Evaluation of the Relationship between C-Reactive Protein and Prostate Cancer

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Abstract
In the last decade, accumulating evidence has supported Virchow’s hypothesis that cancer and inflammation are linked. Many investigators have demonstrated that the presence of a systemic inflammatory response, as evidenced by an elevated C-reactive protein (CRP) level or elevated interleukin-6 (IL-6) levels, are associated with a poor outcome in patients with many types of cancer, including prostate cancer. CRP is a serum acute phase reactant and a well established inflammatory marker. CRP secretion by hepatocytes appears controlled by IL-6. We examined the role of CRP to predict treatment response and tumor recurrence. Thumer et al. have indicated that elevated CRP levels and poor prognosis was independent of other measures of prognosis such as tumor stage, Gleason grading and PSA level at diagnosis. CRP had a specific role in prostate cancer progression and or resistance. Therefore, inhibitors of CRP (Siltuximab) might make for attractive therapeutic agents.

Keywords: CRP (C-reactive protein); IL6; Prostate cancer; Prostate-specific Antigen (PSA)

Introduction
Prostate cancer (PCa) is the most commonly diagnosed cancer and second leading cause of death in men [1]. More accurate and predictive markers should be applied for PCa. Recently, the presence of a systemic inflammatory response, which is measured by an acute-phase reactant has been identified to be associated with a poor prognosis in various types of cancers such as lung cancer, gastric cancer, colorectal cancer, renal cell carcinoma and others [2].

The use of biological tumor markers to help prognosis has appeal. An ideal potential tumor marker should have a long half-life, be measured accurately and precisely by a simple and inexpensive blood test. It is also important that it be sensitive to change so that it can be followed over time through serial measurements. A few biologic marker meet these criteria [3], C-reactive protein (CRP) is one.

CRP
CRP is an acute phase reactant, which reflects tissue injury [4]. The half-life is 19 hours in both health and disease. CRP is a surrogate for interleukin 6 (IL6) action [5]. IL-6 acts on hepatocytes to increase the synthesis of CRP. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) also stimulate CRP synthesis [6]. CRP is a non-specific but fairly sensitive marker of acute-phase inflammation. Major elevation of CRP levels are bacterial infection, inflammatory diseases, cancer, tissue necrosis and trauma. A strong positive correlation between high CRP and high IL-6 levels was shown in advanced pancreatic cancer [7]. Elevated CRP levels have been linked to shorter survival in several cancers [8]. While some studies reported that in PCa patients with a higher CRP level was significantly associated with poor prognosis in PCa [9]. But other studies did not show any significant relationship between CRP and survival in PCa patients [10]. In this paper, we described the review of the relationship between elevated CRP and prostate cancer.

Prostate-specific Antigen Levels (PSA)
PSA is produced exclusively by epithelial cells of prostate gland. Disruption of the cell to cell architecture of prostate epithelium results in increased serum PSA levels [11]. Apart from prostate cancer, nonmalignant condition and prostate manipulation such as benign prostate hyperplasia (BPH), acute/chronic prostatitis elevate serum PSA levels [12]. PSA levels alone are not a reliable parameter between prostate cancer and benign conditions of the prostate. A variety of parameters have been identified and applied for prostate cancer. But PSA is most popular parameter for
the diagnosis of prostate cancer. Other parameters are used to

diagnosis of prostate cancer. Epithelial growth factor receptor, pAKT

nuclear factor-kappa B, macrophage inhibitory cytokine-1, matrix

metalloproteinase-1 and matrix metalloproteinase-9 were used for

the prediction of the prognosis of prostate cancer [13,14]. However,

the above-mentioned biomarkers should be examined in cancerous

issues. Moreover, it is difficult to monitor their levels continuously

in the process of disease progression. In contrast, the inflammation

parameters can be easily assayed in plasma. Therefore, biomarkers

should be carefully selected to improve prognostic accuracy. Recently,

the Glasgow Prognostic Score has been developed to evaluate the

value of an inflammation-based score in patients with metastatic

prostate cancer. The Glasgow Prognostic Score, evaluating elevated

CRP (>10mg) and hypoalbuminemia (<3.5g), appears to be a useful

biomarker in the prognosis of prostate cancer [15].

The possible mechanism by which CRP is associated with the

worse outcome in prostate cancer.

- Tumor growth itself can cause inflammation of surrounding

tissue and increase CRP [16].

- Tumor cells produce various cytokines and chemokines that

attract leukocytes. Some cancer cells express CRP and secrete

interleukin-6 and interleukin-8, which stimulate liver CRP

production [17]. IL-6 blocks p-53 induced apoptosis. CRP

positivity develops a favorable microenvironment for the

tumor cells through acute inflammatory cytokine network

system maintenance [18].

An elevated CRP identifies those patients with an impaired

T-lymphocytic response, since poor infiltration of tumor appears to

be associated with poor outcome [19,20]. Liu [21] reported a total of

nine studies (n=1497) were evaluated in meta-analysis (five for overall

survival (OS), four for CSS (cancer-specific survival) and two for PFS

(progression-free survival). They reported that an elevated CRP level

could predict poor survival in patients with PCa and associated with

OS, CSS and PFS.

In Aldemir’s study [22], CRP is significantly higher in the

PCa patients with PSA>20ng/ml, compared to the subjects with

PSA<20, and is significantly higher in patients with Gleason

score>6, compared to the patients with Gleason score <6. Therefore,

they also concluded that elevated CRP level demonstrate their

diagnostic value in advanced stage prostate cancer. Thumer [23]
evaluated 261 prostate cancer patients treated with 3D-conformal

radiotherapy. They concluded an elevated plasma CRP (>8.6mg)

has been identified as a prognostic factor for poor CSS, OS and DFS

in prostate cancer patients undergoing radiotherapy. The association

between elevated CRP levels and poor prognosis was independent of

other measures of prognosis such as tumor stage, Gleason grading

and PSA level at diagnosis.

Targeting IL-6, Siltuximab (CNTO328)

If CRP had a specific role in prostate cancer progression and or

resistance, direct inhibitors of CRP might make for attractive

therapeutic agents. A chimerised monoclonal antibody targeting

IL-6, named CNTO328, was developed in recent years. It contains

the constant region of a human IgG1 κ immunoglobulin and the

antigen-binding variable region of the murine anti-IL-6 antibody. This

feature enables it to inhibit the binding of IL-6 to the IL-6

receptor. This area still holds promise for inhibitors of IL-6 signalling

pathways to be anti-metastatic agents, most probably combined with

other agents.

Siltuximab (CNTO328), a monoclonal antibody against IL-6,

has been studied in combination with chemotherapy [24] and as a

single agent [25]. Although these phase 2 studies were not designed to

yield definitive results, neither use in combination with mitoxantrone

nor single-agent treatment with CNTO 328 appeared to improve

clinically important end points, despite the fact that CNTO328 led to

expected decrease in IL-6 and CRP.

Conclusion

CRP had a specific role in prostate cancer progression and or

resistance. Therefore, inhibitors of CRP (Siltuximab) might make for

attractive therapeutic agents. To date, no such agents have been

developed. Recently, clinical trial have focused on targeting

inflammation. Siltuximab (CNTO328), a monoclonal antibody

against IL-6, has been studied in combination with chemotherapy

and as a single agent.

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