Enzalutamide in Castration-Resistant Prostate Cancer

TO THE EDITOR: In the double-blind, randomized, placebo-controlled PROSPER trial conducted by Hussain et al. (June 28 issue),[1] enzalutamide treatment was assessed in men with nonmetastatic, castration-resistant prostate cancer. The authors found that metastasis-free survival was prolonged, but overall survival was not prolonged nor was quality of life improved. Major adverse cardiovascular events were reported to be more common in patients who received the antiandrogen agent enzalutamide (48 of 930 patients [5%]) than in those who received placebo (13 of 465 [3%]). Furthermore, 9 patients in the enzalutamide group died from cardiovascular adverse events, as compared with 2 in the placebo group.

The authors report that patients with clinically significant cardiovascular disease were excluded from the trial, but they do not discuss how this was assessed or whether echocardiograms were performed before the enrollment of patients. Since the rates of major adverse cardiovascular events and development of hypertension were elevated with the new medication, we expect that patients also had subclinical cardiotoxic effects. A recent position paper regarding cardiotoxicity[2] recommends the use of cardiac imaging and biomarkers for the early detection of cardiotoxic effects during cancer treatment. How many patients had subclinical cardiotoxic effects during the trial, and were these patients treated with cardioprotective medication?

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1. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465-74.
2. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768-801.

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TO THE EDITOR: Nonmetastatic, castration-resistant prostate cancer is defined by biochemical recurrence after locoregional treatment in the absence of visible metastases. The mainstay of treatment is androgen-deprivation therapy. In the PROSPER trial, 1401 patients with nonmetastatic, castration-resistant prostate cancer were randomly assigned to receive either enzalutamide at a dose of 160 mg or placebo. The primary end point was metastasis-free survival. The median prostate-specific antigen (PSA) doubling time at baseline was 3.8 months in the enzalutamide group and 3.6 months in the placebo group. Enzalutamide significantly prolonged metastasis-free survival, leading to a 71% lower risk of metastatic, castration-resistant prostate cancer or death. Notwithstanding these results, the external validity of the trial is weakened by the placebo control group.

In our opinion, current clinical practice regarding patients who have nonmetastatic, castration-resistant prostate cancer with a short PSA doubling time should be maximal androgen blockade with bicalutamide.[1] In a phase 3 trial that compared bicalutamide plus luteinizing hormone–releasing hormone (LHRH) with LHRH alone, the risk of death was approximately 20% lower in the combination-therapy group.[2] The benefit of enzalutamide in patients with nonmetastatic, castration-resistant prostate cancer could be better interpreted if it were compared with standard treatment. Trials involving patients with prostate tumors and a short PSA doubling time would benefit from comparison with an active-treatment group.

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1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: prostate cancer. Fort Washington, PA: National Comprehensive Cancer Network, 2016.
2. Akaza H, Hinotsu S, Usami M, et al. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer 2009;115:3437-45.

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THE AUTHORS REPLY: In response to Anker et al.: during screening for our trial, patients underwent a full physical examination and a 12-lead electrocardiogram. Patients were excluded from the trial if they had bradycardia, uncontrolled hypertension, hypotension, congestive heart failure, a history of clinically significant ventricular arrhythmias, Mobitz type II second-degree or third-degree heart block without a permanent pacemaker in place, myocardial infarction in the 6 months before screening, or uncontrolled angina in the 3 months before screening (see the protocol, available with the full text of our article at NEJM.org). During the trial, patients underwent a history and physical examination every 16 weeks. Patients were seen by a local cardiologist for any new cardiovascular symptoms. Information on subclinical cardiotoxic effects and the use of cardioprotective medications was not collected.

Bregni et al. are correct that the mainstay of treatment for prostate cancer with biochemical recurrence after locoregional treatment is androgen-deprivation therapy. However, our trial enrolled patients with castration-resistant prostate cancer. More than half the patients had received bicalutamide previously. The trial cited by Bregni et al. enrolled patients with advanced prostate cancer who had not previously been treated,[1] and therefore, the results cannot be extrapolated to the population enrolled in PROSPER. Until the Food and Drug Administration approved both apalutamide and enzalutamide in 2018,[2,3] no therapies had been approved for the treatment of patients with nonmetastatic, castration-resistant prostate cancer. Before that time, the National Comprehensive Cancer Network guidelines recommended clinical trials for such patients, since there was no treatment with level 1 evidence that had shown a meaningful clinical benefit.[4] In the randomized, bicalutamide-controlled, phase 2 STRIVE trial of enzalutamide in men with castration-resistant prostate cancer who had not received chemotherapy previously, treatment with enzalutamide resulted in a 76% lower risk of radiographic progression or death than treatment with bicalutamide.[5] Although the results of the STRIVE trial are limited owing to the small number of patients (139), the lower risk that was observed in that trial is consistent with that observed in PROSPER, which supports the benefit of enzalutamide over bicalutamide in this population of patients.

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1. Akaza H, Hinotsu S, Usami M, et al. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer 2009;115:3437-45.
2. Erleada (apalutamide) prescribing information. Horsham, PA: Janssen Pharmaceutical, 2018 (package insert) (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf).
3. Xtandi (enzalutamide) prescribing information. Northbrook, IL: Astellas Pharma US, 2018 (package insert) (https://www.astellas.us/docs/12A005-ENZ-WPI.PDF).
4. Jana BRP. Prostate cancer guidelines: prostate cancer screening. Medscape. July 31, 2017 (https://emedicine.medscape.com/article/2259453-overview).
5. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34:2098-106.

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