Initial experience with abiraterone acetate in patients with castration-resistant prostate cancer

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Abstract

Objective: To describe the results obtained in 25 men with metastatic castration-resistant prostate cancer (MCRPC) treated with abiraterone (AA). A comparative analysis of abiraterone effectiveness and safety between our results and data published in the literature was conducted.

Materials and method: Bi-institutional prospective analysis of 25 consecutive patients with MCRPC undergoing treatment with abiraterone, with a mean follow-up 7.9 (3–15) months was carried out. Treatment effectiveness and safety analyses regarding baseline characteristics of patients (age, prior treatments, basal PSA, performance status, pain, and metastasis) were conducted.

Results: At 13.6 months of follow-up, the overall survival is 80% (CI 95%: 11.8–15.4). Clinical and radiological-free progression survival is 9.5 ± 1 months (CI 95%: 7.7–11.3) and biochemical response is 6.8 ± 1 months (CI 95%: 5–8.7). Only the treatment with chemotherapy impaired significantly the response time to AA [6.4 months for radiological-free progression survival (CI 95%: 4.2–8.6) and 4.3 months for biochemical-free progression survival (CI 95%: 2.6–6)]. The incidence of adverse drug events was 36%; all of them were of grade 1–2/4 and, in no case, suspension or reduction of the dose of AA was needed.

Conclusions: The treatment with AA has been effective in our series, with a tolerability considerably higher than what other studies published.

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PALABRAS CLAVE
Abiraterona acetato; Cáncer de próstata resistente a la castración; Terapia hormonal secundaria; Nuevas terapias hormonales; CYP17; 17α-hidroxilasa

Experiencia inicial con acetato de abiraterona en pacientes con cáncer de próstata resistente a la castración

Resumen
Objetivo: Describir los resultados obtenidos de la experiencia en el tratamiento con acetato de abiraterona (AA) en 25 hombres con cáncer de próstata metastásico resistente a la castración (CPMRC). Realizamos el análisis comparativo de la eficacia y seguridad de este fármaco en relación con la literatura existente.

Material y método: Estudio biinstitucional prospectivo de una cohorte de 25 pacientes consecutivos que reciben tratamiento con AA por CPMRC, con un seguimiento medio 7,9 (3-15) meses. Análisis de la seguridad y eficacia del tratamiento en relación con las características basales de los pacientes (edad, tratamientos previos, PSA basal, performance status, dolor, metástasis).

Resultados: La supervivencia global es del 80% a los 13,6 meses de seguimiento (IC 95%: 11,8-15,4). La supervivencia libre de progresión clínico-radiológica de la serie es de 9,5 ± 1 meses (IC 95%: 7,7-11,3) y el de respuesta bioquímica de 6,8 ± 1 meses (IC 95%: 5-8,7). Solo el tratamiento previo con quimioterapia empeora significativamente el tiempo de respuesta a AA (supervivencia libre de progresión radiológica 6,4 meses [IC 95%: 4,2-8,6] y bioquímica de 4,3 meses [IC 95%: 2,6-6]). La incidencia de efectos adversos fue del 36%, todos grado 1-2/4, y en ningún caso requiere suspender o disminuir la dosis de AA.

Conclusiones: El tratamiento con AA ha sido eficaz en nuestra serie, con una tolerabilidad considerablemente mayor a la publicado en otros estudios.

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Introduction

Prostate cancer is the second most frequent neoplasm among men and the fifth cause of cancer death.1 Although less than 5% of patients show metastatic disease at diagnosis, approximately 40% of patients are going to develop metastasis after curative local treatment.2 The disease is incurable once metastasis has occurred. Surgical or medical castration is highly effective in shrinking tumor burden, decreasing prostate-specific antigen (PSA) levels, enhancing quality of life, and improving survival.3 However, most patients will eventually experience disease progression despite castration, with a median duration of response of 12–24 months, being the average survival for patients with castration-resistant prostate cancer (CRPC) 2–3 years lower than 20%.3 Three systemic hormonal treatments are able to improve in 1 year the survival rates in patients with advanced CRPC: docetaxel1 as first-line therapy, cabazitaxel1 in second-line therapy and active cellular immunotherapy with sipuleucel-T.6

