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ORIGINAL ARTICLE

Prognostic role of inflammatory biomarkers in metastatic breast cancer

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Summary

Purpose: *The effects of inflammation on the prognosis, life expectancy and several parameters such as response to treatment of breast cancer have been previously studied. The purpose of this study was to investigate the effect of inflammatory markers on prognosis in patients with metastatic breast cancer.*

Methods: *This study was conducted on 81 patients with metastatic breast cancer who have been followed up at the Department of Medical Oncology, Hacettepe University Institute of Oncology, between December, 2009 and March, 2014. For all studied parameters Kaplan-Meier survival estimates and p values computed by log-rank test were calculated. A p value < 0.05 was considered statistically significant.*

Results: *Median follow-up time was 26 months. There were 38 deaths due to disease progression during the follow up. The levels of serum albumin, and erythrocyte sedimentation rate (ESR) were not associated with a significant effect on overall survival (OS). Among patients with a higher serum C-reactive protein (CRP), the estimated mean survival was 84±36 months, compared to 278±113 months among patients with a normal serum CRP (p=0.032). When patients with higher and normal lactate dehydrogenase (LDH) levels were compared, their 2-year OS survival rates were 68.2 and 87.7%, respectively (p=0.034). Among patients with higher serum ferritin levels, the estimated mean survival was 29±10 months, compared to 212±113 months for normal serum ferritin (p=0.01). Among patients with higher serum beta-2 microglobulin (β2-M), the estimated mean OS survival was 28±8 months, compared to 84±57 months for those with normal levels (p<0.01).*

Conclusion: *Serum CRP, ferritin and β2-M can be useful prognostic factors for OS in patients with metastatic breast cancer.*

Key words*: breast cancer, inflammatory markers, metastasis, parameter, prognosis*

Introduction

Elevated levels of serum biomarkers at the time of diagnosis of metastatic breast cancer may be associated with poor prognosis. The role of prognostic and predictive factors in breast cancer has been emphasized in previous studies. Factors such as axillary nodal status, tumor size, tumor type/grade, lymphatic and vascular invasion, proliferation markers, ethnicity and patient age at diagnosis have been defined as prognostic factors [1].

Recently attention has been paid to the renaissance of the inflammation–cancer connection, stemming from different lines of work and leading to a generally accepted paradigm [2–4]. According

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to epidemiological studies, chronic inflammation can predispose to different forms of cancer. The relationship could be supported by the fact that the hallmark of chronic inflammation being white blood cells are prominently tumor-associated macrophages (TAMs), the presence of polypeptide messengers of inflammation [cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, chemokines such as CCL2 and CXCL8] and the occurrence of tissue remodeling and angiogenesis [2,3].

Schematically, inflammation and cancer are connected by two pathways: 1) the intrinsic pathway activated by genetic alterations (including activation of oncogenes by mutation, chromosomal amplification, inactivation of tumor-suppressor genes) leading to neoplastic transformation that cause inflammation and neoplasia; and 2) in the extrinsic pathway, inflammatory conditions facilitate cancer development – inflammatory or infectious conditions are primary regulators of tumor inflammation, augmenting the risk of developing cancer [3,7]. The convergence of these two pathways results in the activation of transcription factors and primary proinflammatory cytokines, and finally a tumor-related inflammatory microenvironment is generated. However, it should be emphasized that not all inflammations play a role in carcinogenesis. For example, in some tumors the adaptive immune response plays a role in immune surveillance [2,7,8]. The role of specific immune and inflammatory cells in epithelial neoplastic transformation is not completely understood. It has been proposed that either the tumor can alter the immune response, becoming a protumorigenic inflammation, or continuous chronic inflammation is the key orchestrator in transforming tissue stem cells into cancer cells. Furthermore, cancer tissue-derived signals and chronic sustained inflammation can play a part in accumulating bone marrow derived cells that can give rise to stroma and tumor cells, contributing to tumor growth and progression [7,9].

Defining prognostic factors at the time of diagnosis of metastatic breast cancer has been a growing concern since metastasis to various organs can affect both the OS and disease-free survival (DFS) of patients with metastatic diseaseses. Follow up of patients with metastatic disease requires a great deal of laboratory work up and the place of inflammatory markers is undeniable. We considered the easy access to lab work and studied its potential role in predicting the prognosis in patients with metastatic breast cancer.

