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ORIGINAL ARTICLE

Impact of inflammatory markers on the prognosis of patients with operable breast cancer

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Summary

Purpose: *To investigate the effect of inflammatory markers on the prognosis of patients with operable breast cancer.*

Methods: *This study was conducted on breast cancer patients followed up between December 2009 and December 2012 at the Division of Medical Oncology, Department of Internal Medicine, Hacettepe University Medical School. A total of 704 patients with stages I to III disease whose inflammatory markers were assessed at the time of diagnosis were included the study. Serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, ferritin, β2 microglobulin (β2-M), and lactate dehydrogenase (LDH) levels were evaluated as inflammatory markers.*

Results: *The median age at diagnosis was 50 years (range 25-92). Of the patients 42.8% were premenopausal and 48.2 % postmenopausal. Invasive ductal carcinoma was the most common histology (76.5 %). Serum ferritin, LDH, β2-M, ESR, and CRP were higher than the normal values in 1.0, 4.3, 9.5, 32.4 and 36.4 % of the patients, respectively. Serum albumin levels were lower than the normal values in 1.7 % of the patients. The median patient follow-up period was 22 months (range 3-227). During follow-up, metastatic disease developed in 31 patients (4.4%) and 11 patients (1.56%) died due to disease progression. Two-year overall survival (OS) and disease free survival (DFS) rates were not statistically different among patients with normal and abnormal values with respect to albumin, ferritin, LDH, β2-M, CRP, and ESR.*

Conclusion: *Our study is the first study to investigate the effect of inflammatory markers on the prognosis of operable breast cancer patients. We showed that inflammatory markers such as ESR, CRP, ferritin, β_2-M, albumin and LDH have no effect on prognosis.*

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

Introduction

Breast cancer is the most frequently diagnosed and the leading cause of cancer-related deaths in women globally. Over the past few decades its incidence has increased but a fall in the death rate has been observed due to improved survival. Improvement in survival is associated with earlier detection of disease, multidisciplinary therapeutic approach and biological changes that have made the disease more susceptible to hormonal therapy [1].

In recent years, earlier detection of the disease (both through screening and earlier symptomatic presentation) has led to a rise in the number of operable breast cancer cases. Early detection of patients during the early stage of disease, progress in surgical procedures, adjuvant hormonal therapy and polychemotherapy are some of the factors that contributed to a decrease of breast cancer associated morbidity and mortality. An increase in the treatment choices for breast cancer can be attributed to factors such as the perception of breast cancer as a systemic disease right after diagnosis and the current ongoing debate on patient selection for neoadjuvant and adjuvant systemic therapy. In this way, staging that had already begun in patients, prognostic factors associated with

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survival and the response to treatment are among factors that have recently drawn attention.

In addition to the role of inflammation in the development of breast cancer, it has also been shown to influence parameters such as prognosis, survival and response to therapy.Chronic inflammation is thought to trigger carcinogenesis and as such is regarded as a predisposing factor for the development of cancer [2]. The prognostic value of the systemic inflammatory response in metastatic breast cancer is known [3]. Increased expression of Interleukin-6 and high serum CRP levels have been associated with tumor stage and metastasis. However, the understanding of the tumor–host interaction remains complex and unclear. Notwithstanding this dilemma, assessment of the host systemic inflammatory response by examining the changes in the concentrations of acute phase proteins, such as elevated serum concentrations of CRP and low concentrations of albumin is now accepted [4]. Be it single or combined, the prognostic values of these factors in patients with advanced cancers have been described to be stage-independent [5].

There has been evidence regarding the prognostic value of systemic inflammatory response in patients with metastatic breast cancer. As an example, high serum concentrations of CRP and low albumin levels have been associated with poor prognosis and short term survival in many studies [6]. In a propective study, lower preoperative albumin concentrations, but not elevated CRP concentrations, were found to be associated with OS and cancer-specific survival in patients undergoing potentially curative surgery for primary operable breast cancer [3]. Low level of preoperative serum albumin is known to be a poor prognostic factor in breast, colon, head-neck, lung, liver and a number of gynecologic malignancies. Levels below 4 g/dL are also known as independent prognostic factors in patients with colorectal cancer. In a prospective study conducted by Alphs et al. mortality was observed to increase by two-fold in peritoneal and ovarian cancer patients who had an albumin level of less than 3.7g/dL [7].

