Emerging Therapies in Metastatic Castration-Resistant Prostate Cancer: A Regulatory Perspective

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Abstract: Worldwide, prostate cancer (PC) is the most commonly diagnosed cancer and the second cause of cancer death in men. During the past decade, metastatic prostate cancer patients were usually treated with androgen deprivation therapy (ADT), and once they progressed to a castration-refractory disease status docetaxel-based chemotherapy was the main option. Recently, the therapeutic armamentarium for the treatment of patients with metastatic castration-resistant prostate cancer has been shaken with the appearance of new attractive pharmacological therapies. New treatments have shown benefits in the progression free survival and the life expectancy with an acceptable and, in general terms, a rather manageable safety profile. This review is aimed to describe how new emerging therapies in metastatic castration-resistant prostate cancer have obtained the marketing authorisations in Europe and to discuss on the imminent challenges to be faced due to the changes in the treatment paradigm/strategy for prostate cancer

Keywords: Abiraterone acetate, Cabazitaxel, Docetaxel, Enzalutamide, regulatory aspects.

INTRODUCTION

Prostate cancer is one of the most important medical problems in males, and is the second cause of death by cancer in the occidental world [1]. In Europe, the annual incidence is estimated in around 69.5 cases per 100.000 men with a mortality of 12.1 cases per 100.000 men [2].

Carcinoma of the prostate is frequently associated to elderly men, with a higher risk in subjects older than 50 years. Besides the age, other risk factors have been studied, even though for the time being only ethnic origin and heredity seem to be well-established as risk factors. The possible role of diet, obesity, physical activity and prostate swelling is not totally elucidated and continue being investigated [3].

Prostate cancer induced death is associated with tumor progression and the development of metastasis. Whereas only a minority of patients have metastasis at diagnosis and most of the patients will be diagnosed with localized prostate tumors, many neoplasms will progress to a metastatic status and eventually lead to prostate cancer-specific death. Many men present with symptoms, including cancer-related pain, and that is the underlying reason for seeking medical care that leads to the diagnosis. Androgen deprivation therapy (ADT) is the mainstay of treatment in metastatic prostate cancer since 1940s [4], when castration of a prostate-cancer patient was associated with a significant tumor regression. Castration has demonstrated an effect in the natural history of the disease and a significant improvement in symptoms (bone pain, renal failure, anemia, pathologic fractures, spinal cord compression). However a formal prospective comparison of the effect of castration is not available, nor will it likely be, due to ethical reasons. In this respect, all guidelines, including the guidelines on prostate cancer of the European Association of Urology [5], NCCN [6] and ESMO guidelines [7], recommend androgen suppression using bilateral orchiectomy or LHRH agonists as first-line treatment. There are no demonstrated differences between different ADT alternatives and their timing for the management of these patients [5], although current clinical practice tends to favor LHRH agonists. Once patients progress following hormonal therapy, their life expectancy is approximately two years with a significant risk of developing complications of bone metastases, which include skeletal related events (SREs), bone pain, pathologic fracture, and spinal cord impingement with potential neurological compromise.

In 2004 docetaxel-based chemotherapy demonstrated an improvement in overall survival (OS) in metastatic castrate-resistant prostate cancer (mCRPC). Two prospective randomized phase 3 trials, SWOG-99-16 [8] and TAX327 [9] compared docetaxel-based chemotherapy with mitoxantrone plus prednisone in mCRPC and observed and increase in most efficacy endpoints, including overall survival, and

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quality of life. However not all patients are good candidates to docetaxel therapy, and the treatment is usually preferred in symptomatic and fit mCRPC patients. Nowadays, the treatment of mCRPC patient is split in two big settings, pre-docetaxel and post-docetaxel therapy, and the vast majority of new treatments have been focused on, firstly to show positive results in the post-docetaxel setting and more recently in those patients not candidate to receive docetaxel.

This article is aiming to review the new approved treatments in the European Union for mCRPC both in pre-docetaxel setting and post-docetaxel scenario.