Our study focused on the effect of inflammatory markers such as serum CRP, β2-M, and ferritin at the time of diagnosis of metastatic breast cancer on the disease prognosis.

CRP is an acute phase reactant produced in the liver, predominantly under transcriptional control by the cytokine interleukin-6 originating from the site of insult [6]. The microenvironment of tumor cells which can serve as a trigger of inflammation in actual fact helps facilitate tumor progression via invasion and metastasis [2,4,7,8]. In view of this, IL-6 which functions as a trigger of chronic inflammation and also seen as a mediator of CRP proliferation could be responsible for elevated levels of CRP in metastatic disease. Patients with higher levels of CRP at the time of metastatic disease should therefore be expected to present with a worse disease progression.

The prognostic use of CRP and other inflammatory markers has been demonstrated in many forms of cancer, such as prostate and colorectal, but the epidemiological evidence for a diagnostic or an etiological role of circulating CRP in cancer has been inconsistent to date. Although previous cohort studies have shown that elevated pretreatment levels of CRP are associated with poor prognosis in patients diagnosed with breast cancer, findings from other studies reveal no clear relationship between circulating levels of CRP and breast, prostate or colorectal cancers but rather a link between CRP and colorectal or lung cancers. These prospective studies provided no strong evidence for a causal role of CRP in cancer [5,6].

β2-M is a serum protein found in association with the major histocompatibility complex (MHC) class I heavy chain on the surface of nearly all nucleated cells. It is necessary for antigen presentation but may also bear proto-oncogene properties. Its role has been described in the pathogenesis of colorectal cancer stratified by mismatch repair [9,10]. Elevated levels of β2-M may as such suggest the presence of proliferating metastatic cells which in turn raises the point of a poor disease prognosis.

Recent studies have proposed a pivotal role of deregulated iron metabolism in the initiation of breast cancer [11,12]. Elevated levels of ferritin have been reported in leukemia and Hodgkin's disease and, in the case of acute leukemia, this is associated with increased synthesis and high concentrations in malignant cells [13]. Marcus and Zinberg suggested that breast cancer tissue might produce its own characteristic ferritin. Elevated levels of ferritin in this respect could be

considered as a marker for metastatic disease [13]. However, current evidence on the clear relationship between the ubiquitous intracellular protein and metastatic disease is far from plausibility.

After the development of cancer, malignant cells and cells found in their microenvironment evoke inflammatory responses via many pathways. A few studies have reported the probable relationship between inflammatory markers such as CRP, ESR, albumin, β2-M, ferritin, LDH and the prognosis, survival and response to chemotherapy. Our study is the first to investigate the effect of inflammatory markers on the prognosis of metastatic breast cancer patients.

Methods

This study was conducted on 81 patients with metastatic breast cancer who had been followed up at the Department of Medical Oncology, Hacettepe University Institute of Oncology, between December 2009 and March 2014. Ethical approval for the study was received from the Hacettepe University ethics committee on 28 November 2012 (Decision No: LUT 12/144-33). Included into the study were patients with metastatic breast cancer at the time of diagnosis. Patients with known inflammatory conditions (acute bacterial and viral), rheumatologic diseases (rheumatoid arthritis, lupus etc.) were excluded from the study.

Serum CRP (mg/dL) levels were measured by using the selective multi-protein analyzer (BN-II-Dade, Malvern, PA, USA) Serum lactate dehydrogenase (LDH (U/L) and albumin (mg/dL) levels were measured spectrophotometrically (Abbott C16000 brand device). β2-M (U/mL) levels were calculated using the nephelometric method (Siemens BN Prospect brand device); Carcinoembryonic antigen (CEA) (ng/mL) and cancer antigen (CA) 15-3(U/mL) levels were calculated by immunoassay (Siemens device).

Serum ferritin (mg/dL) levels were measured via the electro-chemiluminescent immunoassay (ECLIA) method, based on the sandwich principle. Serum ESR (mm/h) measurements were made using the Alifax test system and capillary photometric kinetic technology.

Diagnosis and staging of disease were made based on physical examination, mammography, ultrasonography, computed tomography and bone scintigraphy findings. Routine hemogram and a biochemistry panel were performed before every cycle of chemotherapy. Evaluation of hematologic, liver and kidney toxicities that developed as a result of chemotherapy was based on the results of the hemogram and serum biochemistry profiles.

