Current management of castrate-resistant prostate cancer

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ABSTRACT

Prostate cancer (PCa) is the most frequently diagnosed cancer in North America. Castrate-resistant PCa presents a spectrum of disease ranging from rising PSA levels in the absence of metastases or symptoms and despite androgen-deprivation therapy, to metastases and significant debilitation from cancer symptoms. Castrate-resistant PCa is usually suspected in patients with new symptoms on androgen deprivation therapy, with a rising PSA, or with new evidence of disease on bone scans or computed tomography scans. Institution of treatment and the choice of systemic or local therapy depend on a number of factors. This review discusses the various currently available treatments for patients with castrate-resistant PCa, from secondary hormonal manipulations to options for post-docetaxel systemic therapy.

KEY WORDS

Castrate-resistant prostate cancer, systemic treatment

1. INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed cancer in North America. It is the fourth most common cause of cancer death overall and the third most common cause of cancer death in men [1]. One in four men diagnosed with PCa eventually dies from the disease. Men with PCa that has recurred after local therapy or that has disseminated distantly usually respond to androgen deprivation therapy (ADT); however, despite this treatment, most patients eventually experience disease progression within a median of 18–24 months [2].

2. DISCUSSION

2.1 Definition of Castrate-Resistant Prostate Cancer

Castrate-resistant PCa (CRPC) is defined by disease progression despite androgen-deprivation therapy (ADT) and may present as one or any combination of a continuous rise in serum levels of prostate-specific antigen (PSA), progression of pre-existing disease, or appearance of new metastases.

Advanced PCa has been known by a number of names over the years, including hormone-resistant PCa (HRPC) and androgen-insensitive PCa. Most recently, the terms "castrate-resistant" or "castration-recurrent" PCa were introduced with the realization that intracrine and paracrine androgen production plays a significant role in the resistance of PCa cells to testosterone-suppression therapy [3].

In their second publication, the Prostate Cancer Working Group (PCWG2) defined CRPC as a continuum on the basis of whether metastases are detectable (clinically or by imaging) and whether serum testosterone is in the castrate range because of a surgical orchiectomy or medical therapy [4]. The resulting clinical-states model can be used to classify patients. Within the rising PSA states (castrate and non-castrate), no detectable (measurable or non-measurable) disease has ever been found. Alternatively, in the clinical metastases states (castrate and non-castrate), disease has to have been detectable at some point in the past, regardless of whether it is currently detectable.

Castrate-resistant PCa presents a spectrum of disease ranging from rising PSA levels without metastases or symptoms and despite ADT, to metastases and significant debilitation from cancer symptoms. Prognosis is associated with several factors, including performance status, presence of bone pain, extent of disease on bone scan, and serum levels of alkaline phosphatase. Bone metastases will occur in 90% of men with CRPC and can produce significant morbidity, including pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common, including anemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection.

2.2 Management of CRPC

2.2.1 Determination

Castrate-resistant PCa is usually suspected in patients with new symptoms on ADT, with a rising PSA, or with

new evidence of disease on bone scans or computed tomography scans. To determine the castrate-resistant state and to properly assign a clinical state, it is imperative that patients have a testosterone level drawn. If patients are non-castrate, androgen ablation therapy should be instituted or maximized. If patients have testosterone levels in the castrate range, the diagnosis of CRPC can be made.

2.2.2 Secondary Hormonal Manipulations

In patients who develop CRPC and who are relatively asymptomatic, secondary hormonal treatments may be attempted. To date, no study of secondary hormonal treatment has shown a benefit in terms of survival, but most trials have been smaller and heavily confounded by future treatments used. In patients treated with monotherapy using luteinizing-hormone releasing-hormone agonist or in those who have had an orchiectomy, total androgen blockade with testosterone antagonists such as bicalutamide can offer PSA responses in 30%–35% of patients [5,6].

For patients who have undergone total androgen blockade and are showing signs of progression, the anti-androgen may be discontinued in an attempt to obtain an anti-androgen withdrawal response, which can be observed in 20%–30% of patients. Other options may include a change to a different anti-androgen, such as nilutamide or flutamide, or the use of ketoconazole [7]. For all these modalities, transient PSA reductions have been reported in approximately 30% of patients.

