Abiraterone acetate and enzalutamide received regulatory approval in the USA for the treatment of chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) in 2012 and 2014, respectively, based on impressive results of Phase III studies [1,2]. While multiple other agents have demonstrated survival benefit and thus received regulatory approval as front-line mCRPC therapies (including sipuleucel-T [3], docetaxel [4] and radium-223 [5]), abiraterone and enzalutamide remain the most commonly used drugs. The National Comprehensive Cancer Network (NCCN) guidelines and American Clinical Society of Oncology (ASCO)/Clinical Cancer Ontario (CCO) clinical practice guidelines, endorse this approach [6,7]. These widely used clinical guidelines, developed from systematic reviews of randomized controlled data and expert consensus, can be helpful to clinicians and patients seeking the best treatment options for advanced prostate cancer. However, there are important limitations that must also be considered.

In each of the Phase III trials above, drugs were compared with placebo; docetaxel was the exception, as it was compared with mitoxantrone, a drug with no survival benefit in prior studies. While one can argue the merits of placebo as the control arm in these studies, what cannot be debated is that none of these drugs have been compared against each other. Comparison across trials is difficult given that the different patient populations in each of these trials. TAX-327 (docetaxel) included symptomatic patients and compared docetaxel and prednisone to mitoxantrone and prednisone. Only asymptomatic patients were included in IMPACT (sipuleucel-T). ALSYMPCA (radium-223) required eligible patients to be symptomatic, and required patients to either have been treated with docetaxel or ‘refused’ docetaxel. COU-AA-302 (abiraterone) excluded patients with visceral metastases, while the same patients were included in PREVAIL (enzalutamide). Given these disparities, how can clinicians help patients determine the best option?

Clinicians draw information from multiple domains in their decision-making process. There is the clinical literature – primary sources as well as reviews and practice guidelines. Guidelines developed not only based on evidence of clinical efficacy, but also the potential harms and quality of life (QoL) benefits such as the ASCO/CCO clinical practice guidelines [6], may be more useful to practicing oncologist. Depending on the practice setting, there may be ‘clinical pathways’ or clinical decision support tools [8]. Oncologists may also draw upon previous clinical use of androgen receptor signaling-targeted therapies in chemotherapy-naive metastatic castration-resistant prostate cancer: a call for patient-centered studies

“We currently live in an era of unprecedented choice in the treatment of metastatic castration-resistant prostate cancer; however, to truly improve the quality of care our patients receive, we must improve our collective decision-making process.”

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experiences and familiarity with particular treatment options. Additionally, there may be patient-specific scenarios that lead clinicians to particular decisions (avoiding enzalutamide in patients with a history of seizures, for example). All of these contributing factors play important roles in the treatment decision-making process.

The choice between the AR-targeted therapies abiraterone and enzalutamide presents a special challenge, even for expert clinicians. Clinical efficacy, measured by overall survival, appears comparable between the two drugs in both pre- and post-chemotherapy Phase III clinical trials [1,2,9,10]. Both are administered orally. Differences include the necessary concomitant administration of prednisone with abiraterone (optional for enzalutamide) and differences in types of adverse events (although the overall adverse events rate, for any grade and any grade ≥3 are similar); cardiac events and transaminitis appear to be more common with abiraterone, while falls appear to be more common with enzalutamide, for example.

“One potential paradox within this spectrum of disease burden is that although the cost of therapy may be higher in the lower disease burden patients ... the cost–effectiveness may also be higher.”

A randomized clinical trial directly comparing the two agents (or any of the other approved agents, for that matter) to compare clinical efficacy is impractical for many reasons. However, patient-centered comparative effectiveness studies focusing on QoL benefits and patient-reported outcomes and adverse events (PROs) are both possible and necessary in order to better identify patients who are more likely to obtain clinical benefit (or be harmed) from a particular treatment. Such studies would offer high-level evidence that can provide clinicians and patients with additional data to inform the decision-making process. That patient-reported QoL benefits and PROs be the primary endpoints of such studies is critical, clinicians may underreport incidence and severity of symptoms, and patients report their underlying health status better than clinicians, given the subjective nature of these measures. Tools such as the PRO-CTCAE [11] and multiple QoL measures [12] are available for assessment of these endpoints. Patient-centered studies would enhance physicians’ understanding of the impact of cancer therapies on patients’ lives beyond what is typically reported in registration studies. Factors that impact patient’s QoL that are relatively underevaluated include the impact of costs of monitoring, physician visits and the burden of cost in patients who do versus do not experience clinical benefit from the therapy. Another important facet impacting the cost–effectiveness of therapy is the timing of therapy initiation. The clinical status of chemotherapy-naive CRPC is highly variable, and the registration studies for abiraterone and enzalutamide enrolled patients with a burden of disease that ranged from minimal to extensive. One potential paradox within this spectrum of disease burden is that although the cost of therapy may be higher in the lower disease burden patients (because they receive it longer), the cost–effectiveness may also be higher — as early intervention may be associated with a higher rate or response and the prevention of morbid and costly complications. Although modeling of these questions can be performed from existing datasets, such approaches are impaired from the fact that they are retrospective and were obtained in an international environment, where costs of supportive care and treatment of complications are likely to be highly variable.

The results of such studies should be disseminated to the public in an easily understood format so that patients can truly participate in a shared decision-making process with their physicians [13,14]. We currently live in an era of unprecedented choice in the treatment of mCRPC; however, to truly improve the quality of care our patients receive, we must improve our collective decision-making process.

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Androgen receptor signaling-targeted therapies in chemotherapy-naive mCRPC: a call for patient-centered studies

Editorial