However, recent research suggests that CRPC remains dependent on a signaling pathway androgen receptor, which is active for cell survival and tumor growth.7 As consequence, new treatments have been developed, like abiraterone acetate (AA) which has changed metastatic CRPC treatment paradigm. AA is a selective oral inhibitor of androgen biosynthesis that potently blocks cytochrome P450 CYP17 (17α-hydroxylase and C17,20 lyase), in the adrenal glands and testes and within the prostate tumor.8 In phase III clinical trials have demonstrated an increase in overall survival in patients with metastatic castration-resistant prostate cancer after chemotherapy,9 and delay the chemotherapy if it is used before docetaxel.10

Materials and method

Bi-institutional prospective study of 25 consecutive patients with MCRPC treated with AA from February 2012 until April 2013; mean follow-up 7.9 ± 0.7 (3–15) months.

Patients’ characteristics

Mean age 70 years (59–87) when starting treatment with AA. 60% of them showed metastasis at the diagnosis of prostate adenocarcinoma. All patients had received at least 2 hormonal treatment lines before AA treatment; 16% of them (4 patients) received third-line hormonal treatment with ketoconazole. 36% of patients received chemotherapy before AA treatment (12% of whom received 2 treatment lines with docetaxel and cabazitaxel).

48% of patients were defined as asymptomatic: visual analog scale score (VAS)11 ≥ 3 requiring additional treatment with strong opiates or 89SrCl and/or palliative radiotherapy.

Series characteristics are resumed in Table 1.

Treatment

All patients received 1.000 mg of AA, 10 mg of oral prednisone every 24 h and a GnRH analog. AA treatment was interrupted when radiological and clinical or biochemical progression was confirmed.

At the diagnosis of metastatic bone disease, all patients were supplemented with calcium-vitamin D and zoledronic acid (68%) or denosumab (32%).
### Table 1  Distribution of the different clinical variables in the overall series and in groups treated with abiraterone acetate post-chemotherapy and pre-chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Overall series</th>
<th>Pre-chemotherapy treatment</th>
<th>Post-chemotherapy treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients (%)</strong></td>
<td>25</td>
<td>16 (64%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiological progression</strong></td>
<td>13 (52%)</td>
<td>5 (31%)</td>
<td>8 (89%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Biochemical progression</strong></td>
<td>15 (60%)</td>
<td>7 (44%)</td>
<td>8 (89%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Follow-up (months)</strong></td>
<td>7.9 (±0.7)</td>
<td>8.2 (±0.8)</td>
<td>7.3 (±1.3)</td>
<td>0.568</td>
</tr>
<tr>
<td><strong>Duration of treatment (months)</strong></td>
<td>7.5 (±0.7)</td>
<td>8.2 (±0.8)</td>
<td>6.1 (±1)</td>
<td>0.126</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>70.6 (±1.5)</td>
<td>71.3 (±1.8)</td>
<td>69.3 (±2.5)</td>
<td>0.524</td>
</tr>
<tr>
<td><strong>Gleason 9–10</strong></td>
<td>14 (56%)</td>
<td>10 (62.5%)</td>
<td>4 (44.4%)</td>
<td>0.434</td>
</tr>
<tr>
<td><strong>Time from diagnosis to AA (months)</strong></td>
<td>47.6 (±9.7)</td>
<td>44.4 (±14.5)</td>
<td>53.1 (±9.1)</td>
<td>0.677</td>
</tr>
<tr>
<td><strong>Hormone response time (months)</strong></td>
<td>34 (±9.8)</td>
<td>35.3 (±14.5)</td>
<td>31.7 (±10.1)</td>
<td>0.863</td>
</tr>
<tr>
<td><strong>Response to previous hormonal treatment ≤ 12 months</strong></td>
<td>7 (28%)</td>
<td>5 (31.3%)</td>
<td>2 (22.2%)</td>
<td>0.626</td>
</tr>
<tr>
<td><strong>Previous</strong></td>
<td>4 (16%)</td>
<td>2 (12.5%)</td>
<td>2 (22.2%)</td>
<td>0.602</td>
</tr>
<tr>
<td><strong>Ketoconazole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visceral metastases</strong></td>
<td>5 (20%)</td>
<td>5 (31.3%)</td>
<td>0 (0%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>ECOG PS:</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>ECOG 0</strong></td>
<td>10 (40%)</td>
<td>7 (43.8%)</td>
<td>3 (33.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG 1</strong></td>
<td>10 (40%)</td>
<td>4 (25%)</td>
<td>6 (66.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG 2</strong></td>
<td>5 (20%)</td>
<td>5 (31.2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic</strong></td>
<td>12 (48%)</td>
<td>6 (37.5%)</td>
<td>6 (66.7%)</td>
<td>0.161</td>
</tr>
<tr>
<td><strong>PSA pretreatment (ng/dl)</strong></td>
<td>125.2 (±40.9)</td>
<td>125.5 (±59.3)</td>
<td>124 (±47.1)</td>
<td>0.993</td>
</tr>
<tr>
<td><strong>% PSA reduction</strong></td>
<td>46.1 (±6.9)</td>
<td>40.1 (±10.1)</td>
<td>55.6 (±6)</td>
<td>0.223</td>
</tr>
<tr>
<td><strong>PSA reduction &gt; 50%</strong></td>
<td>10 (40%)</td>
<td>6 (37.5%)</td>
<td>4 (44.4%)</td>
<td>0.734</td>
</tr>
<tr>
<td><strong>Length of biochemical response (months)</strong></td>
<td>6.2 (±0.9)</td>
<td>7.4 (±1.2)</td>
<td>4.3 (±0.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Length of clinical-radiological response (months)</strong></td>
<td>9.5 (±1)</td>
<td>11.5 (±1.1)</td>
<td>6.4 (±1.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Type of radiological response</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.263</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>5 (25%)</td>
<td>4 (33.3%)</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>8 (40%)</td>
<td>5 (41.7%)</td>
<td>3 (37.5%)</td>
<td></td>
</tr>
</tbody>
</table>