Another study demonstrated overexpression of β2-M as the driving factor for epithelial to mesenchymal transition, thus advancing the development of metastasis in bones and soft tissues *in vivo* [8]. Results from these studies demonstrate the role of β2-M in cancer metastasis and lethality, thus making its downstream signaling pathways auspicious prognostic markers of cancer metastases and novel therapeutic targets for cancer therapy. Serum LDH levels were also used as a prognostic factor in follicular lymphoma, chronic lymphocytic leukemıa and metastatic melanoma [9].

An unexplained elevated ESR has been associated with bad prognosis in malignancies like Hodgkin lymphoma, gastric carcinoma, renal cell carcinoma, chronic lymphocytic leukemia, breast cancer, colorectal and prostate cancer [10]. In patients with solid tumors, ESR of ≥ 100mm/h is an indication for metastatic disease, however it is insufficient as a single marker for diagnosis. In patients with Hodgkin lymphoma, elevated ESR that persists 6 months postchemotherapy is predictive of early relapse and poor prognosis [10].

Serum ferritin levels have also been reported to be high in most malignancies including lymphoma, breast, liver, lung and colon. Also, when ferritin levels in tumor tissues of colon cancer, testicular seminoma and breast cancer were compared with normal tissues it was found to be higher in the tumor tissues [11]. Iron deposition has been known to increase with age and is associated with a higher risk of breast cancer in old postmenopausal women [12]. Preoperative serum ferritin levels were higher in 41% of the patients with breast cancer compared to the normal population. Also transferrin and transferrin receptor levels were shown to be elevated in these patients [13]. After the development of cancer, malignant cells and cells found in their microenvironment evoke inflammatory responses via many pathways. Quite a few studies have reported a probable relationship between inflammatory markers such as CRP, ESR, albumin, β2-M, ferritin, LDH and the prognosis, survival and response to chemotherapy [6,10,11].

The present study is the first to investigate the effect of inflammatory markers on the prognosis of operable breast cancer patients.

Methods

This study was conducted on 704 patients with stages I to III breast cancer who have been followed up at the Department of Medical Oncology, Hacettepe University Institute of Oncology, between December 2009 and December 2012. Ethical approval for the study was received from the Hacettepe University Ethics Committee on 28 November 2012 (Decision No: LUT 12/144-33). Patients with stages IA through IIIC breast cancer based on relevant pathology reports, who were operated on and put on adjuvant therapy were included. Patients with metastatic breast cancer and those who had received treatment for metastatic disease were excluded from study. Patients with known inflammato-

ry conditions (acute bacterial and viral), autoimmune diseases (rheumatoid arthritis, lupus etc) were also excluded from study. After exclusion, 704 cases were eligible for analysis. Patient data and information were extracted from a prospectively maintained institutional review board database. Serum CRP levels were measured using the selective multi-protein analyser BN-II-Dade. Serum LDH and albumin levels were measured by spectrophotometry (Abbott C 16000 brand device). β_2-M levels were assessed by nephelometry (Siemens BN Prospect brand device). CEA and CA-15.3 levels were assessed by immunoassay (Siemens device). Serum ferritin levels were measured by the electrochemiluminescent immunoassay (ECLIA) method, based on the sandwich principle. Serum ESR 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 scintigraphic findings. During adjuvant chemotherapy, routine hemograms, and serum biochemistry panel were performed before each cycle of chemotherapy. Evaluation of hematologic, liver and kidney toxicities that developed as a result of chemotherapy were made based on the results of the hemograms and serum biochemistry profiles.

Statistics

All data were 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 disease DFS were analyzed with Cox univariate and multivariate analysis. OS was defined as the period between diagnosis and the last date of follow up or death. DFS was defined as the time period after primary treatment ended until the development of disease relapse (locoregional) or development of metastasis. The estimated probability of survival was assesed using the Kaplan-Meier method and differences were evaluated by log-rank test. Statistical significance was set at $p \leq 0.05$.

