Overview: Much progress has been made in metastatic castration-resistant prostate cancer (CRPC), and multiple new U.S. Food and Drug Administration (FDA)-approved survival-prolonging drugs are now available. In 2004, docetaxel/prednisone was the first therapy shown to prolong survival. In 2010 and 2011, sipuleucel-T, cabazitaxel/prednisone, and abiraterone/prednisone were FDA approved. Two new agents, radium-223 and MDV-3100, have recently reported large phase III trials prolonging overall survival and will be submitted for regulatory approval in 2012. One can now begin to ask, is there an optimal sequence for therapies in metastatic CRPC? Despite the recent progress, there is much we do not know and virtually no information on this important question. We know that abiraterone/prednisone and cabazitaxel/prednisone are appropriate choices for a patient after receiving docetaxel, but we do not know what, if anything, represents the optimal sequence for abiraterone and cabazitaxel. In fact we do not understand how one therapy may affect the response to a subsequent therapy. We are also aware that the pre- and postdocetaxel spaces represent regulatory rather than biologic divisions. In addition, despite the proven role of docetaxel/prednisone, many patients with CRPC are not considered to be suitable for chemotherapy, and worldwide many never receive any form of chemotherapy. What is the optimal management for these patients? Taken together it is reasonable to assess patient preferences, prior therapies and response/tolerance to prior therapies, burden of disease, comorbidities, current symptoms, drug toxicities, out-of-pocket costs, etc., in clinical decision making. Given the many factors we do not know, it is hard to be dogmatic in approaching the therapeutic options for the patient with CRPC. We will likely soon move beyond the current sequencing paradigm and begin to assess new combinations in a systematic and rational fashion. Perhaps one day, in the not too distant future, we will develop molecular “stratification systems” to better guide therapeutic choices in CRPC.

The last several years have seen extraordinary progress in the management of patients with CRPC, with multiple FDA approvals for agents that extend patients’ overall survival. In addition there are several anticipated FDA approvals that might occur in 2012. From a perspective of understanding the current state of affairs, I would first like to review the history of FDA approvals for patients with metastatic CRPC. As seen in Fig. 1, all the FDA drug approvals that occurred before 2004 involved endpoints other than overall survival. In 2004, the combination of docetaxel/prednisone was approved on the basis of a prolongation in survival (as compared with mitoxantrone/prednisone), using data from the pivotal TAX327 study. A separate study with docetaxel in 2004 (SWOG 9916), using docetaxel/estramustine, also demonstrated superior survival in comparison to mitoxantrone/prednisone. Because of the importance of these findings, from both a pragmatic and regulatory perspective, the post-2004 world of metastatic CRPC began to be divided into patients who had or had not received prior docetaxel.

For the next 6 years, no substantial progress was made in prolonging survival in metastatic CRPC. Since 2010, rather remarkably, there have been four new FDA approvals and three of these have involved agents that prolong survival. Unlike a number of other diseases, the underlying mechanisms for these agents are distinct with a novel immunotherapy termed sipuleucel-T, a novel taxane called cabazitaxel, and novel hormone therapy in the form of abiraterone prolonging survival in various pivotal phase III randomized trials. Two of these agents were FDA approved in the postdocetaxel setting (cabazitaxel/prednisone and abiraterone/prednisone). No comparisons between any of these agents have been performed and no direct comparison between docetaxel/prednisone plus an additional agent has ever proven superior to docetaxel/prednisone alone.

A number of trials have tried to improve on docetaxel/prednisone but none have succeeded. Combinations of docetaxel and DN-101 (calcitriol), GVAX, bevacizumab, atrasentan, zibotentan, and lenalidomide all have failed in phase III trials against docetaxel/prednisone. Dasatinib, aflibercept, and custirsen are in current combination trials with docetaxel/prednisone, and in each case the control arm is docetaxel/prednisone. These agents target the src kinase (dasatinib), vascular endothelial growth factor (aflibercept), and clusterin (custirsen), and each of these targets are supported by preclinical data in various systems. Whether or not these combinations will be an improvement on the current standard of care is unknown at the time this was written, but some results may be available during the 2012 ASCO Annual Meeting. Both the dasatinib and aflibercept trials are fully accrued and awaiting maturation of survival data at this time. The trial with custirsen is still accruing as of spring 2012.

One trial is going head to head with docetaxel/prednisone. That trial will compare cabazitaxel/prednisone (two doses of cabazitaxel are being tested, 20 or 25 mg/m²) compared with docetaxel/prednisone. The primary endpoint is overall survival. This trial (FIRSTANA) is currently accruing patients. In 2011 and early 2012, two new agents have resulted in prolonged survival in large phase III trials. These agents include the novel targeted alpha-particle emitter radium-223 and a novel antiandrogen MDV-3100. Taken together there are now six agents that have prolonged survival in phase III trials conducted in metastatic CRPC (Fig. 2).

