

Prescription pattern of abiraterone in Brazil - a survey of medical oncologists

Padrão de prescrição de abiraterona no Brasil - uma pesquisa com médicos oncologistas

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ABSTRACT

Introduction: Abiraterone acetate is widely used for the treatment of prostate cancer. In Brazil, the label dose is not affordable to most patients due to its elevated cost. Mounting data supports the efficacy of abiraterone acetate low-dose with food. Little is known regarding the pattern of prescription of abiraterone acetate in Brazil and its use of low-dose. **Objective:** To describe the prescription patterns of abiraterone acetate in Brazil, including the percentage of prescribers who are knowledgeable about the literature, supporting the prescription of its low-dose. **Material and Methods:** We created a questionnaire and distributed to oncologists and urologists through a social media app (WhatsApp). Questions included demographics, characteristics of practices and awareness of the literature supporting abiraterone acetate low-dose. Logistic regression was employed to identify factors associated with the prescription of abiraterone acetate low-dose. **Results:** Forty-eighty responses were received. Of the medical oncologist respondents, 86% had read the Szmulewitz et al. trial, supporting the use of abiraterone acetate low-dose, and 80% were aware of National Comprehensive Cancer Network recommendations acknowledging its prescription. Most prescribers were willing to use abiraterone acetate low-dose for patients from the public system, and 50% were already using abiraterone acetate-low dose in their practices. Prescribers who had read the Szmulewitz et al. trial and were aware of the National Comprehensive Cancer Network guidelines were more likely to prescribe abiraterone acetate low-dose OR=9.61 [CI 95%=1.75-52.74] - $p=0.02$ and OR=9.8 [CI 95%=1.09-88.2] - $p=0.04$, respectively. **Conclusion:** Our study shows a high percentage of Brazilian prescribers willing to use abiraterone acetate low-dose in their practices. Abiraterone acetate low-dose is an attractive option particularly for the Brazilian public system which frequently cannot afford the label dose.

Keywords: Prostatic neoplasms; Abiraterone acetate; Developing countries.

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RESUMO

Introdução: O acetato de abiraterona é amplamente utilizado para o tratamento do câncer de próstata. No Brasil, a dose da bula ou dose aprovada não é acessível à maioria dos pacientes devido ao seu custo elevado. Dados cada vez maiores apoiam a eficácia da dose baixa do acetato de abiraterona com alimentos. Pouco se sabe sobre o padrão de prescrição de acetato de abiraterona no Brasil e o uso deste em baixa dose. **Objetivo:** Descrever os padrões de prescrição do acetato de abiraterona no Brasil, incluindo a porcentagem de prescritores que conhecem a literatura, apoiando a prescrição do mesmo em baixa dosagem. **Material e Métodos:** Elaboramos um questionário e distribuímos para oncologistas e urologistas por meio de um aplicativo de mídia social (WhatsApp). As perguntas incluíam dados demográficos, características das práticas e conhecimento da literatura que apoia a baixa dose de acetato de abiraterona. A regressão logística foi empregada para identificar os fatores associados à prescrição do acetato de abiraterona em baixa dose. **Resultados:** Foram recebidas 48 respostas. Dos médicos oncologistas entrevistados, 86% leram o estudo de Szmulewitz et al., apoiando o uso de baixa dose do acetato de abiraterona, e 80% estavam cientes das recomendações da National Comprehensive Cancer Network, reconhecendo sua prescrição. A maioria dos prescritores estava disposta a usar o acetato de abiraterona em baixa dosagem para pacientes do sistema público, e 50% já usavam o acetato de abiraterona em baixa dose em suas práticas. Os prescritores que leram o estudo Szmulewitz et al. e estavam cientes das diretrizes da National Comprehensive Cancer Network eram mais propensos a prescrever baixas doses do acetato de abiraterona OR=9,61 [IC 95%=1,75-52,74] - $p=0,02$ e OR=9,8 [IC 95%=1,09-88,2] - $p=0,04$, respectivamente. **Conclusão:** Nosso estudo mostra uma alta porcentagem de prescritores brasileiros dispostos a usar baixas doses do acetato de abiraterona em suas práticas. A baixa dose de acetato de abiraterona é uma opção atraente, principalmente para o sistema público brasileiro, que frequentemente não pode arcar com a dose da bula.

