Published in final edited form as:

Maturitas. 2011 October ; 70(2): 194–196. doi:10.1016/j.maturitas.2011.07.018.

Recent advances in the therapy of castration-resistant prostate cancer: The price of progress

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Abstract

Within the past two years, three agents have garnered approval from the US FDA for the specific treatment of metastatic castration resistant prostate cancer (mCRPC) – (1) abiraterone, (2) cabazitaxel and (3) sipuleucel-T. In separate phase III studies, each agent led to an improvement in overall survival (OS) of 2–4 months over a suitable comparator. With these costly therapies all having potential application in the patient with mCRPC, multiple entities (industry, government, and the general public) must strategize to determine how the cost burden of these agents can be balanced with the potential gains for the individual patient. Herein, we provide a framework with which to approach this dilemma.

COMMENTARY

On May 19, 2004, the US Food and Drug Administration approved docetaxel in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC).¹ This approval came on the basis of two studies (TAX327 and Southwest Oncology Group Protocol, SWOG, 99-16) that identified an improvement in overall survival (OS) with docetaxel-based regimens as compared to mitoxantrone with prednisone.^{2–3} In the

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two decades that preceded this milestone, only a limited number of other agents garnered FDA approvals (mitoxantrone, strontium-89, samarium-153, and zoledronic acid).⁴⁻⁸ Notably, these approvals were granted on the basis of improvements in quality of life (QOL) metrics or skeletal related events (SREs) as opposed to antitumor efficacy. The data in support of docetaxel led to a revised expectation for novel therapies for mCRPC – specifically, an improvement in OS became the most common primary endpoint in trials positioned for FDA approval. Several agents have tried and failed to reach this high-water mark. Perhaps most notably, an evaluation of docetaxel with bevacizumab in Cancer and Leukemia Group B (CALGB) trial 90401 showed an improvement in progression-free survival (PFS), but no difference in OS.⁹ The ASCENT-II study, comparing docetaxel with prednisone to docetaxel with high-dose calcitriol, actually yielded inferior OS with the experimental therapy.¹⁰ Similarly disappointing, despite encouraging phase II data, a randomized, phase III effort comparing the endothelin A antagonist zibotentan to placebo showed no significant benefit in OS.¹¹ While efforts to explore zibotentan with docetaxel are ongoing, hopes for this class of agents have been dampened by a recent press release for SWOG 0421, a trial comparing docetaxel with or without atrasentan (a distinct endothelin antagonist).¹² A planned interim analysis showed no benefit in PFS or OS, leading to early closure.

While the highlighted studies illustrate the challenge in demonstrating an OS benefit in mCRPC, over the past two years, four agents have been able to achieve this endpoint. In the docetaxel-refractory setting, cabazitaxel with prednisone was compared to mitoxantrone with prednisone in the phase III TROPIC study, and was shown to improve OS from 12.7 to 15.1 months (HR 0.70, 95%CI 0.59–0.83; $P<0.0001$).¹³ In a similar patient population, the COU-AA-301 compared the CYP17 lyase inhibitor abiraterone acetate (given with prednisone) to prednisone alone. The improvement on OS in this study with abiraterone was of similar magnitude (14.8 versus 10.9 months, HR 0.65, 95%CI 0.54–0.77; $P<0.001$).¹⁴ The phase III IMPACT study assessed a different cohort of patients – namely, those with asymptomatic or minimally symptomatic mCRPC.¹⁵ In contrast to the previous two studies, only 19% of patients enrolled on IMPACT had prior chemotherapy exposure. The study randomized patients to receive placebo or the autologous dendritic cell vaccine, sipuleucel-T. Although no difference in PFS was observed, there was an improvement in OS with sipuleucel-T (25.8 versus 21.7 months, HR 0.77, 95%CI 0.61–0.97; $P=0.02$). Data for the fourth and most recent agent to generate an improvement in OS, radium-223 chloride, are available only in the form of a press release at this time. In the phase III ALSYMPCA study, patients with mCRPC were randomized to receive either radium-223 chloride or placebo, both administered in conjunction with best supportive care (BSC). The available press release suggests an improvement in OS from 11.2 to 14.0 months (HR 0.70, $P=0.02$).¹⁶ Potentially used alongside each of these agents are bone-directed therapies. The agent denosumab was recently compared to the bisphosphonate zoledronic acid. In this pivotal phase III trial, denosumab significantly delayed time to a first skeletal related event (SRE; 20.7 versus 17.1 months, HR 0.82, $P=0.004$).¹⁷ Now FDA approved, denosumab has already been incorporated in prostate cancer guidelines, including those from the National Comprehensive Cancer Network.¹⁸

As noted in Table 1, there are slight numerical differences in the extent of survival improvement across the aforementioned studies of antitumor agents. Cross-trial comparisons are virtually impossible in this setting due to the marked differences in trial design. Nonetheless, these data can be incorporated into a construct for treating patients with castration-resistant disease, as shown in Figure 1. In attempting to understand the cost burden associated with therapies for mCRPC, two approaches can be taken. First, each therapy can be considered independently. For instance, estimates related to sipuleucel-T suggest that the agent costs an approximate \$290,000 per quality adjusted life-year