As noted above, the disease state for these therapies has varied. For instance, sipuleucel-T is indicated for use in the asymptomatic or minimally symptomatic metastatic CRPC.
state. The eligibility requirements for the phase III trials with MDV3100, cabazitaxel, and abiraterone all required docetaxel pretreatment. The radium-223 study was unique, though the majority of patients had received prior docetaxel, the trial was also open to patients with bone-metastatic CRPC, patients who were not deemed ineligible for docetaxel, and for those patients who refused docetaxel. This is the first trial to evaluate this group of patients. Because not all patients with metastatic CRPC go on to receive docetaxel, this is an important group of patients to include in prospective studies.

There are several questions about the management of the patients with metastatic CRPC. The first is a very practical one: is there an optimal sequence for the FDA-approved therapies? Is there a proper way to pick the right therapy for the right patient at the right time? Is there any way to risk stratify patients to maximize their opportunity for response? The short answer to these reasonable questions is that we are poorly informed on what might constitute an optimal sequencing strategy for using new agents.

One can perhaps imagine that sipuleucel-T could be administered to a patient with small-volume asymptomatic disease, followed by docetaxel at progression, followed by cabazitaxel and/or abiraterone at progression. This would be a logical series. Despite the excellent logic of such an approach, there is very limited clinical data on patients that might be treated in this manner. We have reports of docetaxel following sipuleucel-T, and certainly that appears to be a safe combination, but we have no real data on abiraterone response rates postcabazitaxel or cabazitaxel response rates postabiraterone. Though MDV-3100 has yet to be approved by regulatory authorities, it is not too soon to ask what will be the activity of this agent postabiraterone (and vice versa). Will resistance to one of the newer hormonal therapies result in resistance to the other? We do not know.

At the same time that therapeutic decisions are made, it is an important reminder that a bone-targeted therapy, such as zoledronic acid or denosumab, might be integrated into the treatment regimen for appropriate patients. External beam radiation could be used to palliate focal pain on an “as needed” basis. Growth factors and various other supportive care options are also considerations in selected settings.

Taken together, there is little that we are certain of when it comes to optimal drug sequencing in this disease state. Further, the best choice of therapies—when choices clearly exist (such as the current postdocetaxel setting)—is not at all clear and one is simply left to conjecture. It is reasonable to assess patient preferences, prior therapies and response to prior therapies, performance status, pace of progression, burden of disease, comorbidities, tolerance/intolerance of prior therapies, drug toxicities, neuroendocrine status, and current symptoms in clinical decision making. It is also critical to understand the availability of clinical trials, patient compliance, travel distances, and out-of-pocket costs. Taken together, at this time, no simple algorithm can suffice when it comes to making clinical decisions, and any dogmatic approach to this problem cannot be justified.

We all realize that none of the therapies for CRPC to date are curative, and in my practice, I try to ensure that patients have the opportunity to be treated with as many of the active therapies as possible during the course of their disease. Our ability to predict who will and who will not respond to various therapies is poor, and many of my grateful patients have benefited from a treatment plan that was not judged a priori to have a high rate of success. Perhaps one day our molecular markers will guide us to the right choice of

KEY POINTS

- Patients with metastatic castration-resistant prostate cancer (CRPC) have more options than ever before, including new agents that have been shown to prolong survival.
- New Food and Drug Administration–approved agents for CRPC that prolong survival include sipuleucel-T, cabazitaxel, and abiraterone, and more are on the way.
- Optimal choices and sequences are much discussed in CRPC but comparative data are absent; thus, dogmatic views of sequences are inappropriate.
- Patient preferences, current symptoms, responses and tolerance of prior therapies, pace of the disease, burden of disease, drug toxicities, performance status, comorbidities, out-of-pocket costs, compliance, and various clinical trial options are some of the choices that guide practical considerations in treatment management.
- Combination therapies are beginning to be explored in a systematic fashion.
therapy at each juncture, but today we are often humbled by how poorly we predict patient outcomes.

What about combination therapy? Is the metastatic CRPC state to be restricted to a sequencing therapeutic paradigm? Though combination therapy has a certain attraction in CRPC, other than the agents designed to inhibit skeletal-related events (zoledronic acid and denosumab), there are minimal data on combination therapies using the survival-prolonging agents. Until new data exist, the current sequencing paradigm may be optimal for patients in nonclinical trial settings.

It is clear from phase I/II studies that patients with nondocetaxel-pretreated metastatic CRPC are quite responsive to the newer hormonal agents, such as abiraterone and MDV-3100.9,10 This emphasizes that our division of metastatic CRPC into pre- and postdocetaxel spaces is one based on regulatory and not biologic concerns. Trials are ongoing to further assess both abiraterone and MDV-3100 in the predoctaxel space and perhaps there will be results from one of these trials by the 2012 ASCO Annual Meeting.

All of the FDA-approved agents to date have been approved in a metastatic CRPC setting, yet many patients present to a physician with a rising prostate-specific antigen, a castrate level of testosterone, and no radiographic evidence of metastatic disease. What do you do in this case? The answer is not yet clear and there are no FDA-approved treatments. In my practice, a variety of secondary hormonal agents, such as nilutamide, bicalutamide, low-dose diethylstilbestrol, and ketoconazole are used despite no phase III evidence to support their use. Good clinical trials are always an important consideration as well.

**Author’s Disclosures of Potential Conflicts of Interest**

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