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Research Article

Metastatic hormone-sensitive prostate cancer: A Systematic Review of the Value of Current Therapies

Wafaa Kaikani[1], Mohammed sqalli Houssaini[1] and Khalid Hadadi[2]

[1] *Faculté de médecine, Université Mohammed VI des Sciences de la Santé. Casablanca. Maroc*

[2] *Faculté de médecine, Université Mohammed V, Rabat. Maroc*

Abstract

PROSTATE cancer (PC) is the second most frequent cancer in males. Based on GLOBOCAN 2018 estimates, 1,356,176 new cases of prostate cancer and a mortality of 378,553 are expected in 20201. Despite an overall 5-year survival rate of 98.2%, mHSPC has a dismal 30% 5-year survival rate2. Metastatic hormone-sensitive prostate cancer (mHSPC) is the disease space whereby men have metastatic prostate cancer and have never received (ie. are sensitive to) androgen deprivation therapy (ADT). mHSPC previously constituted ~30% of prostate cancer cases , however, from 2004-2012 secondary to PSA testing, the estimate was ~5% of cases in USA3. Many experts in the field suggest that with decreased PSA screening over the last few years, as a result of the United States Preventative Services Task Force (USPSTF) Grade D recommendation for PSA screening (subsequently upgraded to C 4), that these estimates are likely to once again increase 5. At diagnosis, 77% of prostate cancer cases are localized; in 13%, the cancer has spread to regional lymph nodes, and 6% have distant metastasis. The 5-year relative survival rate for localized and regional prostate cancer is 100%, compared with 30.5% for metastatic cases. 2Conventional treatment of mHSPC has been ADT since the landmark discovery by Huggins and Hodges in 1941 demonstrating the hormonal sensitivity of PC. Since 2015; we have seen several landmark trials published that have added therapies to ADT for these men, favorably impacting overall survival (OS). Men are now faced with decisions of androgen-deprivation therapy alone or combinations with either docetaxel, abiraterone, enzalutamide, or apalutamide, and there are now additional complex decisions around triple combination or sequential therapy with induction androgen-deprivation therapy/docetaxel plus a potent androgen-receptor inhibitor or whether single-agent chemotherapy or androgen-receptor inhibitor use with androgen-deprivation therapy is sufficient. These decisions are presently based on costs, availability and approvals, disease risk/volume, patient age and comorbidity, and of course shared decision-making. This article will discuss the effect of docetaxel and inhibitors of androgen signaling developed in the past 5 years among men with mHSPC and review the subsequent literature following reporting of these trials.

Methods

We performed PubMed and Web of Science database searches of the peer reviewed mHSPC literature on the combination therapies that use ADT with another therapeutic agent .Original studies of this subject as well as a small number of reviews were analyzed for strengths and weaknesses. We provide a comprehensive review of prospective, phase III trials of combination therapy with ADT in the setting of mHSPC,

Combination therapies ongoing and to be considered in the near future are examined.

Results

Agents with proven survival benefit

Docetaxel

Docetaxel is a chemotherapy agent that promotes and stabilizes microtubule assembly, thus inhibiting the mitotic cell division. This was the first drug to demonstrate an improvement in OS in prostate cancer6. The benefit of adding docetaxel to lifelong ADT for mHSPC was established by three phase III trials:

Correspondence to: Université Mohammed VI des Sciences de la Santé. Casablanca. Maroc Tel: 661479990 E-mail: wafaakaikani@yahoo.fr

