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Review

HOW TO OPTIMALLY SEQUENCE AVAILABLE THERAPY LINES IN ADVANCED PROSTATE CANCER

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ABSTRACT: Optimal sequencing of available therapy lines in patients with advanced prostate cancer often poses quite a challenge. The guidelines are sometimes equivocal and clinical trial data are not always applicable to a particular patient. There is a difference in availability of therapy options throughout the world. In decision making, a patient as a whole should be taken into consideration, not just the stage and biology of the disease, but also patient's age, performance status, comorbidities, previous therapy lines, drug's safety profile and patient's preferences. This review article will show certain therapeutic options in the treatment of advanced hormone-sensitive prostate cancer and castration resistant prostate cancer: non- metastatic and metastatic. An attempt will be made to clarify the optimal sequencing.

Key words: *Advanced prostate cancer; hormone sensitive prostate cancer; castration resistant prostate cancer; androgen deprivation therapy; docetaxel; cabazitaxel; Radium 223; enzalutamide; apalutamide; darolutamide; abiraterone.*

Introduction

The patients with advanced prostate cancer present a heterogeneous group. Their tumours are generally classified by sensitivity to castration as hormone sensitive or castration resistant. The patients with advanced hormone sensitive disease can have locally advanced or metastatic disease. Metastatic hormone sensitive disease can further be classified as low or high-volume disease or low or high-risk disease. The patients with castration resistant prostate cancer can have non- metastatic or metastatic disease.

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In the previous few years, a number of drugs have been approved for the treatment of patients with advanced prostate cancer, mostly novel generation antiandrogens. Novel therapies are being moved into earlier therapy lines. It is yet to be defined how to optimally sequence the therapy, but it certainly depends not only on the stage of the disease but also on patient's symptoms, comorbidities, frailty, previous therapy lines, drug's safety profile and drug availability.

In this article, there will be certain available therapeutic options presented and their possible sequencing suggested.

Methods

Literature search by keywords using PubMed was performed.

Results

Hormone sensitive advanced prostate cancer - hsmPC

Hormone sensitive metastatic prostate cancer (hsmPC) is, by definition, a metastatic prostate cancer that is sensitive to androgen deprivation therapy (ADT). It can develop after local therapy or be diagnosed as de novo metastatic disease. The latter accounts for about 5% of prostate cancer cases (1). Based on the site of the metastases, metastatic prostate cancer is classified as M1a lymph node, M1b- bone or M1c- visceral metastases.

In SWOG 8894, the trial patients with hsmPC were stratified into three prognostic groups based on the site of metastases (appendicular vs. axial), ECOG status (0 vs. 1-3), PSA level (<65 vs. 65 or higher) and GS (<8 vs. 8 or higher). The estimated 5-year overall survival rates (OS) were of 46% for patients in good prognostic group, 25% patients in intermediate prognostic group and 14% patients in poor prognostic group (2).

In patients with hsmPC, the addition of docetaxel abiraterone, enzalutamide, darolutamide and apalutamide to ADT has been explored in a number of randomised trials.

Docetaxel

In GETUG AFU 15, the trial patients with metastatic hsPC were randomised to receive ADT only or ADT with docetaxel for up to 9 three- weekly cycles. The stratification with regard to risk groups was performed according to the abovementioned criteria form SWOG 8894 trial. No survival benefit has been observed with the addition of docetaxel to ADT in the overall study population; median OS after 84 months of follow-up being 62.1 months with the addition of docetaxel and 48.6 months with ADT only (p= 0.3). The combination of ADT and docetaxel did not result in better OS, regardless of the volume of the disease, although a nonsignificant 20% reduction in the risk of death was noticed in patients with high volume disease. Both biochemical and radiological progression-free survivals (PFS) were significantly longer in ADT + docetaxel arm (3).

