REVIEW ARTICLE

Pre-chemotherapy abiraterone acetate. A proposal of a treatment algorithm in castration resistant prostate cancer

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KEYWORDS
Castration resistant prostate cancer; Abiraterone; Androgens

Abstract

Context: Prostate cancer treatment remains a challenge for the urologist. Medical control in locally advanced or metastatic prostate cancer is usually performed with LHRH analogs and/or antiandrogens. Different treatments have been proposed when there is biochemical and clinical progression of the disease and other new ones have changed the patients’ perspective and life expectancy.

Objective: This review has aimed to establish the current role of abiraterone acetate in the treatment of castration-resistant prostate cancer and facilitate decision-making by the Urologist by means of a Treatment Algorithm.

Acquisition of the evidence: A search of current evidence on Abiraterone treatment in patients with castration-resistant metastatic prostate cancer was performed in PubMed, mainly analyzing those studies designed as clinical trials. In addition, we reviewed and updated the role of hormone therapy and androgen receptors in prostate cancer.


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The names of the members of the Group of the Andalusian and Spanish Urological Association (AAyEU) are available in Appendix.
Evidence synthesis: There are currently basically two clinical trials that demonstrate the effectiveness of Abiraterone in metastatic prostate cancer compared to placebo. The study COU-AA 302 shows a clear benefit with Abiraterone prior to chemotherapy in patients with castration-resistant prostate cancer, this making it possible to establish an algorithm for initial treatment that facilitates decision-making by the urologist.

Conclusion: Abiraterone is a pre-chemotherapy treatment option in selected patients with castration-resistant metastatic prostate cancer, although it is necessary to improve the cost and to design more multicenter clinical trials to optimize the cost/benefit ratio.

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Acetato de abiraterona prequimioterapia. Propuesta de un algoritmo de tratamiento en el carcinoma de próstata resistente a castración

Resumen

Contexto: El tratamiento del cáncer de próstata sigue siendo un reto para el urólogo. El control médico en el cáncer de próstata metastásico o localmente avanzado se realiza habitualmente con análogos LHRH y antiandrógenos. Cuando se produce la progresión bioquímica y clínica de la enfermedad diferentes tratamientos han sido propuestos y otros nuevos han cambiado la perspectiva y esperanza de vida de los pacientes.

Objetivo: El objetivo de esta revisión es establecer el papel actual del acetato de abiraterona en el tratamiento del cáncer de próstata resistente a la castración y facilitar la toma de decisión del urólogo mediante un algoritmo de tratamiento.

Adquisición de la evidencia: Se realiza una búsqueda de la evidencia actual del tratamiento con abiraterona en pacientes con cáncer de próstata metastásico resistente a castración en PubMed, analizando principalmente aquellos estudios diseñados como ensayos clínicos. Además se realiza una revisión y actualización del papel del tratamiento hormonal y de los receptores andrógenicos en el cáncer de próstata.

Síntesis de la evidencia: Existen en la actualidad fundamentalmente 2 ensayos clínicos que demuestran la eficacia de abiraterona en el cáncer de próstata metastásico con respecto a placebo. En el estudio COU AA-302 se observa un beneficio evidente con abiraterona previo a quimioterapia en pacientes con cáncer de próstata resistente a castración, lo que permite establecer un algoritmo de tratamiento inicial que facilita la toma de decisión por parte del urólogo.

Conclusión: Abiraterona es una opción de tratamiento prequimioterapia en pacientes seleccionados con cáncer de próstata metastásico resistente a la castración, aunque debe mejorarse la oferta económica y diseñar más ensayos clínicos multicéntricos para optimizar la relación coste/beneficio.

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Background

Prostate cancer is the second most common malignant neoplasm in men and the sixth cause of death by cancer. The widespread use of prostate-specific antigen (PSA) in the 1990s corresponded with an increase in the diagnosis of prostate cancer, with characteristics of an epidemic. This situation continues to this day, such that in 2008, 89,900 new cases of the disease were diagnosed worldwide along with 258,000 deaths. In Spain the estimated incidence is 21,000 new cases a year (82.27 new cases/100,000/year). Seventy-two percent of cases and 53% of deaths are reported in developed countries. It is estimated that in 2030, new cases will reach 1.7 million, with deaths reaching 499,000.

The role of hormone therapy in prostate cancer

Since the 1940s when Huggins described the hormonal dependence of prostate cancer, treatment for the disease has evolved in such a way as to significantly alter its natural history. In the mid-20th century, estrogens became the first medical treatment for inhibiting the production of androgen, equivalent to surgical castration, despite significant adverse effects. Although androgenic deprivation, and the consequent reduction in testosterone, results in symptom relief and reduced tumor burden, Huggins described the temporal effect of treatment through androgenic inhibition, where the disease evolves over time independently of hormonal influence.