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GETUG-AFU 15, CHAARTED and STAMPEDE In 2015, the CHAARTED trial changed the landscape of treatment of men with mHSPC. This trial randomized 790 men with mHSPC to receive either ADT + docetaxel or ADT alone, with OS as an endpoint. After a median follow-up of 28.9 months, the median overall survival was 13.6 months longer with ADT-DOCE than with ADT alone . Furthermore, the median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the ADT-DOCE group, as compared with 11.7 months in the ADT-alone group . This trial ushered into clinical practice ADT-DOCE as the standard of care for men with mHSPC7. In 2018, the CHAARTED trial published an updated survival analysis: at a median follow-up 53.7 months, the HR for OS was 0.72 favoring docetaxel over ADT standard of care, a 28% risk reduction of death compared to 39% in the first analysis. In subset analyses, the benefit was observed across all subgroups with two notable exceptions. Specifically,atients with a low burden of disease or those who had prior local therapy did not seem to experience a benefit through the addition fdocetaxel to standard ADT8. Following reporting of the USA led CHAARTED trial , the UK STAMPEDE trial reported their OS outcomes of ADT-DOCE vs ADT alone9. The STAMPEDE study uses a unique phase II/III trial design to investigate new agents under the umbrella of a single trial. Additional arms are added to the study as new approaches are designed. STAMPEDE uses a multi-arm, multi-stage platform, recruiting men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term ADT. Patients were randomized 2:1:1:1 to standard of care (SOC; ADT alone), SOC + zoledronic acid (SOC + ZA), SOC + docetaxel (ADT-DOCE), or SOC with both zoledronic acid and docetaxel (SOC + ZA + Doc). There were 2,962 men randomized between 2005 and 2013, including 1,817 (61%) men with M+ disease, 448 (15%) with N+/X M0, and 697 (24%) men who were N0M0. Over a median follow-up of 43 months (IQR 30–60), there were 415 deaths in the control group, with a median OS of 71 months These results recapitulated the findings of CHAARTED, as well as noting that zoledronic acid did not show an OS improvement when added to ADT alone. A third study using this approach; The GETUG-AFU15 phase III RCT was a French initiative, also testing ADT-DOCE vs ADT alone10. Among 385 patients over a median follow-up of 83.9 months, the median OS was 62.1 months for ADT-DOCE and 48.6 months for ADT alone , thus failing to find a significant OS advantage for the addition of ADT-DOCE. The authors also analyzed several subgroups, post-hoc survival analyses, finding no ADT-DOCE advantage for men with high-volume disease, low-volume disease nor for those with de novo metastatic disease In GETUG-AFU and CHAARTED side effects were more common in the chemohormonal therapy arm. The most common grade 3 or greater adverse events in GETUG-AFU and CHAARTED were neutropenia at 32% and 12%, febrile neutropenia at 7% and 6%, and fatigue at 7% and 4%, respectively. In each study there were negligible grade 3 or greater adverse events in the ADT arm. Diarrhea, stomatitis, and motor and sensory neuropathy were the less common adverse effects, which developed in less than 1% of the population in the CHAARTED study. STAMPEDE reported additional toxicity in the chemohormonal therapy arm compared with that of ADT alone (grade 3 or greater adverse events in 52% vs 32% of patients). This was mostly due to toxicity during the first 6 months on trial, when grade 3 or greater adverse events were reported in 36% of the chemohormonal therapy arm vs 17% in the ADT arm. A 1-year analysis of 1,998 patients with available profiles revealed a balanced rate of grade 3 or greater adverse events of 10% in each arm. There were 2 deaths in the chemohormonal therapy arm and 72 patients (13%) discontinued treatment. A meta-analysis on the individual data of patients who were included in these three trials (GETUG-AFU-15, CHAARTED and STAMPEDE) confirmed the OS benefit obtained with the combination of Docetaxel plus ADT in men with mHSPC11. The combined patient data from these trials showed a 23% reduction in the risk of death, which translated to an absolute improvement in 4-year survival of 9%. A 36% reduction in the risk of progression was also reported, with a 16% reduction in absolute 4-year failure rates.

Abiraterone

Abiraterone (ABI) inhibits cytochrome P-450 CYP17, a critical enzyme in androgen biosynthesis in the testes, adrenal gland and prostate. Its active D4A metabolite contributes to its antitumor effects through blockade of multiple steroidogenic enzymes and antagonism of the androgen receptor. Approval of this drug in the prechemotherapy and post-chemotherapy era led to mHSPC its application to earlier disease 12, 13.The addition of abiraterone to ADT has demonstrated to improve OS in two phase III trials, LATITUDE and STAMPEDE. Both studies randomized participants to ADT alone, or in combination with abiraterone 1000 mg plus prednisone 5 mg daily, until disease progression or unacceptable toxicity. LATITUDE was an international trial evaluating ADT-ABI compared to ADT alone among men with high-risk mHSPC 12. High-risk was defined as meeting at least two of three criteria: (i) Gleason score ≥8, (ii) presence of ≥3 lesions on bone scan, or (iii) presence of measurable visceral lesions. Patients were randomized 1:1 to either ADT-ABI or ADT + placebo . The co-primary endpoints were OS and radiographic progression-free survival (rPFS). Secondary endpoints included time to pain progression, PSA progression, next symptomatic skeletal event, chemotherapy, and subsequent prostate cancer therapy. Over a median follow-up of 30.4 months, patients treated with ADT-ABI had a 38% risk reduction of death compared to ADT + placebo. Median OS was not yet reached in the ADT-ABI arm, compared to 34.7 months in the ADT + placebo arm. There was also a 53% risk of reduction of radiographic progression or death for patients treated with ADT-ABI compared to ADT alone. Additionally, there was a statistically significant improvement across all secondary end points for ADT-ABI. Reporting at the same time as LATITUDE was the STAMPEDE abiraterone acetate arm 13. Inclusion criteria for the STAMPEDE ABI study

