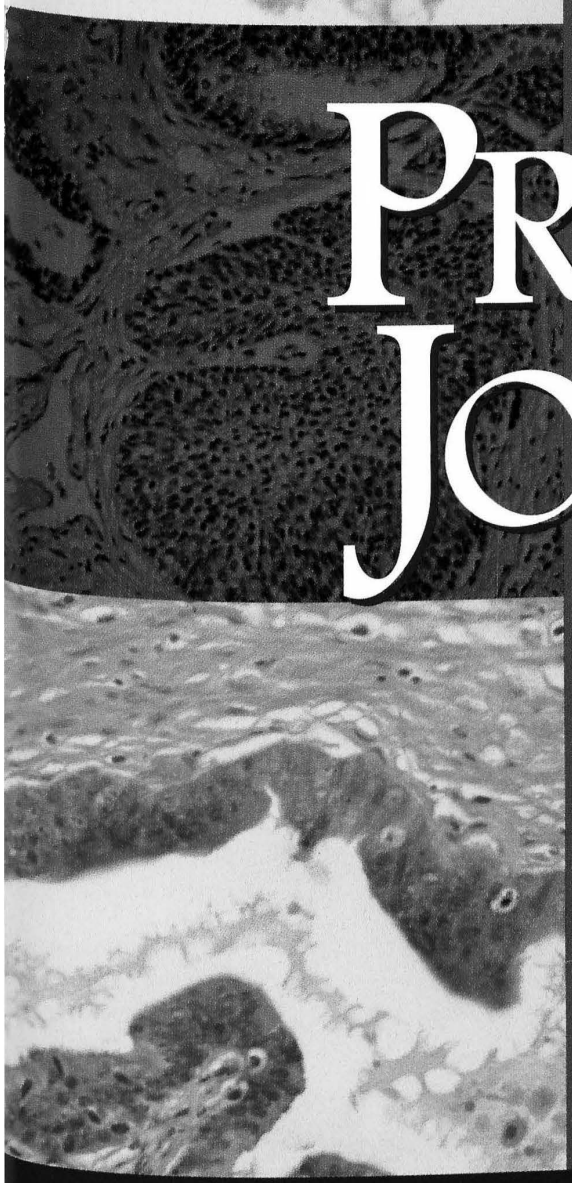

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The Prostate Journal

TABLE OF CONTENTS

Vol. 3, Number 2, April/May/June 2001

Minireviews – Section Editor: Daniel George, MD

HER-Kinase-Directed Therapy of Prostate Cancer 53
D. B. Solit, D. B. Agus

Is Neoadjuvant Hormonal Therapy Before Radical Prostatectomy Indicated? 59
J. Chun, R. S. Pruthi

Original Articles

A Phase II Trial of Humanized Anti-Vascular Endothelial Growth Factor Antibody for the Treatment of Androgen-Independent Prostate Cancer 65
D. M. Reese, P. Fratesi, M. Corry, W. Novotny, E. Holmgren, E. J. Small

Treatment of Metastatic Hormone Refractory Prostate Cancer with Ketoconazole Hydrocortisone, and Cyclophosphamide 71
A. Pecora, F. Richter, A. Pavlick, V. Lanteri, J. Scheuch, S. Levy, G. Rosenberg, J. Vitenson

Structure-Based Androgen Receptor Gene Mutation Database: A Tool to Link Molecular Location and Receptor Function 76
L. Brive, D. B. Agus, K. R. Ely

Expression of Prostate Specific Molecules in Bacille Calmette-Guerin: An Immunotherapeutic Approach to Prostate Cancer 92
C. D. Zeoli, M. Maitland, H. Rose, B. Bloom, A. Mittleman, J. Geliebter

Lack of Effect of Aminoglutethimide and Hydrocortisone Added to High-Dose Bicalutamide for Androgen-Independent Prostate Cancer 98
G. J. Bubley, S. P. Balk, R. M. Joyce, M.-E. Taplin