Descritores: Neoplasias prostáticas; Acetato de abiraterona; Países em desenvolvimento.

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide. It is estimated that by 2030, 1.9 million men will be diagnosed with prostate cancer globally, with around 50.000 deaths. In Brazil, 97,000 new cases were diagnosed in 2020, with approximately 18,000 deaths.⁽¹⁾

Since the 1950s, androgen deprivation therapy (ADT) is the backbone of treatment for metastatic disease.⁽²⁾ However, the duration of response to ADT is often limited and almost all patients will experience disease progression to metastatic castration-resistant prostate cancer (mCRPC) at some point of their course. The two most important mechanisms leading to castration resistance are the androgen receptor (AR) hyperexpression and incomplete blockade of AR-ligand production.⁽³⁾

Abiraterone acetate (AA) was developed in the 1990s and it is a potent selective inhibitor of CYP17A1, member of p450 cytochrome family and involved in androgen production. AA mechanism

of action is based on reducing androgen synthesis, including at the tumor and microenvironment level, and at the adrenal gland.^(4,5) AA was approved by the Food and Drug Administration (FDA) in 2012 initially to mCRPC, based on the phase III study COU-AA-301, which compared AA to placebo in patients already exposed to docetaxel and demonstrated that AA was associated with an increase in overall survival (OS).⁽⁵⁾ The label recommended dose of AA is 1,000mg orally to be taken fasting in association with prednisone 5mg, orally twice daily.

Since the initial AA approval, several indications emerged, including mCRPC pre-docetaxel,⁽⁶⁾ in castration sensitive prostate cancer (CSPC),^(7,8) and more recently in localized nonmetastatic high risk prostate cancer⁽⁹⁾ in combination with ADT and radiation. Of note, akin to its first approval, for all indications the dose of 1,000mg/daily was maintained. Furthermore, in addition to AA, other novel antiandrogens (NAA) such as enzalutamide, darolutamide, and apalutamide, of different mechanism of action (antagonists of the androgen

receptor) have also been approved for similar indications.⁽¹⁰⁻¹²⁾

Despite the dose of 1,000mg fasting has been chosen as recommended phase 2 dose (RP2D), the safety and pharmacokinetics of AA when co-administrated with food was also tested.⁽¹³⁾ When administered with a low-fat meal, AA absorption is increased 5-7 fold. Hence, a dose of 250mg with low-fat meal yields a similar drug exposure in comparison to the standard dose of 1,000mg fasting. Moreover, according to the drug label, a high fat meal leads to a 10-17 times increase in drug concentration.⁽¹⁴⁾

In 2018, Szmulewitz et al.⁽¹⁵⁾ conducted a non-inferiority prospective phase II trial comparing the standard dose of AA (1,000mg/daily) with 250mg/daily with low-fat meal and showed a similar decrease in PSA levels, a similar progression free survival (PFS) and a similar decrease in dehydroepiandrosterone-sulfate (DHEA-S) (pharmacodynamic marker of AA activity) between the two arms. Based on this trial, the National Comprehensive Cancer Network (NCCN) included AA low-dose with food as an acceptable alternative to men with prostate cancer.⁽¹⁶⁾ The use of AA 250mg with food implies in a 75% cost-savings in comparison to the label-dose.

In Brazil, AA at the label dose is not affordable to over 75% of patients treated under the public national health plan (*Sistema Único de Saúde – SUS*). However, a lower dose of 250mg with food may fit into the budget and has already been prescribed at some Brazilian centers.⁽¹⁷⁾ There are no data in regards to the pattern of prescription of AA in Brazil, and whether prescribers (medical oncologists and urologists) are aware of the low-dose AA data, and what are their thoughts in regards to the prescription of such regimen in their practices. We undertook a survey to investigate the pattern of prescription of AA in Brazil, including the uptake of AA low-dose.

