Upon failure of first-line ADT, should second-line hormonal manipulation without survival benefit data still be used?∗

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1. The merits of vintage second-line hormonal manipulation

The androgen receptor (AR) is an important target in castration-resistant prostate cancer (CRPC) as the progression of the disease is still largely dependent on androgen signalling. The recommendation to continue with androgen deprivation therapy is reasonable, as cessation and restoration of testosterone levels may have an adverse impact on survival. Antiandrogen withdrawal may also be attempted in all patients, as some patients are long-term responders. In one study, 19% of patients showed no signs of progression 1 year after antiandrogen withdrawal.1 Bissada et al. reported on a case in which the duration of response was for more than 3 years after antiandrogen withdrawal.2

First-generation antiandrogens such as flutamide, bicalutamide, and nilutamide have shown to be effective against prostate cancer relapse after failure of first-line androgen deprivation therapy (ADT). Studies have indicated PSA responses of 14–48% with bicalutamide and up to 50% with nilutamide.3–9 Among patients with minimal or no bone scan involvement and low baseline prostate-specific antigen (PSA) who were started on high-dose ketoconazole, PSA levels decreased by at least 75%.10 But high doses of ketoconazole have been linked to clinically significant toxicity. Therefore, as shown in a small, retrospective study, low-dose ketoconazole may be an option for patients with biochemical failure who have failed ADT.11 With second-line hormonal manipulation using ketoconazole, response rates of between 11% and 13% were reported. There was also a marked palliation of pain in a subset of patients. Low-dose ketoconazole appears to be well tolerated, is relatively low cost, and easy to administer. For second-line hormonal manipulation with prednisone, approximately 1 in 3 patients had a PSA decrease of > 50%. There may be a dose-response relationship between glucocorticoid dose and PSA decline. Recent data has highlighted a significant benefit of dexamethasone over prednisone in the palliative setting.12

According to international guidelines, second-line hormonal manipulation continued to elicit a biochemical response in CRPC patients without signs of distant metastases.13–15 PSA responses of 14–75% have been reported with these agents, but duration of response was generally less than 6 months, without evidence of survival benefit. Another limitation of this manipulation is its side effect profile. Nevertheless, second-line hormonal therapy continues to be a viable option in limited resource environments. According to the 2015 St Gallen Advances Prostate Cancer Consensus, novel agents such as abiraterone and enzalutamide may be approved but will be unavailable for many patients, especially in the Asia Pacific region, due to cost.16

2. The importance of early initiation of novel agents instead of vintage second-line hormonal manipulation

In recent large, phase III international trials, clear survival benefit has been observed with the use of these novel agents in patients with metastatic castration-resistant prostate cancer (mCRPC) who failed first-line ADT. Before the emergence of the next generation agents these patients were treated with vintage secondary hormones, which include mainly first-generation antiandrogens such as bicalutamide and flutamide, and old secondary hormonal agents such as oestrogens, ketoconazole and corticosteroids.

In the COU-302 clinical trial, the use of abiraterone plus prednisone in chemo-naïve patients who have failed first-line ADT had significantly longer overall survival (OS) than patients who had prednisone alone.17 Abiraterone’s treatment effect was more pronounced when adjusting for prednisone patients who received subsequent abiraterone. Abiraterone also doubled the time to radiographic progression-free survival (rPFS) and there was improvement in all clinical end points including time to opiate use.18
In the Phase III PREVAIL study, the use of enzalutamide after progression on ADT significantly prolonged OS and rPFS. Enzalutamide also delayed median time to chemotherapy by 17 months.\textsuperscript{19} Compared to second-line hormonal manipulation, the early use of novel agents provides significant survival and clinical benefits whilst maintaining quality of life.

Addressing a clinically relevant question, the addition of enzalutamide compared to bicalutamide when patients are progressing on luteinising hormone-releasing hormone (LHRH) therapy alone was recently demonstrated to prolong PFS, time to PSA progression, and time on treatment (TERRAIN trial).\textsuperscript{20} Adverse events observed were consistent with the known safety profile of enzalutamide.

Practice should be based on evidence rather than tradition. Evidence for novel agents is based on large phase III studies, with proven survival and quality of life benefits. Data for vintage secondary hormones are based on small short term phase II studies, with proven benefits on PSA progression only. Therefore, delay in the initiation of the most effective agents may be detrimental.

Both the COU-302 and PREVAIL trials have demonstrated that early initiation of novel agents are associated with improved survival. Although there is no strong evidence to support the use of second-line traditional secondary hormone, there is no strong evidence to exclude their use either.

The 2015 St Gallen Advanced Prostate Cancer Consensus recommends opting for abiraterone and enzalutamide if they are available. Only when these agents are unavailable, should vintage second-line hormonal manipulation be considered, as the use of these traditional antiandrogens first may increase the risk of emergence of resistant tumour clones. Where possible, their use should be limited to selected patients, and avoided in patients with progressive disease.\textsuperscript{16}

3. Summary

The opportunity to change the natural history of prostate cancer is upon us. One of the most common molecular aberrations in the development of castrate resistance is changes in androgen receptor signalling, especially amplification.\textsuperscript{21} Furthermore, changes in message, enhancer and splice variants at the epigenetic and transcription levels are emerging as additional mechanisms for enhanced prostate cancer cell survival. With the arrival of more powerful androgen synthesis and/or receptor pathway inhibitors, delay in progression leading to improvements in overall survival have been demonstrated in early clinical studies. Significant questions remain regarding correlation between this new understanding of molecular pathology and these new targeted strategies; not only in terms of response but more importantly in terms of mechanisms of de novo as well as acquired resistance. Investigators can envisage studies investigating the potential for intermittent compared to continuous therapy; dose modifications according to molecular biomarker correlations and finally the potential for sequential targeted therapy strategies according to the evolution of molecular changes. Close collaboration between academic clinicians, pharma and regulatory authorities is needed to maximise the cost-effectiveness of this rapidly evolving field.

Conflict of interest

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References


