PROSTATE CANCER

Niclosamide jumps the hurdle of enzalutamide resistance

Niclosamide, a drug previously approved by the FDA for the treatment of helminth infections, could be used to treat patients with advanced prostate cancer that has become resistant to enzalutamide, according to a recent study published in *Clinical Cancer Research*.

The launch of next-generation antiandrogen enzalutamide marked a change in the tide of prostate-cancer care, offering an effective second-line therapy for patients with castration-resistant disease in whom docetaxel therapy has failed. However, enzalutamide resistance is inevitable in some patients, drastically reducing their treatment options.

Mechanisms responsible for resistance to the drug include the existence of alternative mRNA splice variants of the androgen receptor (AR), which lack the ligand binding domain, but induce ligand-independent binding of androgen-response-element-driven genes. These variants cause constitutive activation of AR, even in circumstances of effective androgen blockade.

One variant in particular, AR-V7, has been linked to enzalutamide resistance, and was the focus of this new study by Liu *et al.* The researchers showed that AR-V7 was present in a number of prostate cancer cell lines and that it was able to activate the PSA promoter in LNCaP and PC3 cells in the absence of androgen.

The researchers identified niclosamide as an inhibitor of AR-V7 by screening the Prestwick Chemical Library (which contains over 1,100 molecules and approved drugs) in HEK293 cells stably transfected with the splice variant. Niclosamide acts by reducing AR-V7 transcriptional activity and reducing recruitment of AR-V7 to the PSA promoter. Furthermore, niclosamide inhibited prostate cancer cell

Mikhail Kondrashov/Stock/Thinkstock

growth and induced apoptosis of prostate cancer cells, with little effect on normal epithelial cells.

The team then investigated whether niclosamide affected enzalutamide-resistant prostate cancer cells by generating their own enzalutamide-resistant cell line, which expressed higher levels of AR-variant mRNAs than nonresistant parental cells. Treatment of the resistant cell line with niclosamide resulted in a dose-dependent reduction in cell growth, even in the presence of enzalutamide resistance.

Finally, Liu and colleagues investigated the effect of treating prostate cancer cells with both enzalutamide and niclosamide. They found that cotreatment caused synergistic inhibition in a time-dependent manner in both enzalutamide resistant and nonresistant cells.

Enzalutamide resistance has proven to be a real problem in patients with castration-resistant prostate cancer—could niclosamide be the solution?

Annette Fenner

Original article Liu, C. *et al.* Niclosamide inhibits androgen receptor variants expression and overcomes enzalutamide resistance in castration-resistant prostate cancer. *Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-13-32963296