MATERIAL AND METHODS

After ethical approval (CAAE 59172022.1.0000.5415), a survey was created utilizing the questionnaire tool of the Research Electronic Data Capture (REDCap) of *Hospital de Base*.^(18,19) We asked fourteen questions, including prescribers' demographics, and awareness about the literature supporting AA low-dose – Appendix 1. Medical oncologists and urologists treating patients with metastatic prostate cancer were eligible to participate. The survey was distributed through a social media platform (WhatsApp) to approximately 500 prescribers (WhatsApp groups) — medical oncologists and urologists — at two separate dates: September 5th, 2022, and September 26th, 2022.

Study objectives

The primary objective was to evaluate and describe the AA prescription pattern among medical oncologists in Brazil and which percentage of prescribers are knowledgeable of the literature

supporting the prescription of AA low-dose. The secondary objectives included describing demographics of respondents and better understand the pattern of prescription of AA in Brazil.

Statistical analysis

Demographic characteristics were summarized in means, medians, and proportions. Logistic regression was employed to identify factors associated with the prescription of AA low-dose. We used the Peto odds methods for associations with 0-counts. Multivariable analyses were not performed. Data analysis was performed using the IBM SPSS statistical software version v. 28.0.10.

RESULTS

In total, 48 prescribers responded the survey – 45 medical oncologists and 3 urologists. Because of the small sample size, we decided to exclude urologists' response from the statistical analysis. The median age of respondents is 35.5 years old and 55.6% are female (Table 1). Thirty-nine (86.7%) of respondents work at an academic institution (affiliated to a medical school or with a residency program) and 73.3% practice in both public and private healthcare systems (Table 1). Most respondents completed their final specialty within the last 5 years (51.1%) (Table 1). Regarding the volume of prostate cancer patients in their practices, participants responded that 25% (SD 16) of their workload is comprised of patients with prostate cancer (Table 1).

When asked if they had read the phase II study by Szmulewitz et al. (2018),⁽¹⁵⁾ 86.4% of respondents answered “yes” – Table 1. Eighty percent were aware of NCCN recommendations acknowledging the prescription of low-dose AA – Table 1. In terms of willingness to prescribe AA low-dose, 90.9% versus 25% would prescribe AA low-dose in the public (SUS) and private healthcare systems, respectively (Figure 1). Twenty-two medical oncologists (50%) are already using AA low-dose in their practices (Figure 1). Among those who would not prescribe AA low-dose, 50% justified that are not confident on the data supporting AA low-dose, and 50% because AA-low dose is not the standard of care.

Factors associated with AA low-dose prescription

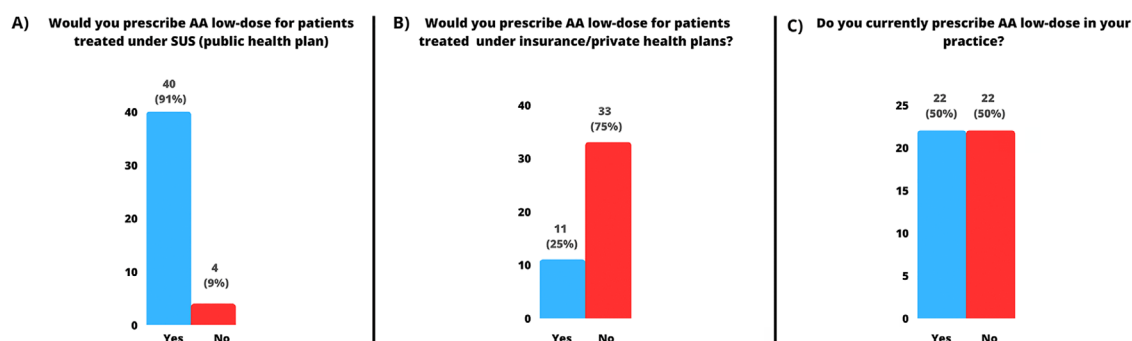
We investigated factors associated with the prescription of AA low-dose (Table 2). Oncologists who read the study by Szmulewitz et al. (2018),⁽¹⁵⁾ as well as the ones aware of the NCCN guidelines acknowledging the use of AA low-dose were more likely to prescribe AA low-dose in their practices OR=9.61 [CI 95%=1.75-52.74] – $p=0.02$ and OR=9.8 [CI 95%=1.09-88.2] – $p=0.04$, respectively.

