Management of Metastatic Hormone-Sensitive Prostate Cancer

Brandon Bernard · Christopher J. Sweeney

Published online: 13 February 2015
© Springer Science+Business Media New York 2015

Abstract In 2014, prostate cancer will affect roughly 15% of American men during their lifetimes with about 230,000 new cases and 29,000 deaths per year. If required, most can be treated with curative surgery or radiotherapy. Upon relapse, androgen deprivation therapy (intermittent or continuous) is the cornerstone of treatment for hormone-sensitive disease. Response is variable and treatment is associated with a significant risk of toxicity. Recently, significant advances in survival have been demonstrated with chemohormonal therapy in men with high-volume disease. In addition, new findings have informed the approach to preventing bone complications in patients on therapy for metastatic hormone-sensitive prostate cancer. Devising clinical prediction tools and biomarkers is needed to select patients most likely to benefit from certain therapies and allow for a personalized approach.

Keywords Metastatic hormone-sensitive prostate cancer · Androgen deprivation therapy · Chemohormonal therapy · Bone health

Introduction

In 2014, an estimated 233,000 men in the USA will be diagnosed with prostate cancer, most presenting with early-stage disease [1]. If low risk, active surveillance and watchful waiting are appropriate strategies in cases detected by prostate-specific antigen (PSA) screening [2•]. For those requiring treatment, cure can be achieved with surgery or radiotherapy plus or minus androgen deprivation therapy (ADT). However, a proportion will recur locally or in distant sites as occult or overt metastatic hormone-sensitive prostate cancer (mHSPC). In addition, approximately 5% of new diagnoses will present as de novo metastatic disease [1]. At such a time, treatment is palliative, with the goal of prolonging quantity and maintaining quality of life. Overall, prostate cancer is the fifth leading cause of cancer death in the USA at about 29,000 deaths per year [1].

Upon recurrence, the mainstay of treatment is ADT by surgical or medical castration with a luteinizing hormone-releasing hormone (LHRH) agonist or gonadotropin-releasing hormone (GnRH) antagonist. This strategy can result in durable and prolonged disease control. An antiandrogen may also be added for complete androgen blockade (CAB) in the setting of rising PSA or clinical progression. Until recently, this has been the standard of care for both low- and high-volume mHSPC [3, 4]. Unfortunately, resistance ultimately occurs and patients die of castration-resistant prostate cancer (CRPC).

This review highlights recent advances in the treatment of mHSPC, specifically evaluating the role of ADT alone, the emerging use of chemohormonal therapy (CHT), strategies to mitigate adverse effects of ADT, and exciting new developments on the horizon.

Androgen Deprivation Therapy

Intermittent vs. Continuous

Early on, it was recognized that castration resulted in regression of prostate cancer [5]. Given its efficacy and relatively low treatment burden, ADT henceforth emerged as the
standard of care for mHSPC, despite a lack of randomized, placebo-controlled trials. Recently, it was found that PSA screening has resulted in stage migration and an improvement in overall survival (OS) in mHSPC [6]. Response to ADT is variable, with some patients living years while others months. Of note, it is recognized that those with a higher volume of metastatic disease and those with visceral metastases or bone involvement beyond the axial skeleton have inferior outcomes [7, 8].

The use of ADT in treating mHSPC is not debatable; its optimal utilization, however, remains unknown. Some disease progresses quickly in the absence of androgen suppression, while some remains quiescent for considerable time. This latter phenotype has been the focus of intermittent ADT, where treatment is only re-initiated at a predetermined time (e.g., increasing PSA). Such an approach provides patients with a treatment-free interval, alleviating side effects associated with therapy. Moreover, time off therapy provides a substantial cost advantage. The ideal patient in which intermittent ADT can be effectively deployed has been a hotly pursued research interest, with two recent trials generating meaningful results [9, 10]. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) PR-7 trial suggested intermittent ADT is non-inferior to continuous treatment in patients with biochemical relapse following radiotherapy [9•]. For patients with mHSPC, the Southwest Oncology Group (SWOG) 9346 trial was inconclusive regarding the potential non-inferiority of intermittent therapy compared to continuous [10•]. The coprimary end point of quality of life at 3 months was, however, significant in favor of intermittent therapy, specifically regarding erectile function and mental health. A recent editorial draws attention to the low rate of cancer-specific deaths in PR-7, suggesting that the findings were in part due to its inclusion of lower-risk patients [11]. Regarding SWOG 9346, concerns have been raised that intermittent ADT may compromise OS given the statistical uncertainty; that said, it is reasonable in men placing a high priority on quality of life at the expense of a possible small effect on survival and for patients where metabolic health may potentially be more compromised with continuous dosing [11, 12].

