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Anticancer Activity and Tolerance of Treatments Received Beyond Progression in Men Treated Upfront with Androgen Deprivation Therapy With or Without Docetaxel for Metastatic Castration-naïve Prostate Cancer in the GETUG-AFU 15 Phase 3 Trial

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Abstract

Background: Androgen deprivation therapy (ADT) plus docetaxel is the standard of care in fit men with metastatic castration-naive prostate cancer (mCNPC) following results from GETUG-AFU 15, CHAARTED, and STAMPEDE. No data are available on the efficacy of treatments used for metastatic castration-resistant prostate cancer (mCRPC) in men treated upfront with ADT plus docetaxel for mCNPC.
Objective: To investigate the efficacy and tolerance of subsequent treatments in patients treated upfront with chemo-hormonal therapy for mCNPC.
Design, setting, and participants: Retrospective data from the GETUG-AFU 15 phase 3 trial were collected for treatments received for mCRPC.
Outcome measurements and statistical analysis: For the first three lines of salvage treatment for mCRPC we investigated the biochemical progression-free survival, maximum prostate-specific antigen (PSA) decline, overall survival, and tolerance.
Results and limitations: Overall, 245 patients received at least one treatment for mCRPC. For docetaxel used in first-line, a PSA decline $\geq$50% was observed in 25/66 (38%) and in 4/20 patients (20%) who had received upfront ADT alone and ADT plus docetaxel ($p = 0.14$). The median biochemical progression-free survival was 6.0 mo (95% confidence interval: 3.6–7.7) and 4.1 mo (95% confidence interval: 1.3–4.9), respectively. For docetaxel used in first- or second-line, a PSA decline $\geq$50% was observed in 36/80 (45%) and in 4/29 patients (14%) who had received upfront ADT alone and ADT plus docetaxel ($p = 0.07$). PSA declines $\geq$50% were observed with bicalutamide in 12/28 (43%) and 4/23 patients (17%) who had received upfront ADT alone and ADT plus docetaxel. Among men treated upfront with ADT plus docetaxel who received abiraterone or enzalutamide for mCRPC, 10/19 patients (53%) achieved a PSA decline $\geq$50%. Few grade 3–4 events occurred. Study limitations include the observational design and retrospective characteristics of this analysis, without standardized therapeutic salvage protocols, and the limited number of patients in some of the treatment subgroups.
Conclusions: Docetaxel rechallenge following progression to mCRPC after upfront ADT plus docetaxel for mCNPC was active only in a limited number of patients. Available data on abiraterone and enzalutamide support maintained efficacy in this setting. The lack of standardized therapeutic protocols for men developing mCRPC limits the comparability between patients.
Patient summary: Rechallenging docetaxel at castration-resistance was active only in a limited number of patients treated upfront with chemo-hormonal therapy for metastatic castration-naive prostate cancer. Anticancer activity was suggested with abiraterone or enzalutamide in this setting.

1. Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of cancer-related death among men worldwide [1]. Until recently, androgen deprivation therapy (ADT) alone was the standard of care for men with metastatic castration-naive prostate cancer (mCNPC), with anticancer activity initially being reported in the large majority of patients after its initiation [2,3]. However, progression to the castration-resistant prostate cancer (CRPC) stage occurs relatively rapidly, within a median of 1 yr in patients with metastatic disease [4–6]. Docetaxel was shown to improve survival in patients with metastatic CRPC (mCRPC) and is the standard of care in these men for more than a decade [7,8]. Another taxane, cabazitaxel [9], two oral androgen-receptor axis targeted inhibitors, abiraterone acetate [10,11] and enzalutamide [12,13], an autologous therapeutic cancer vaccine, Sipuleucel-T [14], and a bone-targeted radio-pharmaceutical, radium-223 [15], have since shown improvement in overall survival in mCRPC patients previously treated with or without docetaxel, and have been approved for use in many countries in this indication.

Since 2015, there has been a paradigm shift in therapeutic sequences for treatment of men with metastatic prostate cancer. Combining docetaxel chemotherapy with ADT became one of the new standards of care in men with mCNPC, based on data from three phase 3 trials (GETUG-AFU 15, CHAARTED, and STAMPEDE) [4–6,16,17]. The addition of docetaxel to ADT significantly improved progression-free survival (PFS) compared with ADT alone in all three trials, and overall survival was significantly improved in the CHAARTED [6,17] and STAMPEDE trials [5]. A recent meta-analysis showed that the addition of docetaxel to standard of care is associated with a 23% reduction in the risk of death [18]. Furthermore, there are currently no available data regarding efficacy and tolerance of treatments used following progression to mCRPC after upfront ADT and docetaxel for mCNPC and this is an unmet need to assist physicians in a treatment strategy.

In this trial, we investigated the efficacy and tolerance of subsequent treatments (chemotherapy and androgen

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