Patterns of corticosteroid prescription with AA

Concerning the corticosteroid prescription associated with AA, 41.9% of respondents use

Table 1. Characteristics of medical oncologist respondents.

	Medical oncologists N=45
Age – yr	
Median	35.5
Range	28-70
Gender – no. (%)	
Female	25 (55.6)
Male	20 (44.4)
Time since the complete of medical specialty – no. (%)	
<5 years	23 (51.1)
5-10 years	7 (15.6)
>10 years	15 (33.3)
Practice characteristic – no. (%)	
Public healthcare system	4 (8.9)
Private healthcare system	8 (17.8)
Public and private healthcare system	33 (73.3)
Work at an academic institution – no. (%)	
Yes	39 (86.7)
No	6 (13.3)
Average proportion of patients with prostate cancer in their practice - % (SD)	25% (16)
Had read the Szmulewitz et al. ⁽¹⁵⁾ trial – no. (%)	N=44
Yes	38 (86.4)
No	6 (13.6)
Awareness of the NCCN guidelines acknowledging the use of AA low-dose – no. (%)	N=44
Yes	36 (81.8)
No	8 (18.2)

**Figure 1.** A) Percentage of medical oncologists who would prescribe and would not prescribe AA low-dose in the public health plan (SUS); B) Percentage of medical oncologists who would prescribe and would not prescribe AA low-dose in the private healthcare system; C) Percentage of medical oncologists who already prescribe AA low-dose in their clinical practices.

prednisone 5mg twice daily for all patients and 23.3% use 5mg twice daily to patients with mCRPC, and 5mg daily to CSPC. When inquired about corticosteroid switch upon PSA progression, 34.9% reported being adept to this practice. The most cited reason not to perform the steroid switch was not being familiar with the literature supporting this practice (75%).

Urologists' responses

We had 3 responses among urologists. All of them were male, aged 49, 29 and 34 years old, and worked at an academic institution. Two of them had completed their final specialties within 5 years, and the other over 10 years after the survey date. Prostate cancer patients represent between 5-20%

Table 2. Characteristics associated with AA low-dose prescription.

	OR (95% CI)	p-value
Age	1.02 (0.94-1.10)	0.59
Gender		
Time since the end of medical specialty	1.44 (0.44-4.75)	0.54
<5 years	Ref	0.33
5-10 years	2.33 (0.41-12.17)	0.07
>10 years	3.50 (0.88-13.92)	
Work at an academic institution Yes	Ref	0.39
No	2.22 (0.36-13.61)	
Had read the Szmulewitz et al. ⁽¹⁵⁾ trial		
Yes	Ref	0.02
No	9.61 (1.75-52.74)	
Awareness of the NCCN guidelines acknowledging the use of AA low-dose		
Yes	Ref	0.04
No	9.8 (1.09-88.2)	

of their clinical practice. All urologists' respondents never had read the Szmulewitz et al.⁽¹⁵⁾ study and were unaware of the NCCN recommendations acknowledging AA low-dose.

DISCUSSION

In our surveyed population, most prescribers were knowledgeable about data supporting the use of AA low-dose. Moreover, over 90% of medical oncologists were willing to prescribe AA low-dose for patients treated under the Brazilian national health plan (SUS) — where resources are scarcer and treatment options are limited — and half were already using AA low-dose as part of their arsenal for prostate cancer treatment. As expected, physicians who had read the article by Szmulewitz et al.⁽¹⁵⁾ and who were aware of the incorporation of AA-low dose as an option by NCCN guidelines were more likely to prescribe AA-low dose in their practices.

