Targeting androgen receptor variants by niclosamide overcoming resistance to abiraterone and enzalutamide

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Background. Use of enzalutamide and abiraterone has improved treatment of advanced prostate cancer. However, development of resistance to these agents frequently occurs. Androgen receptor variants, particularly AR-V7, have been shown to drive resistance to abiraterone and enzalutamide. This study aimed to test whether niclosamide can overcome resistance and improve therapies by targeting androgen receptor variants.

Methods. Resistant prostate cancer cells to enzalutamide and abiraterone were generated by continuous culturing the cells in media containing increasing doses of either enzalutamide or abiraterone. Drug screening was conducted using luciferase activity assay to determine the activity of AR-V7 after treatment with the compounds in the Prestwick Chemical Library, which contains about 1120 FDA-approved drugs. The effects of the identified inhibitors on AR-V7 activity and abiraterone/enzalutamide sensitivity were characterized in CRPC and enzalutamide/abiraterone resistant prostate cancer cells *in vitro* and *in vivo*.

Results. Resistant prostate cancer cells to enzalutamide and abiraterone were generated, respectively. Both resistance cells express high levels of androgen receptor variants including AR-V7. Drug screening identified niclosamide, an anthelmintic agent approved by FDA for the treatment of tapeworm infections, as a potent AR-V7 inhibitor in prostate cancer cells. Niclosamide significantly decreased AR-V7 protein expression by protein degradation through a proteasome dependent pathway. Niclosamide also inhibited AR-V7 transcription activity and reduced the recruitment of AR-V7 to the PSA promoter. Niclosamide inhibited resistant prostate cancer cell growth in vitro and tumor growth in vivo. Furthermore, combination of niclosamide with either enzalutamide or abiraterone resulted in significantly inhibition of enzalutamide/abiraterone-resistant tumor growth. These results suggest that niclosamide enhances abiraterone/enzalutamide therapy and overcomes resistance to abiraterone/enzalutamide in castration resistant prostate cancer cells. Based on these preclinical studies, combination of niclosamide with abiraterone/enzalutamide trials are currently underway.

Conclusions. Our findings offer preclinical validation of niclosamide as a promising inhibitor of androgen receptor variants to treat, either alone or in combination with current antiandrogen therapies, advanced prostate cancer patients, especially those resistant to abiraterone or enzalutamide.

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