Metastatic castration resistant prostate cancer: Current strategies of management in the Middle East

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Abstract

Although most patients with prostate cancer respond to initial androgen-deprivation therapy, progression to castration-resistant prostate cancer (CRPC) is almost inevitable. In 2004, the docetaxel/prednisone regimen was approved for the management of patients with metastatic CRPC, becoming the standard first-line therapy. Recent advances have also led to an unprecedented number of approved new drugs; thus, providing several treatment options for patients with metastatic CRPC. Five new drugs have received US Food and Drug Administration-approval between 2010 and 2012: sipuleucel-T, an immunotherapeutic agent; cabazitaxel, a novel microtubule inhibitor; abiraterone acetate, a new androgen biosynthesis inhibitor; enzalutamide, a novel androgen receptor inhibitor; and denosumab, a bone-targeting agent. Such drugs are either already marketed or about to be marketed in the Middle East. Data supporting the approval of each of these agents are described in this review, as are recent approaches to the treatment of metastatic CRPC.

References.
Biography

Keywords: Prostate cancer; Castration-resistance; Sipuleucel-T; Cabazitaxel; Abiraterone; Enzalutamide; Denosumab

1. Introduction

Prostate cancer is the second most common cancer in men worldwide, with an estimated 900,000 new cases diagnosed and 258,000 deaths in 2008 and with the highest rates recorded primarily in the developed countries of Asia, Europe, and North America [1]. The American Cancer Society estimated that 241,740 American men were diagnosed with the disease and 28,170 men died of it in 2012 [2]. Rates of prostate cancer differ by over 50-fold between different international populations [2]. Interpretation of these data is complicated by dramatic changes in the incidence of prostate cancer in the United States (US) and other Western countries that have taken place over the past two decades. These changes have been primarily driven by the increased frequency of prostate biopsies performed in asymptomatic men because of an elevated serum prostate-specific antigen (PSA) level. In the US, the incidence of prostate cancer dramatically rose in the early 1990s concomitant with the increased utilization of PSA testing [3]. After an initial peak, incidence rates fell, but they have persisted at a rate nearly twice that recorded in the pre-PSA era [3]. Countries that do not utilize PSA testing typically have a much lower rate of prostate cancer compared to those that do. However, unless studies control for the number of prostate biopsies performed, it is difficult if not impossible to be definitive in making such conclusions. Prostate cancer is the most common cancer in males in 24 of 40 European countries with estimated age-standardized rate (ASR) of 96/100,000 in 2012 [4].

Some countries such as Lebanon [7,8] and Libya exhibit a much higher rate than their neighboring countries. Due to the lack of continuous reporting over time, temporal trends cannot be examined. Even in countries that have an established cancer registry, mortality rates and incidence rates prior to 1990 are not available making it difficult to examine the effect of screening tests on incidence and mortality of prostate cancer. Lower median age may represent an additional factor contributing to the low incidence of prostate cancer in the Middle Eastern population. Table 1 represents the incidence (age-standardized rate; ASR) of prostate cancer according to published data in several Middle Eastern countries [8–12]. It is notable that Lebanon represents the Middle Eastern country with the highest recorded incidence rate at 27.6/100,000 [8]. This is likely due to more common use of PSA screening compared with the rest of the region. Out of the six Gulf Countries Council (GCC) states, Bahrain has the highest incidence with

<table>
<thead>
<tr>
<th>Country</th>
<th>ASR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebanon</td>
<td>27.6</td>
</tr>
<tr>
<td>Turkey</td>
<td>13.7–19.1</td>
</tr>
<tr>
<td>Bahrain</td>
<td>13.3</td>
</tr>
<tr>
<td>Kuwait</td>
<td>12.6</td>
</tr>
<tr>
<td>Jordan</td>
<td>11.5</td>
</tr>
<tr>
<td>Qatar</td>
<td>10.3</td>
</tr>
<tr>
<td>Egypt</td>
<td>6.6</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>6.1</td>
</tr>
<tr>
<td>Oman</td>
<td>5.8</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>5.3</td>
</tr>
<tr>
<td>Iran</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Table 1

Age standardized rate (ASR) of prostate cancer in some Middle Eastern countries. Data presented per 100,000 individuals.
an ASR of 13.3/100,000 while United Arab Emirates has the lowest incidence at 4.2/100,000 [12]. In addition, unlike Western countries, prostate cancer ranks lower in incidence among other cancers in men. For example, prostate cancer ranks 4th in Jordan, 3rd in Lebanon, 6th in Egypt, and 5th in GCC nationals [8–12].

In this review, we highlight the most notable advances in the management of patients with advanced prostate cancer. We will focus on those approaches and management options available and utilized in the Middle East region.

