Enzalutamide — A Major Advance in the Treatment of Metastatic Prostate Cancer

Nicholas J. Vogelzang, M.D.

In this issue of the Journal, Scher et al. describe the strikingly positive results of a phase 3 trial of a new nonsteroidal antiandrogen agent, enzalutamide, as compared with placebo in metastatic castration-resistant prostate cancer. Not only was survival significantly improved among patients who had undergone previous chemotherapy with docetaxel (a treatment that is a watershed event in the lives of most patients), but the incidence of adverse events of grade 3 or higher was lower among the patients receiving enzalutamide than among those receiving placebo (a finding that suggests that the “toxicity” of placebo is related to underlying disease-related symptoms). How did the field get to this point, and what are the next steps forward?

The first nonsteroidal antiandrogen agents — flutamide, nilutamide, and bicalutamide — were shown to be less effective than castration in cases of metastatic castration-resistant prostate cancer, but bicalutamide is still widely used as a moderately effective secondary hormone therapy because of an excellent safety profile. Dozens of randomized phase 3 trials then compared testosterone ablation plus an antiandrogen (termed combined androgen blockade) with testosterone ablation alone. Meta-analyses concluded that the addition of flutamide or nilutamide prolonged survival by 2 to 5% at 5 years. One study of testosterone ablation alone as compared with testosterone ablation with bicalutamide showed a survival advantage for the combination. Therefore, since the mid-1990s, bicalutamide has been the standard of care for patients receiving combined androgen blockade.

Subsequently, the androgen receptor was shown to be central to the biologic features of metastatic castration-resistant prostate cancer: it was overexpressed as the cancer progressed; it could mutate, allowing stimulation by a variety of weak androgens; and it could be activated by autocrine production of androgens from tumor cells obtained from patients with the disease. Chen et al. then conducted an elegant series of experiments that involved the synthesis of bicalutamide analogues with improved inhibitory capacity and ultimately led to the discovery of enzalutamide. When phase 1 and phase 2 trials confirmed the safety and activity of enzalutamide, the phase 3 trial was launched; the trial design was virtually identical to that used to obtain Food and Drug Administration (FDA) approval of abiraterone.

Although abiraterone inhibits androgen synthesis and lowers testosterone levels to nearly undetectable levels, it does not affect androgen-receptor signaling, which may remain active and thereby cause disease progression (perhaps by means of alternative androgenic agonists). Enzalutamide does not lower androgen levels but instead inhibits androgen-receptor signaling by competitively inhibiting the binding of androgens without stimulation of the androgen receptor. Tumor-cell growth then requires androgen binding to the androgen receptor, followed by nuclear translocation and DNA binding; enzalutamide inhibits both steps, even in patients with androgen-receptor overexpression and resistance to other antiandrogens. These potentially non-overlapping and synergistic actions of abiraterone and enzalutamide have led to the proposal for a phase 3 trial comparing enzalutamide with enzalutamide plus abiraterone (comparisons with abiraterone alone would also be interesting) (Morris M, Memorial Sloan-Kettering Cancer Center: personal communication).
What are the limitations to the use of enzalutamide (which has just received FDA approval on the basis of the study by Scher et al.)? First, enzalutamide is likely to be active in all patients with metastatic castration-resistant prostate cancer in whom the androgen receptor is still driving the disease, regardless of whether the patients have received treatment with docetaxel. A phase 3 trial involving patients who have not been treated with docetaxel is complete and should be reported shortly (ClinicalTrials.gov number, NCT01212991).

Second, assessment of androgen-receptor activity in patients with metastatic castration-resistant prostate cancer is not clinically available, so all patients deserve a therapeutic trial of enzalutamide. However, Tzelepi et al. recently reported that approximately 25% of analyzed tumors obtained from patients with metastatic castration-resistant prostate cancer have no androgen receptors yet show marked up-regulation of the gene for the ubiquitin-conjugating enzyme E2C and other mitotic genes that are independent of regulation by androgen receptors. The extrapolation of these data indicates that such patients will have no response or only a minimal response to enzalutamide. Characterization of the spectrum of enzalutamide activity as a function of the heterogeneity of the androgen-signaling pathway should be a priority of future translational trials.

Third, enzalutamide crosses the blood–brain barrier and apparently leads to sensitization to seizures in small numbers of patients. The ability to cross the blood–brain barrier may be a therapeutic advantage in patients with advanced epidural or meningeal disease but calls for caution. Another new nonsteroidal antiandrogen, ARN-509, seems to have a similar potency but less penetrance of the central nervous system.

Fourth, this clinical trial enrolled very few patients who had previously received abiraterone, yet abiraterone is used in virtually all patients with metastatic castration-resistant prostate cancer. The relative effectiveness of enzalutamide in patients who have previously received abiraterone is unknown, although as noted above, the two agents are theoretically not cross-resistant.

In conclusion, enzalutamide, a new, highly effective, and safe nonsteroidal antiandrogen, extends survival and will become widely used in patients with metastatic castration-resistant prostate cancer. It will be used sequentially with other active agents, such as docetaxel, abiraterone, cabazitaxel, radium-223, and immunotherapy. It will be studied much earlier in the disease course. In addition, it is likely to supplant bicalutamide in combined androgen blockade after appropriate phase 3 trials have been completed.

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From the Comprehensive Cancer Centers of Nevada, Las Vegas.


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Tiotropium for Asthma — Promise and Caution

Elisabeth H. Bel, M.D., Ph.D.

Anticholinergic agents have been available for the treatment of airways obstruction for many decades. For patients with chronic obstructive pulmonary disease (COPD), many practitioners believe that these drugs have become the bronchodilator of choice. For patients with asthma, anticholinergic agents are less popular, probably because of their slower onset of action as a reliever medication and their generally inferior effect on lung function and symptoms, as compared with inhaled beta-agonists.

Not surprisingly, long-acting beta-agonists...