included men with locally advanced or metastatic prostate cancer, including newly diagnosed with N1 or M1 disease, or any two of the following: stage T3/4, PSA ≥ 40 ng/mL, or Gleason score 8-10. Patients undergoing prior radical prostatectomy or RT were eligible if they had more than one of the following: PSA ≥ 4 ng/mL and PSADT < 6 months, PSA ≥ 20 ng/mL, N1, or M1 disease. These patients were then randomized 1:1 to SOC vs ADT-ABI . Treatment with RT was mandated in patients with N0M0 disease, while strongly encouraged for N1M0 patients. Primary outcomes were OS and failure-free survival (FFS), where failure was defined as PSA failure, local failure, lymph node failure, distant metastases or prostate cancer death. Over a median follow-up of 40 months, there was a 37% relative improvement in OS favoring ADT-ABI. Furthermore, ADT-ABI demonstrated a 71% improvement in FFS as well as significantly decreasing SREs among the entire cohort and specifically in the M1 cohort. Based on the interim analysis findings of LATITUDE, the study was unblinded at the time of the first interim analysis. At the ASCO 2018 annual meeting, longer-term efficacy analyses from this phase III trial were presented 14. Median follow-up at the time of the second analysis was 41.0 months, 10.6 months longer than the initial analysis. There were 205 patients (34%) in the ADT-ABI arm and 70 patients (12%) in the ADT + placebo arm (of whom 57 patients (81%) had crossed over to ADT-ABI) who remained on treatment. Importantly, updated OS results continued to favor ADT-ABI compared to ADT alone (NR vs 36.7 months .The results of the secondary endpoints also continued to favor ADT-ABI: (time to pain progression, time to SRE , time to chemotherapy initiation , time to subsequent prostate cancer therapy)

Enzalutamide

Enzalutamide is a new generation antiandrogen that is approved for the treatment of mCRPC 15,16,17. The benefit of adding enzalutamide to ADT for the treatment of mHSPC patients has been established by two phase III studies, ARCHES and ENZAMET 18,19 . ENZAMET randomly assigned 1,125 patients from March 31, 2014 to March 24, 2017: 562 in the non-steroidal anti-androgen and 563 in the enzalutamide arm. The treatment groups were well balanced for all important baseline factors. In the non-steroidal anti-androgen arm 44% of patients were planned for early docetaxel, compared to 45% in the enzalutamide arm; 53% of patients in the non-steroidal anti-androgen arm were high volume metastatic burden, compared to 52% in the enzalutamide arm. Criteria for early reporting were met at the first interim analysis after a median follow-up of 33 months – 143 deaths in the non-steroidal anti-androgen arm compared to 102 deaths in the enzalutamide arm.

Overall survival was significantly prolonged in the enzalutamide arm compared to the non-steroidal anti-androgen arm. At 3 years, 36% of patients receiving non-steroidal anti-androgen compared to 64% of men receiving enzalutamide were still on their assigned study treatment. Serious adverse events (regardless of attribution) within 30 days of study treatment occurred in 42% in the enzalutamide arm, compared to 34% non-steroidal anti-androgen arm. There were 67% of patients in the enzalutamide arm that received one or more life prolonging CRPC therapies, compared to 85% in the non-steroidal anti-androgen arm, thus the OS benefits noted in this trial are unlikely to be secondary to discrepancies in subsequent therapy 18. The risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT. Similar significant improvements in radiographic progression-free survival were reported in prespecified subgroups on the basis of disease volume and prior docetaxel therapy. Enzalutamide plus ADT significantly reduced the risk of prostate-specific antigen progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and reduced risk of pain progression. More men achieved an undetectable prostate-specific antigen level and/or an objective response with enzalutamide plus ADT . Patients in both treatment groups reported a high baseline level of quality of life, which was maintained over time. Grade 3 or greater adverse events were reported in 24.3% of patients who received enzalutamide plus ADT versus 25.6% of patients who received placebo plus ADT, with no unexpected adverse events.