Statistics

All data was entered and analyzed using the Statistical Package for Social Sciences, version 15.0 (SPSS, Inc. Chicago, IL, USA). Categorical and continuous variables that showed normal distribution were expressed at mean ± SD. Those without normal distribution were expressed as median, minimum-maximum values. Prognostic factors and those affecting OS and DFS were analyzed with univariate and multivariate analysis. OS was defined as the period between diagnosis and the last date of medical follow up or death. DFS was defined as the length of time after primary treatment ended that the patients survived without any signs or symptoms of disease. The estimated probability of survival was

Table 1. Patient and disease characteristics

Characteristics	*n = 81*	*%*
Median age of diagnosis (min-max)	47 (26-83)	
Menopausal status		
Pre-menopausal	43	53.8
Peri- menopausal	35	43.8
Post- menopausal	2	2.5
Histology of the tumor		
IDC	58	76.3
ILC	6	7.9
IDC+ILC	4	5.3
Others	8	10.5
Estrogen receptor		
Positive	52	82.5
Negative	11	17.5
Progesterone receptor		
Positive	42	70.0
Negative	18	30.0
HER2		
Positive	14	23.7
Negative	45	76.3
Subtype		
Luminal A	39	66.1
Luminal B	10	16.9
HER2 over-expression	4	6.8
Triple negative	6	10.2
Grade		
I	3	5.3
II	30	52.6
III	24	42.1
Lymphovascular invasion		
Positive	19	70.4
Negative	8	29.6
Tumor size		
T1	16	19.8
T2	24	29.6
T3	26	32.1
T4	15	18.5
Lymph node status		
N0	18	24.7
N1	17	23.3
N2	18	24.7
N3	20	27.4

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

obtained using Kaplan-Meier method and differences between patient groups with normal and high biomarker levels and positive and negative hormone receptors were evaluated by log-rank test. Statistical significance was accepted as p≤0.05.

Results

A total of 81 patients were included in this study. General demographics of patients are shown in Table 1. The median age at diagnosis of all patients was 47 years (range 26-83). Forty-three (53.1%) patients were premenopausal. Modified radical mastectomy was performed on 35 (43.2%) patients. The most commonly seen primary tumor histological type was invasive ductal carcinoma (n=58;71.6%). Regarding the tumor molecular subtypes, luminal A (n=39;48.1%) was the most common tumor subtype. The most frequent histological grade was grade II (n=30). The percentage of patients with a positive lymphovascular invasion (LVI) was 23.5% (n=19). Tumor size was highest in the T2 group (n=26;32.1%). Lymph node involvement was most frequently seen in the N0 group (n=18;22.2%).

Evaluation of serum inflammatory markers in patients included into the study showed high serum levels of CRP (51;63%), ESR(31;38.3%), ferritin (11;13.6%), LDH (22;27.2%), β2-M(12;14.8%) and low serum levels of albumin 6 (7.4%) (Table 2). During follow up, 38 patients (46.9%) died due to disease progression.

Other laboratory findings which may affect the inflammatory parameters are shown in Table 3. Illustrated in Table 4 is the distribution of patients in terms of normal or abnormal levels of serum inflammatory markers with respect to OS and DFS. Analysis of the 2-year OS and DFS according to other disease parameters is also summarized in Table 5.

Among patients with a higher serum CRP, the estimated mean survival was 84±36 months,

Table 2. Inflammatory markers

Markers	*n = 81*	*%*
Albumin		
Normal	75	92.6
Low (< 4.0 mg/dL)	6	7.4
CRP		
Normal	28	35.4
High (> 0.5 mg/dL)	51	64.6
ESR		
Normal	46	59.7
High (> 25 mm/hr)	31	40.3
Ferritin		
Normal	68	86.1
High (> 300.0 mg/dL)	11	13.9
LDH		
Normal	57	72.2
High (> 480 U/L)	22	27.8
β_2 microglobulin		
Normal	66	84.6
High (> 2400 U/mL)	12	15.4

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase

Table 3. Evaluation of laboratory findings which may affect the inflammatory parameters