Pre-Docetaxel Clinical Setting

Abiraterone Acetate

Abiraterone acetate is a prodrug of abiraterone, an orally active inhibitor of the enzyme, CYP17α (17α-hydroxylase/C17,20-lyase). Abiraterone acts as an androgen biosynthesis inhibitor by blocking 2 important enzymatic activities in the synthesis of testosterone in the testes, adrenals, and within the prostate tumor.

Zytiga™ was authorised for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated [10]. The basis for the approval was the pivotal study COU-AA-302 [11,12]. A phase III, multinational, randomised, double-blind, placebo controlled study conducted at 151 study sites in the US, Europe and Australia comparing the efficacy and safety of abiraterone acetate plus prednisone with placebo plus prednisone in medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who had not received cytotoxic chemotherapy. 1088 men were randomised (1:1) to received abiraterone 1000 mg (4x 250 mg tablets) or 4x placebo tablets orally once daily and prednisone or prednisolone 5 mg orally twice daily. Main inclusion criteria were: histologically or cytologically confirmed adenocarcinoma of the prostate, metastatic disease documented by positive bone scan or metastatic lesions, other than liver or visceral metastasis, cancer progression by PSA, according to adapted Prostate Cancer Clinical Trials Working Group-2 (PCWG2 [13]), or radiographic progression according to modified Response Evaluation in Solid Tumors (RECIST) criteria, asymptomatic or mildly symptomatic from prostate cancer, as defined by a score of 0 or 1 (asymptomatic) or 2-3 (mildly symptomatic) on the Brief Pain Inventory-Short Form (BPI-SF), surgical or medical castration. Subjects were excluded if they received prior cytotoxic chemotherapy or biologic therapy for the treatment of CRPC.

The study had two co-primary endpoints: radiographic progression-free survival (rPFS) and overall survival (OS). rPFS was defined as the time from randomisation to the first occurrence of one of the following: disease progression by bone scan (according to modified PCWG2 criteria), progression by CT or MRI (according to modified RECIST) or death (independent radiographic review of sequential imaging assessments).

Abiraterone acetate substantially decreased the risk of radiographic progression or death (rPFS) 58% compared with placebo (HR=0.425; 95% CI: 0.347, 0.522; p<0.0001). Overall survival data (HR=0.752; 95% CI: 0.606, 0.934; p=0.0097) showed a trend in the same direction as rPFS, although data were too immature to be considered conclusive. Later, in the third interim analysis median OS was 35.3 months (95% CI: 31.24, 35.29) in the abiraterone group and 30.1 months (95% CI: 27.30, 34.10) in the placebo group, HR was 0.79 (95% CI: 0.655, 0.956; p=0.0151). During a second interim analysis the independent-data monitoring committee (IDMC) recommended unblinding the treatment and allowing crossover of subjects.

Results from the secondary endpoints supported the benefit observed for the co-primary endpoints. The subgroup analysis both in PFS and OS went in the same direction, pointing out the robustness of the result.

Regarding the safety profile, treatment with abiraterone was tolerable for the majority of subjects and the safety profile was consistent with previous experience in the post-docetaxel setting (except for the new adverse drug reactions identified - dyspepsia, AST increased, rash and haematuria). Adverse events were generally manageable and no major safety concerns were identified from this study.

Post-Chemotherapy (Docetaxel) Clinical Setting

The randomized study in metastatic castration-resistant prostate cancer comparing docetaxel administered every 3 weeks to docetaxel weekly and to mitoxantrone demonstrated a 2.4 months survival benefit for docetaxel every 3 weeks [9]. Once patients progress on docetaxel, a number of treatments have recently been approved. A brief revision is presented:

Cabazitaxel

Cabazitaxel is the 7,10-dimethoxy analogue of docetaxel that promotes tubulin assembly *in vitro* and stabilises microtubules against cold-induced depolymerization. Cabazitaxel (Jevtana™) is a new member of the taxane family.

