Neoadjuvant therapy for localized prostate cancer: Examining mechanism of action and efficacy within the tumor.

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Abstract

OBJECTIVES: Efforts to improve the clinical outcome for patients with localized high-risk prostate cancer have led to the development of neoadjuvant systemic therapies. We review the different modalities of neoadjuvant therapies for localized prostate cancer and highlight emerging treatment approaches including immunotherapy and targeted therapy.

METHODS: We performed a PubMed search of clinical trials evaluating preoperative systemic therapies for treating high-risk prostate cancer published after 2000, and those studies with the highest clinical relevance to current treatment approaches were selected for review. The database at clinicaltrials.gov was queried for neoadjuvant studies in high-risk prostate cancer, and those evaluating novel targeted therapies and immunotherapies are spotlighted here.

Neoadjuvant chemotherapy has become standard of care for treating some malignancies, including breast and bladder cancers. In prostate cancer, preoperative hormonal therapy or chemotherapy has failed to demonstrate improvements in overall survival. Nevertheless, the emergence of novel treatment modalities such as targeted small molecules and immunotherapy has spawned neoadjuvant clinical trials that provide a unique vantage from which to study mechanism of action and biological potency. Tissue-based biomarkers are being developed to elucidate the biological efficacy of these treatments. With targeted therapy, these can include phospho-proteomic signatures of target pathway activation and deactivation. With immunotherapies, including sipuleucel-T and ipilimumab, recruitment of immune cells to the tumor microenvironment can also be used as robust markers of a biological effect. Such studies can provide insight not only into mechanism of action for these therapies but can also provide paths forward to improving clinical efficacy like with rationally designed combinations and dose selection.

RESULTS: Neoadjuvant chemotherapy has become standard of care for treating some malignancies, including breast and bladder cancers. In prostate cancer, preoperative hormonal therapy or chemotherapy has failed to demonstrate improvements in overall survival. Nevertheless, the emergence of novel treatment modalities such as targeted small molecules and immunotherapy has spawned neoadjuvant clinical trials that provide a unique vantage from which to study mechanism of action and biological potency. Tissue-based biomarkers are being developed to elucidate the biological efficacy of these treatments. With targeted therapy, these can include phospho-proteomic signatures of target pathway activation and deactivation. With immunotherapies, including sipuleucel-T and ipilimumab, recruitment of immune cells to the tumor microenvironment can also be used as robust markers of a biological effect. Such studies can provide insight not only into mechanism of action for these therapies but can also provide paths forward to improving clinical efficacy like with rationally designed combinations and dose selection.

CONCLUSIONS: The use of neoadjuvant androgen-deprivation therapy and chemotherapy either singly or in combination before radical prostatectomy is generally safe and feasible while reducing prostate volume and tumor burden. However, pathologic complete response rates are low and no long-term survival benefit has been observed with the addition of neoadjuvant therapies over surgery alone at present, and therefore preoperative therapy is not the current standard of care in prostate cancer treatment.

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