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Urologists and oncologists: adapting to a new treatment paradigm in castration-resistant prostate cancer (CRPC)

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The treatment landscape for men with castration-resistant prostate cancer (CRPC) is undergoing significant changes; a redefinition of the respective roles of oncologists and urologists will probably occur. In addition, the advent of the multidisciplinary team or coordinated-care approach, which has been gathering momentum over the last decade, will become not simply a preference but a clear necessity. In the present review, we explore the current wave of new treatments and describe the possibility of more complex approaches to combined therapy. New treatment options include abiraterone acetate, cabazitaxel, MDV3100 (in development), radium-223 (in development) and sipuleucel-T. We also present the traditional roles of the urologist and oncologist in caring for patients with CRPC and discuss how these may change. Compounding the new potential for treatment success, as well as the complexity of therapeutic strategies, is the emergence of novel biomarkers to evaluate treatment efficacy and to assist in patient prognosis. The prospects for successful treatment of patients with CRPC have developed considerably so that these patients may soon have a reasonable expectation of therapeutic efficacy and meaningful extension of their lives.

What's known on the subject? and What does the study add?
The interplay between urologists and oncologists in the treatment of prostate cancer has been long standing. Recent paradigm shifts in treatment are reviewed with an emphasis on how these treatments may eventually alter the dynamic equilibrium between urology and oncology specialists.

KEYWORDS

castration-resistant prostate cancer, urologist, oncologist, review, combined therapy

INTRODUCTION

The most common (non-skin) cancer in men in the USA and Europe is prostate cancer [1,2]. Additionally, mortality associated with this disease is the second and third highest of all cancers in these two populations, respectively [1–3]. Within the larger group of men with prostate cancer, there exists a subset of individuals who will require androgen-deprivation therapy (ADT). Although ADT is effective in lowering PSA in most men, the therapeutic response will eventually wane and the disease will progress at some point. For many years, development of new therapies and new treatment strategies were slow to emerge for prostate cancer in general and for castration-resistant prostate cancer (CRPC) in particular. However, that has changed in recent years with the emergence of various new agents accessing several different mechanistic disease pathways. Together with these expanded options for treatment has arisen a commensurate need to redefine both therapeutic strategies and the roles of practitioners from different specialties as well.

As is often the case with the treatment of various diseases and conditions, the type of physician from whom a patient seeks treatment may affect the therapeutic strategy that is implemented on their behalf. This fact is exemplified in a 2009 study from Germany in which urologists and radiological oncologists were surveyed to determine their preferences for treatment should they themselves receive a diagnosis of localised prostate cancer. The authors found that urologists in the survey were significantly more likely to prefer a surgical intervention as opposed to radiological oncologists, who preferred radiotherapy [4]. Similar reports of various prejudices in treatment have been reported from analyses of databases in the USA [5].

In the case of CRPC, the development of treatment options from virtually none to potentially several may result in the application of differing treatment strategies based on whether the treating physician is a urologist or an oncologist. Personal experience suggests that while typical oncologists are more predisposed to i.v. therapies, urologists often favour oral therapies. However, the more immediate impact on treatment is likely to be seen in the ways that urologists and oncologists work together in a changing treatment landscape that is becoming more complex. The present article will examine the changes in the treatment paradigm for CRPC and how this may affect the respective roles of urologists and oncologists.

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PREVIOUS TREATMENT OPTIONS

Until 2004, when the efficacy of docetaxel-based chemotherapy to increase survival in patients with CRPC was first shown, standard care after the failure of ADT was typically limited in its goals to improving palliative endpoints [6–8]. This palliative care primarily focused on alleviating pain, maintaining the best possible health-related quality of life (HRQL), and, when possible, extending survival [8]. Radiation therapy is a well-established component of palliative treatment for metastatic CRPC (mCRPC). External beam radiation may be used to treat painful sites that can be targeted in a single radiation field whereas systemic radioisotopes are more often used for multiple painful sites, with strontium-89 and samarium-153 being the isotopes most frequently used [9].