Apalutamide

Apalutamide, an oral nonsteroidal androgen receptor inhibitor, binds directly to the ligand-binding domain of the androgen receptor, preventing the androgen receptors nuclear translocation and DNA binding and impeding androgen receptor-mediated transcription. Apalutamide is a selective androgen-receptor (AR) antagonist that is approved for the treatment of nmCRPC, based on the SPARTAN study20. The Targeted Investigational Treatment Analysis of Novel Anti-Androgen (TITAN) study was a phase III, double-blind, randomized study designed to determine whether apalutamide, a selective next-generation androgen receptor inhibitor, plus ADT improves radiographic progression-free survival (rPFS) and overall survival (OS) compared with placebo plus ADT in men with metastatic castration sensitive prostate cancer (mCSPC). Kim Chi, MD from the British Columbia Cancer Agency presented the first results of this phase III trial. The Key eligibility of TITAN included patients that were (i) castration sensitive, (ii) had distant metastatic disease by >= 1 lesion on bone scan, and (iii) were ECOG performance status 0 or 1. An on-study requirement was that patients had continuous ADT. Patients with prior docetaxel were permitted, as were (i) patients with ADT <= 6 months for mCSPC or <= 3 years for local disease, and (ii) patients with local treatment completed >= 1 year prior. Patients were stratified by Gleason score (<=7 vs >=8), region (North America and Europe vs other countries), and prior docetaxel use.

Dual primary endpoints were rPFS and OS. Secondary endpoints were time to (i) initiation of cytotoxic chemotherapy, (ii) pain progression, (iii) chronic opioid use, and (iv) skeletal-related event. Time-to-event endpoints were estimated by Kaplan-Meier and Cox proportional hazards methods. Patients were

randomized 1:1 to apalutamide or placebo, added to ADT, in 28-day cycles. This first planned OS interim analysis took place after ~50% of expected events were 525 patients randomized to apalutamide and 527 to placebo. The median age was 68 years, 8% had prior treatment for localized disease, and 11% had prior docetaxel. With regards to disease burden, 63% had high-volume disease and 37% had low-volume disease. At the median follow-up of 22.6 months, 66% of patients on apalutamide and 46% of patients receiving placebo remained on treatment. Apalutamide significantly improved rPFS (HR 0.48, 95% CI 0.39-0.60), with a 52% reduction in risk of death or radiographic progression. Importantly, this benefit was observed across all subgroups analyzed. Median rPFS was not reached in the apalutamide group and was 22.1 months in the placebo group. Second, apalutamide significantly improved OS, with a 33% reduction in risk of death. Median OS was not reached in the apalutamide or placebo group. The TITAN study met its dual primary endpoints, demonstrating significant benefits with apalutamide + ADT in an all-comer mCSPC population; There was a significant improvement in OS, with a 33% reduction in risk of death for apalutamide, There was a significant improvement in rPFS, with a 52% reduction in the risk of progression or death for apalutamide, Secondary and exploratory endpoints also favored apalutamide – prolonged time to cytotoxic chemotherapy (61% risk reduction), PSA progression (74% risk reduction), and second progression-free survival (34% risk reduction). Treatment was tolerable and the safety profile was consistent with the known side-effects of apalutamide. Agents with proven survival benefit – Comparative data

As docetaxel and abiraterone acetate were the first two agents to demonstrate survival advantage, and subsequently be approved, for men with metastatic hormone-sensitive prostate cancer, these agents have subsequently been compared using both network meta-analysis and non-randomized within-trial comparisons from the STAMPEDE cohort. men withm HSPC.To our knowledge, there are no published direct randomized comparisons of these agents, though, undoubtedly, network meta-analyses including enzalutamide and apalutamide will shortly be forthcoming