Sustained Activation of Extracellular Signal-Regulated Kinase (ERK) Signaling in Human Prostate Cancer LNCaP Cells Depleted of Androgen 105
L. Drew, R. L. Fine, A. J. Raffo, D. P. Petrylak

Intermediate-Term Outcome with Radical Prostatectomy for Localized Prostate Cancer: The Cleveland Clinic Experience 118
P. E. Clark, H. S. Levin, P. A. Kupelian, C. Reddy, C. D. Zippe, E. A. Klein

Article Reviews – Section Editor: William Oh, M.D. 126

The Prostate Journal Database - William Oh, M.D. 131

A Phase II Trial of Humanized Anti-Vascular Endothelial Growth Factor Antibody for the Treatment of Androgen-Independent Prostate Cancer

David M. Reese, PhD,[*] Paige Fratesi, BS,[*] Michelle Corry, RN,[*] William Novotny, MD,[†] Eric Holmgren, PhD,[†] and Eric J. Small, MD[*]

[*]Department of Medicine, Division of Hematology-Oncology, Urologic Oncology Program, University of California, San Francisco, California, U.S.A.

[†]Genentech, Inc., South San Francisco, California, U.S.A.

ABSTRACT

Objective: Vascular endothelial growth factor (VEGF) is a glycoprotein that is important in promoting tumor angiogenesis. Recombinant humanized anti (rhuMAb)-VEGF is a humanized murine monoclonal antibody that neutralizes VEGF activity and has shown promise in animal tumor models. **Methods:** To evaluate the efficacy and safety of single-agent rhuMAb VEGF in metastatic androgen-independent prostate cancer (AIPC), we treated 15 patients with 10 mg/kg rhuMAb VEGF every 14 days for six infusions (one cycle), followed by additional treatment for selected patients who had a response or were stable. **Results:** After one cycle, none of the 15 patients who were evaluable for tumor response had an objective complete or partial response. Three possible mixed responses were observed. No patient achieved a >50% decrease in serum prostate specific antigen (PSA) level after one cycle. Four patients (27%) had a PSA decline of <50%, three patients (20%) had a PSA level increase of <50%, and eight patients (53%) had a PSA increase of >50%. The median time to objective progression was 118 days, and the median time to PSA progression was 57 days. Toxicity was generally mild, with asthenia present in 6 (40%) of 15 patients. Severe hyponatremia developed in two patients, although the association with rhuMAb VEGF was unclear. **Conclusions:** We concluded that single-agent rhuMAb VEGF in this dose and with this schedule did not produce significant objective responses in patients with AIPC. Further development of this agent in patients with prostate cancer should focus on earlier stage disease or should evaluate it in combination with other therapies.

INTRODUCTION

Vascular endothelial growth factor (VEGF) is a secreted glycoprotein with potent effects on both normal and pathologic angiogenesis (1). Many solid tumors, including lung, thyroid, breast, colon, kidney, bladder, ovary, and brain cancers, have increased VEGF expression (2). It has been postulated that paracrine growth loops exist whereby tumor cells secrete VEGF, which then interacts with specific receptors (e.g., Flk-1/KDR) on endothelial cells to promote tumor angiogenesis.

Address correspondence and reprint requests to: Eric J. Small, MD, UCSF Comprehensive Cancer Center, 2356 Sutter Street, 5th Floor, San Francisco, CA 94115, U.S.A.

VEGF may play a role in the pathogenesis and progression of human prostate cancer. Flk-1/KDR receptors are expressed in human prostate cancer, and their presence may correlate with higher grade lesions (3). In addition, VEGF is present in both localized and metastatic prostate tumors as well as the plasma of patients with metastatic disease, and increasing expression may correlate with disease progression (4,5). Finally, antibodies to VEGF have caused tumor regression in preclinical animal prostate tumor models (6–8).

