

Resistance Mechanisms in Prostate Cancer after Neoadjuvant Intense Androgen Deprivation Therapy

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ABSTRACT

Background: In a randomized phase II neoadjuvant clinical trial, 58 patients with localized, intermediate to high risk prostatic adenocarcinoma (PCa) received intense androgen deprivation therapy (IADT) combining leuprolide with abiraterone acetate prior to surgery. In this study, we assessed early IADT resistance mechanisms in residual tumors in the radical prostatectomy specimens, with a particular interest in neuroendocrine differentiation and immune modulation after IADT.

Methods: Residual tumor cells and paired benign glands were laser microdissected from 19 trial cases, with two distant tumor foci microdissected from 14 cases. We examined tumor genetic alterations using whole exome sequencing and gene expression profiles using Affymetrix microarray. Potential resistance mechanisms were further examined using immunohistochemical and in situ RNA detection assay for total AR, AR-V7, pS81AR, ERG, NKX3.1, Rb, p53, PTEN, pAkt, pS6, Her3, pHer3, SOX9, LEF1, synaptophysin, chromogranin, Ki67, PD-1, and PD-L1, in 50 trial cases and 50 untreated control cases.

Results: The treated tumors showed remarkable diversity of resistance mechanisms, including foci-specific genetic alterations such as tumor suppressor losses, activation mutations in oncogenes, and foci-specific dysregulation of gene expression and pathway activation. Common resistance mechanisms included partially restored AR transcriptional activity, upregulation of SOX9, and subsequent WNT pathway activation. There was no significant increase in neuroendocrine differentiation or PD-L1 expression in PCa after neoadjuvant IADT.

Conclusions: Our study suggests that pre-existing tumor subclones may survive and expand under selection pressure in the IADT setting and serve as early resistance mechanisms. Early IADT resistance may be overcome by further blockade of AR signaling, inhibition of SOX9-WNT pathway, and precision combinational therapies, but unlikely through addition of immune checkpoint inhibitor.

Reference:

1. Taplin ME, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. *J Clin Oncol.* 2014 32(33):3705-15

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