Results

General patient demographics are shown in Table 1. The mean age of all patients was 50±11 years. Of the patients 298 (42.8%) were premenopausal and 336 (48.2%) postmenopausal. Modified radical mastectomy was performed on 436 (61.9%) patients. The most commonly seen primary tumor histology type was invasive ductal carcinoma (N=535; 76.5%). In the group where tu-

Table 1. Patient and disease characteristics

Characteristics	*N*	*%*
Median age at diagnosis, years (range)	50 (25-92)	
Menopausal status		
Pre-menopausal	298	42.8
Peri- menopausal	63	9.0
Post- menopausal	336	48.2
Recurrence status		
Recurrence +	31	4.4
Recurrence -	673	96.6
Surgical approach		
Modified radical mastectomy	436	61.9
Breast conserving surgery	268	38.1
Histology		
IDC	535	76.5
ILC	42	6.0
IDC+ILC	52	7.4
Others	70	10.0
Estrogen receptor		
Positive	488	76.9
Negative	147	23.1
Progesterone receptor		
Positive	442	70.3
Negative	187	29.7
HER2		
Positive	163	25.8
Negative	468	74.2
Subtype		
Luminal A	393	62.6
Luminal B	111	17.7
HER2 overexpression	52	8.3
Triple negative	72	11.5
Grade		
I	71	11.6
II	283	46.1
III	260	42.3
Lymphovascular invasion		
Positive	222	73.5
Negative	80	26.5
Perineural invasion		
Positive	9	15.8
Negative	48	84.2
Tumor size		
T1	249	35.4
T2	335	47.6
T3	104	14.8
T4	16	2.3
Lymph node status		
N0	336	48.9
N1	191	27.8
N2	103	15.0
N3	57	8.3
TNM stage		
I	185	26.3
II	325	46.2
III	194	27.6

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

Table 2. Inflammatory marker levels

Marker levels	*N*	*%*
Albumin		
Normal	685	98.3
Low (< 4.0 mg/dL)	12	1.7
CRP		
Normal	429	63.6
High (> 0.5 mg/dL)	246	36.4
ESR		
Normal	445	67.6
High (> 25 mm/h)	213	32.4
Ferritin		
Normal	672	99.1
High (> 300.0 mg/dL)	6	0.9
LDH		
Normal	624	95.7
High (> 480 U/L)	28	4.3
B2 microglobulin		
Normal	563	90.5
High (> 2400 U/mL)	59	9.5

Other laboratory findings which may affect the inflammatory parameters are shown in Table 3.

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

Markers	*N*	*%*
Creatinine		
Normal	618	90.4
High (> 0.90 mg/dL)	66	9.6
AST		
Normal	676	96.6
High (> 30 IU/mL)	24	3.4
ALT		
Normal	655	93.6
High (> 30 IU/mL)	45	6.4
White blood cells		
Normal	632	90.2
High (> 10,000 /mL)	69	9.8
Hemoglobin		
Normal	633	90.4
Low (< 11.0 g/dL)	67	9.6
CA 15-3		
Normal	607	87.7
High (> 31.0 U/mL)	85	12.3
CEA		
Normal	646	93.9
High (> 5.0 ng/mL)	42	6.1

mor subtypes were analyzed, Luminal A (N=393; 62.6%) was the moct common tumor subtype. Grade II was the highest histological grade, found in 283 (46.1%) cases. The percentage of patients with positive lymphovascular invasion was 73.5% (N=222). T2 was the biggest tumor size, found in 335 (47.6%) patients. N0 was the most frequent nodal condition found (N=336; 46.2%). Stages I,II and IIIA (early stage) were registered in 510 (72.4%) patients.

Evaluation of serum inflammatory markers in patients included into the study showed high serum levels of CRP (N=246; 36.4%), ESR; (N=213; 32.44%), ferritin (N=6; 0.9%), LDH (N=28; 4.3%), β2-M (N=59; 9.5%), and low serum levels of albumin (N=12; 1.7%) (Table 2).

Other abnormal serum lab values were noticed for AST (N=24; 3.4%), ALT (N=45; 6.4%), CA 15-3 (N=85; 12.3%) and CEA (N=42; 6.1%) (Table 3).

During follow up metastatic disease developed in 31 patients (4.4%) and 11 patients (1.56%) died due to disease progression. Ilustrated 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 summarized in Table 5.

Discussion

The role of inflammation in the pathogenesis and prognosis of breast cancer is known. Recent efforts to identify a possible relationship between inflammatory markers and the prognosis of cancer in general have been widely appreciated. After the development of cancer, malignant cells and cells found in their microenvironment evoke inflammatory responses via many pathways. In our study we found high levels of the inflammatory markers ferritin (1%), LDH (4.3%), β2-M (9.5%), ESR (32.4%) and CRP 36.4%) in patients with operable breast cancer. Low levels of albumin were found in 1.7% of the patients.Two-year OS and DFS rates were not statistically different among patients with normal and abnormal values with respect to albumin, ferritin, LDH, β_2-M, CRP, and ESR.