In CHAARTED trial, docetaxel (up to 6 three-weeks cycles) combined with ADT was compared to ADT alone as well. Upon progression, patients receiving ADT only were given chemotherapy of physician's choice. The patients were divided into risk groups based on the volume of the disease. To be classified as suffering from high volume disease, the patients should have had visceral metastases or 4 or more bone lesions with at least one beyond the vertebral bodies and pelvis. After a median follow-up of 29 months, statistically significantly longer median OS (13.6 months of prolongation) and median time of biochemical, radiographic or symptomatic progression has been observed in all patients receiving docetaxel. The most common adverse event in combination group was febrile neutropenia, grade 3 or 4 occurring in 6% of patients. After a follow-up of 54 months, the overall median OS in months was 57.6 for the combination group and 47.2 for ADT only (p = 0.0018). When stratified according to volume, in patients with high-volume disease, the median OS was 51.2 months with docetaxel vs. 34.4 months with ADT alone (p < 0.001). The patients with low- volume disease had no OS benefit. The evaluation of outcome by disease volume, the interaction with treatments indicated that the impact of early docetaxel differed among the patients according to the volume of the disease. In conclusion, the clinical benefit of adding the docetaxel to ADT was limited to patients with high- volume disease (4, 5, 6).

In STAMPEDE trial, docetaxel, zoledronic acid or the combination was added to standard of care (SOC)- hormone therapy for two years- and compared to standard of care alone (including radiotherapy if stage N0/1M0) in patients with high-risk, locally advanced, metastatic or recurrent prostate cancer. 61% of patients had metastatic disease. The addition of zoledronat to SOC did not contribute to any survival benefit. Median overall survivals in months were 71 for standard of care only, 76 months for combination of SOC +docetaxel+ zoledronat and 81 months for SOC +docetaxel. About half of patients receiving docetaxel, with or without zoledronat, reported grade 3-5 adverse events. The authors have concluded that docetaxel should be added to hormonal therapy in fit men with high-risk prostate cancer (7).

Vale et al. performed a meta-analysis of five randomised trials of docetaxel in men with M1 prostate cancer. In three trials, the addition of docetaxel to standard of care improved survival; absolute improvement in 4-year survival was 9% (8).

EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer strongly recommend that ADT combined with chemotherapy (docetaxel) should be offered to patients whose first presentation is M1 disease and who are fit for docetaxel (9).

Abiraterone

In LATITUDE trial, abiraterone was compared to placebo in patients with newly diagnosed hsmPC receiving ADT who had at least 2 out of three defining factors of high-risk disease: GS 8 or higher, 3 or more bone lesions and/or visceral disease. Primary endpoints were OS and radiographic PFS. The patients receiving abiraterone had both longer median OS (not reached vs. 35 months, $p < 0.001$) and median rPFS (33 vs. 15 months, $p < 0.001$). Secondary endpoints, such as time to pain progression, time to next therapy line, time to PSA progression, time to skeletal event, were all significantly longer in the patients receiving abiraterone. The most common grade 3 adverse events with abiraterone were hypertension and hypokalemia (10).

In STAMPEDE trial, docetaxel was compared to abiraterone in patients with metastatic or advanced hormone sensitive prostate cancer receiving ADT. The patients without metastases were to receive ADT for 2 years or longer and to undergo radiotherapy for primary tumour. After a 4- year follow-up, no difference in overall survival, prostate-cancer specific survival, metastases free survival or skeletal events has been observed between the treatment arms (11).

In a post-hoc analysis, the patients who received abiraterone in the abovementioned STAMPEDE trial were stratified into risk groups, based on LATITUDE criteria; 48% of patients were classified as low risk. In both high and low risk groups of patients, there was an improved OS and failure free survival observed in the therapy with abiraterone, compared to ADT only (12).

Apalutamide

Apalutamide has been compared to placebo in patients with hsmPC receiving ADT in TITAN trial. The patients had to have at least one metastasis detectable on bone scan and performance status ECOG 0 or 1. Prior use of docetaxel was permitted, as well as the use of ADT in less than 6 months for hsmPC. Local treatment had to be completed at least one year before enrolment. Primary endpoints were OS and radiographic progression free survival (rPFS). About one third of patients in both treatment arms had low volume disease and about 10% of patients received docetaxel as previous therapy line. Overall survivals at 24 months were 82% for patients receiving apalutamide and 74% for patients in placebo group ($p< 0.005$). RPFS rate at 24 months was 68% in the apalutamide and 48% in the placebo group ($P< 0.001$). Regarding the secondary endpoints, the time to cytotoxic treatment, the time to pain progression and second progression free survival were all significantly longer with apalutamide. Adverse events occurred in about 40% of patients in each group.The patients receiving apalutamide had rash more often than those receiving placebo (13).