Patient Reported Outcomes

Patient-reported outcomes (PROs) provide meaningful data about disease symptoms, treatment tolerability, and overall HRQoL. PROs are important to both clinicians and patients making treatment choices. They also have increasing importance to regulatory agencies when approving drug therapies23, including pharmaceutical labeling claims, as well as productreimbursement, and health care policy. Given that both ADT-ABI and ADT-DOCE improve OS outcomes, it becomes important to assess the impact on quality of life (QoL) metrics. A published analysis of the LATITUDE data assessing patient reported outcomes showed that patients receiving ADT-ABI had improved outcomes24. The median time to worst pain intensity progression assessed by the BPI-SF score was not reached in either the ADT-ABI group or ADT group , however with an HR of 0.63 favoring ADT-ABI. Similar findings were reported for median time to worst fatigue intensity . Finally, the median time to deterioration of functional status assessed by the FACT-P total score scale was 12.9 months in the ADT-ABI group versus 8.3 months in the ADT alone group. Similarly, QoL data from the CHAARTED trial has also been published25. Among the 790 men randomized, 90% completed FACT-P at baseline, 86% at 3 months, 83% at 6 months, 78% at 9 months, and 77% at 12 months. ADT-DOCE patients reported a statistically significant decline in FACT-P at 3 months but FACT-P did not differ significantly between baseline and 12 months. ADT-DOCE FACT-P scores were significantly lower at 3 months but significantly higher at 12 months when compared with ADT alone FACT-P scores. Furthermore, ADT-DOCE patients reported significantly lower Functional Assessment of Chronic Illness Therapy-Fatigue scores at 3 months than ADT alone patients Feyerabend et al. 26 presented results of an indirect treatment comparison of ADT-ABI and ADT-DOCE on patient-reported outcomes among men with mHSPC. The mean change from baseline was based on differences in FACT-P and BPI scores between active vs control arms in LATITUDE 12 (intention-to-treat ITT population) and CHAARTED 7. The probability of ADT-ABI being superior to ADT-DOCE at 3, 6, 9, and 12 months after treatment was based on fixed-effects Bayesian network meta-analysis. The authors found that the benefit in patient-reported outcomes with ADT-ABI vs ADT-DOCE was seen at 3 months and sustained for at least 1 year after treatment. This was consistent at each time point and for both FACT-P and BPI tools. The Bayesian probability of ADT-ABI being the better treatment for patient-reported outcomes ranged from 92.3% to 100%, with higher probabilities noted earlier in follow-up.

Apalutamide

The time to pain progression was a secondary endpoint in TITAN; PRO-related endpoints for fatigue and HRQoL were prespecified exploratory analyses. PRO instruments were collected in a rigorous way using the Brief Fatigue Inventory (BFI), the Brief Pain Inventory-Short Form (BPI-SF), and the Functional Assessment of Cancer Therapy-Prostate (FACT-P)27. These instruments were administered at baseline, frequently during the treatment phase of the study, and at multiple time points after disease progression, providing an in-depth understanding of the patient experience. Fatigue can be particularly debilitating and has been independently associated with pain and depression in patients with prostate cancer treated with ADT.7 Patients in TITAN were relatively asymptomatic at baseline with regard to fatigue. The group mean fatigue scores (based on the BFI) of patients on the TITAN trial remained stable throughout the trial in both the apalutamide- and placebo-treated groups, with no difference seen between the two groups

Cost Effectiveness

Ongoing Trials

One of the most anticipated trials currently ongoing is the PEACE-1 phase III trial (NCT01957436) assessing SOC (ADT +/- docetaxel) vs SOC + abiraterone + prednisone vs SOC + local radiotherapy vs SOC + local radiotherapy + abiraterone + prednisone for men with de novo M1 prostate cancer. The co-primary outcomes are overall and progression-free survival. This trial has a target accrual of 1,168 patients, with more than 80% of

patients already recruited. This trial will ultimately test whether ADT + abiraterone + docetaxel is even better than ADT-ABI or ADT-DOC 29.

Prognostic and Predictive Factors in mHSPC: Risk Factors in Phase 3 Trials

Several prognostic and predictive factors have been proposed in mCRPC30, whereas less information is available for mHSPC. Metastatic burden and metastasis localization, time of metastatic presentation and the Gleason score are the main prognostic factors that have been identified in clinical trials that included patients with mHSPC. However, it is currently unclear whether the prognostic significance of the Gleason score would be strengthened after the introduction of the new International Society of Urological Pathology (ISUP) classification in 2016, which distinguishes five different Gleason grade groups31. A recent meta-analysis of the aggregate data of patient subgroups from the CHAARTED and GETUG-AFU15 studies evaluated overall survival (OS) according to the metastatic tumor burden and time of metastasis occurrence (at diagnosis or after prior local treatment)32. The authors identified three prognostic subgroups: good prognosis for those with prior local treatment and low-volume disease; intermediate prognosis for those with prior local treatment and high-volume disease, or those with low-volume disease and de novo metastases; and poor prognosis for those with de novo high-volume disease. These data were recently confirmed by a retrospective cohort of 436 consecutive patients with mHSPC treated with ADT at the Dana-Farber Cancer Institute between 1990 and 201333.