Chronic inflammation is thought to trigger the process of carcinogenesis and as such is regarded as a predisposing factor for the development of cancer [2]. Chronic activation of bacterial, viral and parasitic infections has been previously stated to be responsible for the development of tumors in the bladder, liver and different regions of the body, including the head and neck regions [14-16]. Non infectious chronic inflammation has also been associated with a great number of colorectal, lung and esophagogastric tumors [17,18]. As the degree of inflammation increases, the concentration of acute phase proteins also increases and remains high as long as the inflammation lasts. ESR,CRP, albumin, β_2-M, ferritin, and LDH are known to be some of these associated acute phase proteins [19].

The aim of this study was to investigate the

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

Markers	*2-year OS* (%)*	*p-value*	*2-year DFS* (%)*	*p-value*
Albumin				
Normal	98.1	0.66	95.4	0.88
Low	-		-	
LDH				
Normal	98.5	0.23	96.3	0.46
High	95.2		88.4	
β_2 microglobulin				
Normal	98.5	0.69	95.8	0.81
High	98.0		96.5	
CRP				
Normal	97.8	0.83	95.3	0.63
High	98.1		95.6	
ESR				
Normal	99.0	0.32	96.4	0.79
High	97.3		95.5	
Ferritin				
Normal	98.0		96	
High	-		-	

*log-rank test, OS:overall survival, DFS:disease free survival. For other abbreviations see text

impact of inflammatory markers on the prognosis of patients with operable breast cancer and discuss their place in accordance with recent reports in the current literature [20].

The median follow up period for all of the patients was 22 months (range 3-287).

In a study conducted by Albuquerque et al. no relationship between ESR and response to therapy in patients with metastatic breast cancer disease was found [6]. In another study that evaluated 81 patients with metastatic breast cancer, ESR was not found to be associated with survival [21]. In our study, serum inflammatory marker ESR was not associated with prognosis (OS, p=0.32 and DFS, p=0.79). This absence of an ESR-prognosis association in our study could be explained by the fact that most of the patients (N=510; 72.4%) had early-stage disease. Furthermore, for a short median follow up period of 22 months adequate immunologic and inflammatory events might not develop to make inflammatory markers' levels reach statistical significance. Another reason could be the non uniform blood sampling times after surgery (within an one month period).

In a prospective study done by Albuquerque et al., CRP was shown to be a predictive factor in the prognosis of 85 newly diagnosed patients with metastatic breast cancer [6]. In our study serum levels of CRP in patients with operable breast cancer were not associated with prognosis (OS, p=0.83; and DFS, p=0.63).

Table 5. Overall survival and disease free survival of patients with respect to other parameters which might affect inflammatory markers

Parameters	*2-year OS (%)*	*p-value*	*2-year DFS (%)*	*p-value*
Surgery				
Mastectomy	97.3		93.6	
BCS	99.6	0.09	98.0	0.02
CA 15.3				
Normal	98.2		96.6	
High	97.9	0.99	87.7	<0.001
CEA				
Normal	98.6		96.4	
High	90.9	0.04	85.5	<0.001
Hemoglobin				
Normal	98.9		95.6	
High	95.4	0.09	95.3	0.7
ER				
Negative	96.8		96.9	
Positive	98.8	0.4	95.7	0.78
PR				
Negative	96.4		96.1	
Positive	99.0	0.2	95.9	0.57
HER2				
Negative	98.2		95.3	
Positive	98.7	0.4	97.9	0.14
LVI				
Present	98.6	0.98	95.5	
Absent	-		94.9	0.73
Grade				
I	98.6		-	
II	98.4		95.3	
III	98.1	0.92	96.8	0.22
Lymph node status				
N0	99.1		97.7	
N1	992		94.6	
N2	95.0		95.8	
N3	95.4	0.19	88.8	0.12
Histological type				
IDC	98.2		95.0	
ILC	97.1		97.1	
IDC+ILC	-		-	
Other	97.1	0.47	98.6	0.19
Subtype				
Luminal A	98.5		95.0	
Luminal B	-		98.1	
HER2 overexpression	96.6		97.7	
Triple negative	96.3	0.45	96.8	0.40
TNM stage				
I	-		97.1	
II	95.7		95.6	
III	95.8	0.031	91.8	0.08

BCS:breast conserving surgery, LVI: lymphovascular invasion. For other abbreviations see text

The prognostic value of the systemic inflammatory response in metastatic breast cancer is known [3]. Increased expression of Interleukin-6 and serum CRP levels have been associated with tumor stage and metastasis. In fact, in a study of the general population, individuals with CRP

levels with highest vs lowest levels were shown to have a 1.3-fold increased risk for cancer of any type and a 2-fold increased risk for lung cancer [22]. A high serum CRP concentration together with hypoalbuminemia are 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 [23]. 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 [22]. Our study 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. In contrast, in another study that we conducted we found serum CRP levels to be associated with survival and prognosis in patients with metastatic breast cancer (p=0.049) [21].

