Prostate cancer neoadjuvant intensive androgen deprivation therapy selects for tumor foci with diverse oncogenic alterations

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Background:
Based on the hypothesis that early use of androgen deprivation therapy (ADT) may improve outcomes, we conducted a phase 2 trial of neoadjuvant leuprolide for 24 weeks in combination with abiraterone acetate and prednisone (referred to subsequently as leuprolide plus abiraterone) for 12 or 24 weeks prior to radical prostatectomy (RP). As reported recently, we confirmed that the addition of abiraterone further markedly reduced intraprostatic androgen levels and appeared to improve responses relative to historical controls using single agent GnRH agonists. Nonetheless, residual prostate cancer (PCa) was found in the majority of patients, with only a small number of patients demonstrating complete pathological responses. Moreover, substantial nuclear and cytoplasmic AR expression was detected by immunohistochemistry in most cases, suggesting that AR activity still may persist and contribute to residual disease.

Methods:
Residual PCa foci in RPs from 18 men treated with neoadjuvant intensive androgen deprivation therapy (leuprolide, abiraterone acetate, prednisone) were microdissected and analyzed for resistance mechanisms.

Results:
Transcriptome profiling showed reduced but persistent androgen receptor (AR) activity in residual tumors, with no increase in neuroendocrine differentiation. Unexpectedly, proliferation was negatively correlated with AR activity, but positively correlated with decreased *RB1* expression, and whole exome sequencing (WES) further showed enrichment for *RB1* genomic loss. In 14 cases where 2 tumor foci were microdissected, WES confirmed a common origin, but identified multiple oncogenic alterations unique to one focus.

Conclusions:
Primary PCa can have extensive microheterogeneity, but its contribution to the later emergence of metastatic castration-resistant PCa (mCRPC) has not been clear. These findings indicate that therapy selects for subclonal genomic alterations, including *RB1* loss, which may be the origin for metastatic castration-resistant PCa, and are selected for by neoadjuvant intense androgen deprivation therapy. This study indicates that subclonal *RB1* loss may be more common than previously appreciated in intermediate to high risk primary PCa, and may be an early event, independent of neuroendocrine differentiation, in the development of mCRPC. Comprehensive molecular analyses of primary PCa may detect aggressive subclones, and possibly inform on adjuvant strategies to prevent the emergence of mCRPC.

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