Our survey share similarities with the work conducted by Patel et al. (2020)⁽⁴⁾ interrogating AA prescription patterns in India. In their study, of 118 respondents, 58.8% were aware of NCCN's recommendation of AA-low dose and 6.8% were prescribing AA low-dose in their practices. While our numbers are more encouraging, most physicians we surveyed were from academic centers, and were younger than the average Brazilian oncologists (35.5 vs. 45.7 years old).⁽²⁰⁾ Furthermore, our population was acquired by convenience through the distribution of the survey in WhatsApp groups. We speculate that our respondents were more likely to be update with the oncology literature and therefore aware of data on AA low-dose, which is not necessarily generalizable to all (or even most) oncologists from Brazil. In addition, the longer time between the Szmulewitz et al.⁽¹⁵⁾ publication and our work in comparison to Patel's et al.,⁽⁴⁾ may have had impact in the observed differences, with more time

available for spreading the message of the research findings.

While most of our surveyed oncologists would prescribe AA low-dose in the public health system (SUS), only 50% had already adopted AA low-dose in their practices. The reasons for that are likely multifactorial and are beyond the scope of this project. In a recent literature review, concerns about erratic exposure of AA under diverse dietary patterns are amongst potential reasons.⁽²¹⁾ In low-middle income countries (LMICs), food insecurities are always an important concern and need to be taken in consideration before treatment planning. Nevertheless, regardless of the motives, implementation science is needed to improve AA low-dose access to Brazilian patients.

Lower doses of AA can result in up to 75% cost savings which is highly relevant to LMICs such as Brazil. Several data support the use of AA at a lower dose with food.^(13,14,16,17,22) In addition to Szmulewitz et al.⁽¹⁵⁾ trial, a retrospective study conducted at the Princess Margaret Cancer Center showed no statistically significant differences in PSA response rate, biochemical progression free survival (bPFS), and OS in patients with mCRPC between who received AA low-dose (250mg or 500mg) versus the standard dosing.⁽²²⁾ In Brazil, Zucca et al. (2020),⁽¹⁷⁾ reported results of 49 patients with mCRPC treated with AA low-dose post docetaxel. They found a PSA response rate ≥50% in 51% of patients which is in keeping with data from the COU-AA-301 trial.⁽⁵⁾

The dosing conundrum of oncology agents has been the subject of recent scrutiny by several groups including the Optimal Cancer Care Alliance (OCCA — <https://optimalcancercare.org/>)⁽²⁴⁾ and even the FDA.^(23,24) Project Optimus is an FDA-led initiative stimulating a more comprehensive dose exploration strategy to oncology agents during their

early phase of development, before moving to the formal assessment of efficacy endpoints. It has been postulated that most oncology treatments, particularly oral tyrosine kinase inhibitors (TKI) and monoclonal antibodies, are overdosed at their currently approved label doses. Furthermore, the role of food exposure for oral agents has systematically been relegated in drug development and is often not reported (when not conducted) in phase 1 trials. The Methodology for the Development of Innovative Cancer Therapies (MDICT) guidelines recommends that novel agents should consider the initial dosing with food unless there is strong evidence that food may importantly impair absorption.⁽²⁵⁾

In reference to corticosteroid therapy, our study showed AA is most frequently prescribed (41.9%) in association with prednisone 5mg twice daily regardless of the treatment scenario, in line with the prescription patterns of the pivotal trials COU-AA-301 and COU-AA-302^(5,6) and in opposition to the LATITUDE trial that used 5mg/daily to CSPC.⁽²⁶⁾ The strategy of using 5mg twice daily is also supported by the work of Attard et al. (2019),⁽²⁷⁾ suggesting that in comparison to other corticosteroid treatment possibilities, 5mg bid is more efficient in avoiding excess of mineralocorticoids. Regarding the switch from prednisone to dexamethasone upon progression, only a minority of respondents adhere to this practice. Nevertheless, data suggests that up to 30% of patients who progress on AA and prednisone can experience a PSA decrease simply by switching corticosteroids.⁽²⁸⁾ While little is known about the true impact of this practice in survival, this is a convenient and well tolerated approach that can yield some additional time to patients on AA without switching to a new line of treatment or even exclusively palliative care.