The respective roles of urologists and oncologists in the palliative setting have been to a large extent distinct and delineated, although the roles in the USA and in certain European countries differ to some extent. Typically, urologists have been responsible for urinary tract issues and local symptoms including dysfunctions of the male reproductive system. They often treat prostate cancer up to and through hormonal therapy, and surgical intervention has always been their domain. The responsibilities of oncologists in palliative care have been determined by a given physician's particular oncological specialty. The medical oncologist has usually, if not always, been responsible for chemotherapy, while radiation oncologists have generally undertaken radiation therapy (in some European countries, such as Germany, urologists provide chemotherapy to patients with CRPC). In general, oncologists are responsible for bone pain in patients with mCRPC. This pain is the most common source of discomfort and degradation of HRQL in this setting [10,11]. Oncologists and urologists are also both responsible for working with their patients to select and coordinate the application of additional therapies that may prolong survival.

The emergence of docetaxel as an effective therapy, and the development of a new generation of agents for patients with CRPC, including those who have failed docetaxel, have altered the treatment paradigm for this patient population and, consequently, affected the respective roles of urologists and oncologists as they have begun to adapt to the new treatment landscape. Even before the positive survival data from the docetaxel studies, some urologists expressed an interest in taking a larger responsibility for the provision of chemotherapy in patients with CRPC. A 2003 survey of urologists who treated patients with CRPC found that while only 4% offered their patients i.v. chemotherapy (and less than one-third referred their patients to oncologists), nearly 48% of respondents expressed a high degree of interest in learning about chemotherapeutic regimens [12]. The fact that this survey was conducted at a time when clinical trial data suggested only limited efficacy for chemotherapy further indicates the possibility of even greater interest in chemotherapy among urologists at present.

From 2004, the new survival data began to change the standard of care for chemotherapy, although the impact on actual treatment was slower to materialise. Given the 2010 emergence of two additional agents that have shown efficacy in providing patients with better palliation and in extending survival, the standard of care has now shifted once again [13,14]. These agents will be discussed further below.

TREATMENT OPTIONS BEFORE 2010

Since the publication of the 2004 docetaxel efficacy data, the standard treatment in patients with mCRPC for whom hormonal therapy no longer is effective has been docetaxel-based chemotherapy plus prednisone [15]. Even before the publication of these data, a multidisciplinary approach to treating patients with CRPC had become ever more the focus of practitioners as reflected in the many articles published on the subject. The ways in which this cooperative model has been applied to docetaxel therapy in patients with mCRPC, and been primarily contingent upon communication between urologists and oncologists, revolve around two key therapeutic decisions (beyond the decision of appropriate patient selection): when to initiate therapy and when to discontinue it.

For initiating docetaxel therapy, the updated 2010 clinical treatment guidelines produced by the European Association of Urology advocate the introduction of chemotherapy after all reasonable trials of hormonal therapy have been exhausted [16]. At a minimum, this would amount to two rounds of hormonal therapy, although multiple considerations may be applied to the decision of when to start chemotherapy, including the patient's overall health and co-morbidities. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology advocate more than one round of hormonal treatment before determining failure of hormonal response [17]. When secondary hormonal therapy has been discontinued, the NCCN guidelines recommend docetaxel-based chemotherapy as the preferred chemotherapeutic option based on Level 1 Evidence [17]. Primary treatment with LHRH agonists or antagonists are recommended to continue in CRPC.

The presence of pain or lack thereof, is one factor in determining when to initiate chemotherapy. Several clinical trials in men with CRPC, including the TAX 327 trial, have shown that pain at baseline is associated with worse outcomes after chemotherapy as well as a shorter period of overall survival (OS) [18–21]. These data would tend to encourage initiating chemotherapy while patients are asymptomatic and possessing a lesser disease burden; however, this must be balanced with the realities of additional therapeutic-induced adverse events (AEs) to asymptomatic patients. The TAX 327 data showed that asymptomatic patients and those with less disease progression achieved greater treatment benefit with early chemotherapy in terms of OS than symptomatic patients and those with greater disease burden [18,21] (Fig. 1).