Alkhateeb et al. examined the distribution of ferritin in malignant breast tissue at different stages of tumor development and found ferritin to stimulate the proliferation of the 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 tumorigenesis. Because ferritin is secreted by the macrophages and not the tumor, ferritin-based therapies may be effective in patients with elevated serum ferritin regardless of tumor site or molecular subtype [24].

In our previous study [21] we reported a high serum ferritin level (p=0.01) in patients with metastatic breast cancer. Yet, in that study the impact of serum ferritin levels on prognosis did not reach statistical significance (OS, p=0.74 and 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. The absence of a serum ferritin-prognosis relationship in our study could be attributed to the fact that only few patients enrolled into the study had high serum ferritin levels. Morever, since the majority of our patients had early-stage disease we didn't expect a higher level of the inflammaroty indicator ferritin. Furthermore, the high risk of iron defficiency anemia in our patients (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 statistically significant relationship between β2-M levels with prognosis and survival in patients with metastatic breast cancer (p<0.01) [21]. The present study, however, could not show any statistically meaningful association between β2-M levels and prognosis and survival (OS, p=0.69 and DFS, p=0.81). The role of β2-M as a growth factor and a signalling molecule in malignant cells has been previously reported and its levels are known to increase in multiple myeloma and lymphoma [25]. β2-M expression increases during progression of prostate cancer, breast cancer, renal cancer, lung cancer, and colon cancer. 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.Therefore, β2-M and its downstream signaling pathways could serve as promising novel therapeutic target for cancer therapy [26].

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 hematologic diseases and solid tumors is known [27]. Serum LDH levels are used as a prognostic factor in follicular lymphoma,chronic lymphocytic leukemia and metastatic melanoma [8]. High serum LDH levels have been suggested as a marker of relapse in asymptomatic non Hodgkin lymphoma patients and are also known to be an important factor in determining an appropriate treatment strategy [28]. In our study, no statistically significant difference was seen between serum LDH levels and survival (OS, p=0.23 and DFS, p=0.46).

In a prospective study conducted by Alphs et al., mortality was observed to increase by twofold in peritoneal and ovarian cancer patients who had an albumin level of less than 3.7g/dL [9]. Low levels of serum albumin have been reported to adversely affect survival in 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 reported to be related

with decreased mortality [29]. In our study low levels of serum albumin did not show any effect on prognois (OS, p=0.67 and DFS, p=0.89). Conditions such as chronic liver diseases, malabsorption and malignancies are known to decrease serum albumin levels [20]. Low level of preoperative serum albumin is known to be poor prognostic factor in breast, colon, head-neck, lung, liver and a number of gynecologic malignancies. Levels below 4 g/dL are also known as independent prognostic factor in patients with colorectal cancer.

In this study serum ferritin, LDH, β2 -M, ESR, and CRP were higher than the normal values in 1.0, 4.3, 9.5, 32.4 and 36.4 % of the patients, respectively. Serum albumin levels were lower than the normal values in 1.7 % of the patients. Two-year OS and DFS rates were not statistically different among patients with normal and abnormal values with respect to albumin, ferritin, LDH, β2-M, CRP, and ESR.

Conclusion

Our study is the first in the medical literature to investigate the effect of 6 inflammatory markers on the prognosis of operable breast cancer patients. The patient median follow-up period (OS and DFS) was 22 months (range 3-227). We were able to show that the 6 inflammatory markers have no effect on prognosis; however, we suppose that these markers might have an influence on the results of our study should the follow up time be long enough, and the number of events be higher. This hypothesis makes it hard to draw a precise conclusions. All of the patients had early-stage disease that could not evoke the inflammatory process. Another reason that might have affected our results is that blood sampling time after surgery was not uniform. In conclusion, we believe that further studies with a longer follow-up and adequate number of events should be conducted.

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