special articles

Low-Dose Abiraterone in Metastatic Prostate Cancer: Is It Practice Changing? Facts and Facets

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abstract

PURPOSE It is projected that approximately 50,000 new cases of prostate cancer will be diagnosed in 2020 in India. Survival has improved because of the development of effective drugs such as abiraterone acetate, but universal accessibility to treatment is not always possible because of cost constraints in lower- and middle-income countries. Recently, the National Comprehensive Cancer Network (NCCN) has included low-dose abiraterone (250 mg/day) with food as an alternative treatment option to full-dose abiraterone (1,000 mg/day) fasting.

METHODS The Science and Cost Cancer Consortium conducted a survey to evaluate the use of abiraterone in India and the opinions of medical oncologists about using low-dose treatment. Modeling was used to estimate potential financial benefits to individual patients and to estimate overall costs of health care in India if low-dose abiraterone is prescribed.

RESULTS Of 251 Indian medical oncologists who were invited to participate in the survey, 125 provided their e-mail address and received the survey; 118 responded (47% of the total). Of these, 25% were not aware of the recent NCCN recommendation, 55% were already prescribing low-dose abiraterone when resources were limited, 7% had already changed their practice, and 29% agreed to switch to a universal practice of using low-dose abiraterone with food; 9% of practitioners would not use low-dose abiraterone. Estimated mean per patient savings was US$3,640, with annual savings of US$182 million in India.

CONCLUSION Use of lower-dose abiraterone would increase access to treatment in India and globally and lead to large cost savings.

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INTRODUCTION

Prostate cancer is the second most common cancer in men. It is estimated that 1.7 million men will be diagnosed with prostate cancer globally, and approximately 500,000 deaths will occur by 2030. It is projected that approximately 50,000 new cases of prostate cancer will be diagnosed in India annually by 2020.[1] The rise in incidence of prostate cancer is attributed primarily to longevity and to improvement in the human development index.[2,3] In India, it is the second most common malignancy in the population-based cancer registries of Delhi, Kolkata, Pune, and Thiruvananthapuram, and third most common in Mumbai and Bangalore[1]; it is among the top 10 cancers in other registries. Mortality rates (50% to 60%) reported from developing countries are higher than those in high-income countries[4-6] for reasons including lack of health awareness among patients, poor availability of diagnostics, poor access to appropriate health care, cost of treatment, and strained national resources for treatment expenditures. Around 70% to 85% of prostate cancers present in the advanced or metastatic stage in India.

As members of the Science and Cost Cancer Consortium, we evaluate here the national practice in India and the potential benefits of prescribing low-dose abiraterone, which has recently been included in the National Comprehensive Cancer Network (NCCN) guidelines.[7] This strategy has a huge financial implication in resource-constrained countries like India.

Brief History of Abiraterone

The Institute of Cancer Research in London developed abiraterone in the early 1990s, and after 15 years of research, it was approved for treatment of men with metastatic castration-resistant prostate cancer (mCRPC) in 2011.[8] It is a selective and irreversible inhibitor of the steroid 17alpha-monooxygenase (17alpha-hydrolase/C17,20 lyase complex [CYP17A1]). The 17alpha-hydrolase is a member of the cytochrome p450

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CONTEXT

Key Objective

Is low-dose abiraterone a rational strategy for metastatic prostate cancer in a resource-constrained setting?

Knowledge Generated

In a survey of 118 medical oncologists in India, 93.2% were either already using low-dose abiraterone or were considering using it. Most felt that using low-dose abiraterone would improve compliance and would result in substantial cost savings; 29% were willing to consider a change in their practice.

Relevance

The use of lower-dose abiraterone is likely to increase with time, considering the above advantages along with the pharmacokinetic and pharmacodynamic data. This strategy is likely to significantly improve compliance and reduce financial toxicity for patients. A simple survey can be used to understand current practice and knowledge about use of low-dose abiraterone in the oncology community.

family, which catalyzes the 17alpha-hydroxylation of steroid intermediates in the testes and adrenal glands. Early phase I studies demonstrated anticancer activity of abiraterone at 250-, 500-, 750-, 1,000-, and 2,000-mg doses in fasted as well as fed men.[9,10] In the first phase I study, the variability in maximum plasma concentration was greater with the 1,000 mg dose, although it did not consistently change with dose.[11] Chi et al[12] compared the pharmacokinetics (PK) of abiraterone in fasting and fed healthy participants and in men with metastatic prostate cancer and found that food effects were on average more modest among patients, but there was substantial variation in drug levels, and the investigators did not evaluate target inhibition. Overall, the mean maximum concentration (C_{max}) and area under curve of abiraterone are 5 to 7 times higher when administered with a low-fat meal (7% fat, 300 calories) and approximately 10 to 17 times higher when administered with a high-fat meal (57% fat, 825 calories).[13] The recommended dose of abiraterone for further development was 1,000 mg on an empty stomach, but this was an arbitrary decision, given the available evidence.