In bold clinical factors with differences statistically significant in both groups (pre- and post-chemotherapy).

a Time elapsed in months from diagnosis of prostate adenocarcinoma to the beginning of abiraterone acetate treatment.

b Symptomatic patient definition: any patient with VAS scoring ≥ 3 who needs opioids drugs for pain control or support treatment for cancer in day hospital regime.

c Radiological assessment is only performed in doubt or suspected progression.

### Patients follow-up

First control was carried out at month 1 of treatment, and subsequently every month or 2 months, according to general condition of the patient, the presence or absence of adverse effects of treatment, the need to adjust the dose of opioid or support treatment.

If there is a biochemical progression and/or clinical worsening, radiological assessment is performed by computerized axial tomography, according RECIST criteria and/or with bone scintigraphy according Prostate Cancer Clinical Trials Working Group 2 (PCWG2) modified criteria. The presence of one or more of following criteria is defined as clinical response: partial or total reduction of analgesic...
therapy for oncological pain, or of other support treatments for cancer patient, a reduction ≥ 2 scores in pain assessment scale (PAS) and improvement in ECOG performance status (PS) scoring.\textsuperscript{14} Biochemical response is assessed according PCWG2 criteria.\textsuperscript{15} Adverse effects are defined according to CTCAE.\textsuperscript{16}

In those cases in which all sorts of, i.e., radiological, clinical and biochemical progression are proved, treatment with AA is suspended.

Statistical considerations

Statistical analysis is carried out using SPSS 21.0 software (SPSS, Inc. Headquarters, Chicago, IL, USA). In first place a descriptive analysis of the variables is performed. Afterwards, univariate analysis with chi-square test was performed for qualitative variables and with T-student for quantitative variables (Mann–Whitney U for variables without normal distribution). The survival rates were analyzed using Kaplan–Meier functions and the log rank statistic if necessary. For all cases a 95% confidence interval and beta-error of 0.2 (power of 80%) were used.

Ethics considerations

Personal data have been subjected to confidentiality and secret in any phase of the treatment according Organic Law 15/1999 of 13 December about Protection of Personal Data.

Results

Overall follow-up from first day with AA is 7.9 (±0.7) and mean length of treatment 7.5 (±0.7) months. From the start of therapy with AA, biochemical progression at 4.1 (±0.8) months was 60%, and biochemical, clinical and radiological progression at 6.8 (±0.9) months was 52%. No patient shows clinical progression without radiological progression and biochemical progression. At 13.6 months of follow-up, overall survival is 80% (CI 95%; 11.8–15.4).