Enzalutamide

In ARCHES trial, enzalutamide + ADT has been compared to ADT alone in patients with hsmPC who had at least one metastasis and ECOG PS 0-1. Previous use of docetaxel was allowed. Patients were stratified according to the volume of the disease and previous cytotoxic therapy. Enzalutamide was given until the radiographic progression, unacceptable toxicity or the initiation of new therapy for prostate cancer were confirmed. After 24 months of follow-up, the risk of radiographic progression was significantly reduced with enzalutamide (median not reached vs. 19 months, $p < 0.001$). This risk reduction has been observed in patients with low volume disease and in those who previously received docetaxel as well. The risk of PSA progression, initiation of new therapy line, time to first symptomatic skeletal event, time to development of castration resistance, and the risk of pain progression were all reduced in the group of patients receiving enzalutamide and maintaining the quality of life. The reduction of risk of death by 19% was observed in the patients taking enzalutamide, but it was not statistically significant. About a quarter of patients in both treatment arms reported adverse events. After 44 months of follow-up, the trial update was published. Statistically significant difference in 4- year overall survival has been observed, with 4- year OS rates being 71% in patients receiving enzalutamide vs. 57% in patients receiving placebo ($p< 0.001$) (14, 15).

In ENZAMET trial, enzalutamide was compared with nonsteroidal antiandrogen (bicalutamide, nilutamide, flutamide) in patients with hsmPC receiving ADT. Overall survival was the primary endpoint. 45% of patients received concurrent docetaxel;the maximum of 6 cycles was allowed. After 34 months of follow-up, when compared to control, the patients receiving enzalutamide had 33% reduced risk of death, 60% reduced risk of clinical progression and 61% reduced risk of PSA progression. Both clinical and PSA progression free survivals were longer in patients receiving enzalutamide, regardless of docetaxel administration.

Fatigue was more often associated with enzalutamide. 1% of patients receiving enzalutamide had seizures, compared to none in the control group. However, in patients with high volume disease who received docetaxel, there has been no difference between enzalutamide and nonsteroidal antiandrogen observed with regard to overall survival. (16).

In the absence of parallel controlled randomised clinical trials, network meta-analysis can be performed in order to compare efficacy and safety of different therapeutic agents.

In the network meta-analysis, the data related to 7287 patients with hsmPC enrolled in 7 randomised trials were analysed. The patients were given ADT with docetaxel, abiraterone, enzalutamide, apalutamide, a standard nonsteroidal antiandrogen (bicalutamide, nilutamide, or flutamide), or placebo. In terms of the effect on overall survival, abiraterone has shown the greatest benefit reducing the risk of death by 39%. Abiraterone was followed by apalutamide and then by docetaxel. No survival benefit has been observed with enzalutamide, but at the time when this network meta-analysis was made, the update of the aforementioned ARCHES trial was not available. Regarding safety, the incidence of serious adverse event was the highest with docetaxel, followed by abiraterone. In conclusion, abiraterone and apalutamide might provide the largest impact on overall survival with acceptable safety profile (17).

De- novo metastatic hsPC

De- novo metastatic hsPC accounts for about 4- 5% of all patients with metastatic hsPC and it is associated with worse prognoses compared to recurrent hsmPC. It is associated with a greater risk of progressing to metastatic castration resistant prostate cancer (CRPC) and a greater risk of death. In a series of 90 patients with hsmPC, 38 patients with de novo disease had higher median PSA level (63 vs. 13 ng/mL), shorter median duration of hormone sensitivity (372 vs. 1613 days) and shorter median overall survival (6.2 vs. 11.6 years). All observed differences were statistically significant. All of the above-mentioned could lead to the conclusion that a more aggressive therapy should be used in this subset of patients (18, 19).

In LATITUDE trial, all patients had de novo mhsPC. In other aforementioned trials, 50- 80% of patients had de novo mhsPC (Table 1) (23?)