Because the androgen receptor remains active in most patients who have developed castration-resistant disease, groups such as the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario's Program in Evidence-Based Care, and others recommend that ADT should be continued. Consequently, most if not all clinical trials of patients with CRPC have mandated continued ADT.

Novel agents that potently affect the androgen axis have recently been developed and have renewed the enthusiasm for effective hormonal manipulation. A phase III clinical trial in men with early CRPC that has recently completed accrual is looking at whether survival can be improved with prednisone and abiraterone acetate, a potent and irreversible inhibitor of CYP17 (a critical enzyme in androgen biosynthesis), as compared with prednisone and placebo [9–11].

2.2.3 Systemic Corticosteroid Therapy

Corticosteroid therapy with low-dose prednisone or dexamethasone may also offer improvements in PSA values or palliative outcomes in up to 30% of both symptomatic and asymptomatic men [8]. As a palliative measure, prednisone can be used to improve symptoms such as bone pain; it may also exert an anti-neoplastic effect on PCa cells themselves. The latter effect is most likely achieved by inhibition of adrenal androgen production through negative feedback inhibiting the secretion of adrenocorticotropic hormone. Other postulated mechanisms include the modulation of cellular growth factors and the downregulation of androgen receptor–dependent transcription.

Several studies have evaluated prednisone therapy in CRPC patients, although most of them address the symptomatic patient [12]. The PSA response rates, which are defined as a post-treatment decrease in PSA of 50% or more from baseline, have varied from 21% to 34%. In asymptomatic men, Heng and Chi reported a 22.4% response rate to prednisone (defined as a 50% or greater PSA decline) [13]. An additional 16.3% of patients had a PSA decline of less than 50%. In 90% of patients, no side effects were documented. Of all PSA responders, 27% had a time to progression of more than 1 year, and 45% did not require chemotherapy for the duration of the study.

2.2.4 First-Line Systemic Chemotherapy

Currently, only CRPC patients who have detectable macroscopic metastatic disease should receive systemic chemotherapy outside of a clinical trial. Patients with advanced PCa should be referred early to a medical oncologist and should optimally receive multidisciplinary care to maximize survival and optimize quality of life. Because any treatment for advanced disease remains palliative, patients with advanced PCa should be encouraged to participate in clinical trials.

Combined docetaxel (a taxane drug that induces polymerization of microtubules and phosphorylation of the Bcl-2 protein) and prednisone is currently considered the standard of care for men with CRPC and detectable metastatic disease, based largely on the simultaneous publication of two large randomized controlled trials comparing this combination with the previously established standard of mitoxantrone and prednisone [14,15]. Tannock *et al.* [15] randomized 1006 patients to one of three treatment arms: intravenous docetaxel 75 mg/m^2 every 3 weeks, intravenous docetaxel 30 mg/m^2 5 times weekly for 5 of 6 weeks, or control therapy with mitoxantrone. All patients also received oral prednisone 5 mg twice daily. Petrylak *et al.* [14] reported on 666 eligible patients randomized to docetaxel–estramustine or mitoxantrone–prednisone. In addition to dexamethasone pre-medication, patients in the docetaxel arm also received warfarin or acetylsalicylic acid as thrombosis prophylaxis during the course of the trial. Men in both trials had clinical evidence of metastases with or without symptoms and had undergone anti-androgen withdrawal response. Overall survival was the primary endpoint in both trials.

Tannock *et al.* reported improved survival with docetaxel (every-3-weeks dosing) compared with mitoxantrone–prednisone [median survival: 18.9 months vs. 16.5 months; hazard ratio (HR): 0.76; 95% confidence interval (CI): 0.62 to 0.94; two-sided

$p = 0.009$]. No overall survival benefit was observed with docetaxel given on the weekly schedule (HR: 0.91; 95% CI: 0.75 to 1.11; two-sided $p = 0.36$).

Petrylak *et al.* reported longer survival time with docetaxel–estramustine combination chemotherapy as compared with mitoxantrone (median survival: 17.5 months vs. 15.6 months; HR: 0.80; 95% CI: 0.67 to 0.97; two-sided $p = 0.02$). That trial also reported a median progression-free interval of 6.3 months versus 3.2 months (HR: 0.73; 95% CI: 0.63 to 0.86; two-sided $p < 0.0001$) favouring docetaxel–estramustine over mitoxantrone.

