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Original article

C-reactive protein as an adverse prognostic marker for men with castration-resistant prostate cancer (CRPC): Confirmatory results

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Abstract

We previously reported that higher serum concentrations of C-reactive protein (CRP) are associated with shorter survival in men with castration-resistant prostate cancer (CRPC). To confirm this finding in an independent data set, we used 119 CRPC patients enrolled in 6 phase II clinical trials and examined the relationship of CRP, alkaline phosphatase, hemoglobin, age, ECOG PS, and prostate specific antigen (PSA) with survival. Median follow-up was 19.7 months (0.9–98.5 months), and 89% have died. After analyzing the form of the risk function using the generalized additive model method, univariate and multivariate Cox proportional hazard models were used to assess associations between baseline individual categorical and continuous variables. Quartiles of CRP were: 0–1.0, 1.1–4.9, 5.0–17.0, and 17.1–311 mg/L. In a Cox multivariate model, $\log_2$ (CRP) (HR 1.106, $P = 0.013$) as well as hemoglobin and alkaline phosphatase were independently associated with survival, confirming that higher CRP is associated with shorter survival in CRPC. Since CRP is a marker of inflammation, this finding suggests that inflammation may play an important role in the natural history of advanced prostate cancer. CRP is a readily measurable biomarker that has the potential to improve prognostic models and should be validated in a prospective clinical trial.

Keywords: Prostate cancer; C-reactive protein; Prognosis; Inflammation; Survival

1. Introduction

The complex relationship between inflammation and cancer has been well-described since the late 1800s [1]. The principal purpose of an acute inflammatory response is to create a protective tissue microenvironment that allows for recognition and attempted repair of cell damage, as well as the elimination of pathogens and permanently damaged cells. Persistent inflammation, however, may promote tumor formation [2,3].

The intricate molecular and cellular mechanisms responsible for the association between inflammation and cancer have recently become subjects of intense study. Chronic inflammation is thought to induce carcinogenesis through a variety of mechanisms, including irreversible cellular and DNA damage through the generation of free radicals, and the promotion of rapid cellular growth through DNA and cellular replication [4]. Finally, a microenvironment rich in angiogenesis-promoting growth factors is created with the intent of repairing inflamed tissue, but instead establishes the ideal conditions conducive to tumor growth [2,3,5,6].

Well-established epidemiologic studies have demonstrated that inflammatory diseases increase the risk of developing cancer. For example, gastric infection with *Helicobacter pylori* [7], inflammatory bowel disease [8], and chronic hepatitis [9] have all been linked to malignancies of the affected organs. In fact, it has been estimated that infections and inflammatory responses may be linked to upwards of 15% of worldwide cancer deaths [10]. Specifically regarding prostate cancer, it has been hypothesized

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that chronic intraprostatic inflammation—such as that associated with chronic prostatitis—may contribute to its development [11]. Several retrospective case-control studies have reported a positive association between prostatitis and prostate cancer [12]. Further supporting the link between chronic inflammation and cancer is the evidence that treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) has been found to decrease the incidence not only of prostate cancer [13,14] but also of several other solid tumors [15–17], although not all studies have upheld this finding [18–21].

C-reactive protein (CRP), an acute-phase reactant first described circa 1930, is a sensitive marker of tissue damage and inflammation [22,23]. A growing body of literature has described a correlation between circulating CRP serum levels and poor prognosis in patients with various solid tumors. Elevated CRP has been associated with shorter survival in melanoma [24], colorectal cancer [25], non-Hodgkin's lymphoma [26], esophageal carcinoma [27], cervical cancer [28], endometrial cancer [29], ovarian cancer [30], and renal cell carcinoma [31].

We previously reported that higher serum concentrations of CRP are associated with shorter overall survival (OS) in patients with CRPC, and that it also predicts a lower probability of PSA response to docetaxel-based therapy [32]. In this study, we sought to confirm these findings in an independent data set.

2. Materials and methods

2.1. Patients

Patients with castrate-resistant prostate cancer (CRPC) from 6 institutional phase II clinical trials were included in this analysis. Detailed eligibility criteria and the treatment in each of these studies have previously been described [33–38]. Regimens tested included calcitriol + docetaxel, calcitriol + docetaxel + estramustine, calcitriol + carboplatin, imatinib and zoledronic acid, and abarelix. All patients had evidence of progression after standard androgen suppression therapy; 90.8% of patients had metastases and 15.5% had prior chemotherapy exposure. The median follow-up time was 19.7 months (range 0.9–98.5 months), and 89.1% of patients have died. Institutional Review Board approval was obtained for all studies and for biomarker analyses, and informed consent was obtained from all patients contributing samples.

