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The Role of C-Reactive Protein as a Prognostic Biomarker in Patients with Early Breast Cancer Treated with Neoadjuvant Chemotherapy

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Keywords

C-reactive protein · Biomarker · Early disease · Breast cancer · Neoadjuvant therapy

Abstract

Background: C-reactive protein (CRP) is an acute phase reactant influenced by inflammation and tissue damage. Elevated CRP levels have been associated with poor outcome of various cancers including breast cancer. However, evidence regarding a potential impact of CRP levels on outcome of neoadjuvant chemotherapy (NACT) in patients with early breast cancer (EBC) is insufficient. ***Methods:*** Patients who had received NACT for EBC and had available data regarding CRP levels before therapy, pathologic complete remission (pCR), and follow-up were included. The association between CRP at baseline and outcome parameters was analyzed. ***Results:*** 152 women were included in this analysis; median follow-up was 5.8 years. No association between CRP at baseline and pCR rates could be detected. 6.6% of the patients developed a local recurrence, 10.5% developed a distant recurrence, and 5.2% died from breast cancer. A negative correlation (Spearman-Rho) between CRP at baseline and overall survival (OS) (correlation coefficient (CC) −0.255; $p = 0.45$), disease-free survival (DFS) (CC −0.348; $p = 0.075$), local recurrence-free survival (LRFS) (CC −0.245; $p = 0.327$), and distant DFS (DDFS) (CC −0.422; $p = 0.057$) was not statistically significant, although especially in DFS and DDFS a strong trend was detected. The probability of death from breast cancer was 2% if the CRP was <0.08 mg/dL and 40% if the CRP was >2.08 mg/dL; this association was highly statistically significant (χ^2; $p < 0.001$). These results were independent from age, estrogen and progesterone receptor status, HER2 status, nodal status, and grading. The hazard ratio for OS was 5.75 ($p = 0.004$) for CRP <0.08 mg/dL versus CRP >2.08 mg/dL. ***Discussion/Conclusion:*** CRP at baseline is not predictive for pCR in EBC after NACT in our patient dataset. However, an association of parameters of long-term prognosis with CRP could be demonstrated. Although the correlations of higher CRP levels at baseline and shorter OS, DFS, LRFS, and DDFS were not significant, a strong trend could be detected that was reproduced in the analysis of different groups of CRP levels and the probability of breast cancer mortality. Higher CRP levels are indicating a worse prognosis in EBC after NACT in this retrospective analysis. These results justify further investigation of CRP not as a predictive parameter for pCR but as a biomarker of long-term prognosis in EBC in prospective trials and may lead to therapeutic approaches with the aim of lowering CRP levels.

Introduction

C-reactive protein (CRP) is a plasma protein that is synthetized in response to infectious and noninfectious inflammatory reactions. Synthesis of CRP is located in the

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liver and mainly regulated by interleukin-6 [1]. CRP as an acute-phase protein is elevated by any tissue damage by infection, tumor, surgery, or trauma [2–4]. CRP is not only associated with infection but also with diseases such as cardiovascular disease, arteriosclerosis, rheumatic disease, autoimmune disease, trauma, and cancer [5]. The first postulation of an interaction of inflammation, carcinogenesis, and tumor progression goes back to Rudolf Virchow in 1863 and an association between chronic inflammation and cancer has been described by many authors since then [6, 7].

The exact role of CRP in carcinogenesis is not fully understood yet. It is currently subject to discussion whether the association of CRP and the development of cancer is causal or coincidental. However, the rationale for the investigation of the role of CRP in carcinogenesis is on the one hand the hypothesis that chronic inflammation plays a role in the development of malign tumors and on the other hand the fact that CRP is easy to measure and relatively cheap [8, 9].

More robust than the data regarding an association of CRP and carcinogenesis is the evidence for the prognostic value of CRP as a biomarker in numerous malignancies. Apart from breast cancer, elevated CRP levels in serum are associated with a decreased overall survival (OS) in renal cell carcinoma [10], gastric cancer [11], nonsmall-cell lung cancer [12], and chronic lymphatic leukemia [13]. Especially for metastatic or recurrent gastric cancer, elevated CRP levels are not only a prognostic but also a predictive biomarker [14].