Markers	*n = 81*	*%*
Creatinine		
Normal	72	93.5
High (> 0.90 mg/dL)	5	6.5
AST		
Normal	74	92.5
High (> 30 IU/mL)	6	7.5
ALT		
Normal	77	95.1
High (> 30 IU/mL)	4	4.9
WBC		
Normal	76	93.8
High (> 10.000 /mL)	5	6.2
Hemoglobin		
Normal	63	77.8
Low (< 11.0 g/dL)	18	22.2
CA 15-3		
Normal	38	46.9
High (> 31.0 U/mL)	43	53.1
CEA		
Normal	47	58.8
High (> 5.0 ng/mL)	33	41.3

AST: aspartate aminotransferase, ALT: alanine aminotransferase, WBC: white blood cells, CEA: carcinoembryonic antigen

Table 4. Overall survival and disease free survival in patients with respect to inflammatory markers

Markers	*2-year OS * (%)*	*p value*
Albumin		
Normal	84	0.396
Low	66.7	
LDH		
Normal	87.7	0,034
High	68.2	
β_2-microglobulin		
Normal	87.9	<0.001
High	50	
CRP		
Normal	96.4	0.032
High	76.5	
ESR		
Normal	89.1	0.299
High	77.4	
Ferritin		
Normal	88.2	0.006
High	54.5	

*log-rank test; OS: overall survival. For other abbreviations see text

Table 5. Overall survival with respect to other parameters which might affect inflammatory markers

Markers	*2-year OS (%)*	*p value*
CA 15.3		
Normal	84.2	0.947
High	81.4	
CEA		
Normal	83	0.030
High	81.8	
Hemoglobin		
Normal	87.3	0.012
High	66.7	
ER		
Negative	63.6	0.001
Positive	90.4	
PR		
Negative	66.7	0.004
Positive	92.9	
HER2		
Negative	84.4	0.536
Positive	85.7	
LVI		
Present	73.7	0.885
Absent	87.5	
Grade		
I	100	0.403
II	83.3	
III	75	
Lymph nodes		
0	94.4	
1	100	0.037
2	66.7	
3	70	
Histological type		
IDC		
ILC	82.8	0.516
IDC+ILC	10075	
Other	75	
Subtype		
Luminal A	87.2	
Luminal B	90	0.045
HER2 over-expression	75	
Triple negative	66.7	

LVI: lymphovascular invasion , CEA: carcinoembryonic antigen, ER: estrogen receptor, PR: progesterone receptor, IDC: imfiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma

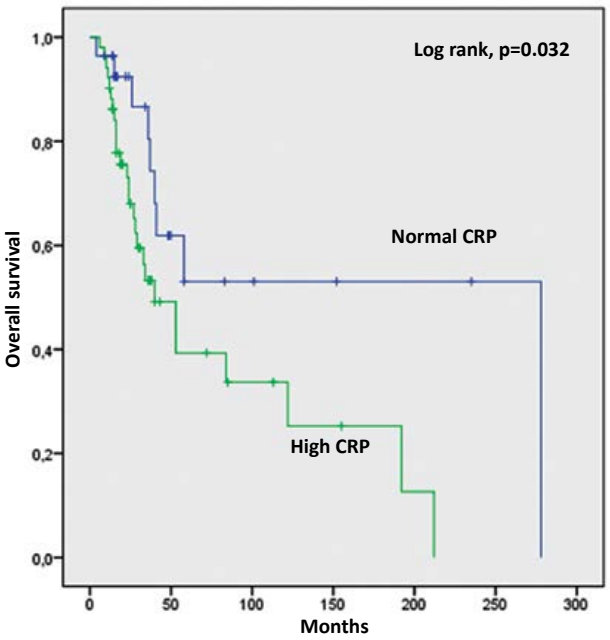

Figure 1. CRP levels and overall survival.