Despite the advantages in survival with earlier chemotherapy, the potentially serious AEs associated with chemotherapy often prevent its premature use. These AEs include asthenia, oedema, peripheral neuropathy, nail changes, anaemia, and neutropenia [7,22]. The impact of AEs and the response to therapy influences the decision of when to start and when to stop chemotherapy treatments. In practice, the choice to begin chemotherapy is dependent on the alternative therapeutic choices available to the patient diagnosed with mCRPC. For patients who have exhausted alternatives, starting chemotherapy may represent the

best choice. Patients with additional secondary hormonal options may choose those instead of starting chemotherapy. For USA patients with metastatic but asymptomatic or minimally symptomatic disease, treating with the newly approved autologous immunotherapy (sipuleucel-T) may represent an option they may wish to consider. For patients with focal pain, external beam radiation may be a good choice. In the end, starting chemotherapy is a decision between the physician and patient after considering the risks, benefits, and various alternatives.

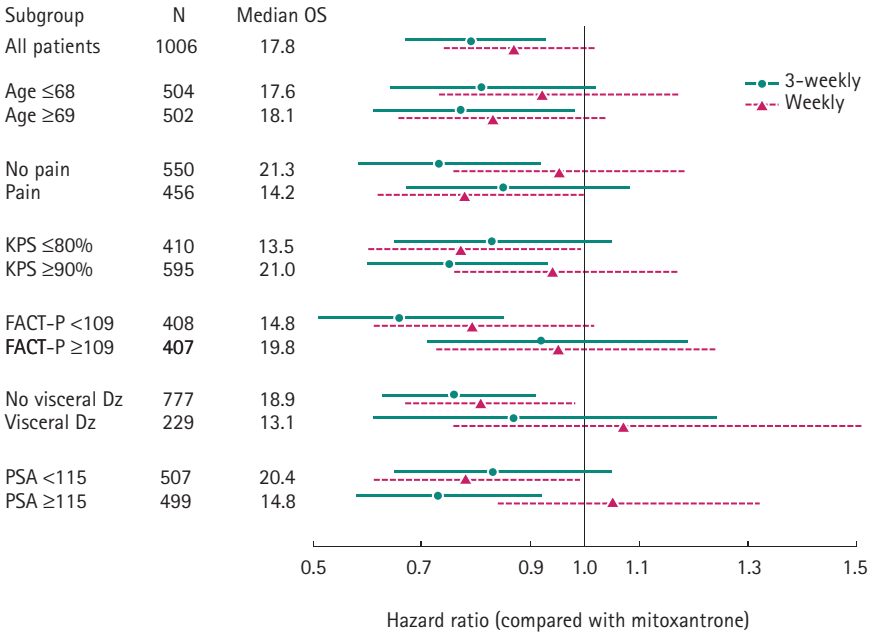
Cessation of chemotherapy also requires an assessment of the risks, benefits, and alternatives. The risks of chemotherapy administration to an individual can typically be assessed accurately after 3–4 cycles are administered. The presence of toxicities may result in deconstruction of chemotherapy altogether, but toxicities may also be mitigated by intermittent use so as to allow the resolution of side-effects [22]. Although intermittent chemotherapy is widely used in the practical management of CRPC, efficacy in specific patient populations and criteria for treatment selection have yet to be elucidated in large clinical trials. Ultimately, deciding how to best balance the potential benefits of chemotherapy with the risk of AEs involves an acknowledgement that not all patients will actually gain significant therapeutic benefits [7,18].

Oncologists may be more inclined to initiate early chemotherapy compared with urologists, in part because it is a key element in their armamentarium, but also because they are often involved in pain management and thus may be more aware of the patients' potential pain status. Awareness that OS benefit with chemotherapy is more likely to occur with early treatment initiation may be a fundamental driver in the oncologist's preference to use chemotherapy.

