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Targeting Metastatic Hormone Sensitive Prostate Cancer: Chemohormonal Therapy and New Combinatorial Approaches.

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PURPOSE: Androgen deprivation therapy alone has been the standard of care for metastatic hormone sensitive prostate cancer for the last 75 years. This review focuses on recent trials and mechanisms which highlight the new paradigm of combining androgen deprivation therapy with other agents, changing the treatment of patients with prostate cancer who have advanced disease.

MATERIALS AND METHODS: We searched the peer reviewed literature on the PubMed® and Web of Science® databases through January 2018 using the key words, "metastatic hormone sensitive prostate cancer," "metastatic castration sensitive prostate cancer," "docetaxel," "abiraterone" and "senescence in cancer." ClinicalTrials.gov was queried for ongoing studies. Relevant data recently presented at major urology and medical oncology meetings were also evaluated.

RESULTS: Recently published, phase III trials using androgen deprivation therapy combinations for metastatic hormone sensitive prostate cancer can be broadly grouped into chemohormonal studies (docetaxel) or trials of androgen signaling inhibitors. The CHARTED (Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) and STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) studies showed a survival advantage when combining androgen deprivation therapy with chemotherapy, as well as increased time to progression to castration resistant status. The abiraterone arm of the STAMPEDE and LATITUDE trials, which analyzed combining androgen deprivation therapy with abiraterone, revealed improved overall and progression-free survival. Androgen deprivation therapy generates a number of phenotypes in resistant cancer cells, including quiescence, autophagy and cellular senescence. Senescent cells represent a metabolic target for synergistic lethality with drugs such as metformin. Ongoing trials are under way to examine the effect of combining newer antiandrogens and novel drugs with androgen deprivation therapy in patients with metastatic hormone sensitive prostate cancer.

CONCLUSIONS: Combination therapy has evolved as the standard of care for metastatic hormone

sensitive prostate cancer. The ideal combination is tailored to patients after individualized counseling taking into account general health and comorbid illness status.

KEYWORDS: antineoplastic agents; castration-resistant; cellular senescence; drug therapy, combination; neoplasm metastasis; prostatic neoplasms

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