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Original article

Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinical trials

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Abstract

Objective: To assess the efficacy and toxicity of androgen-deprivation therapy (ADT) plus chemotherapy in patients with hormone-sensitive metastatic prostate cancer.

Methods: Randomized clinical trials were identified after systematic searching of databases and conference proceedings. A random-effect model was used to determine the pooled hazard ratio (HR) for the efficacy outcomes—overall survival (OS), biochemical progression-free survival (PFS), and clinical PFS, according to the inverse-variance method. Heterogeneity was measured using the Q and I^2 statistics. A narrative review was done to explore the major adverse drug reactions reported for each trial.

Results: After systematic searching, we included 6 trials ($n = 2{,}675$) in this meta-analysis. Estramustine-based chemotherapy plus ADT was not associated with improved OS (HR = 0.64; 95% CI: 0.22–1.89; $P = 0.42$). In contrast, docetaxel plus ADT was associated with improved OS (HR = 0.75; 95% CI: 0.61–0.91; $P = 0.004$) and clinical PFS (HR = 0.64; 95% CI: 0.57–0.72; $P < 0.00001$). There was no significant heterogeneity detected among trials. Regarding adverse drug reactions grade 3 or higher, neutropenia was the most frequent side effect reported in a range from 12% to 32%.

Conclusion: The addition of docetaxel-based chemotherapy to ADT improves OS and clinical PFS in hormone-sensitive metastatic prostate cancer.

Keywords: Androgen; Cancer; Castration; Chemotherapy; Drug therapy; Prostate

1. Background

Prostate cancer is the second most common malignancy in men and it is a leading cause of death from cancer in this sex [1 The growth of prostate cancer is highly dependent on testosterone blood levels. For this reason, androgen-deprivation therapy (ADT) is the standard of care in newly diagnosed metastatic prostate cancer [2]. The hormone ablation can be achieved surgically with castration (orchiectomy) or through medical therapy. Nevertheless, after medical or surgical castration, the vast majority of patients relapse and overall survival (OS) remains poor, especially in young patients with bone metastases, poor performance status, and high-grade primary tumors [3]. For these patients, the addition of chemotherapy to ADT seems reasonable to target the diverse mechanisms of androgen resistance and improve their OS. This approach was firstly introduced with different chemotherapeutic agents several years ago with modest outcomes and high toxicity. Nevertheless, in the last few years, this approach has reemerged with encouraging results from several trials employing docetaxel-based chemotherapy. In contrast with other cytotoxic agents, docetaxel has consistently demonstrated a survival benefit in patients with castrate-resistant prostate cancer [4,5].

The recent publication of phase III trials comparing chemotherapy plus ADT vs. ADT alone has questioned the paradigm of treatment of newly diagnosed metastatic prostate cancer. For this reason, in this systematic review

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and meta-analysis, we aimed to assess the efficacy and safety of chemotherapy in combination with ADT vs. ADT alone for patients with hormone-sensitive metastatic prostate cancer.

2. Materials and methods

2.1. Search strategy and study selection

The 2 authors (A.R.E. and C.F.) independently examined the titles and abstracts retrieved by a search strategy in electronic databases (MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials) from January 2000 to October 1, 2015 (The search strategy is described in detail in a supplementary file). The search was performed in October 2015. Proceedings of the American Society of Clinical Oncology annual meeting, American Society of Clinical Oncology Genitourinary Symposium meeting and European Society of Medical Oncology annual meeting, were searched from 2010 to 2015 for relevant abstracts. In case of reports of the same trial, we only included the most recent results corresponding to longer follow-up. These authors examined full-text articles of potential eligible studies for compliance with the eligibility criteria. Disagreements were resolved in consultation with a third author (Z.Z.). Data extraction tables were designed specifically for this article to aid data collection. Data from relevant studies were extracted and included information on trial design, participants, interventions, and outcomes. The original study authors were contacted in case of unavailable data. Only studies that reported some or all of the outcome measures were included in this article.

2.2. Eligibility criteria

We included published and unpublished randomized controlled trials that enrolled patients (in the whole sample or in a subgroup) with newly diagnosed metastatic prostate cancer. We included the reported comparisons of chemotherapy plus ADT vs. ADT alone. We excluded trials with incomplete data and those trials published in non-English languages.

2.3. Outcomes

The primary outcome was OS, calculated from the date of randomization to the date of death. Secondary outcomes include the following: (1) biochemical progression-free survival (PFS) defined as an increase in the prostate-specific antigen (PSA) level of more than 50% above the nadir reached after the initiation of ADT or a PSA increase of 25% above the nadir in case of patients without a previous PSA decrease of 50% (with a minimum increase of 5 ng/ml); (2) clinical PFS, in general, was considered as an increase of symptoms of bone metastases, progression according to RECIST criteria version 1.0, clinical deterioration due to cancer according to the investigator's opinion or the occurrence of new bone lesions, whichever happen first, or one or more new bone lesions on bone scan or occurrence of a new soft-tissue lesion. The aforementioned definitions varied among trials.

We also evaluated the toxicity profile, defined as the number of patients experiencing any adverse drug reaction (ADR) according to the Common Toxicity Criteria of the National Cancer Institute or the World Health Organization criteria (the criteria used varied among trials).

2.4. Quality assessment

The risk of bias was assessed by 3 reviewers using the Cochrane Collaboration Tool [6], including adequate sequence generation, adequate allocation concealment, blinding, incomplete outcome data addressed, and freedom from selective reporting. Publication bias was visually examined in a funnel plot, in which the standard error was plotted against changes in the hazard ratio (HR). The risk of bias was considered as "low risk," "high risk," or as "unclear risk."

2.5. Data collection and statistical analysis

Treatment efficacy was measured using the HR with its corresponding 95% CI. For time-to-event outcomes (OS, biochemical PFS, and clinical PFS), HRs were employed. We determined the pooled HR through a random-effect model (DerSimonian-Laird method) according to the inverse-variance method, as described by Parmar et al [7]. For trials reporting an unequal intervention, a narrative review was performed to describe efficacy outcomes. To analyze dichotomous data (ADRs), a narrative review was done due to inconsistent and incomplete data from the selected trials. Heterogeneity was determined by the Q and I^2 statistics. Data analysis was performed using RevMan 5.3 software. The PRISMA statement for reporting systematic reviews was followed [8].

2.6. Role of funding source

No funding source had any role in study design, data collection, data analysis, data interpretation, or writing of this article.

3. Results

3.1. Study selection

After applying the search strategy, we identified 6 trials (n = 2,675 M1 patients) that explored the addition of chemotherapy to ADT in hormone-dependent metastatic prostate cancer. Fig. 1 summarizes the selection process