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SHORT COMMUNICATION

The effect of radiotherapy and hormone therapy on osteopontin concentrations in prostate cancer patients

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Summary

Purpose: *To evaluate and compare plasma osteopontin (OPN, a candidate prostate cancer biomarker) levels in prostate cancer patients receiving radiotherapy or combined radiotherapy or hormone therapy.*

Methods: *OPN levels were determined by ELISA in 40 prostate cancer patients eligible for radiotherapy (n=18 radiotherapy alone, n=22 combined radiotherapy and hormone therapy) before the start of irradiation, during treatment, and one month after its completion.*

Results: *OPN levels were significantly higher (p=0.02) in prostate cancer patients after receiving radiotherapy compared to baseline. In a subgroup analysis, there were no differences in OPN levels before and after treatment in patients undergoing radiotherapy alone, but OPN levels were significantly higher in patients after radiotherapy with hormone therapy compared to baseline (p=0.04) and in patients during radiotherapy compared to baseline (p=0.03).*

Conclusions: *Radiotherapy can increase plasma OPN concentrations in patients with prostate cancer, and radiotherapy may interact with hormone therapy to increase OPN concentrations. These differences suggest that OPN is worthy of further study as a predictive biomarker.*

Key words: *osteopontin, prostate cancer, radiotherapy, hormone therapy*

Introduction

Osteopontin (OPN) is a sialoprotein that plays a physiological role in bone tissue reconstruction. OPN also participates in early inflammatory responses, wound healing, angiogenesis, and cell adhesion. In cancer, OPN can influence tumor growth and proliferation and facilitate the formation of bone metastases [1]. Bone metastases are particularly frequent in prostate cancer, and plasma OPN levels are associated with disease progression and a worse prognosis [2], with high OPN levels a possible predictor of bone metastases in prostate cancer patients [3]. In the case of patients qualifying for surgery, OPN levels are also an independent risk factor for biochemical recurrence within 72 months of prostatectomy [4].

The aim of this study was to analyze plasma OPN concentrations in prostate cancer patients receiving radical radiotherapy with or without hormone therapy to evaluate OPN as a potential biomarker of treatment response.

Methods

The study included 40 patients with a confirmed diagnosis of prostate cancer and qualifying for radical external beam radiotherapy. The highest prostate serum antigen (PSA) concentration obtained before starting treatment was documented. All tumors had Gleason's grades documented from histopathological examination, and cancers were staged using the TNM system via prostate digital rectal examination (DRE) and pel-

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vic MRI examination. Hemoglobin concentrations were documented prior to commencing radiotherapy.

Twenty-two patients received neoadjuvant hormonotherapy, a luteinizing hormone analogue, at three-month intervals. The first injection of the hormone was given to the patient at least two months prior to starting radiotherapy. In addition, patients received oral anti-androgens (flutamide) throughout the radiotherapy period.

Peripheral blood was obtained from the basilic vein of the forearm via vene puncture to sterile Vacutainers (Becton Dickinson, Franklin Lakes, NJ) with 3.2% citrate solution for clotting between 7.30 and 8.30 a.m. Test-tubes were centrifuged for 15 min at 4°C at 1500 x g. Prior to analysis, blood samples were divided into sterile Eppendorf tubes and stored at 80°C. Blood was taken three times: before the start of irradiation, in the middle of treatment, and one month after its completion. Plasma OPN concentrations were determined by enzyme-linked immunosorbent assay (ELISA) using the Osteopontin Immunoassay test (R&D Systems, Minneapolis, MN).

Statistics

Statistical analyses were performed using StatSoft® Statistica v.9.0 (StatSoft Inc., Tulsa, OK). $P<0.05$ was considered statistically significant. Normality was examined using the Shapiro-Wilk test. Because the distributions were not normally distributed, the results are presented as medians (Me) and lower (Q1) and upper quartiles (Q3). The Wilcoxon signed-rank test was used to analyze differences between individual measurements of a given parameter. The Spearman coefficient (R) was used to assess correlations between parameters.

Table 1. Clinical characteristics of the tested group

Characteristics	*All (n=40)*	*RT only (n=18)*	*RT + HT (n=22)*
Age (years), mean (range)	68 (56-81)	65.5 (56-80)	69.5 (57-81)
Maximum PSA level before radiotherapy (ng/ml), mean (range)	23 (4.4-100)	10.59 (4.43-51)	16.7 (4.65-100)
Gleason score			
median (range)	6 (3-9)	5 (3-8)	6 (3-9)
divided by groups, n (%)			
2-6	31 (77.5)	16 (88)	15 (68)
7	4 (10)	1 (6)	3 (14)
8-10	5 (12.5)	1 (6)	4 (18)
TNM stage, n (%)			
T2aN0M0	7 (17.5)	2 (10)	5 (23)
T2bN0M0	10 (25)	6 (32)	3 (13)
T2cN0M0	6 (15)	3 (16)	4 (18)
T3aN0M0	14 (35)	8 (42)	7 (33)
T3bN0M0	3 (7.5)	0 (0)	3 (13)
Prostate volume (cm^3), mean (range)	69 (26.9-143.3)	66.7 (26.9-134.9)	58.55 (36.1-143.39)
Hemoglobin level (ng/dl), mean (range)	13.8 (11.7-16.8)	14.5 (12.4-16.8)	13.3 (11.7-15.7)