2. Castration resistant prostate cancer (CRPC): management options

Advanced prostate cancer has been known by several names over the years, including hormone-resistant/refractory prostate cancer (HRPC) and androgen-insensitive prostate cancer. Most recently, the term ‘castrate/castration-resistant/recurrent’ prostate cancer (CRPC) was introduced along the realization that intracrine and paracrine androgen production plays a significant role in the resistance of prostate cancer cells to gonadal androgen-deprivation therapy (ADT). Thus, CRCP is defined by disease progression despite ADT and may present as one or any combination of: a continuous rise in serum levels of PSA, progression of pre-existing disease, or appearance of new metastases. In their second publication, the Prostate Cancer Working Group 2 (PCWG2) defined CRPC as a continuum on the basis of whether metastases are detectable (clinically or on imaging) and whether serum testosterone is in the castrate range because of a surgical orchietomy or medical therapy [13]. The resulting clinical-states model was recommended to classify patients. Within the rising PSA states (castrate and non-castrate), no detectable (measurable or non-measurable) disease is 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 [13].

The European Association of Urology defines CRPC as follows: serum castrate levels of testosterone, three consecutive rises of PSA two weeks apart resulting in two 50% increases over the nadir, anti-androgen withdrawal for at least four weeks, PSA progression despite secondary hormonal manipulations, and progression of osseous or soft tissue lesions. Anti-androgen withdrawal or one secondary hormonal manipulation should have failed in order to fulfill the criteria for CRPC [14].

Thus, it is agreed that CRPC 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 [15]. 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 [15].

3. Second-line hormonal treatment

One-third of patients with prostate cancer will ultimately develop metastatic disease. Hormonal therapy (HT), medical or surgical, is the standard initial therapy for advanced disease. Luteinizing Hormone Releasing Hormone (LHRH) agonists as well as antagonists with or without anti-androgens are used for medical castration. Despite initial profound responses in the majority of patients, responses are not durable and patients will progress biochemically then radiologically as they develop CRPC [16]. Therapeutic options at this stage depend on the patient’s performance status, PSA doubling time, Gleason score, extent of metastasis, and patient’s expectations [17,18]. As previously discussed, CRPC is not hormone refractory and suppression of gonadal androgens needs to be continued in the form of LHRH agonists or antagonists if the patient has not undergone previous orchiectomy [19]. Since a great number of patients present with asymptomatic, non-metastatic, biochemical CRPC, second-line hormonal therapy seems a logical next step to delay progression before recommending cytotoxic chemotherapy. Second-line hormonal manipulations include:

3.1. Antiandrogens

For patients progressing on LHRH agonists/antagonists alone, the addition of low-dose or high-dose antiandrogen could result in a 50% decrease in PSA in 54% of patients with advanced disease [20]. However, median response to this combined androgen blockade is only between 4 and 11 months [21–23].

3.2. Antiandrogen withdrawal

A significant but short duration biochemical and clinical response has been observed in patients progressing on combined androgen blockade when the antiandrogen is stopped [24,25].

3.3. Ketoconazole/aminoglutethimide

Both inhibit the first step of steroid biosynthesis from cholesterol to pregnenolone. Ketoconazole, an antifungal agent, when used in high doses (800–1200 mg) has shown activity in 30–60% of CRPC patients with a median response of 7 months [26,27]. Side effects, mainly hepatic toxicity, limit its use.
3.4. Estrogens

Diethylstilbestrol reduces testosterone production by inhibiting LHRH and LH production. Around 50% PSA decrease has been observed in 20–40% of patients [28,29]. Cardiovascular side effects limit its use and concomitant anticoagulation or antiplatelet agents should be given due to an increased risk of venous thromboembolism.

3.5. Glucocorticoids

Prednisone, dexamethasone, and hydrocortisone have been used alone or in combination with other medications. Biological effects are unknown but palliation is always noted.

4. More novel agents

4.1. Abiraterone

Abiraterone acetate (Zytiga, Janssen) is an oral inhibitor of CYP17A1, a key enzyme in the testosterone biosynthesis pathway. Inhibition of CYP17A1 results in reduction of testosterone both from adrenal steroid precursors and intratumoral production. The use of single-agent abiraterone leads to a rebound increase in LH, hence the development of abiraterone for use in combination with medical or surgical castration [30]. The observation that the addition of low-dose glucocorticoid resulted in normalization of mineralocorticoid levels and an improvement in blood pressure control in early-phase studies led the investigators to recommend that abiraterone acetate should be used with prednisone in further clinical trials.

In the pivotal phase III study published in 2011 (COU-AA-301), abiraterone plus prednisone was shown to prolong survival in men with CRPC who had progressive disease following docetaxel chemotherapy [31]. Approval from the US Food and Drug Administration (FDA) for the use of abiraterone in the post-docetaxel setting followed in April 2011 [32]. The primary endpoint of COU-AA-301 was overall survival (OS), and the study was halted when the planned interim analysis met pre-specified criteria for efficacy. The initial analysis reported a 3.9 month improvement in median OS, but at the final analysis the benefit had extended to 4.6 months [33]. All secondary efficacy endpoints favored the experimental arm at the time of study unblinding, including time to PSA progression (10.2 vs. 6.6 months; \( p < 0.001 \)), progression-free survival (PFS; 5.6 vs. 3.6 months; \( p < 0.001 \)), and PSA response rate (29% vs. 6%; \( p < 0.001 \)). Abiraterone was generally well tolerated; however, mineralocorticoid-related adverse events were reported more frequently in the group of patients receiving abiraterone [31]. Significant improvements in patient-reported fatigue, pain relief, delayed pain progression, and prevention of skeletal-related events were also noted [34,35].

