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PROSTATE CANCER

Enzalutamide—differential cross resistance with taxanes

The past few years have seen a revolution in the treatment of metastatic castration-resistant prostate cancer, with the introduction of new therapies targetting the androgen receptor (AR), such as enzalutamide and abiraterone. Although originally used as a second-line treatment option after docetaxel, more recent data have shown that enzalutamide is effective in chemotherapy-naive patients, with both drugs providing new first-line treatment options for some men with prostate cancer.

However, these new options have also introduced a novel challenge—treatment sequencing. Some studies have suggested that the prior use of abiraterone can cause cross resistance to docetaxel in men whose tumours progress and go on to need chemotherapy.

In a paper published in *European Urology*, van Soest *et al.* report for the first time *in vivo* cross resistance between enzalutamide and docetaxel, but not between enzalutamide and cabazitaxel.

Studies were performed using patient-derived enzalutamide-naive PC346C and enzalutamide-resistant PC346Enza tumours in castrate male mice. Docetaxel treatment resulted in a tumour response in mice harbouring enzalutamide-naive tumours (mean tumour volume change from baseline [TVC] –78%), but not in those mice bearing enzalutamide-resistant tumours (TVC 364%), suggesting *in vivo* resistance to docetaxel in tumours already treated with enzalutamide. This effect was also observed in terms of serum PSA response to docetaxel treatment, with reduced serum PSA levels in docetaxel-treated mice harbouring PC346C tumours, but not in those with the enzaluatmide-resistant PC346Enza tumours.

Interestingly, this was not the case in mice treated with cabazitaxel, which did not seem to be resistant to treatment regardless of prior enzalutamide status. Mice with PC346C tumours and PC346Enza tumours responded similarly to cabazitaxel therapy, with a TVC of –70% in PC346Enza mice and an associated PSA response.

Investigation of AR expression showed that it was similar between treatment groups but that docetaxel inhibited AR nuclear translocation and the AR target gene *PSA* in PC346C tumours, but not in those resistant to enzalutamide. This effect was also oberved with cabazitaxel; however, cabazitaxel displayed stronger antiproliferative effects that docetaxel, determined via *Ki67* expression.

The results suggest that the effects of cabazitaxel are less dependent on the AR pathway than those of docetaxel, possibly owing to their differential ability to suppress microtubule dynamics. The data provide a rationale for the potential use of cabazitaxel in men whose cancers progress despite enzalutamide treatment.

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Original article van Soest, R. J. *et al.* Targeting the androgen receptor confers *in vivo* cross-resistance between enzalutamide and docetaxel, but not cabazitaxel, in castration-resistant prostate cancer. *Eur. Urol.* doi:10.1016/j.eururo.2014.11.033