RT: radiotherapy; HT: hormone therapy; PSA: prostate-specific antigen; TNM: tumor-node-metastasis staging system

Table 2. Osteopontin levels in prostate cancer patients treated with radiation therapy alone or with neoadjuvant hormone therapy (blood collection before radiotherapy, during radiotherapy and one month after radiotherapy)

Time of measurement	*All group Median (Q1-Q3)*	*RT only Median (Q1-Q3)*	*RT + HT Median (Q1-Q3)*	*p value*
Before RT (1)	101.49 (85.93-131.18)	96.49 (82.74-115.48)	105.82 (94.28-151.3)	RT vs RT+HT 0.3
During RT (2)	109.64 (76.89-145.44)	111.57 (91.35-144.90)	108.23 (74.64-141.84)	RT vs RT+HT 0.82
After RT (3)	117.85 (87.64-16.84)	99.51 (81.92-133.74)	144.4 (99.46-191.49)	RT vs RT+HT 0.08
p value	ANOVA 0.05 1vs 2 p=0.56 **1 vs 3 p=0.02**	ANOVA 0.04 **1 vs 2 p=0.03** 1 vs 3 p=0.19	ANOVA 0.01 1 vs 2 p=0.3 **1 vs 3 p=0.04**	

Bold numbers indicate statistical significance

Results

The patient characteristics are presented in Table 1.The average age of all patients was 68 years (range 56-81). Only hemoglobin concentrations differed between subgroups, with hemoglobin levels significantly higher (14.5 mg%) in patients treated with radiotherapy than those treated with radiotherapy and hormone therapy (13.3 mg%, p=0.02).

The median OPN concentration was 101.49 ng/ml (Q1-Q3: 85.93-131.18) pre-radiotherapy, 109.64 ng/ml (76.89-145.44) during therapy, and significantly higher at 117.85ng/ml (87.64-162.84; p=0.02) one-month after therapy (Table 2).

When comparing differences in OPN values between different treatment groups, patients treated with radiotherapy alone showed a small but statistically significant increase in OPN during therapy (96.49 vs. 111.57 ng/ml; p=0.03), which returned to baseline values after therapy (96.49 ng/ml vs. 99.51 ng/ml; p=0.19; Table 2). In patients treated with combined hormone and radiotherapy, there was a significant increase in OPN after the end of treatment (105.82 vs. 144.4 ng/ml; p=0.04).

Discussion

Radiotherapy is a highly effective treatment for prostate cancer and is comparable to surgery. However, the details of the impact of ionizing radiation on the tumor tissue and its microenvironment remain only partially characterized. OPN is a negative prognostic factor in prostate cancer, and studies evaluating the influence of surgical treatment on OPN levels suggest that radiotherapy should similarly lower OPN concentrations [2-5]. Therefore, the increase in OPN concentration after irradiation observed here is surprising. This is the first study of OPN concentrations in prostate cancer patients treated with radiotherapy with or without neoadjuvant hormone therapy. Hormonal treatment significantly increased OPN concentrations under the influence of irradiation, while in patients undergoing radiotherapy alone, the OPN concentration did not change significantly before and after treatment.

The exact mechanism underlying the observed changes is not clear. However, our results suggest that hormone therapy amplifies the effects of irradiation with respect to OPN release. Vergis et al [5] reported that OPN results after prostatectomy could not be extrapolated to patients receiving radical radiotherapy. Evaluating tumor hypoxia factors such as VEGF, HIF-1α, and OPN in surgical (n=201) and radiotherapy (n=289) prostate cancer patients, OPN was only associated with a shorter time to biochemical recurrence in surgical patients [5]. Thoms et al [6] only observed a statistically significant decrease in OPN after surgery in the subgroup of patients with a low risk of disease recurrence. For patients undergoing radiotherapy, OPN values did not change significantly under the influence of treatment [6]. Patients with a high risk of recurrence had radiotherapy combined with hormone therapy, which was associated with a statistically significant increase in OPN after completion of therapy. It is thought that OPN may be associated with the acute radiation-induced reaction and inflammation after irradiation. High OPN values are not necessarily caused by cancer progression, but instead may be the result of activated macrophages and other inflammatory cells [6]. OPN may be a useful biomarker of radiation response, but larger studies with outcome data are needed.

In patients with head and neck cancer, OPN and hemoglobin were correlated [7], and OPN and HIF-1α expression have also been shown to be correlated in prostate cancer patients [5], suggesting that hypoxic cells generate higher amounts of OPN. In our own study, the subgroup treated with combination therapy had significantly lower hemoglobin levels, which might explain the observed higher OPN values in this subgroup.

In conclusion, radiotherapy increases plasma OPN levels in patients with prostate cancer. OPN may be a predictive biomarker of radiotherapy responses, but these changes need to be associated with outcome data. There were greater dynamics of OPN changes in patients receiving radiotherapy combined with hormone therapy, but the reason for this remains uncertain.

Conflict of interests

The authors declare no conflict of interests.

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