The South European Uroncological Group (SEUG) 9901 trial was a phase 3 trial in men with locally advanced and mHSPC randomized to intermittent ADT with the anti-androgen cyproterone acetate or continuous CAB with cyproterone acetate plus an LHRH agonist [13]. With a total of 918 patients, intermittent therapy was found to be non-inferior to CAB (hazard ratio (HR) 0.90 (95% confidence interval (CI) 0.76–1.07); p=0.25). In addition, men on the intermittent arm described better sexual function, with 28% being off treatment for greater than 5 years. This trial has come under criticism, specifically regarding the use of cyproterone acetate, the heterogeneity of the patient population, the treatment of locally advanced disease, and the fact that non-cancer deaths were roughly twofold higher than those due to prostate cancer, possibly dampening the effect of therapy on disease-specific outcomes [11]. While this study further contributes to the body of evidence evaluating intermittent ADT in select patients, its use of outdated drugs (cyproterone acetate) and treatment paradigms (ADT monotherapy for T3 disease) in an 89% M0 population makes interpreting and applying the results to patients with mHSPC challenging.

Earlier this year, a meta-analysis sought to consolidate data on intermittent compared to continuous ADT in locally advanced, recurrent, or mHSPC [14]. Thirteen trials were captured containing 6419 patients with HSPC. As a whole, no difference was observed for OS, cancer-specific survival, and time to progression (TTP) between intermittent and continuous ADT. Unfortunately, only four studies focused exclusively on metastatic disease, and of these, only two had survival data allowing for meta-analysis; OS was comparable with intermittent or continuous treatment (fixed effect: HR 1.10 (95% CI 0.98–1.24; p=0.11)) with no heterogeneity (chi²=0.02, df=1, p=0.88, I²=0%). Importantly, there appeared to be a lower death rate due to cardiovascular events with intermittent therapy (fixed effect: RR=0.80 (95% CI 0.67–0.94); p=0.007; NNH=33), but trials contained a high degree of heterogeneity (chi²=6.67, df=3 (p=0.08); I²=55%). Sexual activity as a measure of quality of life seemed higher in those on intermittent therapy, while the prevalence of hot flushes was the only adverse event that was lower on random-effects model analysis. As expected, the authors proposed that those with a low burden of disease may be the ideal candidates for an intermittent therapy strategy.

Moving forward, the use of intermittent vs. continuous ADT in men with mHSPC will depend on patient factors (e.g., emphasis placed on quality of life), disease factors (e.g., Gleason score and PSA), response to initial therapy, and competing risks of death—specifically in those with a history of cardiovascular disease or metabolic syndrome. Careful discussion with the patient surrounding the risks and benefits of a given strategy is required, and constant re-evaluation is warranted.

Agnostic vs. Antagonist

Another consideration when administering ADT is the use of an LHRH agonist vs. a GnHR antagonist. Degarelix is an intramuscular antagonist FDA approved for the treatment of advanced prostate cancer in 2008 [15]. At that time, results of the CS21 trial showed comparable efficacy of degarelix in terms of maintaining castrate levels of testosterone at 1 year as the LHRH agonist leuprolide. Follow-up results of an extension trial with crossover from leuprolide to degarelix are available; degarelix continued to be well tolerated at 5 years, and crossover appeared to confer a significant PSA progression-free survival (PFS) gain (HR 0.20 to 0.09; p=0.002) [16]. The authors
concluded that the benefit afforded by degarelix at 1 year persisted at year 5. Caution should be exercised, though, in interpreting the clinical significance of a PSA PFS gain, as this end point was almost entirely driven by PSA failure as opposed to death. Moreover, only 20% of patients had metastatic disease, so no definitive conclusion can be made for this subgroup.