Ultimately, each patient must be evaluated based on their specific presentation. The variability in chemotherapy response between different patients is based on several different factors, and so the risks and benefits of therapy must be individualised as much as possible, matching the treatment to the patient and to optimal timing, the 'right patient, right treatment, right time'. In fact, not only must the current disease status be taken into consideration when determining the appropriateness and timing of chemotherapy, but also the presenting symptoms, co-morbidities, previous treatments, prior responses, the rate of disease progression, location of pain, and available alternative therapies. With the introduction of new agents, moreover, the possibility of using a different treatment before or after docetaxel therapy is now a reality, and a potential area of debate between oncologists and urologists.

There can be no overall statement about whether an oncologist or a urologist should, *in general*, take charge of a patient with CRPC. Ideally, the team approach allows for the development of an initial patient-specific treatment strategy and an understanding of which specialist would be most appropriate to provide a given treatment within that strategy. The team approach would further allow for revisiting the strategy at appropriate intervals, whereupon a decision would be made about the need to continue or revise the strategy. Where a change of strategy, or therapy, is agreed upon, this may also involve a change in the specialist providing treatment. In any given case, it maybe that a patient is largely under the care of an oncologist or a urologist, or the patient may need to move between specialists as their disease status develops.

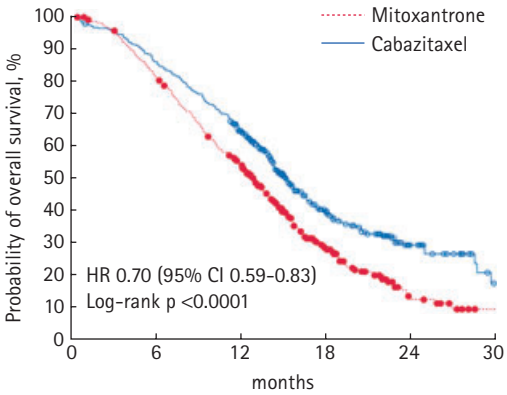
FIG. 1. Effect of baseline disease and symptom status on survival among patients in the TAX 327 Trial. The 30-week TAX 327 trials involved 1006 men with CRPC randomised to one of three treatment groups: docetaxel 75 mg/m2 every 3 weeks, docetaxel 30 mg/m2 weekly 5 weeks out of 6 weeks, and mitoxantrone 12 mg/m2 every 3 weeks. Patients in all three groups also received prednisone 5 mg twice daily [18]. Reprinted from the Journal of Clinical Oncology: Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26: 242–6. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. OS in months (median OS column describes survival in subgroups independent of treatment); KPS, Karnofsky performance status; FACT-P, Functional Assessment of Cancer Therapy–Prostate; Dz, disease.



NEW TREATMENT OPTIONS

Several new and emerging therapies for patients with CRPC have fundamentally altered the treatment landscape. These new treatment options include, among others, a new cytotoxic agent, immunotherapy, and androgen receptor-signalling inhibitors. While it is beyond the scope of the present article to assess all of these agents' efficacy and safety in detail, we will discuss several new and emerging agents for their impact on the CRPC treatment paradigm.

FIG. 2. Kaplan–Meier estimate of OS for patients with CRPC receiving cabazitaxel or mitoxantrone in the TROPIC trial. Probability of survival in all patients randomly assigned to treatment with cabazitaxel plus prednisone or mitoxantrone plus prednisone [13]. Reprinted from The Lancet: de Bono, JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147–54. Copyright (2010), with permission from Elsevier.



Number at risk						
Mitoxantrone	377	300	188	67	11	1
Cabazitaxel	378	321	231	90	28	4

CABAZITAXEL

Cabazitaxel is a novel taxane agent that was recently approved by the USA Food and Drug Administration (FDA) as a second-line agent combined with prednisone for patients with mCRPC who have undergone previous docetaxel-based therapy [23]. It is the first and only cytotoxic agent to show OS benefit in patients with mCRPC after docetaxel. In pre-clinical models, the agent was as potent as docetaxel in cell lines and showed antitumor activity in models resistant to paclitaxel and docetaxel [24–26]. Cabazitaxel also effected complete regression and long-term survival against prostate, head and neck, and pancreatic human tumours in murine xenografts using an intermittent dosing schedule [27].