The description of the hypothalamic–pituitary–gonadal axis and the development of gonadotropin-releasing hormone (GnRH) analogs puts an effective therapeutic tool for the treatment of prostate cancer in the hands of the urologist. For decades, a blockade using luteinizing hormone releasing hormone (LHRH) analogs, alone or combined with antiandrogens, has been the only available treatment for the group of patients with no indication for initial treatment with curative intent. The initial response to hormonal blockade is close to 100%, although the disease will progress over a varying time interval in a high percentage of patients,
depending on several factors including the tumor histology and burden, with the mean time at approximately 2–3 years.\textsuperscript{8,9} Once the disease progresses and despite androgen deprivation, the prostate cancer is considered to be in a castration-resistant situation (CRPC). This term has been coined in recent years and has replaced others such as hormone resistance and hormone independence, given that the disease should continue to be sensitive to androgen stimulation. Metastatic CRPC has a poor prognosis, with a mean survival of 16–18 months. It is not known whether there are castration-resistant cell clones in hormone-resistant prostate cancer, although the prolongation of androgenic deprivation can cause changes in the disease that involve the onset of androgen deprivation resistance.\textsuperscript{10} CRPC is still influenced by androgens. Research on the treatment of the disease has therefore delved into understanding the changes caused in the androgen receptor (AR) and the intratumoral synthesis of antiandrogens, in order to identify therapeutic targets that enable the development of drugs that can act in this disease state.

The role of the androgen receptor

ARs remains active in the CRPC and generally overexpress in CRPC, a fact that might be related to the development of androgenic deprivation resistance.\textsuperscript{11} In normal tissues, ARs depend on ligands that stimulate the transcrip­tion of the receptor when its expression is reduced. Once the ARs recover an appropriate level, transcription is halted through a negative feedback mechanism. In tumor tissues subjected to low levels of androgen, the transcription of AR is overstimulated, but the inhibition mechanisms are not sufficient to suppress the receptor.\textsuperscript{12}

Combined with an increased expression of AR, CRPC presents a change in the AR signal, which enables its stimulation by molecules other than androgens. Exposure to low levels of androgens and the interaction with antiandrogens promote the development of AR mutations, which enable AR activation by estrogens, progesterone and corticosteroids.\textsuperscript{13,14}

Another mechanism involved in resistance to androgens is the coding of incomplete receptors, the AR splice variants (AV), of which 2 have been identified in human tissues. One of these, the AR-V7, depends on normal AR for transcrip­tion and is therefore sensitive to drugs that achieved a profound androgenic blockade, such as abiraterone acetate. The other ARV, known as AV-v567ex, is independent of nor­mal AR; therefore the tumors that express it do not respond properly to drugs based on androgen blockade.\textsuperscript{12}

The role of androgens

The discovery of the intratumoral synthesis of androgens in prostate cancer, as an extratesticular source of androgen, has motivated the search for a new terminology for the disease in this situation, because CRPC remains sensitive to androgens although they do not result from testicular production. Intratumoral androgen levels in patients with CRPC are similar to those of patients with hormone-resistant prostate cancer.\textsuperscript{15} The intratumoral synthesis of androgens arises from 2 pathways. In the first, cholesterol esters are fragmented (in response to the hormonal blockade) in cholesterol and fatty acids, which are metabolized to arachidonic acid. This in turn stimulates (through CYP11A) the production of pregnenolone from cholesterol. A second pathway consists of the stimulation of androgen synthesis by insulin, a treatment that patients who have androgen blockade frequently require.\textsuperscript{16,17}

The conversion of androstenedione to 5-alpha­androstenedione has recently been described. This, in turn, is converted into dihydrotestosterone, without the need for testosterone synthesis in the metastatic CRPC.\textsuperscript{18}

Abiraterone acetate reduces testosterone concentrations in blood and in the tumor at levels in the range of picograms per milliliter.\textsuperscript{19} Conventional antiandrogens present partial agonist activity; new antiandrogens such as MDV3100 lack this activity and act at various levels,\textsuperscript{10} as is the case for this drug, which inhibits the binding of AR to the nuclear chromatin. This drug has an affinity for AR that is 5–8 times higher than bicalutamide.

The majority of conventional antiandrogens bind to the C-terminal end, which is lacking in ARVs. However, the N-terminal end is present in both complete ARs and in ARVs. Binding to the C-terminal end prevents the translocation to the nucleus and blocking of the receptor region known as AF2 (activation function 2).\textsuperscript{20} Research on molecules that use binding to the N-terminal end to inhibit AR, such as the EPI-001 drug, has revealed considerable activity.