Abiraterone has also been tested in chemotherapy-naïve patients in the phase III COU-AA-302 study which randomized 1088 patients to receive abiraterone plus prednisone or placebo plus prednisone. The co-primary endpoints of this study were radiographic PFS (rPFS) and OS. The study was unblinded and patients receiving placebo offered abiraterone when a planned interim analysis showed a statistically significant improvement in rPFS and a strong trend for increased OS in the abiraterone arm. Median rPFS was 8.3 months in the placebo arm and had not been reached in the abiraterone arm; median OS was 27.2 months in the placebo arm and again had not been reached in the abiraterone arm [36]. In December 2012, The US FDA has expanded the approved use of abiraterone acetate to treat men with metastatic CRPC prior to receiving chemotherapy. This was shortly followed by its approval pre chemotherapy by the European Medicines Agency (EMA). Thus, abiraterone may offer an attractive therapeutic option for patients reluctant or unable to tolerate toxicities associated with cytotoxic chemotherapy.

4.2. Enzalutamide

Enzalutamide (MDV3100, Xtandi, Medivation) is an oral novel androgen receptor antagonist that binds to the androgen receptor more avidly than first generation anti-androgens. Enzalutamide prevents DNA binding, induces apoptosis and has no agonist activity when the androgen receptor is overexpressed [37]. The phase III AFFIRM study of enzalutamide 160 mg daily vs. placebo for patients with metastatic CRPC who had progressed after docetaxel chemotherapy showed a significant survival benefit associated enzalutamide treatment. A planned interim analysis of the study showed a 4.8 month improvement in median OS with enzalutamide compared to placebo (18.4 months vs. 13.6 months; hazard ratio [HR] = 0.631; \( p < 0.0001 \)). Enzalutamide was generally well tolerated; however, five seizures were documented in patients receiving enzalutamide, including two patients with intracranial metastases, whereas no seizures were observed in the placebo arm [38]. A potential advantage of enzalutamide over androgen biosynthesis inhibitors such as abiraterone is the fact that concurrent steroids are not required; however, approximately 30% of patients in each arm of the AFFIRM study received concurrent corticosteroid treatment [38]. According to its insert package, seizures might occur in 0.9% of patients on enzalutamide; patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. In September 2012, the US FDA approved enzalutamide as a once-daily oral therapy for men with metastatic CRPC that has either spread to other organs or recurred, despite prior surgical or medical treatment. However, it is expected that enzalutamide will also benefit patients at earlier stages of disease. The phase III PREVAIL study is examining the effect of enzalutamide on OS and PFS benefits in patients with progressive metastatic prostate cancer after androgen
deprivation therapy who have not yet received chemotherapy (ClinicalTrials.gov identifier: NCT01212991).

Following a trend of selectivity in cancer treatment in general, CRPC is witnessing a new surge of second-line hormonal manipulation drugs affecting both the ligand and receptor for improved effectiveness.

5. Chemotherapy for CRPC

Prior to 2004, few options were available for men with CRPC, and no single agent or combination chemotherapy had been proven to prolong survival in these patients. However, data derived from the TAX327, SWOG 99-16 and recent TROPIC studies (featured in subsequent sections) have demonstrated that patients with CRPC may have a survival benefit from chemotherapy. These results have changed expectations although while introducing new sequencing dilemmas.

5.1. The Pre-Taxane Era

In the early 1990s PSA assays became available, and response to agents in clinical trials began to be measured and reported in terms of PSA response [39–41]. Two consecutive trials in the late 1990s demonstrated that the combination of mitoxantrone plus corticosteroids could relieve pain and improve quality of life more frequently than corticosteroids alone, but neither demonstrated a survival benefit [42,43].

5.2. Taxanes

Taxanes have significant antitumor activity in men with CRPC, when administered either as single agents or in combination with estramustine. Initial studies using single-agent paclitaxel administered as a 24-h infusion at a dose of 135–170 mg/m² every 3 weeks were disappointing with only a response rate of only 4% [44]. In contrast, when docetaxel was evaluated in men with CRPC at 75 mg/m² every 3 weeks, a greater than 50% decline in PSA was observed in 46% of treated patients, while 28% of patients with measurable disease had a partial response [45]. The promising activity of docetaxel administered either as a single agent or in combination with estramustine [46–51] provided the basis for two multi-institutional phase III trials, SWOG 99-16 and TAX327 [17,18].

In the TAX327 trial, 1006 patients with CRPC were enrolled in a three-arm study comparing two dosing schedules of docetaxel plus prednisone with the standard mitoxantrone plus prednisone therapy. Patients in the control arm were treated with mitoxantrone 12 mg/m² every 3 weeks plus prednisone 5 mg orally twice-daily continuously. The experimental arms consisted of docetaxel 75 mg/m² every 3 week or docetaxel 30 mg/m² weekly for 5 of every 6 weeks. Prednisone 5 mg orally twice-daily continuously was given in both experimental arms. In an intent-to-treat analysis, at a median follow-up of 28 months, the median OS for patients treated with docetaxel every 3 weeks was 18.9 months, compared with 16.4 months for patients in the control arm (p = 0.009). Weekly docetaxel did not result in a significant survival benefit. Most importantly, the every 3-week schedule of docetaxel was associated with a 24% reduction in the risk of death (p = 0.009), compared with the control regimen. An updated survival analysis confirmed these findings [52]. Docetaxel therapy was also associated with significant improvement in pain relief and in PSA decline. There were no significant differences between the docetaxel arms in terms of response rate. The most common toxicity was neutropenia, which occurred more frequently in the every 3-week docetaxel regimen (32% vs. 21.7%) [18].