A pooled analysis sought to clarify if a safety and efficacy discrepancy exists between LHRH agonists and degarelix [17]. Five randomized trials including 1925 patients with advanced prostate cancer were analyzed. On multivariate analysis, the PSA PFS (HR 0.71 (95% CI 0.54–0.94); p=0.017) and OS (HR 0.47 (95% CI 0.25–0.90); p=0.023) advantage conferred by degarelix persisted when accounting for disease stage. In this retrospective study, there were 37 deaths, of which only 4 were a consequence of prostate cancer. Just shy of one third of patients analyzed had baseline cardiovascular disease, and this subset trended toward improved OS with degarelix over LHRH agonists (HR 0.40 (95% CI 0.16–1.01); p=0.051). This study first and foremost illustrates the overall excellent outcome for patients with locally advanced or relapsed prostate cancer, and no strong statements can be made about the impact of these agents on prostate cancer deaths. Furthermore, as only 23% of a heterogeneous patient population had metastatic disease, so no definitive conclusion can be made for using degarelix or intermittent ADT in this subgroup.

Cost-utility is another factor that requires consideration when implementing ADT. A cost-effectiveness model was designed to evaluate degarelix and LHRH agonists plus anti-androgen flare coverage use in the UK based on data from the CS21 and its associated extension study [15, 16, 18]. The authors assessed two subgroups: the entire intention-to-treat (ITT) population and those defined as a high-risk subgroup with a PSA >20 ng/mL. This analysis found degarelix to have superior cost-effectiveness over LHRH agonists plus temporary anti-androgen use in the treatment of locally advanced and metastatic prostate cancer in both the entire ITT cohort and the high-risk subgroup. This finding persisted even when narrowly examined in the context of testosterone flare prevention. The authors rightly recognized limitations such as the use of a single trial cohort of uncertain quality and limited duration, minimal inclusion of patients with metastatic disease, and that most patients in the LHRH agonist arm of CS21 did not receive concomitant anti-androgen therapy to prevent flare. They interpreted the cost savings from degarelix as stemming from a lower likelihood of progression and thus less utilization of health-care resources and subsequent lines of therapy. However, it should be recognized that projected cost is an ever-changing landscape with hormonal agents such as abiraterone acetate and enzalutamide moving to the prechemotherapy setting. Moreover, it can be argued that data is lacking in both maturity and quantity to make such conclusions regarding the purported benefit of degarelix on PFS.

Lastly, the generalizability and applicability of this data to a US setting is unknown given differences in health-care delivery costs between the USA and the UK National Health Service.

Given the low rate of prostate cancer-specific mortality in the studies evaluated, questionable clinically meaningful benefit of degarelix in terms of outcomes, and higher upfront cost of degarelix, it is an option but currently cannot be justified as the standard of care in mHSPC. Based on the data, consideration can be made for using degarelix or intermittent ADT in patients with underlying cardiovascular disease; as both are viable options, choice is dependent on patient preference (including frequency of dosing) and cost. Moreover, it is a safe and effective option as an induction agent prior to transitioning to a longer-term LHRH agonist and thus is an alternative to concomitant use of anti-androgens in the prevention of the flare phenomenon from transient rises in circulating testosterone seen with LHRH agonists [19].

Chemohormonal Therapy

The role of docetaxel chemotherapy in improving OS in men with metastatic CRPC was established in 2004 [20, 21]. Over the years, the definition of “high volume” has varied, with one study classifying extensive disease as that which includes the appendicular skeleton and/or viscera, while another labeled it as three or more bone metastases and/or visceral involvement [7, 8]. Recently, the E3805 (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)) trial defined high volume as visceral metastases, four or more bone metastases with at least one beyond the pelvis and vertebral column, or both [22••].