The database for CRP and breast cancer is heterogenous. A meta analysis of 15 studies concluded that elevated CRP levels increased the risk of breast cancer after menopause. Only in 4 of the included studies this association was statistically significant on study level, 9 studies only found a strong trend. The included trials had very heterogenous designs and the results of the meta analysis have to be interpreted with caution [15]. The association between obesity and the development of a chronic subclinical inflammation with a consecutive increase of CRP in postmenopausal women is well known [16]. It cannot be excluded that obesity leading to chronic inflammation could be a key driver for the development of breast cancer and the elevated CRP level is only a coincident phenomenon.

The evidence for the association of serum CRP and breast cancer prognosis is much more homogenous. In a study investigating the prognostic value of CRP and interleukin-6 in early breast cancer (EBC), patients with a baseline CRP level of ≥0.12 mg/dL had worse recurrence-free survival probabilities compared to patients whose baseline CRP was <0.12 mg/dL. This prognostic value was independent of tumor size, nodal involvement, and grading [17]. In a cohort of node-negative EBC patients, an elevated serum-CRP before surgery was independently predicting a worse disease-free survival (DFS) and OS [18]. An analysis of a cohort of patients with metastatic breast cancer demonstrated a strong trend for a negative impact of elevated CRP levels on OS without reaching statistical significance. However, the authors concluded that CRP may be helpful as an additional prognostic parameter regarding OS [19]. Data regarding a predictive value of CRP levels at baseline regarding the achievement of a pathological complete remission (pCR) after neoadjuvant chemotherapy (NACT) are missing as well as data on the prognostic value of CRP in a cohort of patients treated with NACT.

Table 1. Baseline characteristics

Parameter	*N*	%
T-stage		
T1	68	44.7
T2	75	49.3
T3	4	27
T4	5	3.3
cN stage		
cN0	139	91.4
cN1	13	8.6
SLNB		
pN0	85	61.2
pN1	54	38.8
Grading		
G1	3	2
G2	80	52.6
G3	69	45.4
Menopausal status		
Premenopausal	53	34.9
Postmenopausal	99	65.1
Receptor status		
ER positive	93	61.2
PR positive	75	49.3
HER2neu positive	55	36.2

ER, estrogen receptor status; PR, progesterone receptor status.

Material and Methods

This retrospective analysis included patients treated in our breast cancer center between 2009 and 2015 who received NACT for EBC according to standard of care at that time. Patients were included if the dataset of predefined baseline characteristics including age, menopausal status, tumor size, nodal status, estrogen receptor status, progesterone receptor status, HER2neu status, grading, pCR status, and CRP level at baseline was completely on the file, if a CRP level in serum at baseline was recorded, and if follow-up data were available. Patients with incomplete datasets or treatment with investigational drugs in a clinical trial were excluded. Neoadjuvant therapy regimens consisted of 4 cycles of epirubicin and cyclophosphamid q3w followed by 12 weeks paclitaxel q1w in hormone receptor-positive HER2neu-negative patients and triple-negative patients (in cases of germline BRCA mutation with addition of carboplatin) and of 6 cycles docetaxel and carboplatin q3w in combination with trastuzumab

Table 2. Probability of death and association with different levels of CRP

	CRP [mg/dL] before NACT					Death						Death of breast cancer					
	groups of CRP levels	mean	min	max	SD	no		yes		total		no		yes		total	
						N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
CRP before NACT	Low	0.04	0.01	0.08	0.02	49	98.0	1	2.0	50	100.0	49	98.0	1	2.0	50	100.0
	Intermediate	0.41	0.09	1.79	0.39	91	93.8	6	6.2	97	100.0	92	94.8	5	5.2	97	100.0
	High	4.63	2.08	11.21	3.80	2	40.0	3	60.0	5	100.0	3	60.0	2	40.0	5	100.0
	Total	0.43	0.01	11.21	1.06	142	–	10	–	152	–	144	–	8	–	152	100

q1w and (after approval of pertuzumab) pertuzumab q3w. Patients with dose reductions and dose delays were included whereas patients who terminated neoadjuvant therapy early were excluded. Surgery, radiation, and endocrine therapy were performed according to the historical standard of care. pCR was defined as no invasive tumor in breast or lymph nodes; total pCR (tpCR) was defined as no invasive or noninvasive tumor in breast or lymph nodes.

