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Platinum Priority – Editorial

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Sequencing Systemic Therapies in Advanced Prostate Cancer: Spoiled for Choice But Not for Evidence

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Since 2004, six new life-prolonging systemic therapies have been introduced into clinical practice for patients with metastatic castration-resistant prostate cancer (mCRPC) (Table 1). Five of these have been introduced since 2010 and were developed almost simultaneously and largely in isolation. Thus we have no formal and only limited informal evidence to support the use of these new therapies in sequence with one another, so doctors and their patients must make decisions about treatment sequencing in the absence of significant evidence. In this month's issue of *European Urology*, Pezaro et al. present important data from a retrospective analysis of patients who had received cabazitaxel as second-line chemotherapy having previously failed new-generation hormone therapy [1]. These data are important because they justify the use of this potentially toxic agent in a therapeutic era that has changed dramatically since the pivotal TROPIC trial was conducted and support a sequence of therapy commonly used in modern oncology practice.

1. Evidence-based sequencing

Six therapies provide 720 different possible sequences, presenting no real opportunity to establish level 1 evidence for optimal sequencing. Abiraterone, enzalutamide, or cabazitaxel are each effective if given after the failure of prior docetaxel, providing level 1 evidence for these two-drug sequences [2–4]. In addition, enzalutamide and abiraterone are effective when given to patients who have not previously received chemotherapy, from which it is inferred that either of these drugs followed by docetaxel will be an active sequence because many patients had received subsequent docetaxel prior to the data cuts in these trials [5,6]. However, the true activity of subsequent docetaxel is not categorically proven, and we have no direct data comparing the sequence docetaxel then hormonal therapy with hormonal therapy then docetaxel. Subgroup analysis supports the use of radium 223 after docetaxel, although this analysis was insufficient to demonstrate statistical significance within the subgroup [7]. Little is known about the activity of subsequent therapies in patients who have received prior sipuleucel-T.

2. Use the "most active agent" first

In most cancers this form of decision making is guided by direct comparative trials demonstrating the superiority of one agent compared with another. In mCRPC we have clear evidence to demonstrate that docetaxel should be used in preference to mitoxantrone, and similarly that cabazitaxel should be used in preference to mitoxantrone, but there are no head-to-head comparisons between any of the six agents in common use today. Thus conclusions about relative activity may only be drawn from indirect comparisons between trials that were conducted in distinct patient populations using controls of varying activity. Therefore, the "most active agent" remains poorly defined.

3. Use the "least toxic" first

Faced with a choice of agents with little else to separate one from another, many patients and doctors choose the treatment with the least likelihood of toxicity. This is entirely reasonable when there is no likelihood of using

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Table 1 – Systemic therapies with proven survival advantage in metastatic castration-resistant prostate cancer

Therapy	Study
Docetaxel	Tannock et al. [10]
Cabazitaxel	de Bono et al. [4]
Abiraterone	de Bono et al., Ryan et al. [2,5]
Sipuleucel-T	Kantoff et al. [11]
Enzalutamide	Scher et al., Medivation [3,6]
Radium 223	Parker et al. [7]

these agents in sequence. However, where there is, there may be some logic in choosing the more arduous, such as chemotherapy, early rather than deferring to a time when the patient's performance status and tolerance may be diminished. In the case of mCRPC, although it is clear that docetaxel and cabazitaxel will have a significant burden of toxicity in some patients, enzalutamide, abiraterone, radium 223, and sipuleucel-T all have generally good toxicity profiles, making it difficult to choose between them on this basis.

4. Rational sequencing

It is rational to choose an agent that is not expected to have cross-resistance with previous therapy in preference to one that may. Relatively little is known about cross-resistance between therapies used to treat mCRPC. Although it is reasonable to expect cross-resistance between treatments with similar mechanisms of action, one of the few pieces of level 1 evidence we have is that cabazitaxel retains activity in patients who have previously received the related taxane docetaxel [4]. The expected cross-resistance between enzalutamide and abiraterone has not been formally explored, but what data we do have would support the assertion that there is at least a degree of cross-resistance, albeit there may be some patients who benefit from one where the other has previously failed [8]. In this issue, Pezaro et al. present retrospective data strongly suggesting that the activity of cabazitaxel seen in the era before abiraterone and enzalutamide (when the TROPIC trial was conducted) is retained in patients who have received either or both of these drugs as well as prior docetaxel [1]. Thus it seems there is no clinically significant cross-resistance between the new hormone therapies and cabazitaxel.

5. Is sequential therapy feasible?

One consequence of recent progress is that patients will now spend a greater proportion of their survival time on therapy than previously. In mCRPC, the total duration of therapy, if all are given in sequence, may be >3 yr. A recent estimate of median survival time with advanced prostate cancer was 42 mo from diagnosis [9], so it is likely that many patients will not survive long enough to receive all of these therapies in sequence after castration has failed. Those that do will have to start therapy early and remain on therapy for much of their remaining life. The solution to this problem may ultimately lie in combination therapy. However, one inevitable consequence of combining continuous oral therapies is that patients will spend greater periods of time on combination than they would have done on either agent had it been given alone, thus increasing the potential for cumulative, as well as additive, toxicity.

6. Conclusions

It is clear that we will never have a complete evidence base to guide sequential therapy in mCRPC. Nonetheless, while curative treatment remains evasive, there will always be the need to use one palliative therapy after another, and so it will be necessary to use what evidence we do have to help define acceptable and active therapy sequences. The data of Pezaro et al. go some way to reassuring us that one recently adopted sequence of therapy, namely docetaxel followed by hormone therapy and then cabazitaxel, is valid.

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