In vivo studies in mouse models demonstrated an improvement in TTP with the use of concurrent ADT and paclitaxel chemotherapy compared to a sequential approach [23]. Early efforts to harness this strategy failed to show benefit in a randomized, controlled trial [7]. However, this trial suggested a potential benefit of chemohormonal therapy (CHT) in the subset of patients with high-volume disease (defined as three or more bone metastases or visceral involvement) but lacked statistical significance.

The CHAARTED trial was presented at the 2014 ASCO Annual Meeting and was the first trial to demonstrate an improvement in OS in patients with high-volume mHSPC [22••]. The rationale for this study was that targeting de novo androgen-independent clones up front with chemotherapy may permit more prolonged prostate cancer control with ADT. Moreover, a proportion of patients are too frail to receive chemotherapy if a sequential approach is employed. A theoretical disadvantage of CHT is that ADT halts cell cycling, thereby decreasing cellular sensitivity to cytotoxic...
chemotherapy. Furthermore, there is currently no predictive model to identify patients that will achieve a prolonged response to ADT alone. In the future, serial biopsies of metastatic sites or assessment of circulating tumor DNA may assist in selecting patients most likely to benefit from CHT [24].

In CHAARTED, 790 men with mHSPC were randomized one to one to ADT plus docetaxel 75 mg/m² every 21 days for a maximum of 6 cycles or ADT alone. Patients were stratified by metastases volume (high vs. low), age, ECOG performance status, history of CAB, skeletal-related event (SRE) prevention, and prior use of adjuvant ADT. The primary end point was OS. After a median follow-up of 29 months, it was found that ADT plus docetaxel conferred a 13.6-month median OS benefit over ADT alone (HR 0.61 (95 % CI 0.47–0.80); p=0.0003). On subgroup analysis, patients with high-volume disease derived a 17-month gain in median OS (HR 0.60 (95 % CI 0.45–0.81); p=0.0006); median OS in the low-volume population has not yet been reached. Additionally, secondary end points of median time to CRPC and median time to clinical progression were both in favor of CHT (HR 0.56 (95 % CI 0.44–0.70) and 0.49 (95 % CI 0.37–0.65), respectively). This effect was even more pronounced in high-volume patients, where median time to symptomatic or radiographic progression was 32.7 months with CHT vs. 19.8 months with ADT alone. Overall, treatment was well tolerated. This study demonstrated a significant improvement in OS for men with mHSPC, especially in those with high-volume disease. Eligible patients should be robust enough to tolerate docetaxel, and the benefit in those with low-volume disease remains to be seen. Speculation exists as to whether early docetaxel use permitted more non-LHRH therapy in high-volume disease with consequent decrease in early prostate cancer deaths. Furthermore, it is unknown whether relapsed disease after greater cytoreduction with CHT is more sensitive to second-line chemotherapy or other hormonal agents such as abiraterone acetate and enzalutamide. Chemohormonal therapy is now currently recommended by the National Comprehensive Cancer Network (NCCN) as first-line therapy for high-volume mHSPC [25].

Interestingly, the results of CHAARTED contrast those in the French study GETUG-AFU 15 [26••]. Here, a similar randomization and treatment algorithm was used, a difference being that patients were eligible for up to 9 cycles of docetaxel in the CHT arm. A total of 385 patients were randomized to either CHT or ADT alone, with a median OS of 58.9 months in the CHT arm vs. 54.2 months in the ADT-alone arm (HR 1.01 (95 % CI 0.75–1.36); p=0.955). While no OS benefit was seen with CHT, combination therapy was associated with an improvement in TTP. Interestingly, the progression-hazards model was not proportional, suggesting a waning effect of docetaxel prior to progression. The authors speculated that a lack in statistical power due to an underestimation of survival in the ADT-alone arm may, in part, have accounted for the discrepancy in outcomes. Notably, only 20 % of patients were Glass prognostic group poor (appendicular disease, performance status of 1 or greater, and PSA 65 ng/mL or greater), and this might possibly explain the higher-than-expected survival rates [27]. Additional considerations include the contribution of non-cancer deaths in an elderly population with comorbidities and the effect of serious adverse events on survival in the CHT arm. Indeed, there were four treatment-related deaths and five non-cancer deaths in the CHT compared with none in the ADT-alone arm, effectively diluting the effect of CHT on OS.

