VIEWPOINT

The Abiraterone Dosing Chess Match With Johnson & Johnson—Back in Check

Russell Z. Szmulewitz, MD
Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, Illinois.

Walter M. Stadler, MD
Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, Illinois.

Mark J. Ratain, MD
Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, Illinois.

Corresponding Author: Russell Z. Szmulewitz, MD, Section of Hematology/Oncology, Department of Medicine, The University of Chicago, 5841 S Maryland Ave, MC2115, Chicago, IL 60637 (rszmulew@medicine.bsd.uchicago.edu).

Prostate cancer is the second most common cancer worldwide, estimated to account for more than 1 million cases and more than 350 000 annual deaths.[1] Although metastatic prostate cancer remains a lethal malignant neoplasm, the therapeutic landscape has changed drastically during the last decade, most notably with the development of highly potent, orally bioavailable, hormonal therapies targeting the androgen receptor pathway. The first of this class, and the most commonly used, is abiraterone acetate, a selective irreversible inhibitor of CYP17A1, which metabolizes multiple steroid substrates and is responsible for the production of multiple androgens. Abiraterone is approved for use in the US across the spectrum of metastatic prostate cancer, including in combination with androgen deprivation therapy for castration-sensitive disease and in castration-resistant disease before or following docetaxel chemotherapy. As such, many if not most patients with metastatic prostate cancer will be offered treatment with abiraterone at some point in their disease course.

Like most oral oncology drugs, abiraterone is an expensive medication with a July 2020 US monthly average wholesale price of more than $13 000 (for branded abiraterone or Zytiga), and the generic version (which is not available in many countries, including all of Europe) costs thousands of dollars per month.[2] Despite generic availability in the US, Johnson & Johnson's branded abiraterone sales were more than $1.8 billion for the 9 months ending September 27, 2020, with approximately 85% of sales coming from outside the US.[3]

The US Food and Drug Administration (and other global regulatory agencies) approved abiraterone at a dose of 1000 mg/d, to be taken without food (modified fasting conditions). But given that it was well documented that food enhanced the bioavailability of abiraterone, we conducted an international, multiinstitution randomized phase 2 clinical trial of low-dose (250 mg/d) abiraterone with a low-fat breakfast vs standard dosing.[4] We showed noninferiority with respect to pharmacodynamic biomarkers, including prostate specific antigen response and time to prostate specific antigen progression, and decrease in circulating androgen levels. Based on these results, low-dose abiraterone with food is now listed as an alternative dosing strategy endorsed by the National Comprehensive Cancer Network. Widespread adoption of low-dose abiraterone would have substantial pharmacoeconomic impact, saving billions of dollars globally.

Although initially manufactured only in 250-mg uncoated tablets, branded abiraterone is also now available in 500-mg film-coated tablets (generic abiraterone is only available in 250-mg tablets). While it may be a convenient coincidence, it has been suggested that the branded 250-mg tablets were withdrawn from the European market because our randomized trial suggested that prescribing 25% of the labeled dose could maintain efficacy and reduce sales by 75%.[5] Thus, in countries without 250-mg tablets, it is not possible to use low-dose abiraterone using the low-fat breakfast strategy.

In what feels like a game of chess with Johnson & Johnson, we now propose a simple alternative to our previously published regimen: 500 mg with food every other day. We argue that given the abundant pharmacokinetic and pharmacodynamic data for this important drug that 500 mg every other day is safe and effective, and there is no need for a clinical trial to show this. The primary justification for lower-dose abiraterone is that the CYP17A1 target is sufficiently targeted at doses well below those recommended in the prescribing information, with no evidence that the labeled dose leads to greater inhibition of androgen production.[6,7] Thus, there would be little concern about toxicity or differences in efficacy with abiraterone, 500 mg every other day, with or without food. This is further supported by the experience in the phase 1 trial, which showed safety of this dose, irrespective of food.[8] Moreover, in our randomized study, although we showed pharmacodynamic noninferiority, the abiraterone trough concentrations in the low-dose arm were roughly half those in the standard arm.[4] Thus, doubling the dose from 250 mg to 500 mg (with food) would be expected to achieve plasma concentrations comparable to the labeled dosing regimen. Furthermore, there is no pharmacodynamic justification for daily dosing of abiraterone. The first-in-human study showed that a single dose of abiraterone, 500 mg, resulted in sustained suppression of the testosterone/androstenedione axis, as evidenced by decreased androgen levels sustained for up to 9 days.[6] In another study in women with aberrantly elevated androgen levels resulting from 21-hydroxylase deficiency, after 6 days of abiraterone, 100 mg or 250 mg administered without food, androgen levels were appropriately suppressed 48 hours following cessation of dosing.[9] Thus, 500 mg every other day with food will likely be sufficient to sustain CYP17 enzyme inhibition, sustain diminished hormone levels, and maintain efficacy—and include a 75% cost savings, the same as with our previously published regimen of 250 mg every day.[4]

While we encourage physicians practicing in cost-constrained environments without abiraterone 250-mg tablets to consider 500 mg every other day at this time, it would be desirable to gain additional clinical pharma-

cology data using this approach. Given the established mechanism of action and a reliable pharmacodynamic biomarker in extragonadal androgen levels, a relatively small, single-arm clinical trial examining dehydroepiandrosterone sulfate levels after 4 weeks of 500 mg every other day with food would be sufficient to show suppressed androgen synthesis of this alternative dosing strategy. Note, this study could also test whether 500 mg even less frequently could maintain efficacy, perhaps enabling abiraterone, 500 mg with food, to be administered every 3 to 4 days, a potential 87.5% decrease in prescribing costs.