Pain response was assessed in both trials. Significantly more patients treated with docetaxel (every-3-weeks dosing) than patients receiving mitoxantrone achieved a pain response (35% vs. 22%, $p = 0.01$). A trend toward improved pain response was observed with the weekly schedule docetaxel as compared with mitoxantrone (31% vs. 22%, $p = 0.08$).

Quality-of-life response, defined as a sustained 16-point or greater improvement from baseline on 2 consecutive measurements, was higher with every-3-weeks (22% vs. 13%, $p = 0.009$) or with weekly-schedule docetaxel (23% vs. 13%, $p = 0.005$) than with mitoxantrone. In their trial, Petrylak *et al.* reported no difference in patient-reported pain relief between the arms and did not assess quality of life. In both trials, PSA response rates were also statistically significantly higher with docetaxel than with mitoxantrone. Measurable disease was present in 27% ($n = 412$) and 29% ($n = 196$) of patients in the two trials. Objective response rates for every-3-weeks docetaxel and mitoxantrone were 12% and 7% respectively. Petrylak and colleagues reported objective response rates of 17% and 11% favouring docetaxel–estramustine over mitoxantrone. The differences in objective response rate between the arms were not statistically significant in either trial.

Based on the results of those two trials, it is now recommended that, for men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m^2 administered intravenously every 3 weeks with 5 mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation, and quality of life [16].

Although patients in the two pivotal trials received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted, duration of therapy should be based on an assessment of benefit and toxicities. A rising PSA should *not* be the sole criterion for progression; assessment of response should incorporate clinical and radiographic criteria. The PCWG2 recommends a minimum exposure of 12 weeks for trials in the pre-chemotherapy or first-line chemotherapy setting, recognizing that declines in serum PSA, if they occur, may not do so for several weeks and that a robust PSA-based surrogate for clinical benefit has yet to be identified. Further, to avoid discontinuing a treatment prematurely, PCWG2 suggests erring on the side of continuing treatment in equivocal cases in which there is no clear evidence of either progression or clinical deterioration and in which patient safety is not compromised. Although these recommendations are targeted at clinical trials and clinical investigators, they are also likely to be of benefit to clinicians [4].

In the first-line setting, alternative therapies that have not demonstrated improvement in overall survival but that can provide disease control and palliation and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (or hydrocortisone).

To date, docetaxel-based chemotherapy remains the only treatment that has demonstrated an overall survival benefit in most men with metastatic CRPC regardless of whether they are symptomatic or have visceral metastases. The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients and be individualized based on their clinical status and preferences. In both the TAX 327 and Southwest Oncology Group 9916 trials, the men enrolled continued on gonadal androgen suppression and discontinued the use of anti-androgens. These maneuvers are recommended for men with HRPC who receive chemotherapy. Men with HRPC should receive treatment to optimize symptom control. Use of estramustine in combination with other cytotoxic agents is not recommended because of the increased risk of clinically important toxicities without evidence of improved survival or palliation [16].

Patients with high-grade disease (Gleason 9–10) nonresponsive to first-line ADT and patients that progress clinically or radiologically without significant PSA elevations may have neuroendocrine (small-cell) differentiation. The NCCN guideline suggests that biopsy of accessible lesions should be considered to identify these patients, who should then be treated with combination chemotherapy such as cisplatin–etoposide or carboplatin–etoposide [17].

2.2.5 Immunotherapy

In April 2010, sipuleucel-T became the first immunotherapeutic agent to approved by the U.S. Food and Drug Administration for PCa, based on consistent observed improvements in overall survival. Sipuleucel-T is an autologous "vaccine" that requires collection of white blood cells from individual patients to obtain antigen-presenting cells. These antigen-presenting cells are then exposed to the prostatic acid phosphatase/granulocyte–macrophage colony–stimulating factor fusion protein and re-infused into the patient.

Patients entered into the studies of sipuleucel-T have had excellent to good performance status (Eastern Cooperative Oncology Group 0–1), have been asymptomatic or very minimally symptomatic, and have not had visceral metastases. Although no

differences were observed in any trial for clinical parameters such as decline in PSA, tumour regression, or time to progression, improvements in overall survival were noted in the integrated analysis of D9901 and D9902A, which demonstrated a 33% reduction in the risk of death (HR: 1.50; 95% CI: 1.10 to 2.05; log-rank $p = 0.011$) [18]. The treatment effect remained strong after adjustments for imbalances in baseline prognostic factors, post-study use of treatment chemotherapy, and deaths not related to PCa. The Food and Drug Administration approval was finally granted when the confirmatory trial D9902B that randomized 512 patients to sipuleucel-T or placebo in a 2:1 ratio also found a 22.5% improvement in mortality risk (median survival: 25.8 months vs. 21.7 months; HR: 0.775; 95% CI: 0.614 to 0.979; $p = 0.032$) [19]. Treatment with sipuleucel-T appears to be well tolerated; the most common complications include mild-to-moderate chills, pyrexia, and headaches, which are transient.