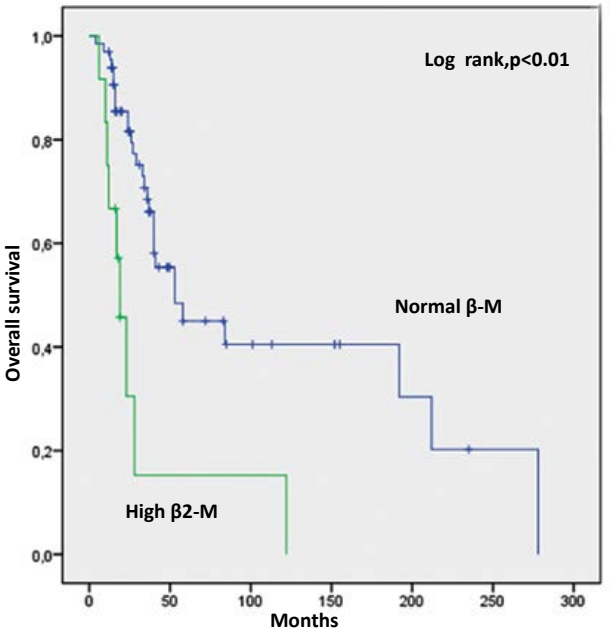

Figure 2. β2 microglobulin levels and overall survival

compared to 278±113 months among patients with normal serum CRP (p=0.032; Figure 1). The patients with higher serum β2-M levels had shorter estimated mean survival time compared to those with lower levels (28±8 months and 84±57 months, respectively, p<0.01; Figure 2). Among patients with higher serum ferritin levels, the estimated mean survival was 29±10 months, compared to 212±113 months for normal serum ferritin (p=0.01; Figure 3). When patients with higher and normal LDH levels were compared, their 2-year OS rates were 68.2% and 87.7%, respectively (p=0.034; Figure 4). On the other hand the levels of serum albumin and ESR were not associated with a significant effect on OS.

The estimated mean survival was 84±36 months and 278±113 months among patients with high and normal serum CRP levels, respectively (p=0.032). The estimated mean survival was 29±10 months and 212±113 months for high and normal serum ferritin levels, respectively (p=0.01). Patients with higher β2-M had mean survival of 28±8 months.

Discussion

Breast cancer is the most frequently diagnosed and the leading cause of cancer death in

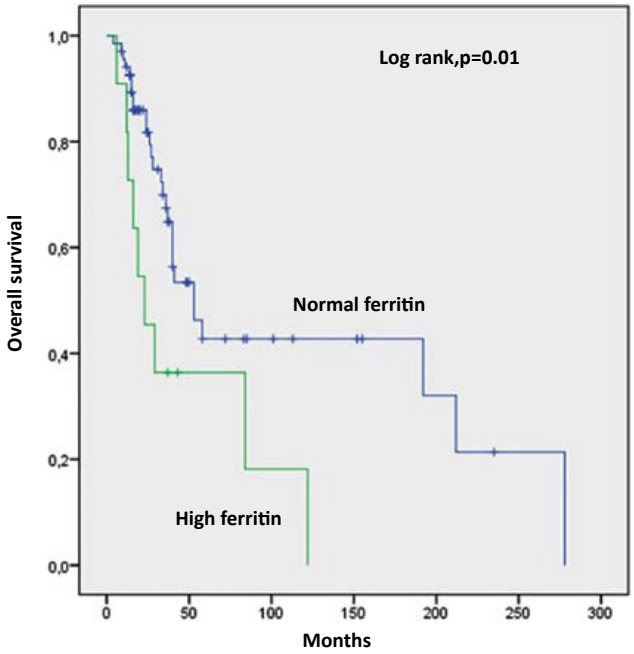

Figure 3. Ferritin levels and overall survival.

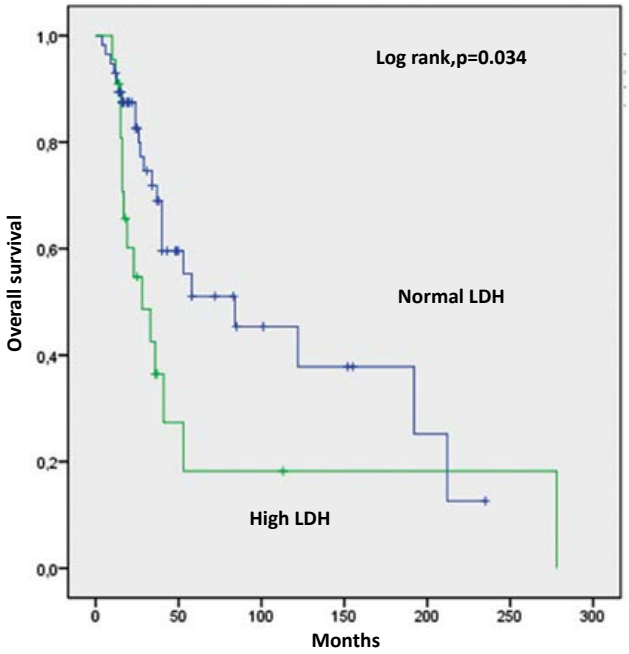

Figure 4. LDH levels and overall survival.