Low Dose Versus Standard Dose

Szmulewitz et al[14] compared low-dose abiraterone (250 mg after a low-fat meal) to a standard dose (1,000 mg, fasting) in men with mCRPC in a randomized clinical trial. The primary objective was to compare the antitumor activity at the two dose levels as assessed by change in serum levels of prostate-specific antigen (PSA). Secondary objectives were to compare PK, PSA response rate (50% reduction in PSA after 12 weeks of therapy), progression-free survival (PFS), and safety profile. They also studied the pharmacodynamic (PD) effect by analyzing testosterone and dehydroepiandrostenedione levels. This study used a noninferiority trial design with analysis of PSA change as a continuous variable. Seventy-two patients with mCRPC were randomly assigned in a 1:1 ratio to each treatment arm. Interestingly, the magnitude of reduction in PSA from baseline to 12 weeks was slightly greater in the low-dose group (the mean log change was 21.6 in the low-dose group *v* 21.2 in the standard-dose group, with a pooled standard deviation of 1.62.) Although noninferiority could not be established with statistical rigor because of the low power of the trial, it was supported strongly by the PSA data and by similar PD effects of the low and standard doses.[15] On the basis of this trial, the NCCN added low-dose abiraterone with food as an acceptable alternative to the standard dose for treatment of men with prostate cancer.

With this background, we undertook a survey under the Science and Cost Cancer Consortium to understand practices in India, and we discuss the financial implications of changing practice in favor of low-dose abiraterone.

METHODS

The purpose of the survey was to understand current practice and review opinions among medical oncologists in India regarding the use of low-dose abiraterone for men with mCRPC. We posed five pertinent questions with multiple-choice answers (Fig 1A-E). The questions were put in an easily accessible form on the Google Forms platform (freely available on the Internet). The survey information was circulated through a WhatsApp group of 251 medical oncologists and was conducted from April 1, 2019, to July 31, 2019. The survey did not require approval by the institutional review board, according to Indian ethics guidelines, but the survey stated that personal information about respondents would not be revealed in any report. Participants were representative of medical oncologists from across the country from various age groups and both sexes. They self-selected for the survey.

We also estimated the potential cost savings of using a quarter dose of abiraterone by using a model with the following seven assumptions: (1) estimated number of Indian men with new diagnosis of prostate cancer per year was 50,000,[1] (2) number of patients with metastatic or advanced cancer with an indication for abiraterone was 42,500 (85% of 50,000),[6,16] (3) number of patients with