CYP17 inhibition

CYP17 inhibition is a key target in the treatment of CRPC. Ketoconazole has been used as a second-line hormonal maneuver because it inhibits 11-beta-hydroxylase, the metabolism of cholesterol to pregnenolone and the CYP17 enzyme. In a phase 3 study of 260 patients with CRPC, in progression after antiandrogen withdrawal, keto­conazole was associated with a reduction in PSA levels > 50% in 27% of the patients. There was no difference in overall survival, but those patients who demonstrated a reduction in PSA levels > 50% had a survival of 41 months, compared with 13 months in the patient group with no reduction in PSA levels.\textsuperscript{21} Another recently published study\textsuperscript{22} observed that the preparation of a risk profile for patients with CRPC could be useful in predicting the response to treatment with ketoconazole.

Abiraterone acetate is an antiandrogen that inhibits synthesis through the irreversible inactivation of CYP17A, leading to a profound androgen blockade. Phase 3 studies have shown that this antiandrogen is initially effective in patients in progression after chemotherapy. Study COU AA-301 randomized patients with CRPC who had been treated previously with docetaxel: 797 patients were treated with 1000-mg abiraterone combined with 10-mg prednisone, and 398 patients were treated with placebo combined with 10-mg prednisone. The treatment arm achieved greater overall survival (14.8 vs. 10.9 m; HR 0.65; 95% CI: 0.54–0.77; \(p < .001\)). The secondary objectives achieved an equal level of significance in terms of time to PSA progression (10.2 vs. 6.6 m), progression-free survival (5.6 vs. 3.6 m) and PSA response rate (29% vs. 6%).\textsuperscript{13} COU AA-302, a phase
3, prospective, randomized study, assessed treatment with abiraterone in patients with prechemotherapy CPRCm. This study randomized 1088 patients to daily treatment with 1000-mg abiraterone combined with 10-mg prednisone (546 patients) or to placebo combined with prednisone (542 patients). The primary objectives were overall survival (OS) and radiological progression-free survival (RPFS). After assessing the results of the second interim analysis, which was expected to reach 43% mortality with a mean follow-up of 22.2 months, the study decided to unblind the patients due to the favorable results of the abiraterone arm. In terms of RPFS, the mean time to progression was 16.5 m in the abiraterone arm vs. 8.3 m in the placebo arm (HR: 0.53; 95% CI: 0.45–0.62; p < .001). With regard to the OS, greater mortality was observed in the placebo arm (34% vs. 27%). The mean survival was not achieved in the abiraterone arm, which was 27.2 m in the placebo arm. A 25% reduction in the mortality risk was observed in the abiraterone arm (HR: 0.75; p = .01), although the preestablished significance level was not reached (p = .005). A statistically significant benefit was also observed in the secondary objectives in the abiraterone arm. The time to a lower ECOG score (by at least 1 point) was 12.3 m in the treatment arm vs. 10.9 m in the placebo arm (HR: 0.82; 95% CI: 0.71–0.94; p = .005). The time to the start of cytotoxic chemotherapy was 25.2 m in 16.8 m (HR: 0.58; 95% CI: 0.49–0.69; p < .001). The mean time to the use of opioids was not reached in the abiraterone group but was 23.7 months in the placebo group. The time to PSA progression was 11.2 m vs. 5.6 m (HR: 0.49; 95% CI: 0.42–0.57; p < .001). The safety parameters were similar to those reported by the 301 study; the drug is therefore considered to be well tolerated. More recently, data obtained after 55% mortality were reported in the 2013 American Society of Clinical Oncology Genitourinary Cancers Symposium. With a mean follow-up of 27.1 months, the OS remained favorable in the abiraterone treatment arm (35.3 m vs. 30.1 m) (HR 0.79; 95% CI: 0.66–0.96; p < .0151). The RPFS was 16.5 m in the abiraterone arm vs. 8.3 m in the prednisone-only arm (HR 0.53; 95% CI: 0.45–0.62; p < .001). The time to the use of opioids did not reach the median in the abiraterone arm, which was 23.7 m in the placebo arm (HR 0.71; 95% CI: 0.59–0.85; p = 0.002). The time to cytotoxic chemotherapy was greater in the abiraterone arm (26.5 m vs. 16.8 m) (HR 0.61; 95% CI: 0.51–0.72; p < .001), as was the time to worsening of the ECOG score (12.3 m vs. 10.9 m) (HR 0.83; 95% CI: 0.72–0.94; p = 0.0052) and the mean time to PSA progression (11.1 m vs. 5.6 m) (HR 0.5; 95% CI: 0.43–0.58; p < .001).