women globally. Over the past few decades its incidence has increased but a fall in mortality has been observed due to improvement in survival which is associated with earlier disease detection, a multidisciplinary approach to treatment and biological changes that have made the disease more susceptible to hormonal therapy.

The role of inflammation in the pathogenesis and prognosis of breast cancer has been investigated. Recent efforts into identifying a possible relationship between inflammatory markers and the prognosis of cancer have been widely appreciated. After the development of cancer, cells found in the malignant microenvironment evoke inflammatory responses via many pathways. A few studies have reported the probable relationship between inflammatory markers such as CRP, ESR, albumin, β2-M, ferritin, LDH and the prognosis, survival and response to chemotherapy.

In this study we found high levels of the inflammatory markers (CRP, ESR, ferritin, LDH β2-M) and low serum levels of albumin in patients with metastatic breast cancer. The median follow up period for all the study groups was 26 months. OS and DFS rates were not statistically different among patients with normal values and abnormal values with respect to albumin, ferritin, LDH, β2-M, CRP, and ESR. To the best of our knowledge, this study is the first to investigate the effect of inflammatory markers on the prognosis of metastatic breast cancer patients.

Inflammation has been shown to influence parameters such as prognosis, survival and response to therapy in breast cancer. Chronic inflammation is thought to trigger the process of carcinogenesis and as such is regarded as a predisposing factor for the development of cancer [13]. The prognostic value of systemic inflammatory response in metastatic breast cancer has already been established [14]. Increased expression of interleukin-6 and triggered serum CRP levels have been associated with tumor stage and metastasis. Nevertheless, the understanding of the tumor–host interaction remains complex and unclear. Notwithstanding this dilemma, an assessment of the host systemic inflammatory response by examining the changes in the concentrations of acute phase proteins, such as elevated circulating concentrations of CRP and low concentrations of albumin is now accepted [15]. Be it single or combined the prognostic values of these factors in patients with advanced cancers have been described to be stage-independent [16].

Noninfectious chronic inflammation has also been associated with other forms of cancer such as colorectal, lung and esophago-gastric tumors [17,18]. The concentration of acute phase proteins stay high as the degree of inflammation increases. ESR, CRP, albumin, β_2-M, ferritin and LDH are known to be the other associated acute phase proteins [19]. This study aimed to investigate the effect of inflammatory markers on prognosis among patients with metastatic breast cancer and discuss its place in accordance with recent reports in the current literature [20-22]. Albuquerque et al. could not find in their study any relationship between

ESR and response to therapy in patients with metastatic breast cancer, however they were able to show CRP as a predictive factor in the prognosis of 85 newly diagnosed patients with metastatic breast cancer [23]. In another study that evaluated 81 patients with metastatic breast cancer , ESR was found not to be associated with survival [24]. Similar to the findings from these studies, our study could not reveal any association between serum inflammatory marker ESR and OS (p=0.32) and DFS (p=0.79) and prognosis.

High serum CRP concentrations together with hypoalbuminemia are proven to be independent prognostic factors for lung cancer. The prognosis of patients with metastatic breast cancer has been shown to worsen in the presence of high CRP concentrations [25]. Patients with invasive breast cancer and CRP levels >3 mg/L at diagnosis had a 1.7-fold increased risk of death from breast cancer compared to patients with CRP levels <1 mg/L at diagnosis [5]. In our study we found serum CRP levels to be associated with survival and prognosis in patients with metastatic breast cancer (p=0.032). In contrast, findings from our previous study which investigated the effects of inflammatory markers in early-stage breast cancer [26] did not reveal any association between CRP and prognosis and this can be attributed to an early-stage inflammation during the early stages of disease.