2.2.6 Second-Line Systemic Chemotherapy

Unfortunately, no treatment has been shown to improve survival or quality of life in patients who have progressed on or soon after docetaxel-based chemotherapy. Participation in a clinical trial should be encouraged.

Currently, mitoxantrone can be considered *de facto* second-line chemotherapy, but published series suggest that it has limited activity and increased toxicity in that setting, with response rates from retrospective series ranging from 9% to 20% [20–22]. Mitoxantrone has been used as the standard treatment in least two published randomized trials [23,24]. In the first trial, mitoxantrone induced a PSA response in 20% of patients, with a median treatment duration of 2.3 months, a 63% rate of grades 3 and 4 neutropenia, and a median survival of 9.8 months. In the second trial, the median number of cycles delivered was 2, and time to progression was 1.1 months. No PSA responses were seen, and the rate of grades 3 and 4 febrile neutropenia was 31%. Based on those results, mitoxantrone appears to have limited benefit, with clear toxicity and questionable palliative benefit post docetaxel. It should likely be reserved for symptomatic patients for whom clinical trials are not an option.

For patients who have not demonstrated definitive evidence of resistance to docetaxel, re-treatment with this agent can be considered [25–28]. In published reports of highly selected individuals who had shown previous sensitivity to docetaxel, PSA declines of at least 50% were observed in 32%–45% of patients. Eymard and colleagues recently published a multicentre retrospective series [28]. Of the 148 patients who responded to first-line docetaxel, 50 received further therapy with docetaxel and were analyzed. The median response duration to first-line docetaxel was 10.3 months (range: 4.6–45.7 months), and the median docetaxel-free interval was 18.4 months (range: 5.0–46.7 months). Docetaxel was reintroduced as second-line therapy in 52% of patients and as further lines in 48%. After docetaxel reintroduction, 24 patients (48%) had a 50% decline in PSA (95% CI: 34.1% to 61.8%). The median overall survival from docetaxel reintroduction was 16 months (95% CI: 13 to 20 months). In most patients, docetaxel appeared to be well tolerated, with a grades 3 and 4 hematologic toxicity rate of 6%.

Cabazitaxel is a potent taxane agent that has been selected in preclinical studies by virtue of its high cytotoxicity and low affinity for the adenosine triphosphate–dependent drug efflux pump P-glycoprotein 1, which can be responsible for resistance to docetaxel [29]. Results from a large phase III trial evaluating the efficacy of cabazitaxel were recently presented at the ASCO Genitourinary Cancers Symposium in March 2010 [30]. This randomized placebo-controlled trial recruited 755 docetaxel-pretreated CRPC patients. Overall survival was the primary endpoint of the study, and PSA response, progression-free survival, response rate according to the Response Evaluation Criteria in Solid Tumors, and pain response were secondary endpoints. Patients were randomized to receive prednisone 10 mg daily with either 3-weekly mitoxantrone 12 mg/m^2 or cabazitaxel 25 mg/m^2. Treatment caused a high rate of grades 3 and 4 neutropenia, which was observed in 81.7% of patients in the cabazitaxel arm and in 58.0% of patients in the mitoxantrone arm, with febrile neutropenia incidences of 7.5% and 1.3% respectively. Results relating to pain response and to quality of life were not reported. A statistically significant and clinically relevant advantage in survival emerged in favour of the cabazitaxel group, with a median survival of 15.1 months compared with 12.7 months in the mitoxantrone group (HR: 0.70; 95% CI: 0.59 to 0.83; $p < 0.0001$). In light of those positive results, cabazitaxel may soon play a prominent role as second-line treatment in CRPC patients.

