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Hard Problems Need "Soft" Science: Integrating Quality of Life into Treatment Decision Making

Alicia K. Morgans [a,*], *Charles J. Ryan* [b]

[a] *Division of Hematology/Oncology, Department of Medicine, Northwestern University, Chicago, IL, USA;* [b] *Department of Medicine and Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA*

Improved efficacy of treatment in metastatic castration-resistant prostate cancer (mCRPC) has dramatically increased the duration of exposure to potential treatment side effects. Given this, quality of life (QOL) considerations in treatment choice must be considered alongside efficacy. Moving forward, harmonization of QOL outcome measures, analytic methods, and reporting styles, as well as integration of assessments of contributing biological factors are needed to accelerate improvements in our understanding of the role of QOL for patients receiving systemic therapy. In this month's issue of *European Urology*, Khalaf and colleagues [1] report a comparison of patient-reported QOL outcomes in men with mCRPC randomized to treatment with abiraterone or enzalutamide. This investigation, the first prospective direct comparison of patient-reported outcomes (PROs) between these therapies, provides clinicians and patients with a more nuanced view of the treatment experience. In addition, the study sheds light on the heterogeneity of the patient experience seen in clinical practice by demonstrating a difference in QOL by age group.

Khalaf and colleagues [1] reveal a striking dichotomy between the QOL reported by men aged $\geq$75 yr treated with abiraterone and that reported by men of the same age group treated with enzalutamide, reporting superior QOL with treatment with abiraterone by FACT-P compared with treatment with enzalutamide. No QOL difference was reported in men aged $<$75 yr between treatments. Whether the difference in PROs is related to changes in organ function and drug metabolism, frailty and tissue senescence, patient perception of the experience and reporting, or other factors deserves further investigation. Addressing factors contributing to these differences may improve the experience for those with poor QOL on treatment, regardless of chronological age. Future studies assessing QOL should integrate correlative studies aimed at understanding the biology driving this difference, to more fully characterize the patient experience and identify possible levers for improvement.

Based on their mechanisms of action, it is not surprising that enzalutamide and abiraterone resulted in divergent outcomes in older patients. Abiraterone reduces testosterone production, which may have little effect on the signaling of the central nervous system (CNS), whereas enzalutamide directly antagonizes the androgen receptor (AR), a molecule expressed not only on tumor cells, but throughout the CNS also [2]. Prior work from our group and others has implicated the AR in a variety of cognitive and other CNS effects, including the development of dementia, which are particularly pronounced in aging and relatively testosterone-depleted brains [3]. It is not surprising, therefore, that more subtle effects could result during direct inhibition of the AR in aged men. Further work in aging populations, and other potentially vulnerable populations such as men with mild cognitive impairment at baseline, will be important in the quest to personalize treatment approaches to individual patients.

Whether cognitive change occurs as a consequence of treatment for prostate cancer is debated [4–7]. The current study reported no difference in cognitive function after 12 wk of therapy between the two treatments. It should be noted, however, that this finding was based on the relatively insensitive Montreal Cognitive Assessment test, a screening test with a limited range of scores from 0 to 30. It is possible that more intensive assessments with tests dedicated to

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* Corresponding author. 676 N. St. Clair St., Suite 850, Chicago, IL 60611, USA. Tel. +1 312 695 2381; Fax: +1 615 343 7602.
E-mail address: alicia.morgans@northwestern.edu (A.K. Morgans).

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multiple cognitive domains (eg, short-term memory, spatial reasoning, executive function, etc.) may identify differences between the groups, if they exist, but are more time and resource intensive. Additionally, separate investigations of cognition in cancer populations have integrated patient-reported outcome measures (PROMs) of cognitive function to provide an expanded and complementary view of cognitive function that is based on the patient's perception. To fully characterize cognitive function, routine incorporation of sensitive objective cognitive assessments and PROMs for cognition should be standardized, as both patients' perceptions and their objective measures may influence treatment choice in this critical aspect of daily life.

Major challenges exist in adequately measuring and reporting QOL data in prostate cancer clinical trials. Although assessments of QOL have been incorporated more consistently in prospective trials, there is no consensus on which PROMs and analytic methods should be considered the gold standard. Many recent trials utilize the FACT-P instrument, used by Khalaf et al. [1] to assess emotional, physical, functional, social, and overall QOL, and the brief pain inventory that assesses pain severity and interference. However, although multiple trials utilize these instruments, the methods of analysis and reporting from these instruments differ vastly across trials. As shown in this paper, some reports address the proportion of patients experiencing clinically meaningful change from baseline, whereas others report on maintained or improved QOL over time, time to deterioration in QOL, or a comparison of QOL at study landmarks [8,9]. The lack of standardization in methods of analysis and reporting, even in the setting of studies that include the same PROM, results in studies that report QOL data that appear to be harmonized on the same measure, but cannot be compared with the same outcomes. The methods of analysis and reporting must be standardized to allow meaningful interpretation and comparison of QOL results for high-quality treatment decision making.

Consistent and definitive integration of QOL information into clinical decision making for men with advanced prostate cancer can greatly improve our ability to deliver high-quality care. Investigations into subgroups that may be more or less vulnerable to poor QOL outcomes must be performed for personalization of treatment, and to identify subgroups (such as the elderly) that may benefit from modifications to treatment regimens to optimize efficacy and QOL outcomes. Finally, QOL is more than a single instrument assessing a few general domains. Sensitive measures of cognition should be integrated as standard assessments in prospective studies, as should explorations of genetic, biochemical, and neurophysiological factors that drive these phenomena. Our patients demand these data, just as they require information on the efficacy of the treatments before them. It is time for the field to transform its view of QOL as an extra, perhaps unnecessary, "soft" science and to routinely provide this information to the men who need these data as they face hard choices each day.

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