correspondence

Impact of Novel Hormonal Therapy on Cognitive Function: Essential to Measure, Difficult to Present

TO THE EDITOR:

Stockler et al[1] reported effects on health-related quality of life (HRQoL) in ENZAMET (ANZUP 1304), a randomized, phase III, cooperative group trial of enzalutamide versus an active control (physician's choice of bicalutamide, nilutamide, or flutamide), in addition to testosterone suppression, in metastatic, hormone-sensitive prostate cancer. The authors carefully analyzed the impact of enzalutamide compared with the active control regarding different aspects of HRQoL, including cognitive function. Cognitive function impairment, potentially related to androgen deprivation treatment and novel hormonal therapy (NHT), is a worrisome adverse event occurring in patients with prostate cancer[2] that needs to be carefully investigated in both clinical trials and clinical practice. Cognitive impairment, by its very nature, especially if mild or moderate, is particularly at risk of under-reporting by physicians if not systematically assessed with adequate and reproducible instruments.[3] Therefore, evaluation of patient-reported outcomes, fundamental to assess the value of anticancer drugs in general, is even more important to fully understand the impact of treatments on the cognitive function of patients. We really appreciated the effort by Stockler et al,[1] considering that—as we have previously shown—evaluation of cognitive function by patient-reported outcomes is lacking in most trials with NHT.[3]

In detail, the authors assessed cognitive function over time by different methods: (1) a repeated measures model and (2) the deterioration-free survival. Deterioration-free survival is heterogeneously defined in the literature.[4] In the ENZAMET trial, it was defined as the time from random assignment until the earliest of the following events: a 10-point or greater deterioration from baseline in the pertinent aspect of HRQoL (without a subsequent 10-point or greater improvement compared with baseline), clinical progression, treatment discontinuation, or death from any cause, thus representing a composite end point summarizing both HRQoL and efficacy outcomes. When looking specifically at the cognitive functioning, the authors found a greater drop in the curve of deterioration-free survival for enzalutamide over the first 3 months and a subsequent crossing of the curves beyond 6 months, with improved deterioration-free survival rates at 3 years (31% *v* 20%) and log-rank *P* values comparing the whole distributions ($P < .001$) favoring enzalutamide over control. However, the latter information may be misleading for readers. In fact, as shown in the Data Supplement (Supplementary Figure 6) of the manuscript, which splits the events of HRQoL drop from the events of treatment failure, deterioration of cognitive function is clearly and constantly worse with enzalutamide, as well as deterioration of fatigue and physical functioning. This is coherent with the difference in overall mean scores of cognitive functioning, which favored control over enzalutamide (+4.0; 95% CI, +2.5 to +5.5; $P < .001$). We suggest that, to be performed correctly and to avoid misinterpretation, time-to-deterioration analysis should treat other events (including deaths or clinical progressions) as competing events and not as events considered on a par with cognitive worsening.[3] The higher efficacy of enzalutamide in terms of disease control, which is well documented by other end points, should not dilute the description of its impact in terms of tolerability and adverse events.

Understanding the real impact of NHT on cognitive functioning is of utmost importance, considering the progressively earlier and longer administration of treatment to patients affected by prostate cancer. Research regarding cognitive training programs for cognitive dysfunction in patients with prostate cancer is still an under-investigated field, and only a few attempts have been made to date.[5] Dissecting the real contribution of NHT to cognitive dysfunction is fundamental for the early recognition of this potentially disabling side effect, for the proper management of these drugs and for appropriate planning of studies aiming at establishing cognitive training programs for patients with prostate cancer.

As the authors stated, the assessment of HRQoL only until clinical progression (like in most clinical trials) is a limitation of the study, and this is especially true for potential long-term and long-lasting adverse events. Understanding the evolution of cognitive functioning over time, not only during therapy but also after suspension of treatment, by using HRQoL follow-up assessment, should become an integrative part of HRQoL evaluation for future trials testing NHT for prostate cancer. In addition, composite end points, mixing events related to tolerability and events related to efficacy, may jeopardize the interpretation of results, underestimating the HRQoL drop associated with the most effective treatment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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