Table 1. Proportion of patients participating in de novo mhsPC in clinical trials

Clinical trial	Proportion of patients in de novo mhsPC
LATITUDE	100%
STAMPEDE	50%
TITAN	80%
ARCHES	75%
ENZAMET	72%

Peace 1 trial enrolled patients with de novo mhsPC receiving ADT and docetaxel. They were randomised in 4 groups by addition of abiraterone, prostate radiotherapy, or both. The addition of abiraterone resulted in prolonged both median rPFS (4.5 vs. 2 years) and median OS (5.7 vs. 4.7 years, respectively) with the reduction of the risk of death by 18%. In patients with high volume disease, as per CHAARTED criteria (about ¾ of patients), median OS was 5.1 years in patients receiving abiraterone vs. 3.5 years in patients not receiving abiraterone (the reduction of the risk of death by 28%). Safety profile was acceptable; with no synergistic toxicity of abiraterone- docetaxel combination being noticed. Radiotherapy data are still pending (20).

Treatment decision

Upfront treatment of patients with hsmPC undoubtedly delays disease progression, symptoms and complications and should be given to all patients, regardless of the volume of the disease.

In order to help in decision making regarding available therapeutics, the patients with hsmPC can be stratified as per CHAARTED (disease volume- high vs. low) or LATITUDE (disease risk- high vs. low) criteria (4, 10). Prognostic groups can be defined according to the site of metastases (appendicular vs. axial), ECOG status (0 vs. 1-3), PSA level (<65 vs. 65 or higher) and GS (<8 vs. 8 or higher) (2).

The role of novel serum and genomic biomarkers, as well as new imaging modalities such as PSMA PET, in decision making is yet to be defined.

According to EAU-EANM-ESTRO-ESUR-SIOG guidelines, health status, comorbidities and life expectancy of each particular patient should be considered when choosing a treatment. Complete assessment

of comorbidities should be made , with the accent on cardiovascular disease and diabetes.

Some patients will require full geriatric assessment. In frail patients, only the symptom directed therapy is to be offered (9).

Treatment sequencing

ADT is the backbone of therapy. The approach to every patient should be individual. Based on literature data, in case of low volume disease, it would be wise not to offer docetaxel as the first line treatment, but to add novel antiandrogens to ADT. Such patients are also candidates for local radiotherapy as it is proven to prolong survival (21, 22).

Regarding comorbidities, the patients with diabetes and heart failure might not be the best candidates for abiraterone, bearing in mind the need to add prednisone to treatment and abiraterone's safety profile.

In patients with high volume disease, the options include both docetaxel and novel antiandrogens.

Follow-up

Once the treatment of patients has started, it is recommended to perform physical examination and to control PSA level every 3- 6 months. Imaging is indicated based on symptoms and PSA increase (21).

Castration- resistant prostate cancer (CRPC)

Castration- resistant prostate cancer can be classified as non- metastatic or metastatic disease. Non-metastatic castration resistant prostate cancer develops upon biochemical recurrence of hormone- sensitive non- metastatic disease. Metastatic castration resistant prostate cancer develops either from metastatic hormone sensitive prostate cancer or from non- metastatic castration resistant prostate cancer.

Non- metastatic castration- resistant prostate cancer (nmCRPC)

The aim of therapy in patients with non- metastatic CRPC is to delay treatment progression with its complications and to prolong survival while maintaining the patient's quality of life. Non- metastatic CRPC is defined as PSA progression with testosterone in castration levels in absence of radiographic evidence of metastases on conventional imaging (bone scan and CT scan of chest, abdomen and pelvis). According to EAU guidelines, PSA progression is defined as PSA value > 2 ng/mL, with 3 consecutive rises, 1 week apart, with two 50% increases over nadir (23).

According to Smith and al., 42% of patients with nmCRPC will develop bone metastases or die within 2 years. Prior to opting for therapy, it is important to select patients with higher risk of developing metastatic disease. Both absolute PSA level and PSA doubling time (DT) are predictive of bone metastases development and death (24). The patients with nmCRPC and PSA DT shorter than 8 months have a significant risk of metastatic disease and death from prostate cancer (25). In population-based analysis, 243 patients with nmCRPC whose PSA DT was longer than 10 months were classified as low-risk, and 150 patients with nmCRPC whose PSA DT was shorter than 10 months were classified as high-risk patients. Median metastasis free survivals (MFS) were 30.5 in a low-risk group and 15.2 months in a high risk group ($p< 0.0001$), and median overall survivals were 36 and 57.6 months, respectively ($p= 0.0092$) (26).

