5-10-2018

Low-Fat Abiraterone Food Effect Is of Little Consequence

Jill M. Kolesar
University of Kentucky, Jill.Kolesar@uky.edu

Glenn X. Liu
University of Wisconsin - Madison

Low-Fat Abiraterone Food Effect Is of Little Consequence

Notes/Citation Information
Published in *Journal of Clinical Oncology*, v. 36, no. 14, p. 1385-1386.

Digital Object Identifier (DOI)
https://doi.org/10.1200/JCO.2018.78.0684

VOLUME 36 · NUMBER 14 · MAY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Low-Fat Abiraterone Food Effect Is of Little Consequence

Jill M. Kolesar, *University of Kentucky, Lexington, KY*
Glenn X. Liu, *University of Wisconsin–Madison, Madison, WI*

See accompanying article on page 1389

Szmulewitz et al[1] report a phase II noninferiority clinical trial that compared the activity of low-dose abiraterone administered with food (LOW) to the currently US Food and Drug Administration–approved standard-dose abiraterone administered in the fasted state (STD) in patients with castrate-resistant prostate cancer (CRPC). Given that abiraterone commonly is used in the first-line setting of CRPC and that its monthly cost is approximately $10,000, a 75% dose reduction would entail substantial cost savings if the doses achieve equivalent clinical outcomes.

The primary end point in this trial was prostate-specific antigen (PSA) change between study entry and 12 weeks of therapy by comparing the log-transformed mean change in PSA between the STD and LOW groups. The LOW group had a mean log change of −1.59 versus −1.19 in the STD group, which is sufficient to establish the LOW group as noninferior to STD within a 90% confidence limit. Although the prespecified noninferiority margin of 15% was met, the clinical significance of the chosen end point is unclear. As the authors acknowledge, log PSA change over 12 weeks in not a clinically validated surrogate end point.

Reliance on local PSA testing in this trial is a substantial concern, particularly given the noninferiority trial design the investigators chose. PSA results can vary by up to 20%[2] for the same sample, and the Prostate Cancer Working Group has recommended central testing to minimize interassay variability.[3] Of note, the 20% variability in locally obtained PSA tests is greater than the predetermined noninferiority margin of 15%. In addition, when clinical trial end points are variable, the bias is toward the null (ie, not detecting a difference). In a noninferiority trial design, failure to reject the null establishes noninferiority of the treatments.[4] In other words, assay variability may lead to erroneously determining two treatments to be noninferior. Given the large expected interassay variation in PSA results, a conclusion of noninferiority in this trial may be spurious.

Pharmacokinetic inferiority of the LOW group was demonstrated, with significantly lower plasma trough and 2-hour postdose (anticipated maximum serum concentration [C_{max}]) concentrations compared with the STD group. This finding contrasts an early phase I study that demonstrated a significant food effect with abiraterone[5] but is consistent with more recent data.[6] Subsequent to abiraterone's approval, definitive food-effect studies were conducted in both healthy volunteers and patients with CRPC, although published in the same article by Chi et al.[6] In the relatively young healthy volunteers who received a single dose of abiraterone 1,000 mg, significant differences in pharmacokinetic parameters were noted among the fasted state, low-fat meal (an approximately five-fold increase in the area under the curve), and high-fat meal (approximately 10-fold increase in the area under the curve). However, in the older patients with CRPC who received daily abiraterone with pharmacokinetic parameters assessed on day 7, no difference was found between the fasted state and low-fat meal, and only an approximately two-fold increase was found with the high-fat meal. Similar to the population and design of Chi et al, patients studied by Szmulewitz et al[1] were approximately the same age and consumed a low-fat meal, and pharmacokinetics were assessed at approximately the same time. Taken together, both studies suggest a modest food effect of a low-fat meal in patients with CRPC who take abiraterone chronically.

A C_{max} of approximately 100 ng/mL in the STD group was observed and seems lower than previously reported, where fasted patients with CRPC who received 1,000 mg/d achieved a mean C_{max} of approximately 200 ng/mL.[6] This pharmacokinetic difference may be related to the more real-world experience Szmulewitz et al[1] studied. Chi et al[6] served standard low- and high-fat breakfasts, enforced fasting, and observed abiraterone administration on the days of pharmacokinetic sampling. In contrast, patients in the Szmulewitz et al study were instructed to eat a low-fat breakfast and to take their medications. Although the patients completed pill and diet diaries, nonadherence to study medications and dietary recommendations is common in clinical trials and may account for the lower-than-expected plasma concentrations.

