Newly Diagnosed Metastatic Prostate Cancer: Has the Paradigm Changed?

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KEYWORDS

• Prostate cancer (PCa) • Hormone-sensitive prostate cancer (HSPC)
• Androgen deprivation therapy (ADT) • Docetaxel • Androgen axis inhibitors

KEY POINTS

- Median overall survival is almost 4 times the failure-free survival and metastatic castration-resistant prostate cancer (CRPC) makes up most of the survival time in patients with metastatic prostate cancer. Three major phase III studies combining ADT with docetaxel in patients with newly diagnosed metastatic prostate cancer have been recently reported.
- The GETUG-AFU 15 trial failed to show a survival advantage for chemohormonal therapy over ADT alone, although progression-free survival (clinical and biochemical) and prostate-specific antigen control were improved.
- The role of surgery and newer androgen receptor pathway inhibitors in metastatic hormone-sensitive prostate cancer is currently being studied.
- Early chemohormonal therapy for hormone-sensitive metastatic prostate cancer leads to improved overall survival and should be used for good performance patients with moderate and high-volume metastatic disease.

INTRODUCTION

Metastatic prostate cancer (mPCa) carries a dismal 5-year survival rate of 29.3%.[1] This is in stark contrast to the nearly 100% 5-year survival for low-volume organ-confined disease. The conventional treatment of PCa has been androgen deprivation therapy (ADT) ever since the landmark discovery of androgen ablation for metastatic PCa by Charles Huggins and Clarence Hodges in 1941.[2] In a retrospective review from the National Cancer Center, the median time for progression to metastatic castration-resistant PCa (mCRPC) was found to be 13.1 months and 19.3 months in patients with and without radiologic evidence of metastasis at initiation of ADT, respectively.[3] A systematic review of 12 studies including 71,179 patients found that 10% to 20% of patients with

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mPCa develop mCRPC within 5 years of follow-up.[4]

The survival of PCa in metastatic patients is being more clearly defined and has changed in the modern era. James and colleagues,[5] reported a median failure-free survival (FFS) of 11 months (2-year FFS of 29%) for patients with newly diagnosed metastatic PCa enrolled in the recent Systemic Therapy in Advancing or Metastatic PCa: Evaluation of Drug Efficacy (STAMPEDE) trial. The median overall survival (OS) was 42 months (2-year OS was 72%) in this same cohort. The finding that median OS is almost 4 times the median FFS demonstrates that the mCRPC now makes up most of the survival time rather than being a short terminal phase with limited treatment options. Furthermore, in the same study, it was observed that the median time to the next therapy was 20 months for the control arm and 15.4 months for the experimental arm, emphasizing that important time is lost in waiting for CRPC transition. Median OS times in the Southwest Oncology Group (SWOG) trials cited by Tangen and colleagues[6] ranged from 32 months in the oldest trial to 49 months in the more recent one, demonstrating improved survival in more modern studies similar to the results reported in STAMPEDE.[7]

Metastatic hormone-sensitive PCa (mHSPC) is a heterogeneous disease that consists of both androgen receptor (AR)-positive and AR-negative cells. ADT eventually selects a clonal population that is capable of surviving without AR-mediated signaling.[8] The mechanisms of overcoming androgen loss during CRPC transition include autocrine androgen production, amplification of AR protein and mechanisms that bypass the AR, such as coactivators and trans activators. Some of the most important of these biologically heterogeneous mechanisms involve cancer stem cells, receptor tyrosine kinases, and neuroendocrine differentiation (NE). Cells that have a “stemlike” phenotype are potentially resistant to ADT and can differentiate into androgen-independent cells.[9,10] The activation of the PI3/Akt tyrosine kinase signaling by deletion, mutation, and methylation silencing of PTEN tumor suppressor gene function is thought to be caused by selective pressure caused by ADT.[11–13] NE differentiation also occurs in an adenocarcinoma prostate-specific antigen (PSA)-secreting environment under the selection pressure of ADT. These cells effectively progress to CRPC through the production of neurosecretory peptides in potentially up to 25% of advanced cancers.[11,12] AR gene amplification is another important mechanism by which PCa cells acquire resistance to conventional ADT and these cells are a target for second-line hormonal therapy[14,15] Thus, CRPC is now known to be the consequence of selective pressure exerted by ADT on mHSPC, which induces clonal selection and the growth of androgen-independent clones.[16–21]

Docetaxel was initially approved for the treatment of metastatic CRPC in 2004 based on 2 separate studies that for the first time confirmed a survival benefit in that setting.[22,23] Despite the small increase in OS (2.4 months in TAX 327 and 1.9 months in SWOG 99–16, respectively), it was approved for the treatment and paved the way to subsequent studies that saw an increasing number of newer agents for CRPC management.[24] Subsequently, combining docetaxel with ADT in the hormone-sensitive setting emerged as an appealing strategy to delay development of CRPC and prolong survival. The rationale behind this approach was some degree of resistance to ADT is already present at the time of diagnosis, a phenomenon that is thought to be proportional to the tumor burden. Early chemotherapy could potentially eradicate the hormone-resistant subpopulation, thus prolonging the time to CRPC transition. In support of this hypothesis, simultaneous castration and treatment with paclitaxel in mouse models was found to be superior to sequential administration.[25] Engrafted mice receiving chemohormonal therapy showed delayed median time to progression compared with those treated with sequential castration and chemotherapy. The explanation for the synergistic activity of taxanes and ADT was provided by Zhu and colleagues in 2010,[26] when they showed that taxanes blocked the microtubule-mediated AR nuclear localization by androgens, thus effectively blocking AR-signaling pathways. In addition to the potential synergistic effect of taxanes to ADT, a proportion of patients might be too frail at the time of development of CRPC and thus might miss the opportunity to receive treatment with a potent chemotherapeutic agent.[27]

Discussion

To date, 3 large-scale phase III studies have examined the role of docetaxel in HSPC:

- *GETUG-AFU 15* (Groupe d’Etude des Tumeurs Uro-Genital and Association Française d’Urologie)
- *CHAARTED* (Chemo-Hormonal therapy vs Androgen Ablation Randomized Trial for Extensive Disease in PCa)
- *STAMPEDE* (Systemic Therapy in Advancing or Metastatic PCa: Evaluation of Drug Efficacy)