Since according to literature data, 1 in 3 patients with nmCRPC will develop metastases within 2 years in the absence of treatment, and the delaying time to metastasis correlates with overall survival, there is a strong rational for treatment of these patients. It is also shown that PSA decline has an effect on prolonging both metastasis free survival and overall survival (27). With appropriate treatment, median survival of 4- 5 years could be achieved (28, 29, 30).

Treatment options in nmCRPC

Just 3 years ago, back in 2018, the recommendation given in EAU guidelines was not to treat patients with non-metastatic CRPC outside of clinical trials, except for the continuation of androgen deprivation due to remaining activity of androgen receptor. In 2020, three treatment options were recommended: apalutamide, enzalutamide and darolutamide, but only for patients with high risk of developing metastasis- those whose PSA DT is shorter than 10 months. Conventional imaging methods required to rule out metastatic disease should be bone and CT scan. PSA should be repeated every 3 months. Imaging, in absence of symptoms, should be repeated when PSA reaches 2 ng/mL, then again when PSA reaches 5 ng/mL and after every PSA doubling (23).

Enzalutamide

In PROSPER trial, the addition of enzalutamide to androgen deprivation therapy (ADT) was compared

to placebo in the patients suffering from nmCRPC with PSA DT < 10 months. Metastasis free survival (MFS) based on conventional imaging (CT scan, MR scan, bone scan) was a primary endpoint. Median MFS was 36.6 months for enzalutamide and 14.7 months for placebo (HR 0.29), meaning that enzalutamide, compared to placebo, resulted in 71% reduction of the risk of metastasis. Overall survival in months was 67 in the group receiving enzalutamide and 56.3 in the group receiving placebo (HR 0.73). Compared to placebo, enzalutamide prolonged both time to PSA progression (37.2 vs. 3.9 months; p< 0.001) and time to subsequent antineoplastic therapy (39.6 vs. 17.7 months; p< 0.001). There was no difference in patients' quality of life observed between the two treatments. The most common adverse events with enzalutamide were fatigue, hypertension, falls and mental impairment disorders (31).

Apalutamide

In SPARTAN trial, apalutamide was compared to placebo in patients with high-risk nmCRPC whose PSA DT was shorter than 10 months. All patients continued with androgen-deprivation therapy. In this trial, the primary endpoint was also MFS, and significant benefit of apalutamide was observed. Apalutamide reduced the risk of metastases development by 72% compared to placebo; median MFS in months were 40.5 in the patients receiving apalutamide and 16.2 in the placebo group (p< 0.001). Apalutamide also reduced the risk of death by 22%; median overall survivals in months were 73.9 and 59.9, respectively (p= 0.016). Median treatment duration in months was 32.9 for the patients receiving apalutamide and 11.5 for the patients in placebo group. The observed benefit was consistent in all age groups, in patients with both local and regional nodal disease, regardless of shorter or longer PSADT. The quality of life was not significantly different between the treatment groups. The most common adverse events were fatigue, rash, hypothyroidism, fractures and falls (32).

Darolutamide

In the same group of patients, with metastasis free survival being also a primary endpoint, darolutamide was compared to placebo in ARAMIS trial. Compared to placebo, darolutamide led to 59% reduction of the risk of metastasis and 31% reduction of the risk of death. Median MFSs were 40.4 months with darolutamide and 18.4 months with placebo (p< 0,001). The benefit in patients receiving darolutamide was also observed regarding secondary endpoints with longer time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event. More than half of the patients in the placebo group crossed over to darolutamide. Fatigue and mental impairment disorders were significantly more often in patients receiving darolutamide. The patients reported that the quality of life did not differ between the groups (33).

All three above-mentioned drugs have shown benefit compared to placebo when given to patients with high risk nmCRPC while maintaining androgen deprivation therapy. The time to metastases was delayed by around 2 years, and overall survival benefit was observed as well. In the absence of head-to-head comparison outcomes, these drugs cannot be directly compared.

However, network meta-analysis comparing effectiveness of enzalutamide, darolutamide, apalutamide and bicalutamide has been performed. It involved the data from 24 randomised controlled trials where placebo was used as comparator to these 4 drugs. The endpoints were metastases free survival, overall survival, time to PSA progression and time to initiation of cytotoxic therapy. There was no difference observed between enzalutamide and apalutamide regarding all four endpoints. In all endpoints, bicalutamide and placebo were worse than novel antiandrogens. Darolutamide had worse results in metastasis free survival and time to PSA progression compared to enzalutamide and apalutamide. Based on these results, enzalutamide and apalutamide could be considered as equivalent. Darolutamide proved equivalent to enzalutamide in terms of overall survival and time to the initiation of cytotoxic therapy (34).