Recombinant humanized anti-VEGF (rhuMAb VEGF) is a monoclonal immunoglobulin g1 antibody generated by engineering the VEGF-binding residues in a murine antibody into the framework of a normal human antibody (9).

rhuMAb VEGF effectively neutralizes VEGF activity in vivo and inhibits the growth of a variety of human cancer cell lines in nude mouse tumor models (10–12). in Phase I clinical trials in humans, there was minimal toxicity of rhuMAb VEGF (13), and the antibody is now being evaluated for the treatment of a variety of solid tumors.

Based on the above observations, a Phase II trial of rhuMAb VEGF in patients with androgen-independent prostate cancer (AIPC) was conducted. The primary objectives of this trial were to determine whether single-agent rhuMAb VEGF would result in objective responses in patients with AIPC, to test the effect of rhuMAb VEGF on prostate specific antigen (PSA) levels in these patients, and to further evaluate the safety of this antibody.

MATERIALS AND METHODS

Patients

Eligibility criteria for inclusion in the study included histologic diagnosis of prostatic adenocarcinoma and disease progression despite androgen deprivation and antiandrogen therapy withdrawal. Patients had to have documented measurable or evaluable metastatic disease and a serum PSA level >5 ng/ml. Three consecutive increases in the serum PSA level, each measured at least 2 weeks apart, were required. Prior second-line hormonal therapy, chemotherapy, immunotherapy, radiation therapy, surgery, or other investigational therapy was permitted provided that treatment was completed at least 4 weeks before enrollment and that disease progression had occurred despite that therapy. Prior radioisotope therapy (strontium-89 or samarium-153) was permitted provided that treatment had occurred at least 60 days preceding the rhuMAb VEGF therapy. If patients were receiving a luteinizing hormone-releasing hormone analog, this was continued. A life expectancy of ≥6 months and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1 were required. Because of the possibility that rhuMAb VEGF could inhibit angiogenesis in nontumor tissues, patients were excluded if they had clinically significant cardiovascular disease (i.e., uncontrolled hypertension, recent unstable angina or myocardial infarction, congestive heart failure, cardiac arrhythmia requiring medication, or significant peripheral vascular disease). In addition, evidence of central nervous system metastases were excluded. Because Phase I studies with rhuMAb VEGF therapy reported severe episodes of bleeding, the current or recent use of oral or parenteral anticoagulants, including aspirin, was an exclusion criterion. Required values for initial laboratory data included the following: white blood cell count >2500/μl and absolute neutrophil count (ANC) >1000/μl; platelet count >75,000/μl; total bilirubin, AST, and ALT less than twice the upper limits of normal; serum creatinine ≤1.5 mg/dl; and hemoglobin >9 g/dl. The protocol was approved by the University of California, San Francisco, Institutional Review Board, and written informed consent was obtained from all patients.

Treatment Plan

rhuMAb VEGF was supplied by Genentech, Inc (South San Francisco, CA) and was administered intravenously in the outpatient clinic. The antibody was administered at a dose of 10 mg/kg every 14 days for six infusions (one cycle). The initial dose was given over a 90-min period, the second dose over 60 min, and all subsequent doses over 30 min if the prior infusions were tolerated without infusion-associated adverse events. Patients experiencing infusion-related effects such as fever, chills, myalgia, headache, rash, fatigue, dyspnea, or hypotension were treated symptomatically with acetaminophen, diphenhydramine, meperidine, or other medications as clinically indicated. Patients with an objective response or stable disease were eligible to receive additional rhuMAb VEGF treatment beyond one cycle.

Response, Assessments, and Toxicity

A physical examination, vital signs, ECOG performance status evaluation, and laboratory evaluation were performed every 2 weeks. Serum and plasma also were collected every 2 weeks to determine VEGF and rhuMAb VEGF levels.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (Version 1). Response to therapy was assessed with serial serum PSA measurements and imaging studies. Bone scans and, when appropriate, computed axial tomography scans were obtained

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