All patients gave their written informed consent to be included in this analysis. The study protocol was approved by the Ethics Committee of the University of Duisburg-Essen on August 25th, 2020 (Ethics Vote No: 20-9483-BO).

The set of outcome data included local recurrence, distant recurrence, or death of breast cancer or of any cause. Outcome variables were OS, event = any death, DFS, event = any relapse or death, local recurrence-free survival, event = local recurrence or death, distant DFS (DDFS), event = distant disease or death. All data were extracted from the database of the breast cancer center and pseudonymized for the analysis. Statistics: CRP-values, age, and tumor size were analyzed as continuous variables, T-stage, cN-stage, results of SLNB, grading, menopausal status, receptor status were analyzed as categorical variables.

The association between CRP and pCR was examined by the Mann-Whitney U-test because the lacking normal distribution of CRP-values according to the Kolmogorov-Smirnov test demanded a nonparametric test. The correlation of CRP levels and survival variables was calculated by Spearman-Rho-correlation analysis.

A multiple linear regression using a stepwise backward model was performed to test for confounding parameters. Parameters for the multivariate analysis were chosen regarding their clinical relevance as prognostic parameters in clinical practice. For the analysis of the association of CRP-values with the probability of death, CRP-values were grouped as low (= <0.08 mg/dL), intermediate (0.09 mg/dL–2.0 mg/dL), and high (>2.0 mg/dL). The association of grouped CRP-values with the probability of death was analyzed by the χ^2 test. A Kaplan-Meier estimate and a Cox regression analysis were performed for a comparison of OS between the three groups of CRP levels. The statistical analysis was performed using SPSS Statistics version 26.0 (IBM SPSS Statistics for Macintosh, version 26.0. IBM Corp, Armonk, NY, USA).

Results

Baseline Characteristics

152 women were included in this analysis; median follow-up was 5.8 years (322–3,149 days). Mean age of the included patients was 57.04 years (24–85; standard deviation [SD] 12.29), mean tumor size was 2.28 cm (0.28–9.35; SD 1.21), and mean CRP level at baseline was 0.43 mg/dL (0.01–11.21; SD 1.06). The distribution of ordinal baseline characteristics is shown in Table 1 and is representing the relatively high risk of a population receiving neoadjuvant therapy.

C-Reactive Protein and pCR/tpCR

49 patients (32.2%) achieved a pCR; 40 patients (26.3%) achieved a tpCR. Median CRP level was 0.16 mg/dL (0.01–4.43; SD 0.81) in patients who achieved a pCR and 0.15 mg/dL (0.01–4.43; SD 0.86) who achieved a tpCR. No association between CRP at baseline and pCR (p = 0.487) or tpCR (p = 0.338) rates could be detected.

Long-Term Outcome and CRP

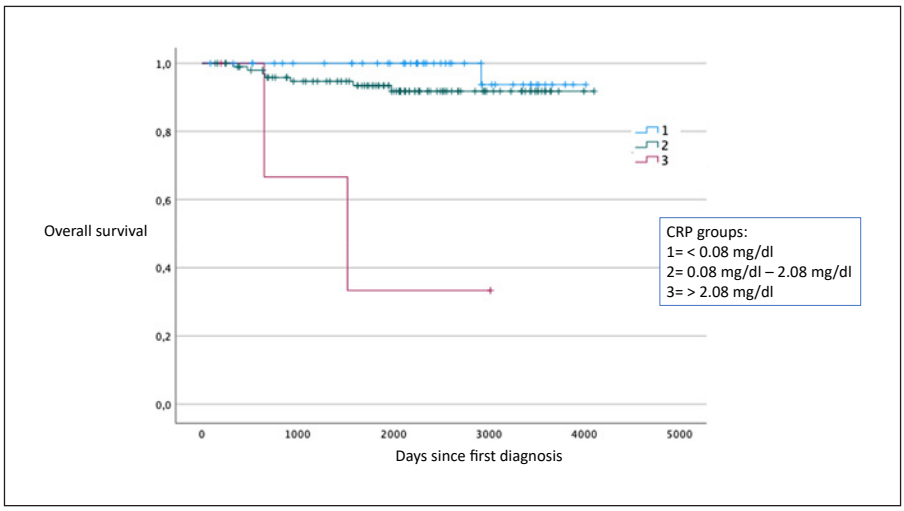
6.6% (n = 10) of the patients developed a local recurrence, 10.5% (n = 16) developed a distant recurrence, 6.6% (n = 10) died, and 5.2% (n = 8) died from breast cancer. A negative correlation (Spearman-Rho) between CRP at baseline and OS (correlation coefficient [CC] −0.255; p = 0.45), DFS (CC −0.348; p = 0.075), local recurrence-free survival (CC −0.245; p = 0.327), and DDFS (CC −0.422; p = 0.057) was not statistically significant, although especially in DFS and DDFS a strong trend was detected.

