Combined Chemohormonal Strategy in Hormone-Sensitive Prostate Cancer: A Pooled Analysis of Randomized Studies

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Abstract

The value of chemohormonal strategies in hormone-sensitive prostate cancer has long been debated. A pooled analysis of randomized studies to evaluate these strategies was conducted. The results of the present analysis indicate that a docetaxel–androgen deprivation therapy combination is associated with prolonged overall survival in patients with metastatic hormone-sensitive prostate cancer.

Background: A meta-analysis of the efficacy of chemohormonal regimens versus standard therapy in the management of advanced hormone-sensitive prostate cancer was conducted. **Materials and Methods:** The eligible studies included randomized studies evaluating chemohormonal regimens in the setting of high-risk localized or metastatic hormone-sensitive prostate cancer. **Results:** The search strategy yielded 900 potentially relevant citations from the searched databases. After exclusion of the ineligible studies, 10 studies were included in the qualitative analysis, among which 5 studies that had evaluated a docetaxel-hormonal therapy combination were included in the final quantitative analysis. For metastatic hormone-sensitive disease, the pooled hazard ratio (HR) for progression-free survival (PFS) was 0.63 (95% confidence interval [CI], 0.57-0.70; $P < .00001$), and the pooled HR for overall survival (OS) was 0.75 (95% CI, 0.65-0.86; $P = .0001$). For high-risk localized disease, the pooled HR for PFS was 0.68 (95% CI, 0.58-0.80; $P < .00001$), and the pooled HR for OS was 0.83 (95% CI, 0.61-1.13; $P = .23$). **Conclusion:** The results of the present meta-analysis have demonstrated that docetaxel-hormonal regimens are associated with superior OS and PFS in patients with metastatic disease and superior PFS but not OS in patients with high-risk localized disease. This option should be considered strongly in fit patients with adequate performance status.

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Introduction

Prostate cancer represents a substantial health burden and is a major cause for cancer mortality and morbidity in men.[1] Many strategies have been used to classify prostate cancer anatomically (TNM staging), histologically, and biologically. Anatomically, it has been classified into 2 main categories, localized and metastatic disease.[2] For localized disease, various risk stratification models have been proposed that incorporate T stage, Gleason score, and prostate-specific antigen level.[3] These models can help direct the therapeutic choices, including surgery, radiation therapy, and systemic therapy.[4] Moreover, the models help direct the dose and volume of radiation therapy.[5]

The approach to the proper management of prostate cancer should start with the assessment of patient- and disease-related characteristics.[6] Because of the specific epidemiologic features of the disease, patients with prostate cancer are often elderly and frail with significant comorbidities. For this group of patients, minimally toxic interventions and/or observation have been the preferred treatment options.[7,8] In contrast, for those patients with competent performance status and organ system function, treatment decisions should be guided by the anatomic and biologic classification described. For low-risk localized disease, surgery or radiation therapy have been the standard active treatments, and for those with high-risk localized disease, combination therapy strategies have been proposed, incorporating definitive radiation therapy or radical surgery plus hormonal therapy.[9] For metastatic disease, androgen deprivation therapy (ADT) has long been considered the first-line therapy of choice. After failure of ADT, a number of different

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therapeutic strategies have been suggested. Docetaxel/prednisone was the first systemic therapy regimen to achieve an overall survival (OS) benefit in the castrate-resistant setting.[10]

Despite the plethora of therapeutic options for advanced prostate cancer in the past decade, major room for improvement still exists in the outcomes for these patients.[11] One of the commonly evaluated strategies in this setting has been to combine systemic chemotherapy with ADT for metastatic hormone-sensitive disease and high-risk localized disease. The aim of the present meta-analysis was to provide an overview of the efficacy and toxicity of chemohormonal regimens in the management of metastatic hormone-sensitive and high-risk localized prostate cancer.

Materials and Methods

Search Strategy

A comprehensive search of studies published in English was performed in the following databases: PubMed/Medline, Cochrane Library, and Google Scholar to identify all relevant citations; the date of the last search was September 10, 2015. The meeting abstracts, including those from the American Society of Clinical Oncology and European Society of Medical Oncology, were also checked. Citations with the following words in their titles or abstracts were assessed: "prostate cancer" AND "chemotherapy" AND "hormonal therapy".