2.2.7 Palliative Radiation

The main source of morbidity for men with CRPC is the pain associated with bone metastases. Narcotics and co-analgesics may help to improve or maintain quality of life, but in many cases, radiation therapy can be used for optimal palliation. The bone metastases from PCa are often radiosensitive, and most men will experience partial or complete pain relief with radiation to a specific lesion. Studies have shown that a single fraction is as effective as 5 fractions in providing palliation [31], but more patients receiving a single fraction require re-treatment for pain recurrence.

In some patients with diffuse bone pain, radioisotopes can be considered. Because of the potential for marrow suppression with radioisotopes, adequate blood counts are required to initiate treatment. The two main isotopes used are strontium and samarium. The main advantage of samarium over strontium is its shorter scatter, which causes less marrow suppression.

2.3 Bone-Targeted Therapy

Bone loss in patients with PCa may be a result of the disease itself (which is a risk factor for osteoporosis) and of therapy with ADT [32,33]. Bone loss associated with ADT has been shown to increase the risk of fracture [34]. Moreover, approximately 70% of patients with advanced PCa will develop bone metastases, which cause local decreases in bone integrity. All of these disease-associated factors lead to a fragile bone state and a significant risk of skeletal complications, including pathologic fractures, debilitating bone pain, and spinal cord compression. The patient's quality of life will likely be affected by these complications [35]. Radiation or radioisotope therapy and bisphosphonates are palliative treatments for patients with bone metastases. Bisphosphonates are inhibitors of osteoclast-mediated bone resorption that can prevent bone loss in patients with PCa receiving ADT; in that setting, they can increase bone mineral density [36,37].

In men with castration-recurrent PCa and bone metastases, intravenous zoledronic acid (4 mg) every 3–4 weeks is recommended to prevent disease-related skeletal complications, including pathologic fractures, spinal cord compression, surgery, or radiation therapy to bone [38].

To reduce the risk of adverse effects on renal function, the infusion time for zoledronic acid should be no less than 15 minutes. Serum creatinine monitoring is suggested before each dose. Results from a randomized study [38] showed that skeletal-related events occurred less often in men receiving zoledronic acid than in men in a placebo group (38% vs. 49%, $p = 0.02$). Zoledronic acid also increased the median time to first skeletal-related event (488 days vs. 321 days, $p = 0.01$). In treated patients, the rate of skeletal-related events showed an overall 36% reduction.

Zoledronic acid should be initiated at reduced dose in men with impaired renal function (estimated creatinine clearance: 30–60 mL/min). Treatment is not recommended for men with a baseline creatinine clearance below 30 mL/min [39]. The optimal duration of zoledronic acid in men with castration-recurrent PCa and bone metastases is undefined. Zoledronic acid and other bisphosphonates are associated with increased risk of osteonecrosis of the jaw (ONJ) [40–42]. Most—but not all—patients who develop ONJ have pre-existing dental problems. Excellent oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk of ONJ.

In clinical trials, zoledronic acid has been used safely with a variety of cytotoxic chemotherapies; preclinical data suggest that docetaxel and zoledronic acid may have additive or synergistic effects on PCa cells [43]. Adverse events reported during bisphosphonate treatment did not appear to increase with concomitant chemotherapy.

Based on the available evidence, several guidelines—including those of the NCCN, the European Association of Urology, and the International Consultation on Urological Diseases—recommend that bisphosphonates be used to preserve bone health and to prevent skeletal complications in patients with bone metastases from CRPC whether asymptomatic or symptomatic. Other bisphosphonates have not been shown to be effective for the prevention of disease-related skeletal complications.

Other bone-targeted agents include denosumab, an inhibitor of receptor activator for nuclear factor κB ligand [44], which has been shown to be effective in preventing bone loss attributable to ADT [45]. The same agent is currently being studied in the setting of prevention of bone metastases in high-risk patients and also in the prevention of skeletal-related events in patients with bone metastases.

2.4 Clinical Trials and Future Directions

Men with CRPC are living longer and with improved quality of life, but most, if not all, eventually succumb to their disease. Better treatments are required.

A phase III study of abiraterone–prednisone compared with prednisone–placebo in men who progressed after docetaxel has recently completed accrual. The results of that trial are widely anticipated. Many other studies are ongoing or planned. Several trials focus on adding a second agent to docetaxel in the first-line setting. Other agents are also under investigation to determine their role in the pre-chemotherapy setting. A number of trials in patients who received previous treatment with docetaxel are evaluating novel antiandrogens, novel cytotoxic agents, and novel targeted therapies. Because CRPC remains an incurable and ultimately fatal illness, participation in clinical trials at all stages of the disease remains paramount.

