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CLINICAL INVESTIGATION **Prostate**

TGFB1 SINGLE NUCLEOTIDE POLYMORPHISMS ARE ASSOCIATED WITH ADVERSE QUALITY OF LIFE IN PROSTATE CANCER PATIENTS TREATED WITH RADIOTHERAPY

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Purpose: To investigate whether the presence of single nucleotide polymorphisms (SNPs) located within *TGFB1* might be predictive for the development of adverse quality-of-life outcomes in prostate cancer patients treated with radiotherapy.

Methods and Materials: A total of 141 prostate cancer patients treated with radiotherapy were screened for SNPs in *TGFB1* using DNA sequencing. Three quality-of-life outcomes were investigated: (*1*) prospective decline in erectile function, (*2*) urinary quality of life, and (*3*) rectal bleeding. Median follow-up was 51.3 months (range, 12–138 months; SD, 24.4 months).

Results: Those patients who possessed either the T/T genotype at position −509, the C/C genotype at position 869 (pro/pro, codon 10) or the G/C genotype at position 915 (arg/pro, codon 25) were significantly associated with the development of a decline in erectile function compared with those who did not have these genotypes: 56% (9 of 16) vs. 24% (11 of 45) ($p = 0.02$). In addition, patients with the −509 T/T genotype had a significantly increased risk of developing late rectal bleeding compared with those who had either the C/T or C/C genotype at this position: 55% (6 of 11) vs. 26% (34 of 130) ($p = 0.05$).

Conclusions: Possession of certain *TGFB1* genotypes is associated with the development of both erectile dysfunction and late rectal bleeding in patients treated with radiotherapy for prostate cancer. Therefore, identification of patients harboring these genotypes may represent a means to predict which men are most likely to suffer from poor quality-of-life outcomes after radiotherapy for prostate cancer. © 2008 Elsevier Inc.

Transforming growth factor β1 (TGF-β1), Single nucleotide polymorphisms (SNPs), Prostate cancer, Radiotherapy, Radiogenomics.

INTRODUCTION

The potential ability to predict both normal tissue and tumor response to a therapeutic intervention is attractive to both patients and oncologists for many reasons. The goal in treating patients is to cure their cancer while rendering a meaningful quality of life. In radiation oncology, maximizing the therapeutic index involves treating the tumor site with a high dose of radiation and minimizing the amount of normal, uninvolved tissue exposed to high radiation doses. Much work is actively proceeding in an effort to elucidate genetic predictors of radiation sensitivity. Our group has previously reported the correlation of ataxia-telangiectasia mutated (*ATM*) sequence variants and the development of adverse normal tissue response after the treatment of both breast and prostate cancer (1, 2). Single nucleotide polymorphisms (SNPs) are defined as DNA sequence variants in which the minor allele occurs in at least 1% of the population and are responsible for approximately 90% of interindividual DNA sequence variation. There is budding evidence implicating polymorphisms as risk factors for developing prostate cancer as well as the response to androgen deprivation therapy (3, 4).

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Single nucleotide polymorphisms are being increasingly studied to investigate how small genotypic variants in the population affect individual patient responses to radiotherapy (5–12).

Transforming growth factor β1 (TGF-β1), the protein encoded by *TGFB1*, is a multifunctional cytokine produced primarily by endothelial, hematopoietic, and connective tissue cells and is implicated in radiotherapy response. Virtually all human cells have receptors for TGF-β1, which regulates various cell functions, such as proliferation, differentiation, embryonic development, angiogenesis, and wound healing (13). Dysfunction of TGF-β1 has been observed in various disease states, including lung, liver, and kidney fibrosis, as well as hypertension (13). Recently, Zacchigna *et al.* (14) have demonstrated that excess TGF-β1 caused blood vessel stenosis and contributed to the development of hypertension in mice through increased peripheral vascular resistance. Previous groups have hypothesized that the TGF-β1 promoter phenotype influences TGF-β1 plasma levels (15). Grainger *et al.* studied two SNPs upstream from the main transcriptional start site: one at −509, where either a cytosine or thymine is present, and the other at position −800, where there is either an adenine or guanine. The −509 C/T genotype in which the patients were heterozygous at this allele was significantly associated with elevated plasma concentrations of TGF-β1. Others have followed, elucidating additional SNPs correlating with elevated TGF-β1 levels (8, 11).