Therefore, the treatment could be guided by drug's safety profile and patient's comorbidities as well as drug's availability regarding different national regulatory and reimbursement status.

Once the treatment has started, PSA and testosterone levels should be controlled on 3- month basis, and CT and bone scan repeated at least annually depending however on symptoms and PSA dynamic (35). In patients with high risk nmCRPC, any increase of PSA requires closer monitoring (36). PSA progression itself should not be a reason to stop or change the treatment. According to EAU guidelines, at least two of the following criteria should be fulfilled: PSA progres-

sion, bone scan progression, CT progression or clinical deterioration (23).

Treatment options in metastatic castration resistant prostate cancer (mCRPC)

Metastatic CRPC is defined as PSA progression, meaning PSA value > 2 ng/mL, with 3 consecutive rises, 1 week apart, with two 50% increases over nadir, with testosterone in castration level accompanied by radiographic evidence of progression: the appearance of at least 2 lesions on bone scan or soft tissue lesion enlargement according to RECIST criteria (23).

Docetaxel

For quite a long time , the combination of mitoxantrone and prednisone was the only therapeutic option in this subset of patients. In 2004, the results of randomised trial comparing docetaxel with mitoxantrone were published. Docetaxel that was given every three weeks prolonged median overall survival time by about 2.5 months compared do mitoxantrone: 18.9 vs. 16.5 months. As far as secondary endpoints are concerned, the improvement after docetaxel treatment was demonstrated in pain relief, PSA serum levels and quality of life (37).

Cabazitaxel

Cabazitaxel was compared to mitoxantrone in patients with mCRPC who had progressed during the treatment with docetaxel in the TROPIC trial. The patients allocated to cabazitaxel group had longer median OS: 15.1 vs. 12.7 months, as well as median progression free survival: 2.8 vs.1.4 months. The most common adverse events associated with the use of cabazitaxel were neutropenia and diarrhoea (38).

Radium 223

In 2013, Radium 223 was approved for treatment of patients with mCRPC who had at least 2 bone metastases in the absence of visceral metastases. the patients either received or declined docetaxel treatment, or were not eligible to receive it. Compared to placebo, Radium 223 prolonged overall survival, with the medians being 14.9 for Ra 223 and 11.3 for placebo. Ra 223 delayed time to the first skeletal event by about 6 months. The most common side effect was myelosuppression (39). The addition of Ra 223 to abiraterone resulted in more bone fractures and deaths then the treatment with abiraterone alone when given to asymptomatic or mildly symptomatic chemotherapy naive patients with mCRPC (bone metastases only). Fractures occurred in 29% of patients who received the combination of Ra 223 and abiraterone, compared to 11% of patients on abiraterone therapy only. Median OS was 30.7 and 33.3 months, respectively (40). According to Ra 223 Summary of product characteristics, safety and efficacy with the combination of Ra 223 and agents other than GNRH analogues have not been established (41).

Novel antiandrogens

Two novel antiandrogens have been approved for the treatment of patients with mCRPC: abiraterone and enzalutamide, both of them in the first line and in the second line of therapy (after docetaxel as first line treatment).

Abiraterone

Abiraterone was initially approved for the treatment of patients with mCRPC progressing on docetaxel. It was given with prednisone and was compared to placebo plus prednisone, with overall survival as primary endpoint. The benefit in OS was observed, the median in months being 15.8 for abiraterone and 11.2 for placebo. There was statistically significant difference noticed in favour of abiraterone for all secondary endpoints: time to PSA progression, radiologic progression-free survival, proportion of patients who had a PSA response and objective response as per RECIST criteria. Most common side effects were fatigue, anaemia and bone pain, latter being more common with abiraterone (42).

When given prior to docetaxel as the first line treatment in patients with mCRPC who were asymptomatic or mildly symptomatic and when compared to placebo, abiraterone led to longer radiographic progression-free survival (16.5 vs. 8.3 months) and overall survival (34.7 vs. 30.3 months) as primary endpoints. The benefit was also observed in secondary endpoints: ECOG performance status, time to chemotherapy, PSA progression and opiate use for prostate cancer pain (43).