2.2. Sample handling and assays

Blood samples were collected from 119 CRPC patients prior to initiation of therapy. All baseline samples were plasma, except for one serum sample. Plasma was separated by centrifugation at 3,000 revolutions per minute (rpm), and samples were stored at −80°C. CRP concentration was measured using turbidimetric measurement of agglutinated anti-CRP antibody/CRP complexes (Roche Diagnostics, Indianapolis, IN).

2.3. Statistical methods

The endpoint of interest was OS, defined as the time from day 1 of the start of therapy to death from any cause. Baseline covariates included in the analyses were age, alkaline phosphatase, Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin, PSA, and CRP. Because the distribution of alkaline phosphatase, CRP, and PSA were skewed, a logarithmic transformation (base 2) was applied. Generalized additive models [39] were used to visually assess functional relationships between the continuous covariates and the risk of death. The risk function of each covariate was analyzed using the GAM package available in the R (www.r-project.org) software. We were thus able to determine if a covariate would be best analyzed as a continuous or categorical predictor in subsequent analyses [40]. Multivariate analysis was performed using stepwise Cox regression in order to assess the association between the above modified covariates and OS. Statistical significance was defined as a $P < 0.05$.

3. Results

3.1. Patient demographics

Baseline characteristics of the 119 patients are shown in Table 1; 90.8% had radiographically demonstrated metastases while the others had CRPC manifested by a rising PSA on androgen suppression therapy only; 57 of these patients were enrolled in clinical trials of docetaxel-based chemotherapy while the remainder received other investigational

Table 1
Baseline characteristics of patients

Treatment regimen	
Calcitriol + docetaxel (*n*)	34
Abarelix + orchiectomy (*n*)	12
Abarelix + LHRH antagonist (*n*)	18
Calcitriol + docetaxel + estramustine (*n*)	23
Carboplatin + calcitriol (*n*)	17
Imatinib + zoledronic acid (*n*)	15
Total (*n*)	119
Median age (range), years	71.9 (45.8–91.5)
ECOG performance status	
0	34.5%
>0	65.5%
Median PSA (range), ng/mL	80.8 (0.8–2113)
Median hemoglobin (range), g/dl	12.4 (8.4–16.7)
Median alkaline phosphatase (range), U/l	113 (33–1304)
Median CRP (range), mg/l	5.0 (1–311)
Metastasis (all sites)	90.8%
Chemotherapy naive	84.5%
Subjects still alive	10.9%
Median follow-up time (range), months	19.7 (0.9–98.5)

regimens. None of these patients received the current FDA-approved regimen of docetaxel and prednisone. Quartiles of CRP were: 0–1.0, 1.1–4.9, 5.0–17.0, and 17.1–311 mg/L, somewhat lower than in our previous study.

3.2. Overall survival

Based on the GAM analysis, the risk function for the $\log_2$ transformed baseline alkaline phosphatase was best analyzed categorically in 2 groups, above or below 238.9 U/L, whereas hemoglobin displayed a decrease in risk. The risk of death increased as $\log_2$ (CRP) increased. Baseline age was categorized into three groups (50–60 years, 60–80 years and >80 years of age). The risk function increased with the $\log_2$ (PSA) and then decreased for $\log_2$ (PSA) >8, thus the $\log_2$ (PSA) variable was categorized into two groups ($\log_2$ (PSA) ≤ 8 or >8).

In the univariate Cox proportional hazard model, $\log_2$ (CRP) was a significant predictor of shorter OS. The impact of an elevated baseline CRP on OS is shown in Fig. 1.

Using multivariate analysis with stepwise Cox regression model, we analyzed age, alkaline phosphatase, Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin, PSA, and CRP. In this multivariate analysis (Table 2), an elevated CRP remained a significant independent predictor of shorter survival ($P = 0.013$), showing a 10.6% increase in risk for every doubling of CRP. Baseline hemoglobin was inversely and significantly associated with OS ($P = 0.006$). Alkaline phosphatase was also significantly associated with OS ($P = 0.014$), showing a 2-fold increase in risk of death for a baseline level greater than 238.9 U/L. Age, ECOG performance status, and PSA were not significant predictors of survival in the multivariate model. A stratified analysis by disease extent (metastatic vs. PSA only) yielded the same results, but lacked power in the PSA only subgroup.

