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ErbB2 Signaling Increases Androgen Receptor Expression in Abiraterone-Resistant Prostate Cancer

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Abstract

Purpose: ErbB2 signaling appears to be increased and may enhance AR activity in a subset of CRPC, but agents targeting ErbB2 have not been effective. This study was undertaken to assess ErbB2 activity in abiraterone-resistant prostate cancer (PCa), and determine whether it may contribute to androgen receptor (AR) signaling in these tumors. Experimental Design: AR activity and ErbB2 signaling were examined in the radical prostatectomy specimens from a neoadjuvant clinical trial of leuprolide plus abiraterone, and in the specimens from abiraterone-resistant CRPC xenograft models. The effect of ErbB2 signaling on AR activity was determined in two CRPC cell lines. Moreover, the effect of combination treatment with abiraterone and an ErbB2 inhibitor was assessed in a CRPC xenograft model. Results: We found that ErbB2 signaling was elevated in residual tumor following abiraterone treatment in a subset of patients, and was associated with higher nuclear AR expression. In xenograft models, we similarly demonstrated that ErbB2 signaling was increased and associated with AR reactivation in abiraterone-resistant tumors, while *ERBB2* message level was not changed. Mechanistically, we show that ErbB2 signaling and subsequent activation of the PI3K/AKT signaling stabilizes AR protein. Inhibitors targeting ErbB2/PI3K/AKT pathway disrupt AR transcriptional activity. Furthermore, concomitantly treating CRPC xenograft with abiraterone and an ErbB2 inhibitor, lapatinib, blocked AR reactivation and suppressed tumor progression. Conclusions: ErbB2 signaling is elevated in a subset of abiraterone-resistant prostate cancer patients and stabilizes AR protein. Combination therapy with abiraterone and ErbB2 antagonists may be effective for treating the subset of CRPC with elevated ErbB2 activity.

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