In the SWOG 99-16 trial, 770 patients were randomized to treatment with docetaxel plus estramustine or with mitoxantrone plus prednisone. The experimental arm was docetaxel 60 mg/m² every 3 weeks and estramustine 280 mg orally 3 times per day on days 1–5. The control arm was mitoxantrone 12 mg/m² every 3 weeks plus prednisone 5 mg orally twice-daily continuously. The trial was designed to detect a 33% improvement in median OS by using a one-sided log-rank test at a p level of 0.025. Secondary end-points were PFS, response rate, and rate of PSA decline. Patients treated with the combination of docetaxel and estramustine had a significant improvement in median OS (18 months vs. 16 months, p = 0.01), longer PFS (6 months vs. 3 months, p < 0.0001), superior median PSA decline, and a 20% reduction in the risk of death [17].

On the basis of the statistically significant improvement in survival observed in patients receiving the docetaxel/prednisone combination in the TAX327 trial, the FDA granted in May 2004 approval for docetaxel 75 mg/m² every 3 week in combination with prednisone as front-line therapy for CRPC. This combination has widely become the standard of care as first-line chemotherapy in CRPC worldwide.

5.3. Cabazitaxel

Cabazitaxel (Jevtana, Sanofi-Aventis) is a novel taxane which has antitumor activity following the development of resistance to paclitaxel and docetaxel. Cabazitaxel has also demonstrated the ability to cross the blood–brain barrier, thus making it potentially effective in patients with cerebral or spinal cord metastases. In June 2010, cabazitaxel was licensed by the US FDA for the treatment of metastatic prostate cancer for patients with progressive disease following docetaxel-based chemotherapy on the basis of the phase III TROPIC study.

The TROPIC study randomized 755 men to receive cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m² on a 3-weekly basis. All patients received prednisone 10 mg daily. The median OS was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group. The HR for death for men treated with cabazitaxel compared to those treated with mitoxantrone was 0.70 (95% CI: 0.59–0.83; p < 0.0001).
There were relatively high rates of grade 3 or 4 neutropenia in both the cabazitaxel (82%) and mitoxantrone (58%) groups. The rates of febrile neutropenia were 8% and 1%, respectively [53]. The use of gold-standard supportive management including growth-factor support and standardized pathways for the management of febrile neutropenia is likely to improve treatment-related morbidity; however, patient selection remains important. Data from 68 patients treated within the expanded access program in the UK showed improvements in pain control and health status associated with cabazitaxel treatment as measured by the EQ-5D quality of life questionnaire and health status visual analog scale (VAS). The proportion of patients reporting no pain or discomfort increased from 22.6% at baseline to 50% at cycle 4 [54]. Data from 111 patients treated with cabazitaxel under the German compassionate-use program has recently been published. Seventy-one patients (64%) were above the age of 65 with 20 patients (18%) above the age of 75. Grade 3/4 treatment-emergent adverse events occurred in 27.5% of patients under 65 and 32.4% of patients above 65 with no statistically significant difference between the two groups. The use of granulocyte colony-stimulating factor (GCSF) was used in 17.1% of patients; however, the rate of febrile neutropenia was significantly lower than that observed in the TROPIC study at 1.8% for the whole cohort. Four treatment-related deaths occurred due to sepsis, two patients under 65 years and two patients over 65 years [55]. A large randomized phase III trial (PROSELICA) is now investigating a lower cabazitaxel dose of 20 mg/m² vs. the licensed dose of 25 mg/m² in CRPC (ClinicalTrials.gov Identifier: NCT01308580).

6. Febrile neutropenia and growth-factor support for patients with CRPC treated with chemotherapy

Occurrence of febrile neutropenia may delay subsequent chemotherapy courses or result in dose reduction that may compromise treatment outcomes. Development of febrile neutropenia also increases diagnostic and treatment costs and often leads to longer hospital stays [56]. Studies have demonstrated that prophylactic use of GCSFs can reduce the risk, severity, and duration of febrile neutropenia, but its cost has prevented its routine use for all patients receiving myelosuppressive chemotherapy. Selective use of GCSFs in patients at increased risk for neutropenic complications may, however, enhance the cost-effectiveness. The GCSFs filgrastim and pegfilgrastim currently have the approval for use in the prevention of chemotherapy-induced neutropenia. In a meta-analysis of 17 randomized trials including 3493 adult patients with solid tumors and lymphoma, showed that G-CSF use as primary prophylaxis reduces the risk of febrile neutropenia (RR = 0.54; 95% CI: 0.43–0.67; p < 0.001) and improves relative dose-intensity of the chemotherapy delivered (average difference between study arms 8.4%; p = 0.001). For the first time, this analysis also reported a substantial reduction in risk of infection-related mortality (RR = 0.55; 95% CI: 0.33–0.90; p = 0.018) and all early deaths during chemotherapy [57].