The approval of cabazitaxel was based on the results of the phase III TROPIC trial, which compared daily i.v. cabazitaxel 25 mg/m^2 plus prednisone 10 mg with i.v. mitoxantrone 12 mg/m^2 plus prednisone 10 mg in 755 men with CRPC at 146 treatment centres in 26 countries [13]. The median follow-up was 12.8 months for both treatment groups. The primary endpoint, OS, was significantly longer in the cabazitaxel group: 15.1 months (95% CI 14.1–16.3) vs 12.7 months (95% CI 11.6–13.7), which corresponds to a 30% relative risk reduction for mortality (hazard ratio [HR] 0.70, 95% CI 0.59–0.83, $P < 0.001$; Fig. 2) [13]. The PSA response rate (defined as reduction in serum PSA concentration of ≥50% in patients with a baseline value of ≥20 μg/L) for cabazitaxel was 39.2% vs 17.8% for mitoxantrone ($P < 0.001$) [13]. The tumour response rate (for patients with measureable disease per Response Evaluation Criteria In Solid Tumors) was 14.4% for cabazitaxel vs 4.4% for mitoxantrone ($P < 0.001$), while progression-free survival as a composite endpoint also significantly favoured cabazitaxel- over mitoxantrone-treated patients (2.8 months vs 1.4 months, $P < 0.001$). The time to PSA progression was 6.4 months in the cabazitaxel group and 3.1 months in the mitoxantrone group ($P < 0.001$) [13].

For AEs, the TROPIC trial investigators reported neutropenia to be very common in both groups, but notably more so in the cabazitaxel group (82% vs 58% for grade ≥3). Among these patients, 1% of the mitoxantrone group and 8% of the cabazitaxel group had grade ≥3 febrile neutropenia. Leukopenia was also common in both treatment groups, and more so among cabazitaxel-treated patients (68% vs 42% for grade ≥3). Grade 3 peripheral neuropathy was uncommon, occurring in 1% of patients in each group and Grade ≥3 diarrhoea was encountered in 6% of the cabazitaxel-treated patients [13].

Viewed as a whole, the AE profile of cabazitaxel reported in TROPIC, although not markedly different from other taxane agents (with the exception of high-grade peripheral neuropathy, which was very rare in TROPIC), can be managed appropriately. However, the frequent occurrence of neutropenia does suggests that the use of granulocyte colony-stimulating factor may be necessary in patients aged > 65 years and others at high risk for febrile neutropenia.

While the role cabazitaxel in therapy is currently defined as a second-line option after docetaxel failure, it is possible that this might change in the future. A multicenter open-label study, the FIRSTANA study, has been initiated to directly compare the relative efficacy of cabazitaxel (at two different doses) compared with docetaxel for OS in chemotherapy-naïve patients with mCRPC [28]. At the same time, a second open-label trial in patients with mCRPC is currently underway with cabazitaxel at its currently approved dose (25 mg/m^2) compared with a lower dose (20 mg/m^2), to determine whether efficacy would be maintained at the lower dose while reducing some of the tolerability issues [29]. Should a lower dose prove to be effective and associated with fewer AEs, the prospects may increase for cabazitaxel to play an earlier role in the developing mCRPC treatment paradigm.

ABIRATERONE ACETATE

The agent abiraterone acetate is a CYP17 inhibitor notable for blocking androgen synthesis in the adrenal glands, testes, and prostate while avoiding adrenal insufficiency [30]. Abiraterone, combined with prednisone, was approved by the FDA in April 2011 to treat patients with late-stage mCRPC who have previously received docetaxel therapy [31]. As an orally administered agent, abiraterone offers the advantage of significant convenience. As a hormonal agent, it offers less toxicity than chemotherapy.

