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Taxanes in the management of metastatic castration-resistant prostate cancer: Efficacy and management of toxicity

Fabio A. Schutz [a,*], Antonio C. Buzaid [a], Oliver Sartor [b]

[a] *Hospital Sao Jose – Beneficencia Portuguesa de Sao Paulo, Sao Paulo, Brazil*
[b] *Tulane Cancer Center, Tulane University School of Medicine, New Orleans, LA, United States*

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Contents

Abstract

Androgen deprivation is the therapy of choice in the majority of patients with metastatic prostate cancer. However, a state of castration resistance ultimately occurs after hormone therapy, thus defining metastatic castration-resistant prostate cancer (mCRPC). mCRPC has historically been considered a relatively chemoresistant tumor. However, due to its ability to improve survival and the quality of life in comparison with mitoxantrone, docetaxel has been established as the standard chemotherapeutic agent for first-line therapy since 2004. Moreover, recent results have shown that the novel taxane cabazitaxel is able to prolong the overall survival of patients with mCRPC previously treated with docetaxel. Even though these taxanes display a favorable toxicity profile, their routine use in clinical practice requires knowledge about the most frequent and distinct adverse events that may result from their administration.

Keywords: Prostate cancer; Docetaxel; Cabazitaxel; Drug toxicity

1. Introduction

Prostate cancer is typically diagnosed at early stages, often through transrectal biopsy triggered by elevated levels of prostate specific antigen (PSA) [1,2]. In part due to the PSA screening programs, it is now the most common

* Corresponding author at: Rua Martiniano de Carvalho 965, Sao Paulo 01321-001, Brazil. Tel.: +55 11 3505 6615; fax: +55 11 3505 6615.
E-mail addresses: fabio.schutz@hospitalsjose.org.br, fabioschutz@gmail.com (F.A. Schutz).

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cancer in the male population in the United States, with an estimated 241,740 new cases in 2012 [2]. Despite its indolent course in most cases and the curability of localized disease by prostatectomy and/or radiation therapy in most patients, nearly over 10,000 men in the US alone are newly diagnosed with metastatic disease each year, and many other recur after local therapy, and it was responsible for an estimated 28,170 deaths in 2012 [2–4]. For these patients, who typically have involvement of the axial skeleton, treatment is done with a palliative intent and often consists in androgen deprivation through surgical or pharmacological means [5]. Due to the reliance of prostate cancer cells on testosterone, androgen deprivation is initially active in 80–90% of patients and is associated with median progression-free survival (PFS) times that range from 12 to 30 months after treatment initiation [5,6]. However, prostate tumor cells eventually acquire the ability to proliferate in a serum androgen-depleted environment [3,7], and a median overall survival (OS) of only 8–16 months has been historically observed after the appearance of such androgen independency [5,6]. Along the years, the terms 'androgen-independent', and 'hormone-refractory', were used interchangeably – but today given the demonstrated sensitivity of CRPC to various androgen-targeted therapies, castrate-resistant is the current preferred term [8] – to denote disease that progresses despite castrate levels of testosterone [9,10]. Over the past 15 years, substantial progress has been achieved in the treatment of patients with of metastatic castration-resistant prostate cancer (mCRPC) with chemotherapy. In the following review, we will present historical developments and current perspectives on the treatment of these patients with taxanes, the most active class of chemotherapeutic agents in this setting.

2. Historical development of chemotherapy for mCRPC

Historically, prostate cancer has been considered a relatively chemoresistant tumor. Until the early 90s, several authors pointed out that the response rates to the agents that were then available were typically low and varied widely [11–13]. Moreover, authors postulated that the documentation of responses in metastatic prostate cancer was complicated by the lack of established criteria, as nearly 80% of patients with this disease have no measurable soft tissue lesions [14]. Thus, objective responses could only be assessed in the minority of patients with measurable disease. In the early 90s, PSA became widely available and was introduced as a measure of response in clinical trials [3,15]. In 1999, a broadly cited consensus conference suggested the criterion for partial PSA responses in clinical trials, namely a decline of at least 50% from baseline levels, as long as there was confirmation at least 4 weeks later and no clinical or radiographic evidence of disease progression [16]. These criteria paved the way for a novel generation of trials in mCRPC. It should be noted, however, that PSA responses have not been validated as surrogates for OS in advanced prostate cancer, including both first and second line chemotherapies, with OS remaining the most accepted regulatory endpoint in phase III trials [17–19]. In addition, PFS and time to tumor progression (TTP) have been used increasingly in selected clinical trials [9], and recent data suggest that PSA progression is able to predict OS in mCRPC after some treatments [20].

Several chemotherapeutic agents that were available before the PSA era, including some anthracyclines, alkylating agents, antimetabolites, platinums, and topoisomerase inhibitors, have been assessed in numerous phase II trials along the years [11,12]. In a landmark review of 26 different agents, the average response rate was only 8.7%, but the combination of vinblastine plus estramustine was regarded as promising [12]. The results of randomized trials with this combination at the time did not seem to establish a reference regimen, and the substantial toxicity remained a concern in the setting of palliative therapy [21,22]. In parallel, phase II trials of both mitoxantrone and low-dose prednisone had suggested modest single-agent activity and good tolerability profiles for these agents [23,24]. In randomized trials, the addition of mitoxantrone to a corticosteroid relieved pain and improved the quality of life more frequently than the same corticosteroid alone [25–27], thus establishing mitoxantrone as the reference chemotherapeutic agent for the treatment of patients with mCRPC [28]. Of note, this approach was not associated with improvements in OS, and additional regimens were sought.

During the 90s, the nascent class of taxanes represented a logical next step in the search for novel agents with activity in mCRPC. Agents from this class were noted to bind beta-tubulin and inhibit the intrinsic instability of microtubules, the dynamic structures involved in the development and maintenance of cell shape, intracellular transport, and cell division; as a result, taxanes exert potent antitumor effects in various preclinical models and clinical settings [29]. In prostate cancer, increased expression of class III beta-tubulin may have a role in progression to the castration-resistant state [30]. Paclitaxel, the first taxane to become clinically available, displayed single-agent activity that was described as modest or encouraging in phase II trials [31,32]. On the other hand, a plethora of phase II trials assessed paclitaxel in combination with estramustine, another agent that is capable of inhibiting the function of microtubules. However, paclitaxel was not widely used in current clinical practice since there was not any phase III trials of paclitaxel, alone or in combination with estramustine, published so far.

3. Docetaxel in the first line

Docetaxel is a semisynthetic taxane that is able to inhibit the depolymerization of microtubules approximately twice as effectively as paclitaxel in pre-clinical models [33]. After the demonstration of its promising single-agent activity in phase II trials in mCRPC [34,35], docetaxel was assessed in