Cabazitaxel has been authorised for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen in combination with prednisone or prednisolone. Thus, cabazitaxel is approved as second-line chemotherapy [14].

Data from a single pivotal study supported this indication [15,16]. The objective of the study was to determine whether cabazitaxel/prednisone could improve overall survival when compared to mitoxantrone/prednisone. A statistically significant difference was observed in favour of cabazitaxel as compared to mitoxantrone in terms of OS, with a 2.4 months increase of median OS, and a 30% reduction in risk of death (HR=0.70). The effect of cabazitaxel was consistent across the majority of subgroups, even if not significant in all of them. However, in subgroup analyses (i) there was no statistically significant difference between cabazitaxel and mitoxantrone in patients who have received 3 cycles or less (225 mg/m²) of docetaxel, and (ii) the effect of cabazitaxel was less pronounced in patients who received two lines of docetaxel.

The results in relevant parameters like progression-free survival (PFS), tumour response rate and tumour progression were consistent with the primary endpoint. A median PFS difference of 1.4 months in favour of cabazitaxel/prednisone was also observed. cabazitaxel/prednisone was also associated with higher response rate and increased time to PSA progression. These results should be taken with caution due to the fact that no independent review of PFS assessment was carried out. Efficacy in patients that had received less than 225mg/m^2 of docetaxel has not been fully demonstrated.

This intravenous chemotherapy is complicated by febrile neutropenia, sepsis, neutropenic deaths, and serious gastrointestinal side effects including diarrhoea.

Abiraterone Acetate

Abiraterone has been approved, in combination with prednisone or prednisolone, for patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. It is noted that abiraterone is also indicated with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

The efficacy of abiraterone acetate was demonstrated in a single pivotal study [17,18]. Treatment with abiraterone acetate decreased the risk of death by 26% compared with placebo (HR=0.740; 95%CI: 0.638, 0.859; p<0.0001), showing a median survival of 15.8 months for the AA group versus 11.2 months for the placebo group. Treatment effect on OS was robust after adjustment for stratification factors in multivariate analysis and was consistently favourable across relevant subgroups.

Consistent effects were found in pre-specified secondary efficacy endpoints: time to biochemical or radiological disease progression was significantly increased, such as time to PSA progression [10.2 months versus 6.6 months in controls, HR=0.58, p<0.0001] or radiographic progression-free survival [5.6 months versus 3.6 months in controls, HR=0.673, p<0.0001]. PSA response rate was significantly greater in abiraterone treated patients compared to the placebo group (38% versus 10%, p<0.0001), also when only confirmed PSA responses were considered (29% versus 6%, p<0.0001), as was objective response rate in the subset of patients with baseline measurable disease (14% versus 3%, p<0.0001). Finally, symptom-related endpoints, such as pain palliation, time to pain progression, skeletal-related events, and quality of life scores also tended to favour abiraterone-treated patients over placebo-control ones.

The efficacy of abiraterone in non-caucasian patients and in patients having received prior ketoconazol therapy has not been studied.

Treatment with abiraterone acetate requires the co-administration of prednisone and is complicated by the side effects of mineralocorticoid excess (hypertension, hypokalaemia, and fluid overload), hepatotoxicity, and adrenal insufficiency. The safety profile is considered acceptable, predictable, and generally manageable with basic medical interventions (oral potassium supplements, diuretics and antihypertensive medication). However, the role of abiraterone in hepatotoxicity is not fully understood, and frequent monitoring of serum transaminases is recommended.

Enzalutamide

Enzalutamide is an oral androgen receptor signalling inhibitor designed to block multiple steps in the androgen receptor signalling pathway. As a consequence, a reduced expression of androgen receptor dependent genes, decreased growth of prostate cancer cells, induction of cancer cell death, and tumour regression might be expected.

Enzalutamide (MDV3100) is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy[19].

