotin-conjugated anti-human antibodies to form immune complex and were left to incubate at room temperature for 1 h. Unbound Streptavidin-HRP was washed away and then a colorless Chromogen solution was added to the wells. At this moment solution turned blue. The intensity of this color conversion was proportional to the amount of ICAM-1 and ALCAM in the sample. The reaction was terminated by adding of acid (stop solution) and the absorbance was measured by an automated ELISA reader (ChroMate, 4300 Microplate Reader, Palm City, FL, USA) at 450 nm. The amounts of ICAM-1 and ALCAM were denominated as and ng/mL.

2.3. Statistical analysis

Continuous variables were grouped using median values as cut-off point. Assessment of relationship and comparisons between various clinical and laboratory parameters and serum ICAM-1 and ALCAM levels were carried out with Mann–Whitney *U* test. Survival was calculated starting from the date of first admission to the date of death of any cause or to the date of the last contact with the patient or any family member. Kaplan–Meier method was used to determine the survival of patients and differences in survivals were assessed by the log-rank statistics. A p value < 0.05 was considered significant. Statistical analysis was carried out using SPSS 16.0 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

Fifty-eight patients with pathologically confirmed diagnosis of gastric cancer were enrolled in the study. The baseline histopathological characteristics and demographic features of patients were listed in Table 1. The median age at diagnosis was 59.5 years, range 32–82 years. Tumor localization of the majority of the patients was antrum ($n=42$, 72.4%) and tumor histopathology of the majority of the patients was diffuse ($n=43$, 74.1%). The majority of the patients had stage IV disease ($n=41$, 70.7%). Thirty six (62.1%) patients had lymph node involvement. We could not reach the chemotherapy data of 12 patients.

The levels of serum ALCAM and ICAM-1 in patients with gastric cancer and healthy controls are shown in Table 2. The baseline