Probability of Death and CRP

The probability of death and death from breast cancer was 2% if CRP was <0.08 mg/dL. If CRP was >2.08 mg/dL, the probability of death was 60% and the probability of death from breast cancer was 60%. Table 2 demonstrates the CRP levels grouped by low (= <0.08 mg/dL), intermediate (0.09 mg/dL–2.0 mg/dL), and high (>2.0 mg/dL) values and the according probabilities of death. These associations were highly statistically significant (χ^2; $p < 0.001$).

Multivariate Analysis

A stepwise backward multivariate linear regression analysis led to a model that allowed exclusion of estrogen



Color version available online

Fig. 1. OS by CRP level at baseline.

and progesterone receptor status, HER2neu status, nodal status, grading, and age, leaving only CRP at baseline within the model with a standardized regression coefficient of $r = 0.229$.

Survival Analysis

The result of a comparison of OS between all three groups by Kaplan-Meier estimate is shown in Figure 1. In a Cox proportional regression hazard model, the hazard ratio for OS was 5.75 ($p = 0.004$) for CRP <0.08 mg/dL compared to CRP >2.08 mg/dL.

Discussion

In our patient dataset, CRP at baseline was not predictive for pCR in patients with EBC after NACT. However, an association between parameters of long-term prognosis and CRP could be demonstrated.

Our results regarding the value of CRP as a biomarker of long-term prognosis are in line with the majority of studies investigating a prognostic value of CRP in cancer [9–14]. Studies in EBC have shown an impact of elevated CRP levels on DFS and OS [20]. In a large cohort study with 2,190 breast cancer patients, the risk of death from breast cancer was increased by factor 3.5 if baseline CRP was at the 95th percentile [21]. These results could be reproduced in a large meta analysis including 10 trials and 4,502 patients [22], but to our knowledge our study is the first analysis in a cohort with patients with EBC receiving NACT. Because of the paradigm that pCR after NACT is predicting an improved long-term outcome [23], we hypothesized that CRP could also be predictive for pCR. The majority of patients in our study were estrogen receptor status and/or progesterone receptor status positive and the decreased predictive value of pCR in hormone receptor-positive HER2neu-negative breast cancer is well known [23]. Furthermore, recent data in triple-negative breast cancer revealed that even in cases of non-pCR the prognosis of patients is significantly different depending on the fact if patients had received an immune-checkpoint-inhibitor in combination with NACT or not [24]. pCR is an important but not the only parameter of prognosis in breast cancer after NACT. This may explain the lacking coincidence of associations of CRP and pCR and long-term prognosis in our dataset.

However, in a study including metastatic breast cancer patients treated with paclitaxel and bevacizumab an impact of baseline CRP levels not only on OS but also on the short-term parameter PFS was demonstrated, indicating that in the metastatic setting CRP may also be predictive regarding short-term outcome [25]. We could not demonstrate this effect in our population of therapy naïve patients receiving neoadjuvant therapy.

Although the exact role of CRP in the course of the disease is still controversial, the majority of theories are postulating a role of CRP in the process of chronic inflammation and a consecutive impact on cancer progression. In a xenograft mice tumor model, the molecular mechanism of sphingosine-1-phosphate-induced transcriptional activation of CRP and its role in the development of an invasive phenotype of human breast epithelial cells in an environment of inflammation was investigated. CRP expression is upregulated by sphingosine-1-phosphate and in a next step CRP induces the activation of matrix-metalloproteinase-9 leading to breast cancer progression [26]. Another approach postulates an association between the stimulation of an inflammatory response by solid tumors and following that the induction of DNA damage leading to disease progression by facilitating invasion and metastasis. In this model, the proteins expressed in the very early phases of inflammation are

involved in the process of disease progression and are thus leading to a worse long-term outcome [27]. These postulated mechanisms rather hint to a long-term impact of CRP and thus may explain why elevated CRP levels in our population were associated with a worse long-term outcome but not with different pCR rates.