**Bone Health**

A diagnosis of metastatic prostate cancer has implications with respect to fracture risk, both from osteoblastic bone lesions and from increased osteoporosis risk with prolonged ADT [28]. As such, attempts to minimize the morbidity associated with treatment-related osteoporotic fracture and disease-related SRE are paramount. Currently, the National Osteoporosis Foundation (NOF) guideline on prevention and treatment of osteoporosis recommends consideration of FDA-approved medical therapies in the following settings: history of vertebral or hip fracture, femoral neck or spine T score of ≤2.5, and Fracture Risk Algorithm (FRAX; http://www.shef.ac.uk/FRAX/) 10-year probability of a hip fracture ≥3 % or 10-year probability of any major fracture ≥20 % [29]. In mHSPC, the question of whether bisphosphonates are beneficial was addressed in the CALGB 90202 (ALLIANCE) trial [30••]. Here, men that started ADT within 6 months of study entry were randomized to zoledronic acid 4 mg intravenously every 4 weeks or placebo. The primary end point showed that zoledronic acid conferred no benefit over placebo in time to first SRE (31.9 vs. 29.8 months, respectively) (HR 0.97 (95 % CI 0.81–1.17); p=0.39). Overall survival was also similar between the two treatment groups. Therapy was generally well tolerated, with equal rates of adverse events. The authors concluded that osteoclast-targeted therapy is not indicated to prevent SRE in the mHSPC setting. As such, treatment recommendations are driven by osteoporotic fracture risk prevention as outlined above rather than skeletal-related events. In general, suplementation with calcium and vitamin D is reasonable in men with mHSPC prior to commencing ADT.

**Side Effects and Their Management**

The detrimental effects of ADT have been well described. Given the widespread use of ADT and continued improvements in survival for men with metastatic prostate cancer, side effect mitigation is vital. The high prevalence of hot flushing and its potential for negatively impacting quality of life were
addressed in a randomized trial looking at venlafaxine and soy protein in men on ADT, with no improvement in severity of symptoms seen with either agent [31]. A review of the effects of exercise in ameliorating ADT-associated adverse events identified ten studies that overall demonstrated an improvement in fitness, lean body mass, and fatigue with exercise [32]. There was insufficient evidence to support a benefit on bone health, metabolic profile, and quality of life. Although the majority of patients in the studies assessed did not have metastatic disease, the multitude of health benefits associated with exercise justifies its recommendation as an adjunctive therapy given a median life expectancy of years in men with metastases.

More broadly, a review by Nguyen et al. aimed to synthesize an inventory of adverse effects of ADT and a variety of strategies to combat them [33]. For each known side effect, studies with the highest-quality evidence were compiled and evaluated. A synopsis of evidence-based tactics included in this review is listed in Table 1. Although this review was concerned with ADT use in all comers, the information presented is pertinent to the metastatic population given the expected amount of time on treatment and a heightened emphasis on quality of life. Of course, many of the strategies listed are vague with target end points that are difficult to measure in clinical trials. Therefore, side effect management should be individualized after a careful discussion assessing severity of symptoms, impact on quality of life, disease status, and co-morbidities. Oftentimes, recruitment of a multidisciplinary team of health-care professionals consisting of physicians, nurses, dieticians, physiotherapists, and counsellors, to name but a few, is likely to yield the greatest results in terms of objective measures and patient satisfaction.