In irradiated cells, TGF-β1 is a key cytokine associated with proliferation, differentiation, and deposition of extracellular matrix proteins (16). There is considerable evidence that TGF-β1 acts as a key mediator of fibrosis, both recruiting inflammatory cells as well as activating fibroblasts to produce extracellular matrix. Transforming growth factor β1 is central in the mitigation of postirradiation injury in various normal tissues and tumor cells (10, 17). It has been observed that a dose as low as 0.1 Gy of ionizing radiation directly induces TGF-β1 activation in less than 1 h (18, 19). In addition, ionizing radiation indirectly activates TGF-β1 by damaging endothelial cells and altering the homeostasis of reactive oxygen and nitrogen species (9). Elevated plasma TGF-β1 levels have been studied in the setting of thoracic radiation for non–small-cell lung cancer as a means of predicting patients at risk for developing radiation-induced pulmonary fibrosis (20, 21). Quarmby *et al.* (12) have reported on a series of 103 breast cancer patients who received radiotherapy and correlated TGF-β1 SNPs at the −509 and 869 positions with the development of severe radiation-induced normal tissue fibrosis. They found patients with either the −509 T/T or 869 C/C genotypes to be 7 and 15 times more likely to develop severe fibrosis, respectively. In a validation study of 167 breast cancer patients treated with radiotherapy, Giotopoulos *et al.* (22) reported that possession of the *TGFB1* −509 T/T genotype was associated with a roughly ninefold increase for the development of fibrosis compared with patients who have the *TGFB1* −509 C/C genotype. Andreassen *et al.* (6) have shown *TGFB1* polymorphisms were associated with late normal tissue skin toxicity in women treated with radiotherapy for early breast cancer. In a study of postmastectomy radiotherapy patients, the aforementioned investigators failed to replicate the initial results indicative of an association between *TGFB1* SNPs and the development of subcutaneous fibrosis (23). However, the different types of breast cancer patients and treatments should be noted, as well as the use of DNA derived from archived formalin-fixed, paraffin-embedded tissue samples for the second study compared with the use of DNA isolated from cultured fibroblasts for the initial study. Both of these differences between their studies could help to account for the contradictory results obtained in their two series.

Because of the growing evidence of the correlation between possession of certain *TGFB1* genotypes and the development of adverse normal tissue response after radiotherapy, we investigated the role of *TGFB1* SNPs in the setting of prostate cancer. We hypothesized that certain candidate *TGFB1* SNPs that result in the −509 T/T, 869 C/C (pro/pro, codon 10), and 915 G/C (arg/pro, codon 25) genotypes may be involved in the development of adverse normal tissue response after radiation. In line with previous findings in breast and lung cancer patients, these genotypes may predispose patients to adverse effects resulting from treatment of prostate cancer with radiation. The purpose of this study was to investigate whether the presence of SNPs located within *TGFB1* might be predictive for the development of adverse quality-of-life outcomes in prostate cancer patients treated with radiotherapy. We explore the potential association between possession of certain *TGFB1* genotypes and the development of three common quality-of-life measures relevant in men treated for prostate cancer: erectile dysfunction, urinary morbidity, and rectal bleeding.

METHODS AND MATERIALS

Patients

Peripheral blood lymphocytes were collected from a consecutive series of 141 patients treated at Mount Sinai Hospital for organ-confined prostate cancer between 1997 and 2005. All patients had biopsy-proven adenocarcinoma of the prostate, with central pathology review performed on all specimens. Patients were staged according to the American Joint Committee on Cancer standard (24). Patient and tumor characteristics are outlined in Table 1.

All but 1 patient was treated with low-dose-rate prostate brachytherapy using a real-time ultrasound-guided technique (25). One patient was treated with salvage external beam radiotherapy after a radical prostatectomy biochemical failure, and 1 patient was treated with a salvage partial ^{103}Pd implant 5 years after external beam radiotherapy. Treatment regimens evolved over time, thus there was overlap among different risk groups being treated by different regimens. Details of the development for these treatment schemas have been previously described (26). The implant prescription dose was 160 Gy (Task Group Report 43) for ^{125}I implants, 124 Gy (National Institute of Standards and Technology Report 99) for full ^{103}Pd implants, and 100 Gy (National Institute of Standards and Technology Report 99) for partial ^{103}Pd implants. Generally, patients at higher risk for extracapsular extension on the basis of pretreatment risk factors underwent partial (67%) dose implantation followed by external beam radiation to 45 Gy. A summary of the