Sequencing Medical Therapy in Prostate Cancer: Not as Easy as 1-2-3

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With the emergence of several new agents for the treatment of advanced prostate cancer, new questions have arisen regarding the optimal sequence or combination of these agents. As we await the results of ongoing and planned clinical trials to answer some of these questions directly, the decision-making process will rely heavily on considerations of side effects and patient characteristics.

In their article in this issue of ONCOLOGY, Drs. Hurwitz and Petrylak have very effectively reviewed recent progress in the treatment of advanced prostate cancer.[1] Enhanced understanding of the biologic drivers of disease progression and treatment resistance has led to prolific research, new therapeutic discoveries, and the timely approval of new agents. The authors note that currently the proper sequencing of these therapies may depend on consideration of the side effects of therapy, as no definitive comparison of efficacy exists. Choosing a treatment involves assessment of both the biology of the disease (ie, sites of metastasis, rate of disease progression, and response to previous therapy) and the characteristics of the patient (ie, physiologic age, residual effects of previous therapy, comorbidities, and goals of treatment). In considering these factors one must remember the broad demographic features of prostate cancer patients, including that the majority of prostate cancer patients are over 65 years old and that the unique needs of an older cancer population must be a priority as these new therapies are integrated into routine care. Another key factor in determining the appropriate sequencing of these agents is the acknowledgement that we are treating a moving target. With the early, prechemotherapy use of abiraterone acetate, and the likely use of enzalutamide in the future, the biologic behavior of the prostate cancer that emerges from “complete” androgen blockade may be different from that of the historically defined and studied entity of castrate-resistant prostate cancer (CRPC).

In the prechemotherapy setting, there are now several approved agents to include in the discussion of therapeutic sequencing, each with a unique mechanism of action. In addition to abiraterone acetate and sipuleucel-T, the radiopharmaceutical radium-223 is also approved and available. Radium 223-dichloride is an agent that builds on a previous therapy with a more direct and effective mechanism, as do abiraterone acetate and enzalutamide. One must remember that soft-tissue disease is not likely to be treated during the 6-month treatment course of radium-223. While the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) clinical trial data do not suggest a difference in marrow toxicity pre- or postchemotherapy, it will be interesting to see whether this changes in standard practice.[2] In particular, there are only limited data on the early use of radium-223, and tolerance of chemotherapy given post radium-223 is not clearly defined. In the post-docetaxel setting, separate sequencing considerations arise. Additional agents available after chemotherapy are enzalutamide and cabazitaxel, since most patients in the future will be treated with abiraterone acetate prior to chemotherapy. Importantly, Hurwitz and Petrylak point out that the efficacy of cabazitaxel and enzalutamide was established in patients who had not previously received abiraterone acetate, a much more effective hormonal agent than other available hormonal therapies. The magnitude of benefit from these agents, now used later in the disease process, may be tempered by early treatment with abiraterone, or equally potent hormone-blocking agents.[3,4] Given the similar mechanisms of action, it is our general practice to avoid immediate sequencing of enzalutamide and abiraterone acetate in either direction at any time. Indications of a feedback mechanism contributing to an increase in androgen receptor copy number or an induction of testosterone in men treated with either of these agents has led to investigation of abiraterone acetate and enzalutamide in combination; combination therapy with abiraterone and enzalutamide apparently addresses the compensatory mechanisms seen when either agent is used alone.[5] Enzalutamide has proven to be active and well tolerated in the postchemotherapy setting regardless of the site of disease, and practitioners are awaiting results of the completed trial of this drug in the
prechemotherapy setting. In choosing this therapy, the risk of seizure or mechanical falls should be considered, especially in older vulnerable patients. Thus, postchemotherapy decision making will be guided by data on combination therapy and continued consideration of adverse effects. Beyond weighing the efficacy and tolerance of available agents for management of CRPC, the oncology community is also beginning to place more emphasis on the cost of therapy. Some have now started to emphasize the physician’s role in this process, stressing that physicians do need to be cognizant of the cost of these agents.[6] The cost of a course of therapy with sipuleucel-T may be $90,000. This is an expensive therapy, but it is a bundled price for the defined course of treatment. Many of the newer oral agents cost $7,500 to $9,000 a month and their financial impact on patients may vary, as insurance coverage is frequently different for oral as opposed to injectable medications. This monthly cost is in addition to lab tests and office visits required for safety monitoring, yet in keeping with the common $10,000/month range for new oncology agents. The newest approved agent, radium-223, also appears similarly priced in terms of cost per month, but experience with total patient costs of this new therapy is still limited. Thus, prescribers must look beyond efficacy alone and understand treatment influences on a patient's time and quality of life, and the need to address patient navigation through the healthcare system. For uninsured patients, or patients for whom the copayment is too expensive, options such as nonsteroidal anti-androgens or ketoconazole still may be reasonable in some cases. Without direct comparison between agents, cost is yet another consideration in sequencing decisions.

In following the realistic sequencing recommendations of Petrylak and Hurwitz, one must continuously keep in mind patient characteristics that may bolster the decision to choose one particular therapy over another, given the similar efficacy of several of these agents. The side effects and administration of these new agents vary dramatically. As noted, the majority of men with advanced prostate cancer are elderly. In this light, one may consider using a geriatric screening tool to assess treatment tolerance—or at least, in deciding how these drugs should be sequenced, the physician should acknowledge factors including altered pharmacokinetics as patients age; decreased marrow reserve, perhaps requiring colony stimulating factor support; the impact of treatment on the patient's functional status; and the impact of clinical follow-up on caregiver burden.

In conclusion, with the emergence of several new agents for the treatment of advanced prostate cancer, new questions have arisen regarding the optimal sequence or combination of these agents. As we await the results of ongoing and planned clinical trials to answer some of these questions directly, the decision-making process will rely heavily on considerations of side effects and patient characteristics. In prostate cancer, given that the majority of patients are elderly, principles of geriatric oncology predominate when making treatment decisions. Beyond these considerations, it is also clear that our understanding of the response and biologic features of prostate cancer are changing with the use of these effective drugs.

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