The efficacy of enzalutamide is based on the results of one single pivotal study (Study CRPR2) that enrolled 1199 patients, randomised 2:1 to enzalutamide or placebo, respectively [20]. Interim results showed a significant improvement in terms of the primary endpoint OS: a benefit of 4.8 months compared to placebo (median time was 18.4 in the MDV3100 arm and 13.6 months in placebo arm). Overall active treatment decreased the risk of death by 37% when compared with placebo (HR: 0.633; 95%CI:0.531, 0.754; p< 0.0001). The study was stopped following pre-specified criteria and patients in the control groups were recommended to cross over to active treatment group. More mature data has shown an overall event rate of 43%.

Additional analyses have been conducted in different subgroups showing consistent results. Time to PSA progression and time to radiologic progression were also significantly improved in favour of active treatment and time to first skeletal-related event also favoured MDV3100.

A clinical relevant reduction of the risk of death (37% relative risk reduction), with an improvement in the median overall survival of 4.8 months, has been convincingly demonstrated.

On the other hand, the safety profile of enzalutamide is characterised by secondary effects to androgen receptor inhibition but also by events not intuitively attributable to that mechanism, such as hypertension, decreased neutrophils/leukocytes and seizure.

In CRPC2 study, the most frequent adverse drug reactions (ADRs) in enzalutamide treatment arm were hot flush (20.3%), headache (11.6%), anxiety (6.4%), hypertension (6.1%), falls (4.0%), pruritus (3.6%), dry skin (3.5%) and non-pathological fractures (3.5%).

Although less common, there is a risk for the following ADRs: seizure, neutropenia, leucopenia, visual hallucinations, cognitive disorder, memory impairment, amnesia, disturbance in attention. The major safety concern identified is the risk of seizure, which is to be minimised by avoiding the use in patients with prior seizures.

But all in all, the safety profile of enzalutamide is considered acceptable and outweighed by the benefits.

DISCUSSION

Prostate cancer is the most common cancer and the second leading cause of cancer deaths among males in most western countries. Prostate cancer-related deaths occur as a result of complications of metastatic disease. Despite the early sensitivity of these tumours to hormonal strategies, castration-resistant progression generally represents a transition to the lethal state of the illness, and most patients ultimately succumb to this disease. The median survival of patients with castration-resistant disease is approximately 1–2 years [21, 22].

Until very recently most patients received 2 or more hormonal manipulations and were then offered chemotherapy as their disease progressed. In this setting, docetaxel with prednisone represent the front-line chemotherapy. However, in recent years, a number of interesting agents have been authorised based on the demonstration of benefits mainly but not limited to survival, in the treatment of patients with castration-resistant prostate cancer. In this regard, it could be raised the question of whether to increase the overall survival should be the goal of any clinical trial in mCRPC setting. Actually, this fact seems to be critical, since the surrogate value of PFS for OS is still a matter of debate and has not been established [23-25]. Undoubtedly, when a new medicinal product cannot offer any advantages in terms of life expectancy in last lines of treatments, the use of PFS instead OS should be related to a better quality of life and not only with an improvement in tumour related symptoms (usually associated to a gain in PFS) given that a hypothetical unfavourable safety profile from that drug would not be reflected in terms of PFS. Fortunately, for the time being, the new therapies recently approved have demonstrated a clinical benefit not only in PFS but also in OS.

Two clearly differentiated clinical settings have been investigated, i.e. patients progressing after docetaxel chemotherapy, which includes cabazitaxel with

prednisone, abiraterone acetate with prednisone or prednisolone and enzalutamide, and patients with castration-resistant prostate cancer asymptomatic or mildly symptomatic not yet candidates to chemotherapy, which include abiraterone and sipuleucel-T (currently not approved in EU) [26-27] or for those patients with symptomatic bone metastases and no known visceral metastatic disease (radium Ra 223; Xofigo; (currently not approved in EU)) [28]. A number of additional new products are currently in the last steps of clinical development or under evaluation by regulatory agencies and might be available in the near future.

These novel therapies have completely modified the treatment strategies in metastatic prostate cancer, some of them offering substantial benefits in survival, disease progression-free survival, symptoms and quality of life, with an acceptable and generally manageable safety profile in most cases.