(QALY).¹⁹ Although independently assessing the QALY associated with each agent certainly has merit, a second approach is to determine the cost associated with the sum of available therapies for mCRPC. Assuming that a patient with mCRPC is (a) exposed to each of the agents in this algorithm and (b) receives the median number of cycles of each agent rendered in pivotal studies, the total cost of therapy would be roughly \$181,000 (US). Of note, this estimate does not incorporate the cost of docetaxel, which has recently been made available in a generic form. Additionally, the fate of radium-223 chloride remains to be decided, at least until formal presentation of this dataset. The cost of this modality will likely emerge if and when the agent gains approval. Perhaps most importantly, it is critical to note that this estimate does not include the expense of supportive modalities that accompany each of these treatments. In the case of cytotoxic therapies such as docetaxel and cabazitaxel, use of growth factor support and hospitalizations for treatment-related complications may add substantial cost. Although the side effect profile of sipuleucel-T may compare favorably, additional expense may occur due to issues related to leukapheresis (i.e., catheter placement and catheter-based complications). Distribution of sipuleucel-T has also been an issue during the infancy of this approval – transportation to sites that provide the vaccine represents a direct-to-patient cost. Albeit orally administered and quite tolerable, abiraterone does not come without associated expense. Frequent laboratory monitoring and office visits (up to twice monthly when initiating the medication) are recommended. Finally, an overarching consideration relevant to all recently approved therapies for mCRPC is their net effect on longevity. As the lifespan of the patient with mCRPC increases, so will the duration of androgen deprivation therapy in patients who are managed with pharmacologic castration. Likewise, supportive care modalities (i.e., pain medications and bone-directed therapies such as zoledronic acid and denosumab) will also be used in a more extended fashion.¹⁷

Sources of overestimation in this scenario are quite obvious – as one example, not every patient will receive each of the approved therapies. For instance, patients may present with symptomatic metastatic disease, and may therefore not be ideal candidates for sipuleucel-T. Furthermore, as patients work their way through the proposed algorithm, their performance status is subject to decline, precluding the use of “downstream” agents. Finally, it is critical to account for patient preference – many practitioners can produce anecdotes of patients refusing cytotoxic therapy after a thorough discussion of risks and benefits. Similarly, patients may balk at the labor-intensive process required to generate autologous vaccines, such as sipuleucel-T. Transportation to and from pheresis centers at specific intervals may prove challenging for those patients with limited social support.

The estimates provided herein are intended primarily to highlight a conundrum in treating mCRPC. With a plethora of therapies currently available to the urologist and oncologist, when does the cumulative cost of these treatments become prohibitive? The available data reflects strong public sentiment favoring increased access to novel mCRPC therapies. For instance, the US Center for Medicare Services (CMS) requested public comments regarding the coverage status of sipuleucel-T – of 657 public comments received, 620 (94.4%) favored extending coverage to this modality.²⁰ Acknowledging this sentiment, the onus falls on the public and their elected officials (at least in part) to devise appropriate means of financing these agents. Although Medicare and Medicaid budgets continue to rise, in the current fiscal climate, a plateau in expenditures is destined to occur in coming years.²¹ When this happens, CMS may have little recourse but to limit expenditures by capping lifetime costs or withholding payments unless criteria for treatment are clearly met. With accountable care organizations (ACOs) lurking in the midst, government and PhRMA may have to form an alliance to prevent the collapse of the current healthcare system due to costly novel therapies.²²

Acknowledgments

Dr. Pal's efforts are supported by the NIH Loan Repayment Plan (LRP), the CBCRP 15IB-0140 (California Breast Cancer Research Program Junior IDEA Award) and NIH K12 2K12CA001727-16A1. The City of Hope Renal Cell Carcinoma Program is also supported by Kure It, Nancy and Ira Norris, the Hoeven family and Richard and Nancy Bloch Kidney Cancer Research Funds.

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Figure 1.

Projected algorithm for sequencing US FDA approved agents for mCRPC. Note that novel antitumor agents are typically used concomitantly with bone-directed therapies (i.e., zoledronic acid or denosumab) and leutenizing-hormone releasing hormone (LHRH) agonists.

Table 1

Recent positive phase III trials in mCRPC and estimated cost of therapy.²³

Agent	ΔOS	OS HR	Median No. of Cycles	Estimated Cost per Cycle	Total Cost
Abiraterone	3.9	0.65	8	\$5,000	\$40,000
Cabazitaxel	2.4	0.70	6	\$8,000	\$48,000
Denosumab	--	--	13	\$1,650	\$21,450
Radium-223 chloride	2.8	0.70		**	**
Sipuleucel-T	4.1	0.77	3	\$31,000	\$93,000

(Note: ΔOS = improvement in OS observed with the agent as compared to its comparator in pivotal phase III studies; OS HR = hazard ratio for OS for the agent as compared to its comparator in pivotal phase III studies; Total cost = the median number of cycles rendered in pivotal studies of the agent × the cost per cycle of therapy;

* Data not publicly available;
** Agent not yet approved for use.)