Enzalutamide

Similar to abiraterone, enzalutamide was firstly approved in the second line of therapy in patients with mCRPC after docetaxel treatment failure, based on the results of the AFFIRM trial. Compared to placebo groups, the patients who received enzalutamide had

longer median OS (18.4 vs. 13.6 months), longer time to PSA progression and radiographic progression-free survival. The patients who received enzalutamide had more often fatigue, diarrhoea, and hot flashes; there were seizures reported in five patients. (44).

In PREVAIL trial, enzalutamide was compared to placebo in asymptomatic or mildly symptomatic patients with mCRPC. Both primary endpoints: radiographic progression-free survival (rPFS) and overall survival (OS) were significantly longer in patients receiving enzalutamide, median in months being 20 and 5.4 for rPFS and 32.4 and 30.2 for OS. The time until the initiation of cytotoxic chemotherapy and the time until the level of PSA had increased were significantly longer with enzalutamide (45). In extended safety analysis, the most common adverse events associated with enzalutamide were fatigue, back pain, constipation and arthralgia. 11% of patients receiving enzalutamide experienced some cardiac adverse events, one third of them being grade 3 or higher (46).

Sequencing treatment lines in patients with mCRPC

According to EAU guidelines, the first-line treatment of mCRPC depends on the treatments used when metastatic cancer was discovered. Since there are no validated predictive factors, no clear-cut recommendation can be made for the most effective drug for the first line (1). ESMO guidelines recommend that the treatment should be started with either enzalutamide or abiraterone in patients with mildly symptomatic or asymptomatic disease who are chemotherapy naive (47).

There are the data obtained in the phase 2 randomised clinical trial available that provide direct comparison of abiraterone and enzalutamide in chemotherapy naive patients with mCRPC. Upon PSA progression, patients would cross over from one agent to another. The primary outcome was the time from randomization to PSA progression after the second line therapy (TTPP2), and the secondary outcomes were the time to progression with the first line therapy and PSA decline by 50% or more from the baseline. Median follow-up was 13 months. The patients starting the treatment with enzalutamide had an improved PSA decline at 12 weeks (77% vs. 55% with abiraterone). Regarding other endpoints, no statistically significant difference has been observed. Since PSA progression should not itself be the reason for treatment discontinuation according to guidelines, these data could not be taken into account as practice- changing. The most common adverse events associated with abiraterone were urinary tract infection, hypokalaemia, hypertension, diarrhoea, peripheral oedema and ALT or AST increase. The most frequent adverse events in patients receiving enzalutamide were hot flushes, hypertension, fractures, falls, asthenia and fatigue. (48).

In the long-term prospective observational study PREMISE, enzalutamide was prescribed in a real-world clinical practice setting as a first- line treatment or following treatment with abiraterone or/and docetaxel. The primary endpoint was time to treatment failure (TTF) and the secondary endpoints were time to PSA progression, PSA response rate, time to disease progression and drug's safety. After a follow-up of 18 months, the median TTF was the longest in patients who received enzalutamide as a first-line treatment. Similar findings were observed in the secondary efficacy endpoints. The patients who previously received both docetaxel and enzalutamide experienced the highest treatment toxicity. The most common adverse event in all groups was fatigue; it has occurred in up to 20% of patients. (49).

Chopra and al. performed an indirect comparison of abiraterone and enzalutamide in both pre- and post- docetaxel setting in a meta-analysis of phase III randomised trials. There was a weak evidence found that enzalutamide outperformed abiraterone in terms of overall survival in both pre- and post-chemotherapy setting. However, there is a strong evidence that enzalutamide outperforms abiraterone in both above-mentioned settings in terms of PSA progression, radiographic progression and PSA response. The frequency of higher-grade adverse events was similar in the treatments (50).

In a randomised phase II trial, quality of life was compared between the treatments with abiraterone and enzalutamide. The patients older than 75 years receiving abiraterone had better quality of life. There was no difference observed between the treatments in younger subgroup of patients. It is to be pointed out that a higher proportion of patients reported worsened physical and functional well-being when treated with enzalutamide (51).