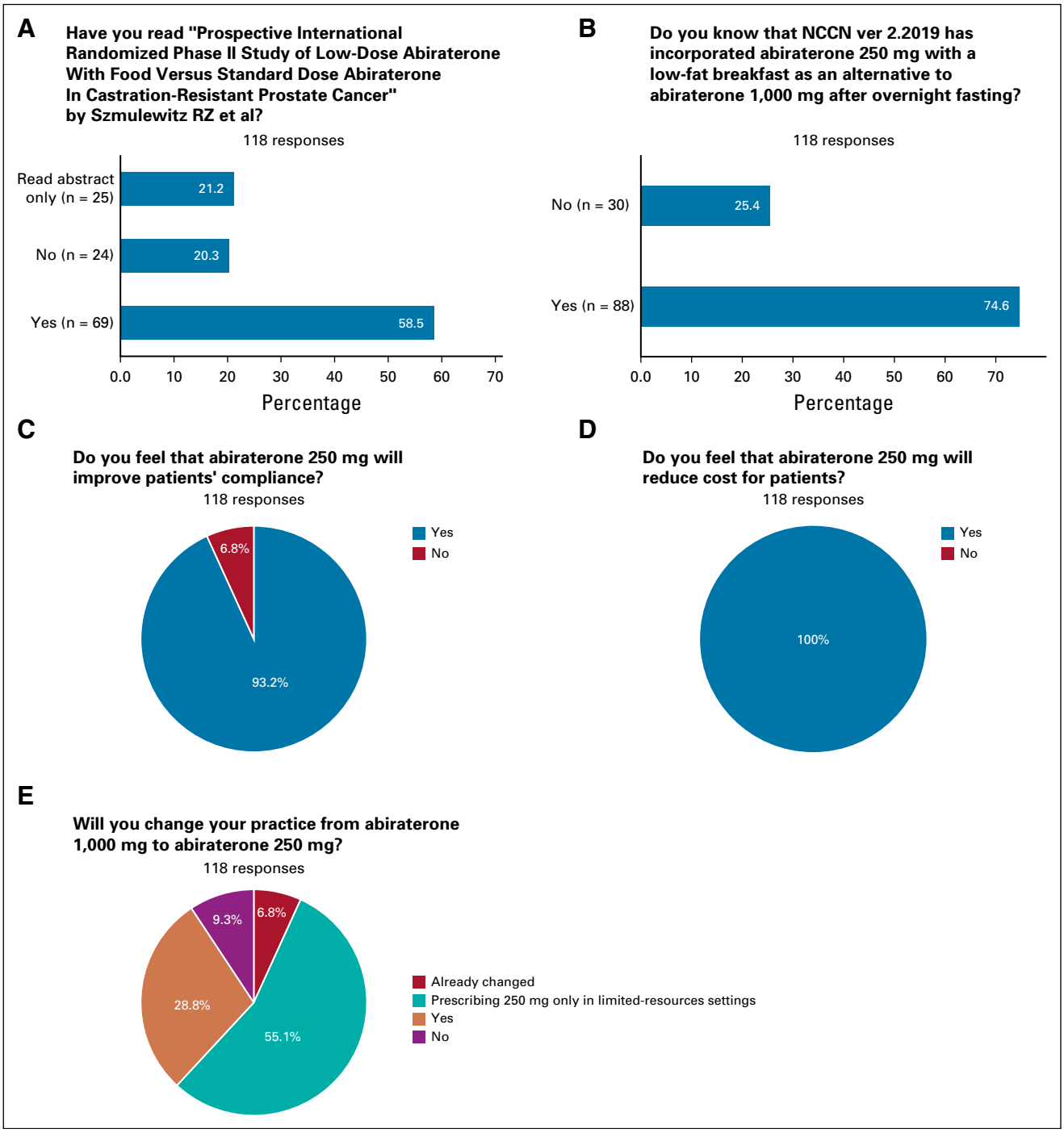

FIG 1. (A-E) Survey questions on use of low-dose abiraterone among Indian medical oncologists.

castrate-sensitive prostate cancer receiving abiraterone was 25,500 (assumed to be 60% of 42,500), (4) number of patients with mCRPC receiving abiraterone as second-line therapy was 17,000 (assumed to be 40% of 42,500), (5) expected PFS for abiraterone in the castrate-sensitive setting was assumed to be 33 months,[17] (6) expected PFS for abiraterone in the castrate-resistant setting was assumed to be 10 months,[18] and (7) the minimum cost of monthly abiraterone in India (cheapest available generic drug) was US$240 for 1,000 mg or US$60 for 250 mg. Cost difference is US$180 per month of treatment.

RESULTS

Results of the Survey

Among 251 medical oncologists who were invited to participate, 125 provided their e-mail address and received the survey by e-mail, and 118 (47% of the total) responded to the survey. Overall, 93.2% of practitioners believed that the

use of abiraterone 250 mg with a low-fat meal would improve compliance, and all agreed that it would reduce costs (Fig 1C-D). However, 25.4% were not aware of the recent NCCN recommendation for reduced-dose abiraterone (Fig 1B). Fifty-five percent of medical oncologists were prescribing low-dose abiraterone only in a limited-resources setting, and that was the major factor for use of low-dose abiraterone. Before NCCN recommendations were made, 6.8% had already changed their practice after publication of the article by Szmulewitz et al,[14] and 28.8% agreed that they would switch to a universal practice of using 250 mg abiraterone with food (Fig 1E). Some practitioners (9.3%) said they would not use low-dose abiraterone.

Cost-Effectiveness Analysis

If all Indian patients taking abiraterone received the lower dose with food, the yearly cost savings to the Indian health care system is estimated to be:

Cost savings per patient × [(number of castrate sensitive × duration of treatment) + (number of castrate resistant × duration of treatment)] that is: \$180 × [(25,500 × 33) + (17,000 × 10)] or US\$182 million.

The average patient would save US\$3,640 over his lifetime, equal to approximately INR260,000. To put this in context, the saved amount is approximately 2.5 times the mean per capita income in India.

DISCUSSION

We report here a survey of the opinions of Indian medical oncologists about prescribing low-dose abiraterone with food; we had a reasonable response rate of 47%. We are unaware of previous surveys of this type, and these simple questions and answers can be used for making medical oncologists aware of changes in NCCN guidelines. Although the type and amount of food intake is variable and dependent on economic status in India, taking abiraterone after any substantial meal would be likely to increase its bioavailability and would provide an effective treatment at reduced price. We can only speculate on why low-dose abiraterone is used by some oncologists only in limited-resources settings. It often takes time for physicians to become comfortable with a change in practice, and we expect that the proportion of respondents who will use low-dose treatment will increase.