Surprisingly, no one of these therapies has been directly compared to docetaxel-chemotherapy. Initially these were developed to fulfil a medical need in patients who progressed after or during docetaxel therapy. In this late line, cabacitaxel showed an effect in terms of overall survival similar to what had been observed with other therapies in late line cancers, where dramatic effects in terms of overall survival are rare due to the advanced stage of the disease. Safety was within that expected for a citotoxic drug and based on efficacy findings and the poor prognosis of these patients, a positive benefit/risk balance was concluded by regulatory agencies. This was followed by the approval of novel antiandrogens, i.e. first abiraterone, a synthesis inhibitor, followed by enzalutamide, an inhibitor of the androgen-receptor. Both medicinal products have shown an increment in survival rates in the clinical settings where have been tested with an acceptable and foreseeable safety profile, according to the mechanism of action. Of note, the safety profile of these new agents seems to be better tolerated than chemotherapy. Importantly, it should be highlighted that at present, enzalutamide can only be used in the post-chemotherapeutic regimen whilst abiraterone has shown benefits in both pre and post-docetaxel.

Therefore, a natural movement to cover the pre-chemotherapy setting by some of these non-citotoxic medicinal products, either in a second step like abiraterone, or directly for sipuleucel-T, has just started. Given its safety profile, delaying chemotherapy is seen as desirable step forward for hormonal or immuno-therapies. So, further developments able to prolong the benefits of androgen deprivation therapy while delaying chemotherapy are awaited in the upcoming years.

Being fully welcomed, this will necessarily add complexity to the current treatment paradigm in advanced prostate cancer. Consequently, a number of relevant questions for the clinical practice emerge and will need to be clarified by additional investigations.

There are no direct comparative data about the relative efficacy and/or safety of any of these agents. Eventually, therapy selection after docetaxel therapy would give priority to hormonal therapies given their apparently better benefit/risk balance over cabazitaxel. Given the lack of a direct comparison between abiraterone and enzalutamide, therapy selection should rely on the safety profile of the available therapies and the differential mechanism of action rather than on their apparently similar efficacy data. Costs and treatment convenience are also important factors to be considered in the decision making phase.

The same would apply in the pre-docetaxel setting if agents such as sipuleucel-T or radium Ra 223, get approved in EU without direct comparative data, and safety may become important when choosing between treatment of similar efficacy. But, further difficulties in treatment selection are recognised given the increasing number of medicinal products with completely different mechanism of actions.

Despite all these uncertainties, it is reasonable to feel that in the clinical practice, novel hormonal therapies can delay the use of chemotherapy (docetaxel and cabazitaxel) and, due to the manageable toxicity profile of these new treatments, they should be also further studied in medically unfit mCRPC patients not suitable for chemotherapy.

Further, at present, the optimal sequence of the available therapies is uncertain. This might be particularly relevant in the case of novel hormonal therapies, given that there is potential risk for cross-resistance [29]. It is deemed necessary to conduct additional studies to generate data able to solve this potential concern. In this regard, some clinical investigations are to be conducted, but the results are not expected in the short-term.

Another relevant opened question is whether a possible synergistic mechanism of action among some of these therapies might occur. This might well happen with the available anti-androgen therapies given their

differential mechanism of action. At present, there is an ongoing study aimed to address this uncertainty for abiraterone and enzalutamide and the results are highly awaited given the potential implications for the management of advanced prostate cancer [30]. Given the increasing number of treatment candidates, additional investigations will be needed.

In summary, the recent advances in the treatment of metastatic prostate cancer are substantial and deemed of important clinical relevance. A number of medicinal products have just been authorised and many others remain under investigation. Significant changes in the treatment paradigm of these advanced and lethal prostate cancers have just started and given the rapidly evolving changes, a number of relevant questions have not yet been solved at this stage but will need to be addressed due to the implications for the clinical practice. For this aim, the compromise and support of the different stakeholders to conduct the appropriate investigations is encouraged.

DISCLAIMER

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