Review article

Abiraterone acetate – 10 clinically relevant facts

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ABSTRACT

Prostate cancer is one of the most frequently diagnosed cancers in men. Number of newly diagnosed cases is increasing due to several factors and the most important ones seem to be: population ageing and more sensitive diagnostic procedures. Secondary – the higher efficacy of treatment with its influence on improving patients' overall survival and the specific mechanism of action of drugs used in systemic therapy lead to growing population of men suffering from prostate cancer in general and, specifically – patients with castration resistance. It is hormone therapy to play the key role in systemic treatment of prostate cancer with increasing significance of novel drugs focused on inhibition of molecular signal transduction mediated by androgen receptor. Abiraterone acetate is the representative of this therapeutic class. The paper describes the most clinically relevant data regarding the drug.

Key words: prostate cancer, systemic therapy, hormone therapy, abiraterone acetate

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INTRODUCTION

Systemic treatment of prostate cancer patients is dominated by hormone therapy – constantly enriched with new, more effective and safer drugs, which are registered for use at earlier and earlier stages of the disease – both in terms of clinical stage of the neoplastic process and its sensitivity to castration. In the face of an increasingly wide choice, albeit limited by available reimbursement provisions, the use of these drugs is challenging from the perspective of both anti-tumor efficacy and toxicity profile. One of the leading and more frequently used drugs from the group of modern hormonal drugs is abiraterone acetate (ABI). Some important facts about this drug from a clinician's perspective are discussed below.

FACT 1. THE DRUG'S MECHANISM OF ACTION ALLOWS FOR EFFECTIVE TREATMENT, TARGETING THE PATHOMECHANISM OF PROSTATE CANCER DEVELOPMENT AND PROGRESSION

In the case of prostate cancer, tumor progression is primarily dependent on molecular signal transduction mediated through the androgen receptor (AR). The receptor itself has the activity of a transcription factor which, upon binding to its ligand, triggers the synthesis of biologically active proteins encoded by its transcription-dependent genes.

Physiological ligands of the androgen receptor are androgens, and among them the most active are testosterone and dihydrotestosterone. Abiraterone acetate, as an inhibitor of two enzymes catalyzing the pathway of their synthesis, 17β-hydroxylase and C17, 20-lyase, has the ability to inhibit androgen formation in the gonads, adrenal glands, and cancer cells themselves [1–4]. Thus, abiraterone eliminates a growth factor for prostate cancer cells from the tissue environment, and the last mentioned mechanism of its action is particularly relevant in the context of the biology of castration-resistant prostate cancer (CRPC) tumors. In this specific case, paracrine and autocrine stimulation of tumor cells has been shown to have a crucial effect on disease progression.

In addition to new generation antiandrogens that inhibit AR itself, abiraterone acetate – as an inhibitor of AR ligand production – forms a group of modern hormonal drugs targeting the androgen receptor (ARTA, androgen receptor targeted agent).

FACT 2. ABIRATERONE ACETATE HAS HIGH ACTIVITY IN THE TREATMENT OF PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PRIOR TO CHEMOTHERAPY WITH DOCETAXEL

Evidence to support this claim comes from the prospective phase III randomized clinical trial COU-AA-302 (ratio 1 : 1), in which abiraterone (1000 mg once daily orally) with prednisone (5 mg twice daily orally) was administered in a group of 1088 sparse metastatic CRPC (mCRPC) patients previously untreated with docetaxel-containing chemotherapy (DXL, *docetaxel*) and compared with placebo with prednisone. Treatment with abiraterone resulted in a clinically and statistically significant benefit with respect to the primary endpoints of median radiographic progression-free survival (rPFS) ($p < 0.0001$) and median overall survival (OS) ($p = 0.0033$) [5]. Similar drug effects have been documented for clinically important secondary and exploratory endpoints such as time to biochemical progression (PSA increase) (PSA TTP, PSA time-to-progression), time to deterioration of overall performance status, time to need for opiate dose escalation, time to deterioration of quality of life, or time to need for chemotherapy.

FACT 3. THERE IS CLINICAL EVIDENCE FOR THE EFFICACY OF ABIRATERONE ACETATE IN THE TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER AFTER CHEMOTHERAPY WITH DOCETAXEL

Results of an analysis comparing the efficacy and safety of treatment with abiraterone acetate plus prednisone (typical dosing) versus placebo plus prednisone, based on data from a randomized phase III clinical trial (ratio 2 : 1) (COU-AA-301) in a population of 1195 men with progression of mCRPC despite prior first- or second-line chemotherapy (one of which contained docetaxel) indicate a clinically and statistically significant positive effect of the drug on median OS and rPFS, as the most important parameters for assessing the efficacy of anticancer therapy [6]. The relative risk of death was reduced by 26% in the study drug group, and the median OS was 15.8 months (compared to 11.2 months in the prednisone placebo group ($p < 0.001$) [7]. The benefit discussed above also applied to men who previously received two lines of chemotherapy. The median rPFS was increased from 3.6 months in the control group to 5.6 months in the study drug group (hazard ratio [HR] and 95% confidence interval [CI], respectively: 0.66 and 0.58–0.76) ($p < 0.0001$). A significant difference in favor of abiraterone acetate was also found for the other study endpoints: biochemical response rate (decrease in serum PSA levels), objective response rate (a parameter

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referring only to measurable lesions in radiographic evaluation according to RECIST [Response Evaluation Criteria in Solid Tumors] criteria).