The distribution of ferritin in malignant breast tissue at different stages in tumor development was examined by Alkhateeb et al. They found ferritin to stimulate the proliferation of epithelial breast cancer cell lines MCF7 and T47D. Moreover they were able to show that this proliferative effect was independent of the iron content of ferritin, thus suggesting an effector mechanism by which inflammatory ferritin, directly stimulates tumor genesis. Because ferritin is secreted by the macrophages and not by the tumor, ferritin-based therapies may be effective in patients with elevated serum ferritin regardless of tumor site or molecular subtype [27].

Findings from our study showed a high serum ferritin level (p=0.01) in patients with metastatic breast cancer, although in another study that we conducted, the impact of serum ferritin levels on prognosis in operable breast cancer; OS and DFS did not reach statistical significance (OS, p=0.74, DFS, p=0.23). Since malignant cells often have a high demand for iron, breast cancer cells may alter the expression of iron transporter genes including the iron importer (transferrin receptor). This can be explained by the high transferrin receptor levels and proliferation index that is seen in aggressive tumors. Serum ferritin levels have also been reported to be high in most malignancies including lymphoma, breast, liver, lung and colon. Also, when serum ferritin levels in tumor tissue of colon cancer, testicular seminoma and breast cancer were compared to that of normal tissue it was found to be higher in the tumor tissues [28]. The absence of a serum ferritin-prognosis relationship in our study could be attributed to the fact that only few numbers of patients enrolled into the study had high serum ferritin levels. Moreover, the high risk of iron deficiency anemia in our study group (females) cannot be ruled out. We considered this situation as a bias in patients who could have higher serum ferritin levels.

We have previously reported a non-statistically significant relationship between β2-M levels and prognosis and survival in patients with operable breast cancer (p=0.69) and DFS (p=0.81) [26]. The present study, however, revealed a statistically significant association between β2-M levels and prognosis and survival (p<0.01).

β2-M has been previously reported as a growth factor and a signaling molecule in malignant cells and its levels are known to increase in multiple myeloma and lymphoma [29]. Its expression increases during progression of human prostate, breast, renal, lung, and colon cancer and a number of non-solid tumors. Overexpression of β2-M in patients with late-stage breast cancer compared to those with early-stage disease has also been reported. Overexpression of β2-M has been associated with proliferation, migration and invasion of breast, lung and renal cancer cells.

β2-M mediates the activation of epithelial to mesenchymal transition, thus promoting lethal bone and soft tissue metastases in host mice. Thus, β2-M and its downstream signaling pathways serve as promising novel therapeutic targets for cancer therapy [30].

Total serum LDH level elevation is a predictive marker of tissue damage and inflammation. Its prognostic value on the follow up of patients with malignant hemopathies and malignancies is well investigated [31]. Serum LDH levels are also used as a prognostic factor in follicular lymphoma, chronic lymphocytic lymphoma and metastatic melanoma [32]. High serum LDH levels have been suggested as a marker of relapse in asymptomatic non-Hodgkin lymphoma patients. Besides, it is also known to be an important factor in determining an appropriate treatment strategy [33]. Similarly, in our study a significant relation-

ship between LDH levels and 2-year survival rate was demonstrated.

Alphs et al. in their study were prospectively able to determine that mortality increases by 2-fold in peritoneal and ovarian cancer patients who had an albumin level of less than 3.7g/dL [34]. Low levels of serum albumin have been reported to adversely affect survival for all stages of breast cancer. A baseline serum albumin level was found to be a powerful prognostic variable and a level greater than 3.5g/dL was described to decrease mortality [35]. Conditions such as chronic liver diseases, malabsorption and malignancies are known to decrease serum albumin levels [36]. Low level of preoperative serum albumin is known to be bad prognostic factor in breast, colon, head-neck, lung, liver and a number of gynecologic malignancies. Levels below 4 g/dL are also known as an independent prognostic factor in patients with colorectal cancer. In our study, levels of serum albumin were not associated with a significant effect on OS.

Conclusion

The present study is the first study in the medical literature that investigated the effect of 6 inflammatory markers on the prognosis of metastatic breast cancer patients. The median follow-up period of the patients (OS and DFS) was 26 months (range 3-227). We were able to show that while ESR and albumin levels were not significantly associated with the course of the disease, inflammatory markers such as CRP, ferritin, β2-M, and LDH can be used to predict prognosis in patients with metastatic breast cancer.

Conflict of interests

The authors declare no confict of interests.

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