We demonstrated an association of elevated CRP levels before NACT and worse long-term outcome in patients with EBC and as we discussed this is reproducible in other breast cancer populations. Looking beyond this demonstration of the value of CRP as a prognostic biomarker, the emerging question is if and if yes how a lowering of CRP levels could influence prognosis leading to a therapeutic approach. In metastatic gastric cancer, it has been demonstrated that patients whose CRP decreased by more than 22% during chemotherapy had an improved OS [14]. It is also known that drug interventions lowering CRP levels such as COX inhibitors, platelet aggregation inhibitors, lipid-lowering agents, and angiotensin-converting enzyme inhibitors and antioxidants are improving the prognosis of patients with cardiovascular disease [20]. However, the biggest prospective randomized trial investigating adjuvant therapy with the COX inhibitor celecoxib in EBC, the REACT trial, was negative [28] and other comparable data are not available for breast cancer.

CRP levels cannot only be influenced by drugs. It has been shown that physical activity can lower CRP levels in breast cancer patients [29, 30] and that regular physical activity improves the long-term prognosis of breast cancer substantially [31]. It has been proposed that the lowering of markers of inflammation by exercise might serve as immunotherapy in breast cancer patients [32, 33] and that an improved insulin pathway regulation also plays a role in this process [34, 35].

However, it is not fully understood if the decrease of CRP levels by physical activity has an active impact on the beneficial effect on breast cancer prognosis or if it is only a phenomenon observed coincidentally but without causal association. If lowering CRP levels by physical or pharmaceutical approaches is a feasible approach for improving the prognosis of breast cancer patients and if yes if this works in all patients or only in patients with elevated CRP levels is still an unanswered question.

Our analysis has limitations that have to be kept in mind when interpreting our results. It was a retrospective single-arm and single-institution analysis with a patient number just over 150. We cannot exclude a selection bias or an influence of the small number on the results. Furthermore, we only had baseline CRP levels in our dataset and could not investigate dynamics of CRP during neoadjuvant therapy. However, ours is the first analysis of CRP in a cohort of patients with EBC treated with NACT.

Conclusion

CRP is a parameter that is easy to measure and comparably cheap. The current literature as well as our analysis supports its value as a prognostic biomarker, but the clinical implications are unclear. Our results justify further investigation of CRP as a biomarker of long-term prognosis in EBC in prospective trials and we propose a concentration on approaches directed at lowering of elevated baseline CRP levels and then implementation of CRP as a biomarker of response as future direction.

Statement of Ethics

All patients gave their written informed consent to be included in this analysis. The study protocol was approved by the Ethics Committee of the University of Duisburg-Essen on August 25th, 2020 (Ethics Vote No.: 20-9483-BO).

Conflict of Interest Statement

H.C.K. received honoraria and travel support from AstraZeneca, Pfizer, Roche, Daiichi Sankyo, Tesaro, MSD, onkowissen, Eli Lilly, SurgVision, Exact Sciences, und Genomic Health and holds stock of Theraclion und Phaon scientific. C.K.L. received honoraria from Roche, Novartis, Pfizer, Amgen, Astra Zeneca, onkowissen, Gilead Sciences, SeaGen, Sanofi-Genzyme, and MSD and research funding from Gilead Sciences. A.K.B. received honoraria and travel support from Amgen, AstraZeneca, Daiichi Sankyo, Hexal, Novartis, Pfizer, Roche, MSD, and SeaGen. O.H. received honoraria and travel support from Amgen, AstraZeneca, Daiichi Sankyo, Hexal, Novartis, Pfizer, Roche, MSD, Riemser, SeaGen, Gilead, and Eisai. A.E., S.W., M.S., and M.S. have nothing to disclose.

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Author Contributions

All authors listed fulfill the ICJME criteria for authorship.

Data Availability Statement

The raw data are on file with the authors and are available upon request.

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