All symptomatic patients show a good clinical response to treatment (83% at month and remaining 17% between first and third month of treatment), with an objective improvement of analgesia and VAS improvement of 1.8 ± 1. In all cases, clinical response is maintained until radiological progression.

In the series, the estimated mean time of clinical-radiological response is 9.5 ± 1 months (CI 95%; 7.7–11.3) (Fig. 1A), meanwhile the time of biochemical response is 6.8 ± 1 months (CI 95%; 5–8.7) (Fig. 1B). Radiological assessment was performed in 20 patients at 5.3 (±2.3) months after the treatment started; the better response obtained was 25% of partial responses.

Biochemical response at month of treatment takes place in 56% of patients (14 patients) and disease-free progression survival showed no significant statistical differences between patients with and without clinical-radiological (8.5 months [CI: 6.3–10.6] vs. 10.7 months [CI: 7.9–13.4], respectively, p > 0.1) (Fig. 2A). At 3 months of treatment, differences statistically significant are identified regarding clinical-radiological free progression survival among patients with (68%) and without (32%) biochemical response (11 months [CI: 9.2–13] vs. 5.4 months [CI: 3.9–6.8], respectively, p < 0.01) (Fig. 2B). Three patients (12%) did not show any biochemical response in controls, but a clinical-radiological progression is observed at 5 months of treatment (CI: 3–7) with clinical response from first month of treatment.

In post-chemotherapy, radiological free progression survival is 6.4 months (CI: 4.2–8.6), and 11.5 months (CI: 9.2–13.7) in patients not undergone to previous chemotherapy (p < 0.01) (Fig. 3A). In patients treated in post-chemotherapy, biochemical-free progression survival was 4.3 months (CI: 2.6–6) meanwhile in those undergone to prior chemotherapy the values were 7.4 months (CI 95%; 5.1–9.7) (p = 0.01) (Fig. 3B). In both post- and pre-chemotherapy groups, clinical factors follow a similar distribution, although pre-chemotherapy group shows a greater frequency of patients with visceral metastases and ECOG PS2 (Table 1). In the subgroup of patients (36%) receiving AA pre-chemotherapy for indication (asymptomatic patient, ECOG 0–1 and without visceral metastases), radiologic-free survival progression (12.6 ± 1.5 months) and biochemical free survival progression (9.6 ± 1.5 months) are even higher than in post-chemotherapy patients (p < 0.01) and in pre-chemotherapy patients not meeting any of these criteria (p > 0.05).

Some adverse effects are observed in 36% of patients. All of them are classified in grade 1–2/4 (Table 2). In no case, discontinuation or doses reduction is required. The most frequent AE was hypercholesterolemia (16%). AE are more frequent in no pre-chemotherapy group (50%) than in post-chemotherapy group (22%); however, it is not statistically significant.

Discussion

In the AA-302\textsuperscript{10} mean time for radiological progression in patients without previous chemotherapy treatment was 16.5 months, higher than the results reported in our series: 11.5 months (all patients who were treated in pre-chemotherapy) and 12.5 months (patients who were treated in pre-chemotherapy with baseline characteristics similar to the clinical trial population). However, 69% of patients of our series continue in treatment with AA. In post-chemotherapy group, median radiological free-survival progression was 6.4 months, slightly higher than published in the COU AA-301\textsuperscript{7} (5.6 months).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>List of side effects reported during treatment with abiraterone acetate and prednisone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect (grades 1 and 2)</td>
<td>No. patients (%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>UTI</td>
<td>1 (4)</td>
</tr>
<tr>
<td>AH</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nauseas</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Global</td>
<td>9 (36)</td>
</tr>
</tbody>
</table>
Biochemical-free survival progression in our series is lower than the published in the trials, both in pre-chemotherapy group (7.4 months vs. 11.1 months) and in the post-chemotherapy group (4.3 vs. 8.7). The discrepancy in the pre-chemotherapy group may be related to a higher percentage of patients of our series showing visceral metastases, PS ECOG 2 and with symptomatology. Regarding post-chemotherapy group, it draws attention the fact that the time of biochemical progression is lower than the one of radiological progression in the clinical trial. This also occurs in our study, both in pre-chemotherapy and in post-chemotherapy, but nevertheless this does not happen in the clinical trial post-chemotherapy. The authors have not explained this discordance.