More importantly, are the pharmacokinetic parameters clinically significant? A trough concentration of 8.4 ng/mL is associated with PSA response, which is defined as a ≥ 50% reduction in PSA at 12 weeks.[7] In Szmulewitz et al,[1] the LOW group had an average trough concentration of approximately 2 ng/mL, whereas the STD group had approximately 8 ng/mL. Although no association was found between abiraterone trough concentration and PSA response, the authors noted that the three individuals with the highest trough concentrations had the best PSA responses. Of note, the majority of patients in both the STD and the LOW groups had trough abiraterone concentrations < 8.4 ng/mL. PSA responses were similar between the LOW (58%) and STD (50%) groups and generally consistent with a prior landmark trial (62%) by Ryan et al.[8] Progression-free survival (PFS) was similar between the

LOW and STD groups at 8.6 months but seems inferior to the PFS achieved with abiraterone in the landmark study at 16.5 months and more similar to the placebo group at 8.3 months. Differences in study population may account for the inferior PFS; in Szmulewitz et al,[1] 11 patients received prior docetaxel and had a performance status of 2, whereas Ryan et al[8] allowed no prior therapy and required a performance status of ≤ 1. However, the contribution of inadequate abiraterone concentrations to the poorer PFS observed cannot be excluded.

In conclusion, we do not agree with the recommendation by Szmulewitz et al[1] that these data should be considered by prescribers, payers, and patients when considering a dose-with-food strategy. The evidence of noninferiority of the regimens is not compelling, the evaluated primary end point is clinically questionable, and both groups did not achieve an average trough abiraterone concentration associated with clinical benefit. The overall poorer PFS observed in this study combined with inadequate abiraterone trough concentrations in the STD group raises the question of suboptimal adherence in the real world outside controlled clinical trials.

We suggest additional investigation of the target abiraterone trough concentration predictive of response and consideration of therapeutic drug monitoring (TDM) or determination of the target plasma concentration of abiraterone and dosing to the target. TDM is most useful for medications that are self-administered, with narrow therapeutic indices, and high interpatient variability,[9] and abiraterone has all three characteristics. The overall goal of TDM is to determine a significant association among drug dose, plasma concentrations (pharmacokinetics), and pharmacodynamic response. Plasma concentrations can be relatively easily and reliably measured, and dose adjustments can achieve the desired concentration. TDM is routinely used in clinical practice for a number of medications, including tacrolimus, but of note, use in oncology is rare despite the deluge of targeted therapies. Determination of the target plasma concentration of a drug during early-phase clinical trials and development of an assay for drug concentration assessment as a companion diagnostic may be a useful strategy to minimize interpatient variability, assess adherence with oral medications, and improve efficacy.

Finally, the low-fat food effect of abiraterone in the target population appears minimal at best and is close to moot as a novel formulation of abiraterone without significant food effect in clinical trials.[10] We can only hope that the new formulation of abiraterone will be priced more reasonably.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. 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 36:1389-1395, 2018
2. Scher HI, Morris MJ, Stadler WM, et al: Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34:1402-1418, 2016
3. Murthy V, Rishi A, Gupta S, et al: Clinical impact of prostate specific antigen (PSA) inter-assay variability on management of prostate cancer. Clin Biochem 49: 79-84, 2016
4. Food and Drug Administration: Non-inferiority clinical trials to establish effectiveness: Guidance for industry, 2016. https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf
5. 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 28:1481-1488, 2010
6. Chi KN, Spratlin J, Kollmannsberger C, et al: Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. J Clin Pharmacol 55:1406-1414, 2015
7. Carton E, Noe G, Huillard O, et al: Relation between plasma trough concentration of abiraterone and prostate-specific antigen response in metastatic castration-resistant prostate cancer patients. Eur J Cancer 72:54-61, 2017
8. Ryan CJ, Smith MR, de Bono MS, et al: Abiraterone in men with metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013
9. Lee JJ, Beumer JH, Chu E: Therapeutic drug monitoring of 5-fluorouracil. Cancer Chemother Pharmacol 78:447-464, 2016
10. Solymosi T, Ötvös Z, Angi R, et al: Development of an abiraterone acetate formulation with improved oral bioavailability guided by absorption modeling based on in vitro dissolution and permeability measurements. Int J Pharm 532:427-434, 2017

DOI: https://doi.org/10.1200/JCO.2018.78.0684; published at jco.org on March 28, 2018.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Low-Fat Abiraterone Food Effect Is of Little Consequence

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Jill M. Kolesar
Stock or Other Ownership: Helix Diagnostics

Glenn Liu
Leadership: AIQ Solutions
Stock or Other Ownership: AIQ Solutions
Consulting or Advisory Role: Janssen, Exelixis, Novartis
Research Funding: Johnson & Johnson (Inst), Novartis (Inst), Madison Vaccines, Pfizer, TRACON Pharmaceuticals
Patents, Royalties, Other Intellectual Property: US 9161720 B2: Quantitative evaluation of total tumor burden using functional and anatomical imaging (Inst)
Other Relationship: Sanofi