Changing pill formulation or vial size is not a new tactic to maintain drug costs. Similar cost-saving approaches are possible for other oncologic therapies, and an entire field to address these issues—interventional pharmacoeconomics—has been created.[10] If academic pursuits into interventional pharmacoeconomics are to continue, we must anticipate the pharmaceutical industry response and continue to be nimble. Fortunately, available clinical pharmacology data suggest that there are multiple approaches to safely lower the cost of cancer drugs and, in turn, care. These include use of food or other agents to enhance absorption, modification of the dosing interval, reevaluation of the minimally effective dose, and consideration of intermittent therapy. The interventional pharmacoeconomic strategy of every-other-day dosing of abiraterone is an example of how academic investigators can keep the pharmaceutical industry in check, but it will undoubtedly not be the last opportunity to do so.

ARTICLE INFORMATION

Published Online: March 4, 2021. doi:10.1001/jamaoncol.2020.8087

Conflict of Interest Disclosures: Dr Szmulewitz reported receiving honoraria for consulting from Astellas Pharma, Bayer, Janssen Pharmaceutica, Pfizer, and Sanofi; research funding from AbbVie, Astellas Pharma, Janssen Pharmaceutica, MacroGenics, and Pfizer; and patent licensing from Corcept Therapeutics. Dr Stadler reported receiving honoraria for consulting from AstraZeneca, Bayer, CVS Caremark, Eisai, Genentech, Merck, Pfizer, and Sotio and research funding from AbbVie, Astellas Pharma (Medivation), AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Calithera Biosciences, Clovis Oncology, Corvus Pharmaceuticals, Eisai, Exelixis, Genentech (Roche), Janssen Pharmaceutica, Merck, Novartis, Pfizer, Seagen, Tesaro, and X4 Pharmaceuticals. Dr Ratain reported receiving honoraria for consulting and serving as an expert witness from multiple generic pharmaceutical companies, including Accord Healthcare, Actavis, Amerigen Pharmaceuticals, Apotex, Argentum, Aurobindo Pharma, Breckenridge Pharmaceutical, Celltrion Healthcare, Dr. Reddy's Laboratories, Fresenius Kabi, Hetero, Mylan, Par Pharmaceutical, Roxane Laboratories, Sandoz, Shilpa Pharma, and Teva Pharmaceutical Industries; honoraria for consulting from Aptevo Therapeutics, Arvinas, Ayala Pharmaceuticals, Cyclacel, Genentech, and Shionogi; receiving research funding from AbbVie, BeiGene, Bristol Myers Squibb, Corvus Pharmaceuticals, Dicerna Pharmaceuticals, Genentech, Oncovalent Therapeutics, Pneuma Respiratory, and Xencor; receiving royalties from The University of Chicago through a patent licensed to Mayo Medical; and serving as director and treasurer of Value in Cancer Care Consortium.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. Published online February 4, 2021. doi:10.3322/caac.21660

2. Information for Vermont prescribers of prescription drugs: Alunbrig™ (brigatinib) capsules. Accessed February 9, 2021. https://www.takeda.com/48fdcc/siteassets/en-us/home/corporate-responsibility/culture-of-compliance/state/vt/alunbrig_lf.pdf

3. Securities and Exchange Commission. Form 10-Q, Johnson & Johnson. Published July 2020. Accessed January 25, 2020. https://www.sec.gov/Archives/edgar/data/0000200406/000020040620000056/jnj-20200927.htm

4. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol*. 2018;36(14):1389-1395. doi:10.1200/JCO.2017.76.4381

5. Peters N, Zameer MZ, O'Reilly S. Low-dose abiraterone, a rare European commodity. *JCO Glob Oncol*. 2020;6:730. doi:10.1200/GO.20.00106

6. O'Donnell A, Judson I, Dowsett M, et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. *Br J Cancer*. 2004;90(12):2317-2325. doi:10.1038/sj.bjc.6601879

7. Attard G, Reid AHM, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563-4571. doi:10.1200/JCO.2007.15.9749

8. Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol*. 2010;28(9):1481-1488. doi:10.1200/JCO.2009.24.1281

9. Auchus RJ, Buschur EO, Chang AY, et al. Abiraterone acetate to lower androgens in women with classic 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2014;99(8):2763-2770. doi:10.1210/jc.2014-1258

10. Ratain MJ, Goldstein DA, Lichter AS. Interventional pharmacoeconomics—a new discipline for a cost-constrained environment. *JAMA Oncol*. 2019;5(8):1097-1098. doi:10.1001/jamaoncol.2019.1341