Second line therapy in mCRPC

EAU guidelines suggest that the patients progressing on docetaxel should be offered a second line treatment: enzalutamide, abiraterone, cabazitaxel or Ra

223. A decision should be made based on performance status, response to previous treatment, symptoms, comorbidities, extent of the disease and patient preference (23).

In a phase 2 cross over trial, the patients with mCRPC were randomised to receive either abiraterone as the first line treatment and then, upon PSA progression, to receive enzalutamide or vice versa. Time to second PSA progression and PSA response were primary endpoints. In conclusion, enzalutamide showed activity when used in the second line after abiraterone, while abiraterone did not. The time to second PSA progression was 19.3 months for abiraterone followed by enzalutamide and 15.2 months for enzalutamide followed by abiraterone. Only 4% of patients had PSA response to the second-line abiraterone compared to 36% of patients on enzalutamide as the second-line treatment (52).

According to available literature data, only one novel antiandrogen should be used in patients with mCRPC because of cross- resistance between abiraterone and enzalutamide when sequencing the therapies. In further therapy lines, chemotherapy should be used. There has been no difference in efficacy of docetaxel observed in regards to whether the patients received abiraterone or enzalutamide as the first line treatment (53). In a retrospective analysis of 74 patients, cabazitaxel showed efficacy after both docetaxel and one antiandrogen received in previous treatment lines. There was no difference in efficacy in patients older than 75 years when compared to younger patients (54).

In PROfound trial, the patients with mCRPC progressing after abiraterone or enzalutamide were given olaparib or the next line of therapy according to physician's choice. They were stratified based on BRCA1, BRCA 2 or ATM alteration. The patients with alterations had better radiographic PFS and OS when given olaparib: 7.39 vs. 3.55 months for rPFS and 18.5 vs. 15.11 months for OS, respectively (55).

Despite all of the above mentioned, the fact is that less than half of the patients actually receive the second line treatment. The third line treatment is given in less than 15% of patients (56).

Third- line therapy

As third line therapy, EAU suggest to offer cabazitaxel if the patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide (23).

ESMO does not recommend the use of second novel antiandrogen (47).

Conclusion

Apart from available clinical trial data, a lot more has to be taken into consideration when choosing a treatment, such as PSA doubling time, time to development of CRPC/mCRPC, burden of the disease (lymph node only, bone, visceral), whether a patient is symptomatic or not, patient's fitness and comorbidities precluding chemotherapy options, previous treatment lines, response to previous treatment lines and the duration of the response. In some cases, the biology of the disease changes becoming anaplastic, or neuroendocrine dedifferentiation can occur. If available, biomarkers should be included in the decision. In the next treatment, the line agents with different mechanism of action are to be used in order to overcome the acquired resistance. If possible, a patient should be enrolled in clinical trial.

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Sažetak

KAKO OPTIMALNO PRIMIJENITI DOSTUPNE TERAPIJSKE LINIJE U LIJEČENJU UZNAPREDOVALOG KARCINOMA PROSTATE

K. Antunac i *L. Beketić-Orešković*

Adekvatno sekvencioniranje dostupnih terapijskih linija u uznapredovalom raku prostate predstavlja velik izazov. Smjernice ponekad znaju biti nedorečene a podaci iz kliničkih studija često se ne mogu točno preslikati na pojedinog bolesnika. Također, sama dostupnost lijeka varira među pojedinim zemljama. Kod donošenja odluke treba uzeti bolesnika u cjelini, ne samo stadij i biologiju bolesti već i dob, opće stanje, druge bolesti od kojih eventualno boluje, ranije linije liječenja, očekivani profil nuspojava lijeka ali i preferencije bolesnika. U ovom preglednom radu će biti prikazane terapijske mogućnosti kod uznapredovalog hormon- senzitivnog raka prostate, te kastracijski rezistentnog raka prostate: nemetastatskog i metastatskog. Pokušat će se razjasniti optimalno sekvencioniranje liječenja za pojedine skupine bolesnika.

Ključne riječi: *Uznapredovali rak prostate; hormon senzitivni rak prostate; kastracijski rezistentni rak prostate; androgen deprivacijska terapija; docetaksel; kabazitaksel; Radij 223; enzalutamid; apalutamid; darolutamid; abirateron.*