The approval of abiraterone in mCRPC was largely based on the results of a clinical trial of abiraterone (1000 mg/day) plus prednisone (5 mg twice daily) compared

with placebo, randomised 2:1, in 1195 patients with mCRPC who had had disease progression after receiving docetaxel-based chemotherapy [14]. The study was conducted at 147 centres in 13 countries and had a median follow-up of 12.8 months. The median duration of treatment was 8 months in the abiraterone acetate group vs 4 months in the placebo group. Abiraterone-treated patients had significantly improved OS, the primary endpoint. The median OS was 14.8 months in the abiraterone acetate group and 10.9 months in the placebo group. The significance of treatment effect on OS was robust after adjustment for stratification factors in a multivariate analysis (HR for death 0.66, 95% CI 0.55–0.78, $P < 0.001$) [14]. The effect on OS was consistent across all subgroups.

In addition, treatment with abiraterone was associated with significantly improved time to PSA progression compared with placebo (10.2 months in the abiraterone group vs 6.6 months in placebo group [HR 0.58, 95% CI 0.46–0.73, $P < 0.001$]), improved radiographic progression-free survival (5.6 months in the abiraterone group vs 3.6 months in placebo group [HR 0.67, 95% CI 0.59–0.78, $P < 0.001$]), and improved total PSA response rate (38.0% in the abiraterone group vs 10.1% in placebo group [$P < 0.001$]) [14].

Common treatment-related AEs in the study included fluid retention and oedema (31% abiraterone vs 22% placebo) and hypokalaemia (17% abiraterone vs 8% placebo), but these events were largely Grades 1 and 2 [14]. There were liver function test abnormalities in 10% of abiraterone-treated patients compared with 8% of placebo-treated patients, and cardiac disorders in 13% vs 11% of abiraterone and placebo patients, respectively. A phase II study of abiraterone in chemotherapy-naïve patients, published in 2010, showed promising results for antitumor activity [32], and a phase III trial in chemotherapy-naïve patients is currently underway [33].

The potential for AEs associated with treatment is an area of concern in attempting to formulate an optimal treatment strategy for the use of abiraterone in patients with CRPC. Further, little is known about treating CRPC after abiraterone failure, and patients for whom abiraterone is not efficacious may be distinct from patients previously studied. That said, the possibility that patients may be able to move directly to abiraterone therapy after hormone treatment failure before or instead of chemotherapy, should the phase III trial in chemotherapy-naïve patients prove successful, represents an alternative treatment strategy and one that may be particularly attractive to urologists. Should abiraterone be found to possess comparable survival benefit to docetaxel, assumptions about the relative role of chemotherapy in mCRPC might shift. That is not to say that the need for chemotherapy would be obviated, but rather that patient selection for appropriate treatment after failure of conventional hormonal therapy would probably require a more sophisticated analysis based on determining which patients would be more likely to respond to the available treatments, chemotherapy or otherwise, and even, for example, whether certain chemotherapeutic options would be associated with better outcomes in patients with particular disease profiles. However, this concept will need to be established via prospective clinical trials.

It is worth noting, in this context, that one of the barriers to smooth cooperation between urologists and oncologists is the concern among the former that when they transfer primary care responsibility to an oncologist they are losing control of their patient's treatment [34]. Thus, the potential for treating patients with abiraterone before chemotherapy may be an attractive proposition to urologists, in that it would provide patients with a potentially effective treatment while still maintaining the urologist's primary therapeutic responsibility. Still, if this treatment strategy proves to be viable based on forthcoming phase III data, there may yet be other considerations that need to be resolved before choosing abiraterone before chemotherapy. One such consideration is whether the efficacy of abiraterone administered before chemotherapy would be sufficiently high to justify the choice. Once again, customising treatment to the particular needs of individual patients, assessing risk and benefits, and understanding therapeutic alternatives all play an important role in choosing the right treatment strategy for the right patient at the right time.