Lastly, patients treated with ADT may be at heightened risk of cardiovascular complications such as myocardial infarction (MI) and stroke. A large cohort study from Denmark identified 31,571 patients with prostate cancer of which 36 % received medical or surgical castration [34]. The study found a 31 % increased risk of MI and 19 % increased risk of stroke associated with ADT on multivariate analysis (HR 1.31 (95 % CI 1.16–1.49) and 1.19 (95 % CI 1.06–1.35), respectively), with a more pronounced effect seen in those without a known history of cardiovascular disease. Surgical castration was not associated with increased risk. As with other studies, numbers with distant disease (classified as T1–4, N0–3, M1) were limited (14 %), and no subgroup analysis was performed in this population. In addition, another limitation listed is a lack of

### Table 1: Adverse events associated with ADT and evidence-based treatments to consider [33]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased bone mineral density</td>
<td>• Calcium 1000–1200 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Vitamin D 800–1000 IU daily</td>
</tr>
<tr>
<td></td>
<td>• Osteoporosis treatment for FRAX risk of hip fracture &gt;3 %</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>• Aerobic and resistance exercise</td>
</tr>
<tr>
<td></td>
<td>• Adherence to the Adult Treatment Panel III and American Heart Association/American College of Cardiology guidelines for lipid monitoring and targets</td>
</tr>
<tr>
<td></td>
<td>• Diabetic screening in high-risk patients as per the American Diabetes Association guidelines</td>
</tr>
<tr>
<td></td>
<td>• Closer diabetic monitoring and glycemic control in diabetics</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Limiting time of ADT necessary to maintain disease control</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Aerobic and resistance exercise</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>• Medroxyprogesterone</td>
</tr>
<tr>
<td></td>
<td>• Venlafaxine</td>
</tr>
<tr>
<td></td>
<td>• Gabapentin</td>
</tr>
</tbody>
</table>

### Table 2: Ongoing or opening trials in mHSPC

<table>
<thead>
<tr>
<th>Group</th>
<th>Phase</th>
<th>Arms</th>
<th>Number of patients</th>
<th>Primary end point</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG-0925a</td>
<td>2</td>
<td>CAB±IMC-A12c</td>
<td>180</td>
<td>PSA&lt;0.2 ng/mL (negative)</td>
<td>Completed</td>
</tr>
<tr>
<td>SWOG-1216b</td>
<td>3</td>
<td>ADT+TAK700f vs. ADT+bicalutamide</td>
<td>1486</td>
<td>OS</td>
<td>Recruiting (USA)</td>
</tr>
<tr>
<td>PEACE-1c</td>
<td>3</td>
<td>ADT±abiraterone; ±local RT; ±abiraterone+local RT</td>
<td>916</td>
<td>OS and PFS</td>
<td>Pending recruitment (Europe)</td>
</tr>
<tr>
<td>Latituded</td>
<td>3</td>
<td>ADT±abiraterone</td>
<td>1270 (&gt;2 poor risk factors: visceral metastases; &gt;2 bone metastases; Gleason score &gt;7)</td>
<td>OS and radiographic PFS</td>
<td>Starting (Europe)</td>
</tr>
<tr>
<td>ENZAMET</td>
<td>3</td>
<td>ADT+enzalutamide vs. ADT+nonsteroidal anti-androgen</td>
<td>1100</td>
<td>OS</td>
<td>Pending (USA, Canada, Australia)</td>
</tr>
</tbody>
</table>

a NCT01120236; b NCT01809691; c NCT01957436; d NCT01715285; e Investigational monoclonal antibody to insulin-like growth factor receptor 1; f Androgen biosynthesis inhibitor
other known cardiovascular prognostic factors such as obesity and smoking. Moreover, a distinction should be made between a potential increased risk of MI and cardiovascular death, as a recent meta-analysis found no association between the latter and ADT use in patients with high-risk, localized disease [35]. Of course, the heterogeneity of a North American population must also be taken into consideration when attempting to apply these results. While this study adds to the growing body of literature linking ADT and increased risk of stroke or MI, there is currently no level 1 evidence indicating a causal link between these variables.

