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The review article of treatments for castration-resistant prostate cancer (CRPC) by Sartor and Gillessen describes available sequencing data in detail with outlines of each agent.[1] Currently, the efficacy of docetaxel, radium-223, sipuleucel-T, abiraterone, and enzalutamide (this is upcoming) as front-line agents and cabazitaxel, radium-223, abiraterone, and enzalutamide as post-docetaxel agents have been confirmed by phase III randomized controlled trials (RCT). While the development of treatment options should be of great benefit to CRPC patients, physicians may need to pay attention to patient selection for each treatment as these agents have not been compared with one another by head-to-head RCT.

It is important to take into consideration that the eligibility criteria for each RCT were different. For example, the RCTs of radium-223, sipuleucel-T, and abiraterone did not include patients with visceral metastasis. Although these studies used the same primary endpoint, i.e., overall survival (OS), there were huge differences in OS even among control groups. Furthermore, the anti-tumor mechanisms of these agents are different. Docetaxel/cabazitaxel, radium-223,

and sipuleucel-T may be classified as chemotherapy, radiotherapy, and immunotherapy, respectively. As CRPC remains androgen receptor (AR)-dependent, abiraterone and enzalutamide target androgen/AR signaling and can be classified as hormone therapy. Both docetaxel and cabazitaxel are microtubular polymerization inhibitors. Nevertheless, cabazitaxel exerts its anti-tumor effect on post-docetaxel CRPC without obvious cross-resistance. Abiraterone is just an inhibitor of androgen biosynthesis. As it inhibits CYP17A1 (both 17α-hydroxylase and 17,20-lyase), addition of prednisone is needed to compensate for the decrease in cortisol level.[2] On the other hand, enzalutamide binds to the AR with greater relative affinity than the clinically used anti-androgen agent, bicalutamide, reduces the efficiency of its nuclear translocation, and impairs both DNA binding to androgen response elements and recruitment of co-activators.[3] In terms of the mechanism, although there may be cross-resistance between these two hormonal therapies, enzalutamide seems to be superior to abiraterone. Actually, prostate-specific antigen response to sequential therapy from abiraterone to enzalutamide was much better than that

from enzalutamide to abiraterone. The another advantage of enzalutamide is that the RCT was terminated at the time of interim analysis due to its higher than expected efficacy. However, mechanisms of enzalutamide resistance in prostate cancer have been reported recently.

As the anti-tumor effect of each single agent may be limited and there may be cross-resistance among agents, it is important to investigate better sequential treatment regimens. Unfortunately, few treatment sequence data are available, especially with more than two sequences or sequential treatment after radium-223 or sipuleucel-T. However, the review article by Sartor and Gillessen clearly shows the current available treatment sequencing data and helps physicians in practice to in treatment planning for CRPC. As the OS of advanced colorectal cancer patients improved with the availability of key agents in the course of treatment,[4] the OS of CRPC patients may similarly be maximized with the availability of key agents. Planned sequential therapies such as those in kidney cancer may establish novel treatment strategies. Additional studies are needed to clarify the optimal treatment sequence as well as head-to-head

studies.

Competing interests

The authors declare no competing interests associated with the content of this manuscript.

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