MDV3100

MDV3100 is an orally delivered androgen receptor antagonist that prevents nuclear translocation of the androgen receptor and its DNA binding [35]. A phase I/II study in 140 patients with mCRPC took place at five USA study centres [36]. Patients were assigned to one of seven doses ranging from 30 mg daily to 600 mg daily, and all patients receiving the two higher doses had previously had disease progression while on chemotherapy [36]. MDV3100 showed antitumor activity and stable disease in soft tissue as well as stable disease in bone to varying degrees at all doses [36]. A phase III trial in ≈1200 patients diagnosed with CRPC who have failed docetaxel-based treatment has recently reported a survival benefit [37]. The occurrence of two or possibly three seizures in patients receiving higher MDV3100 doses in the phase I/II trial caused the study investigators to use a lower dose of 160 mg daily for the phase III trial [36,37]. If MDV3100 were to be approved by the FDA for the treatment of CRPC, its role in therapy remains to be determined, particularly in the context of second-line hormonal therapies. Interactions between abiraterone and MDV3100 have yet to be explored.

SIPULEUCEL-T

Sipuleucel-T is a vaccine-based immunotherapy in which autologous antigen-presenting cells are obtained from the patient, activated through co-culturing with a fusion protein consisting of granulocyte-macrophage colony stimulating factor and prostatic acid phosphatase, and infused into the patient to stimulate a T cell immune response [38]. Three phase III trials have been conducted with sipuleucel-T, all in asymptomatic or minimally symptomatic patients with mCRPC.

In the first phase III trial, 127 patients (115 of whom had progressive disease) were randomised to receive sipuleucel-T or placebo in a 2:1 ratio every 2 weeks over a 6-week period with a 36-month follow-up period [39]. At the end of the evaluation period, patients receiving sipuleucel-T had a median 4.5 month survival benefit compared with placebo ($P = 0.01$) [39]. In the second phase III trial, which had a similar design to the first, 98 subjects with mCRPC were randomised to sipuleucel-T or placebo [38].

Those patients treated with sipuleucel-T had a 20% survival benefit over 3 years compared with placebo. The third trial, the IMPACT study, involved 512 patients with asymptomatic or minimally symptomatic mCRPC randomised to receive three doses of sipuleucel-T or placebo in a 2:1 ratio every 2 weeks over a period of 4 weeks [40]. The median follow-up was 34.1 months, at the end of which time patients receiving sipuleucel-T had a 4.1 month survival benefit compared with those receiving placebo ($P = 0.03$) [40]. There was no benefit in terms of either response rate (≈1%) or progression-free interval [40].

Sipuleucel-T is the first immunotherapy to have shown an OS benefit in the treatment of CRPC. In fact, it is the first immunotherapy to show a survival benefit in an intent-to-treat analysis in any solid tumour randomised trial. In April of 2010, it was granted approval by the FDA with an indication for 'the treatment of asymptomatic or minimally symptomatic' CRPC [41]. It represents yet another option for urologists and oncologists in the treatment of CRPC, and its place in therapy will ultimately need to be determined based upon the limitations of its indication, the geographic confines of its approval, and its relative efficacy compared with other treatment options. However, it should be noted that as sipuleucel-T is only indicated for patients with less-advanced mCRPC, coordination between treating physicians will be particularly critical, as any delay in treatment could mean missing the window of opportunity of sipuleucel-T's utility. Still, for mildly symptomatic or asymptomatic patients with advanced metastatic disease, yet who remain on the earlier end of the spectrum, the preference for either sipuleucel-T or docetaxel will need to take into consideration the status of each particular patient to determine whether they would likely respond better to one or the other treatment. At present, the criteria for making such a determination is difficult as the clinical experience with sipuleucel-T is limited. As more clinical familiarity with sipuleucel-T is obtained and other newer mCRPC treatments accrue, optimising patient selection will become a more viable process. For now, the use of sipuleucel-T is somewhat limited, in that individualised preparation of the sipuleucel-T vaccine can only be conducted at a limited number of centres in certain countries, and the associated costs of sipuleucel-T treatment are high [42].

The desire to avoid using corticosteroids during or after sipuleucel-T is an issue that is much discussed among urologists and oncologists alike. Because abiraterone, docetaxel, and cabazitaxel are all co-administered with steroids, there are significant potential interactions between this novel immunotherapy and other therapies known to prolong survival in CRPC. It is worth noting that MDV3100 which has now shown a survival benefit post-docetaxel, does not require steroid co-administration.