We acknowledge several limitations of this study. First, the response rate of our survey was low, with only 48 respondents. Furthermore, only 3 urologists responded to the survey making our findings most applicable to medical oncologists. Secondly, our sample was acquired by convenience which by default induces biases in interpretation of results. For instance, our population was mostly constituted of physicians working at academic centers, who are more likely to be updated with medical literature. We hypothesize that awareness of AA low-dose is lower than what we found in this survey. Finally, our limited sample size prevented performing multivariable analyses.

It is important to discuss AA low-dose in Brazil and other LMICs, particularly in settings where the standard treatment is unavailable due to cost constraints. Larger studies (e.g., phase 3 trials) investigating AA low-dose are unlikely to occur as these are off the agenda of pharmaceutical industries.⁽²¹⁾ Nevertheless, considering the increased accessibility and the economics involved in using AA-low, we advocate for the implementation of AA low-dose in a near-equivalence fashion.⁽²⁹⁾

CONCLUSION

This survey study showed a trend towards Brazilian medical oncologists prescribing AA low-dose. However, only half of the respondents already use AA-low in their practices. We advocate for broader use of AA low-dose, increasing accessibility.

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AUTHORS' CONTRIBUTIONS

JPHN	Collection and assembly of data, Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing.
LAF	Final approval of manuscript, Provision of study materials or patient
JAS	Final approval of manuscript, Provision of study materials or patient
FLCF	Final approval of manuscript, Provision of study materials or patient
DVA	Collection and assembly of data, Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient

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APPENDIX 1:

The questions and possible answers (when multiple-choice) of the survey applied to physicians:

1 - Demographics data:

- a) How old are you?
- b) Gender;
- c) What is your medical specialty?
Possible answers: urologist or medical oncologist;
- d) Where do you work?
Possible answers: public healthcare system, private healthcare system or both.
- e) How long has it been since the end of your medical specialization?
Possible answers: < 5 years or \geq 5 years;
- f) Do your work at an academic institution?
Possible answers: Yes or No;
- g) What percentage of patients with prostate cancer do you treat in your clinical practice?

2 - AA prescription data:

- a) Have you ever read "Prospective International Randomized Phase II Study of Low Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer" by Szmulewitz RZ et al?
Possible answers: Yes or No;
- b) Do you know that AA low-dose (250 mg/day) with low-fat meal was incorporated by NCCN like an alternative option to the standard dose (1000 mg/day)?
- c) Possible answers: Yes or No;
- d) Would you prescribe AA 250 mg/day with low-fat meal in the public healthcare?
Possible answers: Yes or No. If the answer was No:
 - d.1: Because I do not trust the data;
 - d.2: Because it is not the standard of care;
 - d.3: I would not because I do not know the literature basis;Would you prescribe AA 250 mg/day with low-fat meal in private healthcare? Possible answers: Yes or No;
- e) Do you already prescribe AA 250 mg/day with low-fat meal in your clinical practice?
Possible answers: Yes or No;

3 - Novel antiandrogens prescription data

- f) In which situations do you prescribe the novel antiandrogen therapies?
Possible answers: just to metastatic castration-resistant, to metastatic castration-sensitive AND castration-resistant, to metastatic and non-metastatic high and very high risk.

4 - Corticosteroid therapy data

- g) Do you switch the corticosteroid therapy when PSA progressing?
Possible answers: Yes or No. If the answer was No:
 - g.1: Because I do not know the literature embasament;
 - g.2: Because I do not trust the data;