Discussion

The lack of predictive biomarkers and the absence of direct comparisons among the different agents are the major current issues to be faced when selecting the best treatment for patients with mHSPC. Choices between these agents should not be based on efficacy across trials alone, given their similar benefits. The drug mechanism of action, the route of administration, the duration of treatment, the impact on quality of life and the toxicity profile are important factors to consider when selecting a therapy for a particular patient, as they are quite different among the various strategies The drug mechanism of action, the route of administration, the duration of treatment, the impact on quality of life and the toxicity profile are important factors to consider when selecting a therapy for a particular patient, as they are quite different among the various strategies. Docetaxel is likely the more cost-effective and efficient approach with androgen-deprivation therapy for men with high-volume metastatic hormone-sensitive prostate cancer; it is completed in 18 weeks with reversible—but more intense—short-term chemotherapy toxicities, is now generic and available worldwide, and is less expensive than other options. However, men with low-volume disease do not have a clear benefit from docetaxel in this setting, many men with high-volume disease would prefer not to receive chemotherapy and its toxicities7.Abiraterone is requiring prednisone and associated with mineralocorticoid-associated side effects including hypertension, hypokalemia and hepatic toxicity. Enzalutamide frequently causes fatigue, hypertension and falls; particularly in older men. Apalutamide is associated with increased risk of rash, pruritus, hot flushes, hypothyroidism and fractures. All men face a higher risk of hypertension, mild cardiovascular risk, muscle loss, fatigue, and fracture from these agents, and attention to exercise, cardiac risk reduction, and bone health and monitoring is critical.We can suggest for men with high volume disease – therapy should consist of ADT + docetaxel or abiraterone or ADT alone. For men with low volume disease – therapy should consist of ADT alone or with abiraterone. Therapy should also be chosen based on patient comorbidities, treatment-related toxicities, and patient preferences. Finally, there is still much to be learned on how the earlier use of docetaxel or abiraterone will impact downstream effects on the response in metastatic castrate-resistant prostate cancer (Table 1).The only patients who should not get combination therapy are those with significant comorbidities and a very short life expectancy, such as advanced cardiac disease or dementia, or those who understand the benefit of combination therapy but decline.

	Docetaxel	Abiraterone	Enzalutamide	Apalutamide
The route of administration	Iv	Oral	Oral	Oral
The duration of treatment	18 weeks therapy	Continuous therapy with abiraterone and prednisone (33 months)	Continuous therapy with enzalutamide (33 months)	Continuous therapy with apalutamide (22 months)
Financial issues	Possible time off work Generic and available worldwide	Prescription co-pays Generic	Prescription co-pays	Prescription co-pays
Toxicity profile	Hair loss Myelo-suppression with potential neutropenia, Fatigue Neurotoxicity	Hypertension, Hypokalemia Hepatic toxicity.	Fatigue Hypertension and falls. Patients with a history of or risk factors for seizures were excluded from controlled clinical studies	Increased risk of rash, pruritus, hot flushes, Hypothyroidism and fractures
Concurrent use of steroids	Yes	Yes challenging in diabetic or osteoporotic patients	No	No
Settings	High volume	Any	Any	Any

Conclusions

Treatment options in patients with metastatic hormone-sensitive prostate cancer have dramatically changed in the past five years. Randomized data have demonstrated a significant survival benefit to docetaxel, abiraterone acetate, apalutamide, and enzalutamide in this disease space. Despite the fact that those options are currently implemented in the international guidelines for mHSPC patients, no data on the optimal treatment sequence are available. Treatment choice is based upon indirect comparisons of randomized trials and on the specific characteristics of each patient. New biomarkers are therefore warranted to improve patients 'selection. Results of clinical trials assessing additional combinatorial therapy (ie. PEACE-1) are eagerly anticipated as we continue to strive for improved survival among prostate cancer patients with aggressive hormone-sensitive disease.

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