OTHER KEY ISSUES

TARGETING MULTIPLE PATHWAYS

The above discussion is far from comprehensive in describing the multiple molecular pathways implicated in CRPC's complex manifestations and the emerging agents developed to exploit those pathways. In addition to cytotoxic agents; antiandrogen receptor agents; immunotherapies; various additional agents including endothelial receptor antagonists, radium-223, various tyrosine kinase inhibitors, oestrogens, bisphosphonates, an anti-clusterin agent (custirsen); and several other classes of immunotherapies as well as various compounds have shown potential efficacy in treating CRPC [35,38,43]. We should state that radium-223 has now demonstrated overall survival benefit in a randomized phase III trial [44]. Moreover, there exists the potential to apply combined therapies using agents that address different disease pathways simultaneously and thereby potentially produce greater efficacy than any single monotherapy. Achieving the clinical insight to succeed in such an endeavour will surely require the knowledge and efforts of a multidisciplinary team of practitioners so as to explore the relative and cumulative effects of the safety and efficacy of different agents.

BIOMARKERS

PSA has been the standard measure of treatment efficacy for many years, but has also long been understood to be a flawed measure given that a substantial proportion of patients with prostate cancer have low PSA levels; also, PSA levels can fluctuate unpredictably [38]. Several other potential biomarkers have been proposed as prognostic and efficacy indicators including serum clusterin, fluoro-dihydrotestosterone, and circulating tumour cells [36,45,46].

Identifying reliable biomarkers could have an enormous impact on the ways that CRPC therapies are used and how reliable they are, as well as answer several complex questions, including which agent(s) will be most effective for a given patient, how combined or sequential therapy might be applied for a given patient, and the most efficacious order and timing for administration.

CONCLUSIONS

The emergence of novel therapies for the treatment of mCRPC significantly expands the possibilities for improved outcomes and extended survival in this patient population. With this expansion of therapeutic opportunities arises a commensurate need to adapt standard therapeutic practice to meet the needs of patients and individualise the selection of their treatment. Part of this adaptation includes the need for integrated multidisciplinary teams in which oncologists, urologists, and other colleagues work together to formulate therapeutic strategies, monitor safety and efficacy, and adapt to new treatments as needed. The promise of an expanded armamentarium coupled with useful biomarkers will make the treatment of CRPC not only more effective but more complicated, requiring the clarification of the respective roles of urologists and oncologists, and perhaps an elaboration of the phrase 'right practitioner, right patient, right treatment, right time'. It is likely that there will be significant geographic variation. Vaccines and hormonal therapy may be within the purview of urology in some jurisdictions. Chemotherapy will, in all likelihood, be in the domain of the medical oncologists in most areas. The real key is not the specialist, but rather the circumstance, each patient receiving the best care at the most opportune time. It is the opinion of the authors that this may involve multiple therapies for the best possible outcome; indeed, it is our hope that each patient will receive all available active therapies that are appropriate, as that scenario is likely to be associated with the best outcome. Good

coordination between the various specialists involved in the patient's care is clearly necessary for optimal results.

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CONFLICT OF INTEREST

A. Oliver Sartor is a Consultant for Algeta, Amgen, Bayer, Bellicum, Bristol-Myers Squibb, Celgene, Dendreon, Exelixis, GSK, Johnson & Johnson, Medivation, Oncogenex, Sanofi-Aventis and Takeda, and has received grant/research support from Algeta, AstraZeneca, Bayer, Cougar, Johnson & Johnson, Sanofi-Aventis, Takeda and Exelixis. John M. Fitzpatrick has lectured at meetings organized by, or has sat on the advisory board of, Sanofi-Aventis, GSK, Janssen, Astellas, Orion, Hofman-La-Roche, Pfizer, Takeda and Millenium.

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Abbreviations: **ADT**, androgen-deprivation therapy; **(m)CRPC**, (metastatic) castration-resistant prostate cancer; **HRQL**, health-related quality of life; **NCCN**, National Comprehensive Cancer Network; **OS**, overall survival; **AE**, adverse event; **FDA**, USA Food and Drug Administration; **HR**, hazard ratio.