**Future Directions**

The development of second-generation anti-androgens such as enzalutamide has revived interest in the use of anti-androgen monotherapy for mHSPC. Tombal et al. recently published results of an open-label, single-arm, phase 2 study of first-line enzalutamide monotherapy in M1 prostate cancer or relapsed disease after local therapy [36]. The primary outcome was the number of patients that achieved an 80% or greater reduction in PSA at week 25. On primary analysis, 62 of the 67 men enrolled met the primary end point. Seventy-six percent of patients included had Gleason 7 or less at initial diagnosis, potentially indicating a more favorable risk cohort. That said, study participants were reasonably heterogeneous, with 39% having M1 disease upon study entry. Bone mineral density was maintained although a fair number of patients had grade 1–2 gynecomastia, nipple pain, fatigue, and hot flush. Given its limitation as a phase 2 trial without randomization to ADT as the standard of care, Attard rightly stressed that its present use remains in the domain of clinical trials [37]. It is important to keep in mind, however, that these results do identify a potential signal of efficacy. As such, follow-up in the form of a randomized, phase 3 trial is justified. Given the variety of resistance mechanisms employed in the development of CRPC, the Medical Research Council STAMPEDE trial was designed as a multistage, multiarm study to assess the efficacy of ADT in combination with other agents in any attempt to stymie such compensatory mechanisms and improve disease control (ClinicalTrials.gov Identifier: NCT00268476). Other active or pending trials in mHSPC are listed in Table 2.

Biological interrogation in the form of sequential biopsies or circulating tumor DNA (the so-called liquid biopsy) may provide further insight into the emergence of resistant clones and tailored therapy. The ability to risk stratify based on biomarkers and other prognostic features will allow for improved matching of patient to therapy, such as the possible use of enzalutamide monotherapy in those with low-risk disease compared with CHT for those with high-volume, high-risk disease [37]. Finally, the definition of “high-volume” disease is being refined, with plans for a further cross-trial analysis allowing for a consistent and applicable framework that may better select patients most likely to benefit from CHT.

**Conclusions**

The discovery of new therapies and refinement of existing ones continue to improve outcomes in men with mHSPC. While ADT remains the backbone of treatment, the sequence of other active agents is still unknown. A major breakthrough was seen in 2014 with the finding that first-line CHT with docetaxel and ADT considerably improves survival in men with high-volume mHSPC. While the benefit of CHT in low-volume disease remains to be seen, it is a definite consideration in chemofit patients with high-volume disease. Clinical discretion is warranted in the elderly patient with high-volume disease, with risks and benefits of CHT weighed against comorbidities and competing risks of death. Mindfulness of bone health and adverse effects related to therapy is an important component of care for men with mHSPC. The discovery of new therapies and refinement of existing ones continue to improve outcomes in men with mHSPC. The development of novel biomarkers will further assist clinical decision-making and optimize outcomes long term.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Dr. Brandon Bernard declares no potential conflicts of interest. Dr. Christopher Sweeney is a consultant with compensation from Sanofi, Janssen Pharmaceutical Companies, BIND Therapeutics, Inc., Astellas Pharma, and Bayer.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**References**

Papers of particular interest, published recently, have been highlighted as:
- Of importance
- Of major importance


10. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013;368(14):1314–25. doi:10.1056/NEJMoa1212299. This study was inconclusive as to whether intermittent androgen deprivation therapy was non-inferior to continuous therapy in men with metastatic hormone-sensitive prostate cancer. Thus, no definitive recommendation can be made in the metastatic population. Bearing in mind the possibility of slight inferiority of intermittent therapy with respect to overall survival, quality of life was mildly better and may be a reasonable compromise in patients with bothersome side effects.


22. Sweeney C, Chen Y, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial. ASCO Meet Abstr. 2014;32(15 suppl):LB2. Presented at the plenary session of the 2014 ASCO Annual Meeting; this trial showed an unprecedented survival advantage with the use of upfront chemohormonal therapy in patients with metastatic hormone-sensitive prostate cancer. Those with a high volume of disease derive the greatest benefit. These results were paradigm-shifting for the approach to patients with early metastatic prostate cancer.


26. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(2):149–58. doi:10.1016/S1470-2045(12)70560-0. This manuscript was negative with respect to an overall survival advantage with chemohormonal therapy in metastatic hormone-sensitive prostate cancer. However, it demonstrated the prolonged survival that can be achieved with androgen deprivation alone compared to a study with a larger proportion of higher volume disease.