In general, the pharmaceutical industry promulgates advances in medicine, in terms of newer therapeutics, through conferences and closed meetings of experts. The option of prescribing lower doses of drugs decreases their profit and will be concealed or discouraged in such meetings. However, NCCN guidelines are used widely and are based on a critical review of evidence. Although there has been no formal large equivalence study to compare 250 mg/day abiraterone after food with 1,000 mg/day fasting, the cumulative evidence from smaller phase I studies of PK and PD effects of the drug[9-11] as well as the smaller randomized trial[14] provide strong evidence for similar effectiveness of the lower dose. We are aware that there is no Level I evidence to support noninferiority, especially when abiraterone is used for hormone-sensitive cancer, but PK and PD data suggest that lower-dose abiraterone with food will give similar outcomes, regardless of the stage of disease being treated.

We took the present initiative to encourage effective practice at lower cost, and 28.8% of medical oncologists agreed to change their practice. One tablet after a meal would improve compliance compared with four tablets on an empty stomach and the cost would be reduced by 75%. Other oral drugs such as lapatinib and ibrutinib could also be given with food to save cost and increase access to treatment.[19,20] In the ASCEND 8 study (ClinicalTrials.gov identifier: NCT02299505), a low dose of 450 mg/day of the ALK inhibitor ceritinib in the fed state (low-fat meal) was as effective as and was better tolerated than the standard dose of 750 mg/day fasting for ALK-rearranged metastatic non–small-cell lung cancer, and the low dose is being used in clinical practice.[21] With the current survey, 25.4% of medical oncologists were made aware of a change in recommendations.

In conclusion, a simple survey can be used to understand current practice and physicians' knowledge about use of low-dose abiraterone in the oncology community. Use of lower-dose abiraterone would increase access to treatment in India and globally and would lead to large cost savings. Additional well-planned studies of cost-effective newer therapeutics should be undertaken in oncology in an era in which cancer incidence and the costs of care are rapidly increasing. We urge the oncology community to collaborate by collecting clinical data to better understand the efficacy of this practice in treating prostate cancer.

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REFERENCES

1. Jain S, Saxena S, Kumar A: Epidemiology of prostate cancer in India. Meta Gene 2:596-605, 2014
2. Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893-2917, 2010
3. Sharma R: The burden of prostate cancer is associated with human development index: Evidence from 87 countries, 1990-2016. EPMA J 10:137-152, 2019
4. Center MM, Jemal A, Lortet-Tieulent J, et al: International variation in prostate cancer incidence and mortality rates. Eur Urol 61:1079-1092, 2012
5. India Against Cancer: Globocan 2018: India Factsheet. http://cancerindia.org.in/globocan-2018-india-factsheet/
6. Taitt HE: Global trends and prostate cancer: A review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. Am J Men Health 12:1807-1823, 2018
7. National Comprehensive Cancer Network: Prostate Cancer, 2019. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
8. Institute of Cancer Research: Abiraterone: a story of scientific innovation and commercial partnership. https://www.icr.ac.uk/news-features/latest-features/abiraterone-a-story-of-scientific-innovation-and-commercial-partnership
9. 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
10. Matsubara N, Uemura H, Fukui I, et al: Phase-1 study of abiraterone acetate in chemotherapy-naïve Japanese patients with castration-resistant prostate cancer. Cancer Sci 105:1313-1320, 2014
11. Attard G, Reid AH, 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 26:4563-4571, 2008
12. 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
13. Center for Drug Evaluation and Research: Approval Package for Zytiga (abiraterone acetate). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202379Orig1s005.pdf
14. 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
15. Tannock IF: Low-fat abiraterone food effect is of great consequence. J Clin Oncol 36:3058-3059, 2018
16. Ghagane SC, Nerli RB, Hiremath MB, et al: Incidence of prostate cancer at a single tertiary care center in North Karnataka. Indian J Cancer 53:429-431, 2016
17. James ND, de Bono JS, Spears MR, et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 377:338-351, 2017
18. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011
19. Ratain MJ, Cohen EE: The value meal: How to save $1,700 per month or more on lapatinib. J Clin Oncol 25:3397-3398, 2007
20. Kang SP, Ratain MJ: Inconsistent labeling of food effect for oral agents across therapeutic areas: Differences between oncology and non-oncology products. Clin Cancer Res 16:4446-4451, 2010
21. Cho BC, Kim DW, Bearz A, et al: ASCEND-8: A randomized phase 1 study of ceritinib, 450 mg or 600 mg, taken with a low-fat meal versus 750 mg in fasted state in patients with anaplastic lymphoma kinase (ALK)-rearranged metastatic non-small cell lung cancer (NSCLC). J Thorac Oncol 12:1357-1367, 2017