### Table 2

<table>
<thead>
<tr>
<th>Patient-related risk factors for febrile neutropenia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age over 65 years (most important risk factor for developing severe neutropenia)</td>
</tr>
<tr>
<td>Previous chemotherapy or radiotherapy</td>
</tr>
<tr>
<td>Pre-existing neutropenia</td>
</tr>
<tr>
<td>Tumor involvement in the bone marrow</td>
</tr>
<tr>
<td>Poor performance status</td>
</tr>
<tr>
<td>Comorbidities including renal or liver dysfunction</td>
</tr>
<tr>
<td>Pre-existing conditions such as neutropenia and infection</td>
</tr>
<tr>
<td>History of invasive fungal infection or other clinically-documented infections</td>
</tr>
</tbody>
</table>

6.1. Primary CSF prophylaxis

The indication for prophylactic CSF use depends on the risk of febrile neutropenia or other neutropenic events that can potentially compromise treatment. Febrile neutropenia risk is assigned to a high-risk group (>20% risk of febrile neutropenia), an intermediate group (10–20% risk), and a low risk group (<10% risk). The NCCN, ASCO and EORTC guidelines recommended prophylactic use of CSF if the risk of febrile neutropenia is 20% or greater [58]. Patient risk factors are an important consideration in estimating the overall risk of febrile neutropenia, particularly when chemotherapy regimens are considered an intermediate risk (reviewed by Lyman et al. [59]). Patient risk factors may elevate the overall risk to a high-risk category, where prophylactic CSFs are more routinely recommended. These factors are illustrated in Table 2. Most of these factors have been confirmed as independent risk factors for neutropenic complications in a risk model developed by Lyman and colleagues that was validated in a study population of 3760 cancer patients beginning chemotherapy [60].

6.2. Secondary CSF prophylaxis

After the first cycle, patient evaluation should be performed prior to each subsequent cycle to determine the risk categorization. If the patient experienced a previous episode of febrile neutropenia or a dose-limiting neutropenic event (a nadir or a day-of-treatment count impacting the planned dose of chemotherapy), this patient is now considered in the high-risk group.

6.3. Recommended approach and GCSF dosing

Patients with CRPC receiving docetaxel or cabazitaxel have to be assessed for overall febrile neutropenia risk (including patient risk factors). High risk (>20% risk) patients should receive primary prophylaxis, while secondary prophylaxis is given for those who develop febrile neutropenia or prolonged nadir. In second-line treatment with cabazitaxel most of patients in our region fit in the category of high risk.
for febrile neutropenia because of the aforementioned patient risk factors and primary prophylaxis is advised.

When treatment with GCSF is indicated, initial doses of filgrastim should be initiated within 1–3 days after completion of chemotherapy in a daily dose of μg/kg until post-nadir absolute neutrophil count recovery is to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg, given 1–3 days after administration of chemotherapy, is sufficient per chemotherapy cycle. There is evidence to support use of pegfilgrastim 1 day after completion of chemotherapy given every 2–3 weeks [61,62]. Dose reduction should be considered if CSF support did not achieve the goal.

7. Bone-targeted therapy in advanced prostate cancer

Bone metastases are a major cause of prostate cancer-specific morbidity and mortality. The treatment and prevention of skeletal related events (SREs) in prostate cancer has the potential to impact both symptoms and survival in advanced disease. Bisphosphonates such as zoledronic acid [63] and bone-targeted radiopharmaceuticals such as samarium-153 and strontium-89 are used as monotherapy and in combination with chemotherapy (zoledronic acid) [64,65]. Novel approaches to bone-targeted therapy include an alpha-emitting radiopharmaceutical (radium-223) and a receptor activation of nuclear factor kappa-B ligand (RANK-L) inhibitor (denosumab).

7.1. Zoledronic acid

In men with CRPC and bone metastases, bisphosphonates slow the progression of SREs. Bisphosphonates also protect against the bone loss associated with androgen deprivation therapy. The FDA has approved only one bisphosphonate, zoledronic acid for use in castrate-resistant prostate with bone metastases.

The benefit of zoledronic acid in men with bone metastases and CRPC was demonstrated in a trial in 643 men whose disease was progressing while on ADT [66]. Men were randomly assigned to one of two doses of zoledronic acid (4 mg or 8 mg) or placebo, each given every three weeks. The 8 mg dose of zoledronic acid was reduced to 4 mg early in the trial because of an increased risk of renal toxicity. At an average follow-up of 24 months, there was a significant reduction in the frequency of SREs in men receiving zoledronic acid compared to placebo (38% vs. 49%), and the median time to develop an SRE was significantly longer with zoledronic acid (488 vs. 321 days) [63]. Pain and analgesic scores were significantly higher in men who received placebo than in those who received zoledronic acid, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups.

