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Critical Reviews in Oncology/Hematology 87 (2013) 122–131

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Angiogenesis and anti-angiogenic therapy in prostate cancer

Deborah Mukherji *, Sally Temraz, David Wehbe, Ali Shamseddine

Department of Hematology/Oncology, American University of Beirut Medical Center, PO Box 11-0236, Riad El Solh, Beirut 1107 2020, Lebanon

Accepted 4 January 2013

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Abstract

Inhibition of angiogenic pathways has proven an effective strategy for the treatment of several common solid tumors however its role in the management of prostate cancer is yet to be defined. Advances in clinical research have resulted in five new treatments for metastatic prostate cancer in the last two years. The immunotherapy sipuleucel-T, the cytotoxic cabazitaxel, the androgen biosynthesis inhibitor abiraterone acetate, the radioisotope radium-223 and the antiandrogen enzalutamide have all been shown to improve overall survival in randomized phase III studies treatment paradigms are changing rapidly. Angiogenesis is known to play a central role in the progression of advanced prostate cancer however established antiangiogenic therapies including bevacizumab and sunitinib have failed to improve survival in randomized trials to date. Novel treatment combinations and novel agents such as cabozantinib are showing promising early results and it is hoped that further well-designed studies will validate the strong biological hypothesis for the benefit of antiangiogenic therapy to improve outcomes for patients with prostate cancer.

Keywords: Angiogenesis; Castration resistant prostate cancer; Vascular endothelial growth factor; Bevacizumab; Sunitinib; Cabozantinib

1. Introduction

Prostate cancer is the most common cancer in North American and European men with the exception of non-melanoma skin cancer, and the second leading cause of male cancer-related death after lung cancer [1,2]. Suppression of gonadal

* Corresponding author. Tel.: +961 1350000; fax: +961 1742080.
E-mail address: Dm25@aub.edu.lb (D. Mukherji).

1040-8428/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.critrevonc.2013.01.002

androgens remains the first-line of therapy for patients who relapse following treatment of organ-confined disease and for those with advanced disease at diagnosis, however responses are not durable and metastatic castration-resistant prostate cancer (mCRPC) is invariably fatal. In the last two years, sipuleucel-T, cabazitaxel, abiraterone acetate, radium-223 and enzalutamide have all been shown to improve survival in randomized phase III studies for patients with CRPC [3–7]. The optimal use and sequencing of these new agents has yet to be determined and treatment paradigms for advanced prostate cancer are changing rapidly. Angiogenesis is known to play a central role in the progression of CRPC [8]. Inhibition of angiogenic pathways has proven an effective strategy for the treatment of several common solid tumors such as colorectal, lung and kidney cancer [9–11]. Despite on-going clinical investigation, the role of anti-angiogenic therapy in the management of prostate cancer has yet to be defined. This review will cover the preclinical evidence supporting the use of anti-angiogenic therapy for the treatment of prostate cancer; discuss the challenges of response assessment, current clinical data and future directions for research.

Data for this review were compiled using MEDLINE/PubMed, American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) abstract databases published before July 2012. The search terms included *prostate cancer*, *angiogenesis* and *vascular endothelial growth factor*. Information regarding ongoing clinical trials was obtained using the United Stated National Institute of Health's online resource clinicaltrials.gov. Only articles published in English were considered.

2. Rationale for anti-angiogenic therapy in prostate cancer

Microvessel density in prostate cancer, a histological measure of tumor angiogenesis, has been shown to correlate with Gleason score and predict disease progression [8,12]. Whether neovascularization is a primary pathogenic event or a response to the hypoxic microenvironment of a growing tumor, this observation provides a rationale for investigating anti-angiogenic therapy as a treatment strategy for this disease.

Tumor angiogenesis involves the complex interplay between pro-and anti-angiogenic factors influencing tumor cells, endothelial cells and surrounding stroma. Key angiogenic factors implicated in prostate cancer progression and metastasis include vascular endothelial growth factor (VEGF), angiopoietins, fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) (Fig. 1) [13–17].

The novel androgen biosynthesis inhibitor abiraterone, androgen receptor (AR) inhibitor enzalutamide and taxane cabazitaxel have all shown a survival benefit in phase III studies in castration-resistant prostate cancer (CRPC) [4,5,18]. The success of abiraterone acetate and enzalutamide in the post-docetaxel setting confirms the hypothesis that advanced prostate cancer remains driven by AR signaling and that targeting this pathway remains an effective strategy for disease control. There is also evidence that the tubulin-binding taxane cytotoxic agents inhibit AR signaling by blocking AR nuclear accumulation [19]. The AR can modulate gene expression by directly interacting with specific androgen response elements (AREs) within the regulatory regions of target genes [20]. A dose-dependent increase in the expression of *FLT1* (FMS-related tyrosine kinase 1) encoding VEGFR-1 suggests that *FLT1* is an androgen target gene, linking AR signaling to angiogenesis [21]. The expression of VEGFR-1 has been correlated with higher Gleason score, pathological stage and microvessel density in prostate intraepithelial neoplasia (PIN) and prostate carcinoma when compared to normal prostatic tissue [22]. Genetic polymorphisms in the AR binding site of *FLT1* have been shown to predict survival in a cohort of 601 men with advanced prostate cancer treated with androgen deprivation therapy [23].

Whereas two novel therapies targeting the AR signaling pathway have improved survival in advanced CRPC in randomized studies, several phase III studies of antiangiogenic agents in mCRPC have failed to meet their primary endpoints. A large phase III study investigating the combination of the anti-VEGF monoclonal antibody bevacizumab with docetaxel chemotherapy in CRPC was disappointingly negative [24]. Furthermore, phase III studies investigating the use of the antiangiogenic agents sunitinib and lenalidomide in advanced CRPC were discontinued due to futility [25,26]. Despite this, the rationale for the use of antiangiogenic therapy remains strong and novel agents such as the dual VEGF/MET targeting tyrosine kinase inhibitor cabozantinib have recently shown promising results (Table 1) [27].

3. Challenges of drug development and response assessment in advanced prostate cancer

In 1999, the Prostate-Specific Antigen Working Group (PCWG1) produced the first consensus recommendations for the conduct of clinical trials in prostate cancer [32], these were followed in 2000 by the introduction of the now-familiar Response Evaluation Criteria in Solid Tumors (RECIST) [33]. Since the publication of these guidelines, advances have been made in our understanding of the biology of prostate cancer and with the advent of both new androgen signaling pathway and molecularly targeted therapies, updated recommendations were published in 2008 by the Prostate Cancer Clinical Trials Working Group (PCWG2) [34].

PCWG2 recognized that cytotoxic agents typically produce PSA responses and regression of target lesions, whereas non-cytotoxic agents slowing tumor growth, inhibiting bone destruction or targeting angiogenesis may not. Two types of phase II trial objectives were distinguished: those based on controlling, relieving, or eliminating manifestations of disease present at the initiation of treatment, and those based on preventing or delaying future manifestations of disease.