FACT 4. DESPITE THE LACK OF DATA OF RECOMMENDING POWER REGARDING THE OPTIMAL SEQUENCE OF ATRA USE IN THE TREATMENT OF MCRPC, AVAILABLE DATA SUGGEST THE USE OF ABIRATERONE ACETATE PRIOR TO ENZALUTAMIDE THERAPY

Controversy regarding the feasibility and method of sequential use of the two leading ARTAs in clinical practice, abiraterone (ABI) and enzalutamide (ENZA), continues to persist, as data regarding this issue mainly come, unfortunately, from retrospective, single-center or small population studies.

One of the few prospective studies with randomized sampling is a phase II clinical trial by Khalaf conducted between 2014 and 2018 and evaluating the sequential use of ABI then ENZA or ENZA then ABI in patients with mCRPC. In this study, switching from one drug to another was done when biochemical progression was confirmed, and the endpoints for evaluating the efficacy of the sequence were time to biochemical progression (PSA increase) during second-line treatment and the percentage of biochemical responses consisting of a reduction in serum PSA by at least 30% by the sequential therapy used – also during second-line treatment. The analysis of results in this study seems to confirm previous suggestions of higher efficacy of the "ABI then ENZA" sequence over the reverse order. This is probably a consequence of specific differences in the mechanism of action of both drugs.

On the other hand, meta-analysis of data from eight studies on a total of 643 men showed that the sequence "ABI then ENZA" significantly positively affects PFS (HR = 0.62; $p < 0.001$), PSA-PFS (PSA-progression-free survival) (HR = 0, 48; $p < 0.001$) and biochemical response rate (relative risk [RR, risk ratio] = 0.21; $p < 0.001$) compared to the reverse sequence (ENZA followed by ABI) – nevertheless without impact on OS.

FACT 5. SIDE EFFECT PROFILE INDICATES SAFE USE OF ABIRATERONE ACETATE

Treatment with abiraterone acetate is safe and well tolerated – also in the elderly male population. The most common adverse event of the drug, and resulting from the mechanism of action of ABI are: fatigue and lack of energy (G [grade; here the symptom intensity] 1–2: 44%, G ≥ 3: 8%) fluid retention (31% and 2% respectively), back pain (30% and 6%), nausea (30% and 2%), joint pain (27% and 4%). Hepatotoxicity (with an increase in an activity of hepatic aminotransferases) was found to be relatively rare (10% and 3%), as were hypokalemia (17% and 3%) and hypertension (10% and 1%) [7]. Studies that aimed to comparatively assess the effect of ABI or ENZA treatment on quality of life indicate that quality of life (QoL) based on validated assessment tools in the form of FACT-P HRQoL and PHQ-9 questionnaires, especially in the older male group indicate ABI as the better tolerated one [1]. ENZA has also been shown to cause more frequently fatigue and impaired cognitive function [11, 12].

FACT 6. THE USE OF GLUCOCORTICOSTEROIDS AS CONCOMITANT THERAPY WITH ABIRATERONE ACETATE IS SAFE

Glucocorticosteroids are widely used in the systemic treatment of cancer. Glucocorticosteroids are an important part of supportive therapy or broadly defined premedication in relation to antineoplastic treatment. Their antiemetic, anti-inflammatory, "co-analgetic", antiedematous, anabolic or appetite-enhancing effects are well recognized and used [13, 14]. They are most often used interventively. It is estimated that drugs from this group have been used in 30–80% of patients with prostate cancer [15]. The specificity of prostate cancer here lies not only in the interventional use of glucocorticosteroids, but also in their use as part of causal treatment – alone having a certain antitumor activity (with negligible effect on OS), they are an integral part of anticancer treatment with abiraterone acetate – due to the mechanism of action of the latter. Many doubts have been raised about the safety of this treatment. Studies indicate that prednisolone administered in low doses (10 mg/24 h) together with abiraterone acetate gives concentrations equivalent to physiological cortisol concentrations [14]. Among patients enrolled into the phase III clinical trials COU-AA-301 and COU-AA-302, the incidence of clinically significant adverse events (i.e. in grade ≥ 3) (hyperglycemia, weight gain, skin fragility, diabetes, bone fractures, cataracts etc.) does not exceed a few percent (1–8% depending on the adverse event) and does not increase with the duration of exposure to glucocorticoids [5, 7].