Selection Criteria

The inclusion criteria were as follows: randomized clinical trials that evaluated chemohormonal regimens for the treatment of patients with advanced hormone-sensitive prostate cancer (including both metastatic and high-risk localized disease); and reporting of efficacy measures and/or toxicities. The exclusion criteria were non-English language records.

Data Extraction

The data were extracted, and all eligible articles underwent an initial evaluation for relevance. The following data were extracted, if available: trial investigators, year of issue, treatment plan, number of patients, response rate (RR), progression-free survival (PFS), OS, and the incidence of grade 3 and 4 adverse events.

Outcome Measures

The outcome measures of interest were PFS, OS, RR, and toxicities. Response was estimated using the Response Evaluation Criteria In Solid Tumors, and toxicities were assessed using common Terminology Criteria of Adverse Events. The present meta-analysis adhered to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (PRISMA statement).[12]

Statistical Analysis

For the efficacy analysis, the hazard ratios (HRs) were calculated for the PFS and OS from each study, and the log of the HRs and 95% confidence intervals (CIs) were derived. A meta-analysis of the HRs was then conducted, and the fixed effects model was used, because no substantial heterogeneity was observed among the different studies. An HR of < 1 indicates a benefit for patients receiving chemohormonal regimens. A subgroup analysis according to the treatment setting was conducted (high-risk localized prostate cancer vs. metastatic prostate cancer). The publication bias was assessed using funnel plots. All statistical analyses were conducted using the program RevMan, version 5.3 (Copenhagen, Denmark).

Results

Search Results

The PRISMA diagram for the study selection procedure is shown in Figure 1. A total of 900 results were obtained from the searches in PubMed (n = 600 studies) and other databases (n = 300). Of these results, 320 were duplicates and 560 did not meet the eligibility criteria and were therefore excluded. Of the 20 possibly eligible studies after the initial screening, the full text search resulted in the removal of 10 studies. Hence, 10 studies were included in the final analysis: 7 phase III studies and 3 randomized phase II studies[13-23] (Table 1). Of the included studies, 3 were of high-risk localized prostate cancer and 6 were in of metastatic hormone-sensitive prostate cancer. The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial contained 2 cohorts (metastatic and localized disease). The chemotherapy regimen was docetaxel-based in 6 studies and estramustine-based in 4 studies.

Population Characteristics

A total of 4754 patients were included in the present analysis. Most of the patients had an Eastern Cooperative Oncology Group performance score of 0 to 1, in addition to competent hematologic, hepatic, and renal function. The baseline characteristics and the relevant outcomes in each trial are summarized in Table 1. The funnel plots did not reveal significant evidence of a publication bias (Figure 2).

Efficacy Outcomes

A meta-analysis of the HRs for OS and PFS was conducted of the 5 randomized studies comparing the docetaxel-hormonal combination to standard therapy. The study by Rajan et al[22] was not included, because it did not report the HRs.

Metastatic Hormone-sensitive Disease. The pooled HR for PFS was 0.63 (95% CI, 0.57-0.70; $P < .00001$), and the pooled HR for OS was 0.75 (95% CI, 0.65-0.86; $P = .0001$; Figures 3 and 4). Thus, the results from the available efficacy analyses demonstrated that docetaxel-hormonal regimens are associated with superior OS and PFS compared with standard therapies in metastatic hormone-sensitive prostate cancer.

High-Risk Localized Disease. The pooled HR for PFS was 0.68 (95% CI, 0.58-0.80; $P < .00001$), and the pooled HR for OS was 0.83 (95% CI, 0.61-1.13; $P = .23$; Figures 3 and 4). The PFS benefit has been consistently shown, even after removing the estramustine-containing study by Fizazi et al[14] (data not shown). Thus, the results from the available efficacy analyses demonstrated that docetaxel-hormonal regimens are associated with superior PFS, but not OS, compared with standard therapies for high-risk localized prostate cancer.

Toxicities

Higher rates of hematologic and nonhematologic toxicities have been consistently reported in the combination therapy arms (Table 2). The most commonly reported grade 3 and 4 toxicities in