New prostate cancer drugs: extending and improving life

With the advent of new, life-prolonging therapies in advanced prostate cancer, the effects of therapy on the disease’s most common complications—skeletal-related events and bone pain—and their effect in turn on health-related quality of life should be considered in addition to survival outcomes. AFFIRM1 was a randomized phase 3 study of enzalutamide (an androgen receptor inhibitor) versus placebo in men with metastatic castration-resistant prostate cancer previously treated with docetaxel chemotherapy. Enzalutamide significantly improved overall and progression-free survival, the study’s primary endpoints, leading to US Food and Drug Administration approval for the drug in this patient population. Karim Fizazi and colleagues1 now report the results of some of the secondary endpoints of AFFIRM, specifically time to skeletal-related events, pain progression, pain palliation and health-related quality of life. They found that, compared with placebo, enzalutamide significantly improved median time to first skeletal-related event, pain progression, pain severity, and health-related quality of life.

It is interesting to consider enzalutamide’s effects in the context of corticosteroid and bisphosphonate use in AFFIRM. Historically, corticosteroid use in the control groups of some trials induced prostate-specific-antigen responses and pain reduction, possibly through central androgen-pathway suppression or inhibition of peripheral tumour growth.3,4 For example, in the COU-AA-301 trial, patients with metastatic castration-resistant prostate cancer who had progressed after docetaxel were treated with either abiraterone acetate plus prednisone or placebo plus prednisone.5 In that trial, the control group (prednisone alone) had a median interval of 20·3 months (95% CI 16·9—not estimable) until first skeletal-related event, and only 98 (25%) of 398 patients in the control group had at least one skeletal-related event.6 By contrast, patients in the placebo group of AFFIRM, of whom 45% were receiving corticosteroids, had a median time to first skeletal-related event of only 13·3 months (95% CI 9·9 to not yet reached), and 161 (40%) of 399 had at least one skeletal-related event. Indeed, not only was corticosteroid use in AFFIRM not beneficial but it was actually associated with worse survival in both groups, and increased treatment-emergent grade 3 and 4 adverse events.6 This might be because patients who were started on corticosteroids while on the trial were sicker (more pain, higher prostate-specific antigen, and more metastases), and possibly because corticosteroids might stimulate cancer cells through the glucocorticoid receptor as a mechanism of androgen receptor pathway escape.7 In view of the detrimental survival effects of corticosteroid use in AFFIRM, the authors did a post-hoc analysis to establish if corticosteroid use affected any of the secondary endpoints. They noted no significant difference in time to skeletal-related events, pain, and health-related quality of life between those patients treated with corticosteroids and those not treated; a similar analysis also showed that bisphosphonate use did not significantly affect the benefits of enzalutamide.

An intriguing aspect of this study was that even among patients who did not have disease response according to prostate-specific-antigen level or clinical criteria, enzalutamide improved health-related quality of life outcomes. Similarly, post-hoc analysis showed better health-related quality of life with enzalutamide than with placebo when analysed in all progressors or in all non-progressors of disease (data not shown). This might be because even in patients who did not meet criteria for response or progression, enzalutamide still increased cancer control, and reduced disease volumes, thus improving secondary outcomes. However, it is intriguing to speculate, as the authors do, that enzalutamide might exert tumour-independent biological effects—eg, modulation of the tumour microenvironment. In one report, 8 weeks of enzalutamide increased circulating and bone marrow testosterone concentrations, suggesting that enzalutamide might induce host signalling feedback that might affect the tumour microenvironment.8

Enzalutamide after docetaxel yields significant relief from pain and skeletal-related events, leading to overall improvement in quality of life. Although not practice changing, this knowledge assures clinicians that enzalutamide will provide not just more time, but more quality time: a crucial consideration in the setting of non-curtative therapy. As new treatments are approved in this setting, further research is needed to determine their optimum combination and sequence for delivery. The PREVAIL trial9 showed that enzalutamide...
significantly improves overall survival when given before chemotherapy; would improvements for skeletal-related events, pain, and health-related quality of life also be preserved if enzalutamide was given in this earlier disease state? How would these secondary, but essential endpoints affect our sequencing of enzalutamide with other new hormonal agents (eg, abiraterone) that are also being given before chemotherapy? What is the optimum delivery for these drugs in patients with high-volume, metastatic, hormone-sensitive prostate cancer who, as demonstrated in the CHAARTED study, can benefit from docetaxel as part of first-line therapy? Last, but not least, if skeletal-related events, pain, and health-related quality of life are improved even in patients with no clear disease response, as reported in this trial, what is the most appropriate signal to switch therapy that ensures patients are treated long enough to derive the full benefits of these new drugs? In this era of new therapeutic options, these are the crucial questions that future trials must answer.

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