**Definition of castration-resistant prostate cancer.**

**Treatment of castration-resistant prostate cancer.**

The definition of CRPC involves several conditions: testosterone levels within castration levels (<50 ng/dl); 3 consecutive increases in PSA levels, separated by at least 1 week, with 2 increases greater than 50% above nadir and a PSA level >2 ng/ml; having withdrawn from antiandrogens for at least 4 weeks; PSA progression despite 2 hormonal maneuvers; and progression of bone or soft tissue lesions.

It is essential that the criteria for the diagnosis of CRPC remain clear, given that the disease in this situation includes a heterogeneous group of patients, with or without radiologically obvious metastases (symptomatic or asymptomatic), with various expected survival rates. Additionally, the persistent influence of the androgenic environment has changed the concept of the disease and has opened new avenues of research into the development of effective drugs for the treatment of this disease.

There are several treatment options for patients in progression with CRPC, once the hormonal manipulation maneuvers have been exhausted and depending on their clinical status. Basically, for those patients in rapid progression who are clearly symptomatic, there is a poor prognosis and the use of chemotherapy might be appropriate if their clinical situation allows for it.

A significant group of patients present only PSA progression, with no radiological evidence of metastases, and remain asymptomatic. This patient group can expect a survival of up to 4 years, and there is currently no specific treatment beyond hormonal manipulation maneuvers and the use of corticosteroids. Nevertheless, the development of new radiological techniques and a stricter follow-up can reduce the number of patients in this situation.

Lastly, another group of patients with CRPC present radiological evidence of metastases although they remain asymptomatic or minimally symptomatic. Abiraterone has emerged as a new therapeutic option for these patients, once hormonal manipulation maneuvers have been exhausted.

Abiraterone acetate, as stated earlier, has been approved for the treatment of metastatic asymptomatic or minimally symptomatic CRPC. Currently, the use of the drug is included in clinical guidelines as a grade A recommendation. The European Association of Urology (UA) guidelines recommend abiraterone with a grade A recommendation, although one of the primary objectives regarding overall survival has not reached the expected significance level. In the National Comprehensive Cancer Network guidelines, treatment with abiraterone prechemotherapy has a 1A level of evidence. The recommendation for abiraterone refers to those patients who were included in the phase 3 clinical trial that showed evidence, i.e. patients with metastatic CRPC, with no visceral metastases, who are asymptomatic or slightly symptomatic. Patients indicated for chemotherapy who cannot tolerate it due to their clinical condition, might be candidates for treatment with abiraterone, with a 2A level of evidence. The approval of the drug in this stage of the disease represents an increase in the number of patient candidates for treatment compared with those who had an indication for initial postchemotherapy. In order to make the best use of resources, the indications for administering abiraterone to patients with prechemotherapy CRPC need to be properly established.

Currently in Spain, the pharmaceutical company that owns the patent on the drug is in price negotiations with the Ministry of Health to adjust the cost of the treatment to the new scenario. The current cost for 1 month of treatment is more than 3000 euros, an undoubtedly high price that needs to be negotiated by the health authorities, as has taken place in other countries such as England and Wales, which will improve the cost–benefits of the drug. However, although this negotiation is necessary, the
current available scientific evidence places the indication for abiraterone in CRPC before undergoing chemotherapy. In this context, an expert panel of urologists from the Andalusian Association of Urology and from Spanish hospitals has prepared a protocol to help with decisions about treatment with abiraterone acetate. This decision-making process for hormone therapy is applied in the clinical practice of urologists and is promoted and endorsed by the Spanish Urological Association (the highest governance body for scientific representation in Spanish urology). It is not meant to
undermine the reaching of consensus on recommendations based on available evidence from other medical specialties.54

Treatment protocol and algorithm for castration-resistant prostate cancer

The protocol (available in electronic format on the Andalusian Association of Urology website52) includes the various treatment options for CRPC. Data from the technical sheet on abiraterone acetate are also included.

Based on this protocol, a treatment algorithm for CRPC has been developed, which attempts to facilitate the decision-making process in this group of patients and promote reduced variability in clinical practice (Fig. 1).

Conclusions

The treatment of CRPC has evolved in recent years, from the first indications of cytotoxic treatment starting in 2004 to the development of drugs that deepen the hormonal blockade. Patients with CRPC do not form a homogeneous group, and although a large portion of them can undergo treatment backed by a good level of evidence, there are still patients who have no specific treatment, such as those with only PSA progression. Abiraterone is a prechemotherapy hormone treatment option for selected patients with metastatic castration-resistant prostate cancer. However, the economic proposal needs to improve, and more multicenter clinical trials need to be designed to optimize the cost–benefit relationship.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Addendum 1. AAYEU Group


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