3. SUMMARY

The multifaceted problem of CRPC needs a multidisciplinary approach (Figure 1). Many aspects of the disease—biological, chronological, physical, and psychological—need to be taken into account when deciding on treatment. All specialties involved in the management of CRPC need to be aware that hormone therapy diminishes bone health, chemotherapy with docetaxel can provide a survival benefit, and zoledronic acid reduces and delays skeletal complications. Building on those positive results is necessary to further improve survival, symptom management, and quality of life in these poor-prognosis patients.

4. CONFLICT OF INTEREST DISCLOSURES

FS is an advisor and has conducted research with Novartis, Sanofi Aventis, Amgen. SJH has acted as an advisor and has conducted research with Novartis and Sanofi Aventis. No financial support was given for the work in preparing this article.

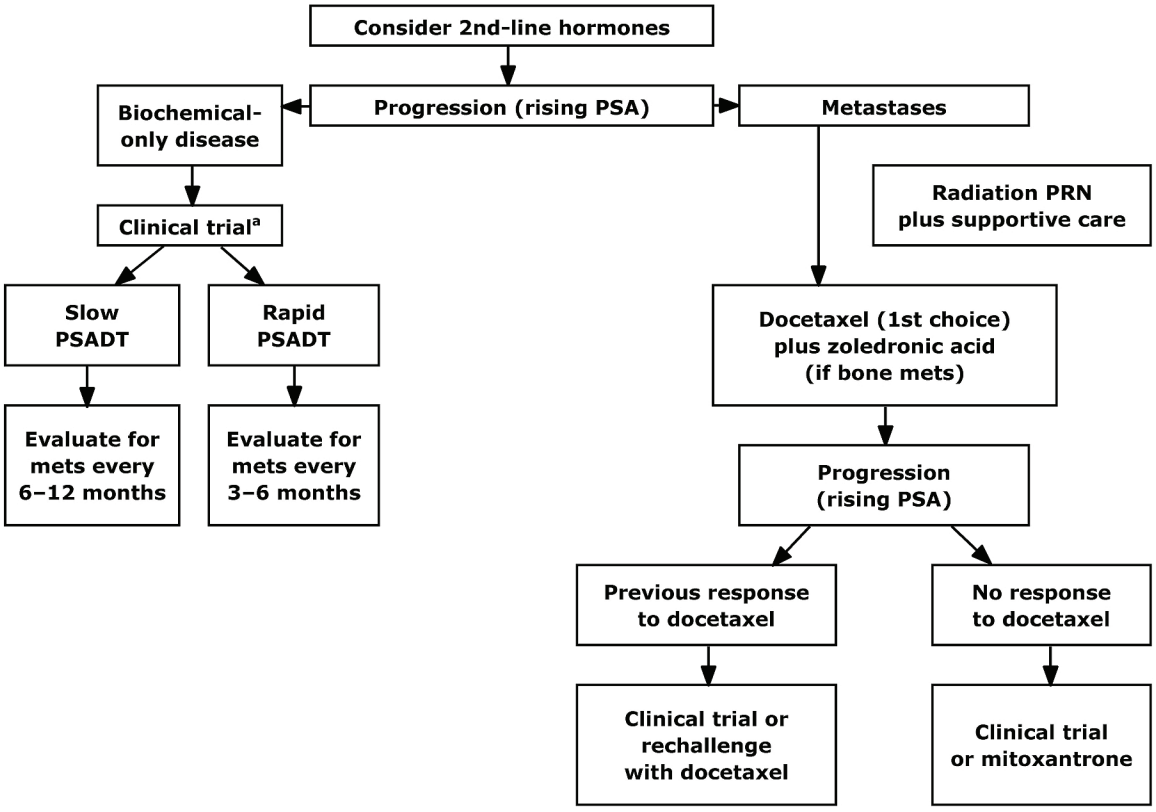

FIGURE 1 Proposed approach for patients with castrate-resistant prostate cancer. PSA = prostate-specific antigen; PRN = as needed; PSADT = prostate-specific antigen doubling time; METS = metastases. [a] In castrate-resistant prostate cancer, clinical trials should be considered whenever possible.

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