In both clinical trials, patients follow a radiological supervision every 8 weeks. In our series radiological controls are performed if there are clinical and/or biochemical progression, being our percentages similar to published data (25% vs. 14.8% in COU AA301 and 36% in COU AA302).

All cases of our series show clinical response. Like in sub-analysis of COU-301, most of our patients experience a significant pain improvement since first month of treatment with AA (60.1% in trial vs. 88% in our series). This higher percentage of clinical response of our series may be due to the fact that in our study all patients received treatment for...
bone metastases with zoledronic acid or denosumab, and 40% of them also received palliative treatment for pain with radiotherapy and/or metastron® during 3 months before the beginning of treatment with AA. However, in EC COU-AA301, only 44.9% of patients received bisphosphonates and 2.6% denosumab.

According to our series, biochemical response appeared mostly at 3 months of treatment, being the data similar to the published by other studies. In the clinical trial, PSA reduction > 50% was 62% in pre-chemotherapy and 29.5% in post-chemotherapy. In our study, the percentage of patients with PSA reduction > 50% is higher in post-chemotherapy (44.4%) than in pre-chemotherapy (37.5%), probably due to higher number of patients with visceral metastases in pre-chemotherapy group; however, global percentage of PSA reduction is near to this 50% (46.1%). In a subanalysis of COU-AA302, 13% of patients do not show biochemical response, which was associated to a significant reduction in the radiological response. This fact happens in 12% of patients in our series. Furthermore, in our series, biochemical response at 3 months is considered a favorable prognostic factor for radiological progression-free survival. We were unable to compare these data with other studies, because it has not been previously evaluated.

As a consequence of the differences in AA efficacy between pre- and post-chemotherapy treatments, clinical guidelines recommend their use in pre-chemotherapy (in asymptomatic or minimally symptomatic patients without visceral metastases). However, a meta-analysis of 3.149 patients concluded that there is a reduced risk of death for hormone treatments (abiraterone and enzalutamide) after docetaxel in patients with ECOG 2 with respect to second-line chemotherapy. In our series and despite a significant increase in the number of patients of pre-chemotherapy group with visceral metastasis and PS ECOG 2, the treatment with AA in pre-chemotherapy has proven significantly more effective than in post-chemotherapy.

In our series AA has been extraordinarily well tolerated with a 36% of AE, and none of them were in grade 3 or 4 (Table 2). However, in both pre- and post-chemotherapy phase III trials, the AE rate grade 3 or 4 was 48%, dose reduction or discontinuation of treatment related adverse events was 13–19% and fatal adverse effects occurred in 1–4%, although in any case significant differences were observed between AA plus prednisone and placebo plus prednisone. Most of the AE related with the use of AA are secondary to mineralocorticoid excess (as fluid retention or edema [28–33%], hypertension [18–22%] and hypokalemia [11–17%]), and due to the co-administration of glucocorticoids at low doses, generally are grade 1 or 2. In our series only one patient showed AE related with a mineralocorticoid excess (AH grade 2). We have identified other secondary effects as hyperkalemia or nausea and hot flashes, which are described as frequent AE in clinical trial (55 and 22%, respectively). In our series, the hepatotoxicity (grade 3 or 4) described in 8% of patients receiving AA, has not been observed. Detected thrombocytopenia and hyperglycemia are probably related to the use of prednisone.

Study limitations: It is a short series with heterogeneous distribution of basal patient characteristics. By the other side, the lack of pre-selection of patients, unlike what happens in clinical trials, can bring us closer to the expected efficacy of this drug in clinical practice.

Conclusions

In this series of patients with CRPC, efficacy results to treatment with abiraterone are similar to the good results reported in clinical trials previously published, especially in the pre-chemotherapy treatment, both referring to the biochemical and radiological response after 3 months of treatment, as well as to clinical improvement experienced by treated patients from the first month. Until biochemical progression, the most of patients maintain a
radiological clinical benefit, even in patients treated with pre-chemotherapy who had visceral metastases, ECOG 2 and symptomatology. Furthermore, the treatment with AA has been safe, with an incidence of AE considerably lower than published. Therefore, the use of AA in the patient with CRPC is supported by our data. However, many questions about this treatment like: patient selection, proper treatment sequence and proper moment to change the treatment, are still unresolved.

Conflict of interests
The authors declare that they have no conflict of interest.

References