7.2. Radium-223

Radium-223 chloride (Xofigo, Alpharadin, Bayer) is a novel bone-targeting alpha-emitting agent that has recently been reported to improve pain as well as survival in patients with CRPC and symptomatic bone metastasis [67–69]. The phase III ALSYMPCA study enrolled men with prostate cancer with symptomatic bone metastasis, no evidence of visceral disease or significant lymphadenopathy and either post-docetaxel or unfit for docetaxel chemotherapy. A planned interim analysis showed median OS of 14 months with alpharadin compared to 11.2 months with placebo (p = 0.0033, HR = 0.699), so the trial was halted and placebo patients were offered treatment with alpharadin [70]. Alpharadin appeared to be well tolerated; however, thrombocytopenia and diarrhea were seen more frequently with alpharadin compared to placebo. On May 2013, the FDA approved Xofigo for the treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease. Whether alpharadin can be safely combined with chemotherapy or novel androgen receptor pathway targeting agents has yet to be determined.

7.3. Denosumab

RANK signaling is a potent stimulus for osteoclast proliferation and bone resorption. Denosumab (Xgeva®, Amgen) is a fully humanized monoclonal antibody targeting RANK-ligand that has recently been shown to be superior to zoledronic acid in preventing or delaying SREs in patients with bone metastases from CRPC [71]. A large double-blind phase III non-inferiority study randomized 1904 patients to denosumab 120 mg subcutaneously monthly or zoledronic acid 4 mg intravenously monthly. The primary end-point was time to SRE as defined by pathological fracture, radiotherapy to bone, surgery to bone or spinal cord compression. The adverse event profile was similar in both arms. Denosumab was shown to be superior to zoledronic acid for prevention of SRE (median time to SRE 20.7 months vs. 17.1 months; HR = 0.82; p = 0.008) [71]. A phase III placebo-controlled study also demonstrated that denosumab significantly improved bone metastasis-free survival in men with CRPC (29.5 vs. 25.2 months; HR = 0.85; 95% CI: 0.73–0.98; p = 0.028); however there was no improvement in OS [72].

8. Treatment sequencing

With four novel therapies (cabazitaxel, abiraterone acetate, enzalutamide, and alpharadin) shown to improve survival in patients with advanced prostate cancer who progress after docetaxel chemotherapy, the pace of clinical drug
development in this field has been unprecedented. Median survival from a diagnosis of CRPC was 13–19 months in the pre-docetaxel era and is now exceeding 30 months with novel treatments [73,74]. With so many therapeutic options now in the clinic and under investigation in clinical trials, strategies for treatment selection, combination and sequencing are urgently required. Since docetaxel became standard of care for symptomatic patients with CRPC following the TAX327 study [18], three artificial ‘spaces’ have emerged. These form the basis of current prostate cancer drug development strategies and are divided into: pre-docetaxel, docetaxel combination therapy, and post-docetaxel spaces. Treatment of metastatic CRPC is nowadays a rapidly changing field and accordingly the treatment options described below may soon change in the near future [75].

8.1. Metastatic CRPC pre-docetaxel

Several options exist for patients with metastatic CRPC before they go on chemotherapy. Sipuleucel-T, a dendritic cell vaccine, has shown in randomized trials prolonged OS compared with placebo in men with minimally symptomatic, metastatic prostate cancer [76]. There are no data on the effectiveness of sipuleucel-T in men whose only evidence of disease is an elevated PSA or in those with symptomatic metastatic disease. Although sipuleucel-T prolonged overall survival, it did not significantly increase progression-free survival or affect the serum PSA. However, due to its high cost, contraindication to the use of corticosteroids for 6 months following treatment, and some controversy regarding the study design [77], the use of sipuleucel-T is likely to be limited.

As previously mentioned, abiraterone plus prednisone can prolong rPFS pre-chemotherapy compared to prednisone alone, however the COU-AA-302 study was unblinded prior to the co-primary end-point of OS showing a significant difference between the two arms [78]. Despite this, abiraterone is FDA approved now for use pre-docetaxel and is an attractive option for patients who wish to avoid the toxicity of chemotherapy. Another option for patients unfit for docetaxel is radium-223 (alpharadin). In the ALSYMPCA study, 42% were chemotherapy naïve [79]. Another drug currently in phase III clinical trials in the pre-docetaxel setting aside from enzalutamide (ClinicalTrials.gov identifier: NCT01212991) is tasquinimod (ClinicalTrials.gov identifier: NCT01234311). Although many of the above mentioned options are presently used in the castrate resistant phase of the disease, ongoing studies are being conducted to assess the efficacy of many of the above agents in the 1st line setting of hormone naïve disease with encouraging results [80].

8.2. Timing of docetaxel chemotherapy

Strict guidelines for the role of docetaxel chemotherapy in asymptomatic metastatic CRPC do not exist. In the TAX 327 trial, those patients without baseline pain were able to receive chemotherapy for a significantly greater duration compared with those with baseline pain (median 27 vs. 21 weeks; \( p = 0.0017 \)) [52]. Moreover, those without baseline pain had significantly greater overall survival than those with pain (HR 0.73 vs. 0.85; 95% CI: 0.57–0.93; \( p = 0.01 \)) [52]. Taken together, these data point to the potential benefits of earlier chemotherapy. Despite this NCCN guidelines require that chemotherapy only be given to patients with symptomatic metastatic disease [81]. On the other hand the European Association of Urology (EAU) guidelines state that patients with asymptomatic metastatic CRPC who have elevated PSA levels or PSA doubling time <6 months should be started on cytotoxic therapy early in order to increase the opportunity for extended survival [82].