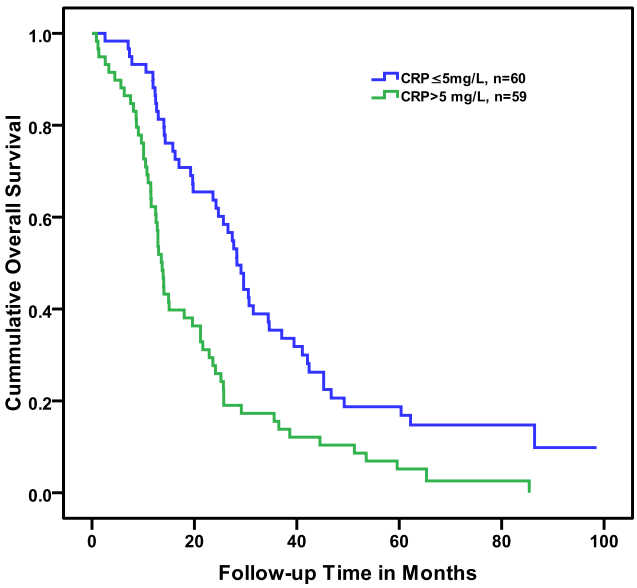

Fig. 1. Kaplan-Meier curve of below the median (≤5 mg/L) or above the median (>5 mg/l) C-reactive protein (CRP) on overall survival in men with castrate-resistant prostate cancer (log rank $P < 0.0001$). (Color version of figure is available online.)

Table 2
Independent risk factors for death

Prognostic factor	HR (95% CI)	P
CRP (continuous, per each doubling of CRP)	1.106 (1.022–1.197)	0.013
Alkaline phosphatase (categorical, above vs. below 238.9 U/l)	1.944 (1.144–3.302)	0.014
Hemoglobin (continuous, per each g/dl)	0.819 (0.711–0.943)	0.006

4. Discussion

In our independent data set of patients with CRPC, we confirmed our initial finding that elevated baseline CRP is associated with shorter OS. Recent evidence has suggested that elevated CRP is not only a marker of inflammation and cancer, but also plays a functional role in the proliferation of tumor cells. CRP has been found to inhibit apoptosis of myeloma cells, thereby directly regulating tumor cell growth and survival [41]. Moreover, HMG-CoA reductase inhibitors, commonly known as statins, decrease levels of circulating CRP [42], a finding which, in addition to the primary lipid lowering properties, may be another mechanism by which statins may decrease the risk of prostate cancer and other solid tumors [43,44]. The possibility that CRP may contribute to the pathogenesis of cancer indicates that CRP (in addition to inflammation) may be a potential target for novel cancer treatments.

Our current study has some limitations. As in our previous study, a sample size of 119 patients is modest for a complete analysis of potential prognostic markers in men with CRPC. Additionally, although prognostic models that predict the OS probability for patients with CRPC are well established in the medical literature [45,46], we were not able to include all of these available predictors in this current study as these data were not uniformly collected in all patients. A larger sample size that includes data from a comprehensive set of prognostic factors would be needed to incorporate CRP into current prognostic models. Our effort was more modest, however, and sought to confirm our initial finding that CRP elevations are associated with shorter survival in an unrelated patient group. For this purpose, our patient sample proved adequate. With only 57 patients receiving docetaxel-based chemotherapy, our study did not have sufficient power to determine if CRP was associated with the probability of PSA decline in response to docetaxel-based chemotherapy in CRPC.

Similar to all studies of CRP, we were unable to determine the specific causes of CRP elevation in these patients and unable to distinguish between increased CRP due to the presence of cancer from increased CRP related to other medical conditions. Although a formal determination of the cause of death in our patient subset was not performed, we would expect that the vast majority of these patients with CRPC die of prostate cancer rather than other co-morbid conditions [47].

Together with our prior results, we now have two retrospective analyses of independent data sets, which demonstrate that baseline elevated CRP is associated with shorter survival in CRPC. This readily measurable biomarker should now be examined prospectively in a larger study that incorporates a broad range of potential prognostic factors. If prospective evaluation further confirms our findings, the inclusion of CRP may enhance the performance of current prognostic models. Unlike many of the other prognostic markers, CRP levels, as well as the underlying inflammation, are potentially modifiable. Thus, a better understanding of how inflammation, and potentially CRP itself, affects cancer progression and treatment resistance may have the potential to point the way toward improved therapies and outcomes in advanced prostate cancer.

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