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Seminar article

The current role and limitations of surrogate endpoints in advanced prostate cancer

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Abstract

Objectives: The identification of appropriate surrogate endpoints for evaluating cancer therapeutics has been of ongoing interest across various tumor types. Metastatic castrate-resistant prostate cancer (mCRPC) has been a particularly challenging area. As more targeted and novel therapies are being developed in this disease space, an urgent need exists to identify surrogate endpoints in mCRPC. The ability to discern patient benefit in the absence of patient death or other complications would facilitate both drug development and more appropriate patient care.

Methods and materials: We reviewed the available literature and guidelines used in the development and approval of recent agents for mCRPC.

Results: The majority of regulatory approvals of new medications have relied on overall survival (OS) or prevention of complications such as skeletal related events (SRE's). Progression-free survival measures, such as bone scans, computed tomography scans, and prostate-specific antigen related changes, have not been validated nor uniformly accepted as outcome surrogates. All of the successful recent pivotal Phase III trials designed to achieve regulatory approval in mCRPC have used either OS or SRE's as the primary endpoint.

Conclusions: There are significant problematic issues that exist associated with defining and implementing surrogate markers in mCRPC beyond survival and complications. Suggestions are made as to how the current situation might be improved. © 2014 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer endpoints; Metastatic castrate-resistant prostate cancer

1. Introduction

The identification of appropriate endpoints for evaluating cancer therapeutics has been a rigorous process across tumor types [1]. Broad guidelines that encompass all solid tumors, as well as tumor-specific guidelines, have been proposed that define standard criteria for measuring patient outcomes [2]. Although agents are approved with endpoints other than survival for some cancers (e.g., breast cancer, renal cell carcinoma) the identification of endpoints as an alternative or addition to overall survival (OS) for advanced prostate cancer is particularly complicated. Confounding factors include the long natural history of the disease, the uncertainties associated with assessing response in bone, controversy surrounding the clinical significance of post-therapy changes in prostate-specific antigen (PSA) levels, the wide range of mechanisms of action for new treatment options, and the lack of standard definitions for progression-free survival (PFS) and time to progression (TTP) [3]. The range of endpoints used to characterize clinical benefit in prostate cancer illustrates the need for different criteria for approval decisions depending on the disease state, question(s) being addressed, type of drug being investigated, and the drug mechanism of action [4].

Prior to 2004, drugs such as strontium-89, samarium-153, and mitoxantrone were approved by the US Food and Drug Administration (FDA) for palliation of painful bone metastases in patients with metastatic castration-resistant prostate cancer (mCRPC) [5]. In 2002, zoledronic acid was approved based on reductions in skeletal-related events (SREs) [6]. In 2010, denosumab was approved based on its improved ability to prevent or delay SREs vs. zoledronic acid [7]. In 2004, docetaxel became the first drug approved

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for the treatment of mCRPC based on a demonstrated OS benefit [8]. Since the approval of docetaxel, the FDA has consistently based approval of agents on OS or reduction of SREs for the active treatment of late-stage prostate cancer. As ondate of this publication, 4 agents have been approved for the treatment of mCRPC based on a demonstrated positive effect on OS.

In addition to the drugs currently approved for the treatment of advanced prostate cancer, there are several promising agents in late-stage clinical development. Some of these agents have demonstrated an OS benefit without any effect on measures of progression, which may make integration of these agents into clinical practice confusing. This article discusses the current predominance of OS as the acceptable endpoint for drug approval in mCRPC by the FDA and the pressing need for the identification of surrogate endpoints.

2. Overview of FDA acceptance of endpoints related to mCRPC

With the exception of reduction in SREs, OS is the current FDA standard for drug approval in the treatment of mCRPC. Bone metastases are common in patients with prostate cancer, and time to SRE is a composite endpoint of local skeletal complications—fracture, spinal cord compression, and complications that require radiotherapy or surgery [6,9]. While not directly treating the prostate tumor, the prevention of SREs is of great importance to patients and physicians and has contributed to the acceptance of this endpoint by the FDA.

Other than denosumab for prevention of SREs, all of the therapeutic agents approved to treat mCRPC because the approval of docetaxel have had OS as the primary endpoint in their pivotal phase III trials (Table 1) [8,10–12]. Almost all of the products in late-stage clinical development for the treatment of advanced prostate cancer also have OS as the primary endpoint. The exceptions are custirsen, an anti-apoptotic factor inhibitor (OGX-011, OncoGeneX, Bothell, WA/USA/Teva Pharmaceuticals, North Wales, PA/USA), and cabozantinib, a tyrosine kinase inhibitor (XL184, Exelixis, South San Francisco, CA/USA), for which durable pain palliation is the primary endpoint in their ongoing phase III studies (Table 2). Secondary endpoints for ongoing phase III trials vary and include time to event or symptom measures.

Custirsen is a clusterin inhibitor being investigated for the first- and second-line treatment of symptomatic mCRPC. In 2008, the FDA granted a Special Protocol Assessment (SPA) for the second-line trial of custirsen (Prostate Cancer SATURN Trial), which at the time had OS as the primary endpoint [13]. The SPA was later amended to include a similar trial of custirsen in the first-line setting with OS as the primary endpoint, whereas the endpoint for the trial of custirsen in the second-line setting was changed to durable pain palliation [14]. Whether this endpoint will be achieved and how the FDA would respond remain to be determined. The manufacturer of custirsen also plans to have a second phase III trial, called the Synergy trial, in the second-line setting, but with survival as the primary objective [15]. Although the exact development plan for custirsen is in the midst of change, it is clear that survival is an acceptable

Table 1
Overview of pivotal Phase III Trials for drugs approved for metastatic CRPC since 2004

	Drug	Trial Name	Trial Design	Primary and Select Secondary Endpoints*
Asymptomatic, Minimally Symptomatic Chemotherapy-Naïve CRPC	Sipuleucel-T [10]	IMPACT	Sipuleucel-T vs Placebo	1°: OS 2°: Time to disease progression†
Symptomatic Chemotherapy-Naïve CRPC	Docetaxel [8]	TAX327	Docetaxel+prednisone vs Mitoxantrone+prednisone	1°: OS 2°: Pain response, PSA response
Second-Line, Docetaxel-Pretreated CRPC	Cabazitaxel [11]	TROPIC	Cabazitaxel+prednisone vs Mitoxantrone+prednisone	1°: OS 2°: PFS‡
	Abiraterone acetate [12]	COU-AA-301	Abiraterone+prednisone vs Placebo+prednisone	1°: OS 2°: TP-PSA, PFS§,PSA response
	Enzalutamide (MDV3100) [49]	AFFIRM	MDV3100 vs placebo	1°: OS, PFS 2°: TFSE

CRPC = castration-resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen; PFS = progression-free survival; TP-PSA = time to progression in PSA.

*Limited to disease progression endpoints.

†Time to disease progression determined by radiographic studies, with one or more of the following criteria used to define progression: an increase in lesion size, the new appearance or unequivocal progression of nonindex lesions, at least two new lesions on bone scanning, and a new pathologic fracture or spinal cord compression.

‡Progression-free survival defined as the time between randomization and the first date of progression as measured by PSA progression, tumor progression by Response Evaluation Criteria in Solid Tumors (RECIST), pain progression, or death.

§Progression-free survival determined by radiographic evidence of prespecified criteria: soft-tissue disease progression according to modified RECIST or progression according to bone scans showing two or more new lesions not consistent with tumor flare.

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