A prognostic nomogram developed by Armstrong et al. [83] and based on results from TAX 327 demonstrated that patients with lower PSA (<114 ng ml\(^{-1}\)) and slower PSA doubling time (≥55 days) had significantly greater survival than patients with higher PSA or faster PSA doubling time. The analysis of clinical trial data by Hussain et al. [84] also revealed that PSA progression, defined as an increase in PSA of at least 25% over nadir, or an absolute increase of 2 ng ml\(^{-1}\) (based on the Prostate Cancer Working Group 2008 definition), was predictive of OS in both patients with CRPC on chemotherapy. Based on this data, the predictive validity of PSA kinetics regarding response to chemotherapy and the threshold for initiation of chemotherapy in asymptomatic patients may, in some cases, be appropriate if their PSA-related values support it regardless if they are metastatic or not [85]; the latter is though discouraged by most treatment guidelines. The availability of other therapeutic options at this interim period, such as immunotherapy or hormonal therapy (discussed above), may be seen as preferable at this stage.

8.3. Can we improve on docetaxel for first-line chemotherapy?

Several large phase III studies investigating the combination of docetaxel with novel therapies for CRPC including bevacizumab (CALGB 90401 trial), lenalidomide (MAINSAIL trial), and Dasatinib (READY trial) have been disappointingly negative [86–88]. So far, despite promising phase II results, no combination treatments have been shown to improve survival over docetaxel alone. Table 3 lists the most important trials using docetaxel in combination with novel therapies [89,86,90–93].

<table>
<thead>
<tr>
<th>Design</th>
<th>Results</th>
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<tbody>
<tr>
<td>DN-101 ± docetaxel [89]</td>
<td>Negative</td>
</tr>
<tr>
<td>Bevacizumab ± docetaxel [86]</td>
<td>Negative</td>
</tr>
<tr>
<td>GVAX ± docetaxel [90]</td>
<td>Negative</td>
</tr>
<tr>
<td>Oblimersen ± docetaxel [91]</td>
<td>Negative</td>
</tr>
<tr>
<td>Atrasentan ± docetaxel [92]</td>
<td>Negative</td>
</tr>
<tr>
<td>Zibotentan ± docetaxel [93]</td>
<td>Negative</td>
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</tbody>
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Table 3

Summary of the most important trials using docetaxel in combination with novel therapies.
8.4. Metastatic CRPC post-docetaxel

In the post-docetaxel space we now have three drugs shown to improve survival in phase III studies and this is arguably the area of most debate due to the lack of head-to-head data. Cabazitaxel, abiraterone, and enzalutamide are all now licensed for use in CRPC following docetaxel [31,38,53]. Pending prospective sequencing studies, one can examine the patient characteristics of the pivotal phase III trials and retrospective data from institutions treating patients with these drugs within serial clinical trial protocols.

One essential question remains, are the results of the pivotal phase III trials in the post-docetaxel space for cabazitaxel, abiraterone, and enzalutamide comparable? The first point to note is that in the TROPIC study, cabazitaxel was compared to the active comparator of mitoxantrone plus prednisone; in the COU-AA-301 study abiraterone plus prednisone were compared to prednisone alone; while in the AFFIRM study, enzalutamide was compared to placebo [31,38,53]. Furthermore in the TROPIC study, PFS was doubled in the cabazitaxel arm compared to mitoxantrone (2.8 months vs. 1.4 months; HR=0.74; p<0.0001). The observed PFS is somewhat shorter than what has been reported with the COU-AA-301 trial for abiraterone acetate (PFS: 5.6 months vs. 3.6 months; p<0.001) [31,53]. One contributing factor to this difference is the definition of PFS, which in the COU-AA-301 trial was a composite end-point defined as time to disease progression including radiographic progression plus symptomatic/clinical progression plus PSA progression. In the TROPIC trial, PFS was defined as time from randomization to PSA progression, tumor progression, pain progression, or death. PSA elevation alone often predates clinical tumor progression by 3–4 months; thus, such a definition may result in a shorter PFS.

Patients recruited in these three trials had progressed following docetaxel with approximately 30% of patients receiving two or more lines of chemotherapy prior to study entry. In the TROPIC trial, nearly two-thirds of patients had progressed on or within 3 months of docetaxel. Prior response to docetaxel was not reported in the COU-301 or AFFIRM trials; however, some retrospective data are available. In an exploratory analysis of the COU-AA-301 trial, approximately 45% discontinued docetaxel due to disease progression in each arm. The OS benefit of abiraterone was maintained when calculated from the first or last dose of prior docetaxel and whether or not patients discontinued docetaxel for progressive disease [94].