FACT 7. ABIRTERONE ACETATE IS AN EFFECTIVE TREATMENT FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Treatment with abiraterone acetate (AA) (1000 mg/24 h) in combination with prednisone (P) (5 mg/24 h) and androgen depriva-

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tion therapy (ADT) was compared to placebo (with prednisone and ADT) in a population of 1199 men with newly diagnosed (≤ 3 months prior to randomization) high-risk mCSPC (castration-sensitive prostate cancer) with no prior exposure to hormone therapy (two out of three high-risk criteria present, which were defined as: Gleason score of tumor histological malignancy ≥ 8, presence of ≥ 3 bone lesions, presence of measurable visceral organ lesions) [16]. The data analysis showed that the relative risk of death was 38% lower in the group treated with AA + P + ADT, and the relative risk of radiographic progression was 53% lower compared to the group receiving placebo + P + ADT. In addition, a significant advantage of ADT + AA + P therapy over ADT + placebo was observed for all secondary end-points such as time to pain progression, time to PSA progression, time to subsequent skeletal-related event (SRE), and time to need for chemotherapy with a significantly higher biochemical response rate (91 vs. 67) ($p < 0.001$).

FACT 8. ABIRATERONE ACETATE SHOULD BE CONSIDERED EARLY IN THE TREATMENT OF SYSTEMIC PROSTATE CANCER

Data from the LATITUDE phase III clinical trial discussed above indicate that the drug is highly active as early as castration-sensitive spread. Although we do not have direct comparisons, meta-analyses of large prospective randomized clinical trials (seven clinical trials on a total population of 7287 patients comparing six treatment options) indicate (in order from most effective treatment to least effective therapeutic option) that the drugs that significantly improve OS are: abiraterone acetate, apalutamide, and docetaxel, and drugs with a significantly positive effect on rPFS are: enzalutamide, abiraterone acetate, apalutamide, and docetaxel. At the same time, the frequency of serious adverse events (SAEs) is relatively highest with docetaxel treatment, slightly higher with abiraterone and not increased with the other ATRAs.

FACT 9. POSSIBLE SEQUENTIAL TREATMENT WITH MODERN HORMONAL DRUGS IN THE CONTINUUM OF THERAPY FOR THIS CANCER

The question of the feasibility of sequential use of modern hormonal drugs is still controversial, a good example being the issue of the use of abiraterone acetate and enzalutamide discussed above. However, data from a phase III clinical trial with apalutamide in patients with non-metastatic CRPC (so-called M0 CRPC) shed a different light on this experience. In this study, if radiographic progression – the appearance of metastatic prostate cancer (and disease progression to mCRPC status) – was detected, it was possible to use subsequent treatment with a documented positive impact on OS. Among the men enrolled into the study, 50% and 64% (from the experimental treatment group and the control group, respectively) experienced progression. More than 70% of them received subsequent abiraterone acetate (enzalutamide was received by 6% and 12%, respectively), and during an analysis dedicated to evaluate one of the exploratory endpoints which was progression-free survival 2 (PFS2 – measured from randomization to progression during subsequent anticancer treatment), the validity of this approach was demonstrated [17].

FACT 10. TREATMENT OF PATIENTS WITH METASTATIC PROSTATE CANCER WITH ABIRATERONE ACETATE AND RADIUM-223 DICHLORIDE INCREASES FRACTURE RISK – ESPECIALLY IN PATIENTS UNPROTECTED WITH OSTEOPROTECTIVE DRUGS

At the 2018 ESMO Congress, data on the efficacy and safety of the combined use of abiraterone acetate (AA) with prednisone (P) and radium-223 dichloride + placebo (Phase III ERA 223 study) were presented for the first time (Smith MR et al. LBA_30, ESMO 2018). The message was dominated by an unexpectedly high incidence of bone fractures, and these were not pathological fractures – because occurred not at sites of localization of prostate cancer metastatic lesion – but rather fractures of the osteoporotic type. The consequence of these events was the recommendation of the Independent Data-Monitoring Committee (IDMC), to unblind the trial in November 2017, followed by the introduction of an amendment to the protocol recommending the use of osteotropic treatment *de novo*, secondly changes in the summary of product characteristics (SmPC), and – in Polish conditions – modifications in so called "drug program" as a procedure for financing treatment with public funds moving that moved the possibility of using α-radinium as the last in the sequence of systemic treatment in mCRPC. A deeper analysis of the reasons for the phenomenon in question revealed a grossly low – in terms of frequency and inconsistent with recommendations – use of osteotropic/osteoprotective drugs. Ultimately, the conclusion of our analysis is that adjunctive bone-targeted therapy should be implemented in every patient with mCRPC and bone involvement – unless there are contraindications for its use.

CONCLUSIONS

The issues discussed above demonstrate the high efficacy and safety of abiraterone acetate, which translate into clinical benefits for patients with prostate cancer. In Poland we expect chang-

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es in the reimbursement of ABI treatment which will reflect the progress made in the field of prostate cancer pharmacotherapy and will be in accordance with the SmPC (summary of product characteristics) as well as international recommendations.

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