When selecting second-line therapy, the potential for cross resistance should also be considered. In vitro studies suggest that one mechanism of action for taxanes is inhibition of microtubule-dependent, androgen receptor translocation to the nucleus, impairing androgen receptor signaling and reducing PSA expression. Abiraterone impairs such signaling by reducing CYP17-dependent androgen production, as well as directly binding to the androgen receptor and reducing its signaling in a dose-dependent manner. This raises concerns regarding the potential for cross resistance between microtubule inhibitors and hormonal therapies such as abiraterone, based on the hypothesis that use of androgen receptor signaling inhibitors may impair the ability of taxanes to subsequently inhibit this pathway [95]. There is a distinction to be made, however, regarding truly docetaxel-refractory CRPC (no response to docetaxel) and those who have an initial response to treatment yet develop progressive disease while still receiving chemotherapy. In a small retrospective series of 44 patients treated with abiraterone post-docetaxel, seven patients were defined as docetaxel-refractory (no PSA response, PSA or radiological progression on treatment). None of these docetaxel-refractory patients had a subsequent response to abiraterone raising questions regarding cross-resistance [96]. In a separate retrospective study looking at the activity of docetaxel post-abiraterone, no responses to docetaxel were observed in abiraterone-refractory patients [97].

Apart from prior response to chemotherapy, other factors such as prior response to endocrine therapy may be taken in to consideration for treatment selection. Loriot et al. reported that duration of sensitivity of ADT ≥16 months is a significant predictive factor for efficacy of subsequent endocrine manipulations in patients with CRPC [98]. Although abiraterone has antitumor activity in patients pretreated with docetaxel and enzalutamide [99], two recent studies showed reduced efficacy of abiraterone acetate in patients who previously received enzalutamide despite their different mechanisms of action indicating the presence of cross resistance [100,101]. There is no doubt that novel treatments are prolonging survival for patients with CRPC with median OS in placebo arm of the AFFIRM study of over 13 months. The majority of these patients went on to receive subsequent therapy including cabazitaxel and abiraterone [38]. In the absence of randomized data on which to base the decision regarding which drug to use first following docetaxel failure in CRPC, clinical criteria to select cabazitaxel include good performance status, aggressive disease trajectory with visceral metastasis and resistance to prior docetaxel and/or short duration of response to ADT. Abiraterone or enzalutamide may be more appropriate options for patients who wish to avoid the toxicity of chemotherapy, particularly those with poorer performance status, medical co-morbidities, and poor bone marrow reserve. In summary, selection of second-line therapy beyond docetaxel and sequencing of therapies in patients with progressive metastatic CRPC should be based on careful evaluation of disease characteristics. In patients likely to poorly respond to abiraterone (e.g., high Gleason score, rapid progression to CRPC with primary ADT; or progression during docetaxel therapy), cabazitaxel might be the preferred first-option in the second-line setting. For patients with less-aggressive metastatic CRPC, cabazitaxel and abiraterone are reasonable treatment options. Treatment
paradigms for advanced prostate cancer are changing rapidly as more data emerges.

9. Conclusions

Men with advanced prostate cancer now have hope when little existed before. While there is no formal sequence to treating CRPC, men have increasing options to help deal with a complex problem. Further, going from one therapy to another may have cumulative benefits and can further prolong survival. Several options have recently demonstrated activity, providing survival improvement, in patients with prostate cancer progressing while on androgen deprivation therapy: chemotherapy (docetaxel, cabazitaxel), sipuleucel-T, abiraterone, and enzalutamide. The availability of new approved agents with different mechanisms of action highlights the need for the coordinated multidisciplinary care approach between different specialties especially urologists and oncologists. It is important to understand that this is a continuously changing field and it is likely that we will see hormonal therapy move from the post-docetaxel phase to the pre-docetaxel phase or even to the hormone naïve phase. The options of chemotherapy among the emerging large number of hormonal therapies need to be clearly defined. There is now emerging data that can help in defining patients who might benefit from chemotherapy beyond symptomatic and metastatic CRPC. There is presently an urgent need to identify predictive factors of efficacy for each of these treatments to assist decision-making in patients with CRPC.

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References


[87] Celgene Celgene Will Discontinue Phase III MAINSAIL(R) Trial in Castrate-Resistant Prostate Cancer, 2011.


**Biography**

**Dr. Shamseddine** is Professor of Clinical Medicine and Head of Hematology–Oncology Division at the American University of Beirut and Medical Center. He is the formal chair of the hospital committee on cancer as well as the director of the Tumor Registry at the Medical Center (1997–2012). He is also the V/P of the National Cancer Registry (NCR) since 2005. Starting October 2012, he is appointed as director of data base & clinical research unit at NK Basile Cancer Institution at AUBMC. He published more than 150 papers in peer review journals. His research focuses on several issues including: Epidemiology of cancer in Lebanon, Breast cancer, Gastro-intestinal and Prostatic cancers. He also published a book dealing with the trends of cancer at the American University of Beirut over 20 years (1983–2003) and recently (May 2010) cancer report 2010 (APOCP). Dr. Shamseddine is an active member in the society. He is a formal president of the Lebanese Society of Medical Oncology as well as the Vice-President of the National Cancer Registry. He is also well known internationally in the field of oncology and he is an active member of the American Society of Clinical oncology (ASCO) and over the last two years he was the chair of the Best of ASCO meeting in Beirut. He is also member of the European Society of Medical Oncology (ESMO) and the European Association of Hematology (EHA). He is a co-founder and chair of the advisory board of the Arab Collaborative Hematology–Oncology Group (ACHOG). Dr. Shamseddine chairs the EASO (European Arab School of Oncology) prostatic committee in Lebanon. On May 1st, 2012, Dr. Shamseddine was elected as a fellow of the Royal College of Physician in London (FRCP).