Original Study

Prevalence of Measurable Disease in Metastatic Castration-resistant Prostate Cancer

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Abstract

Measurable disease was significantly more frequent in phase III trials accruing after 2000. Because of the subjective nature of prostate-specific antigen and bone scan changes and the robust association of objective measurable disease changes with survival, Response Evaluation Criteria in Solid Tumors changes should be a major end point in phase II trials to obtain a firm signal of efficacy before launching phase III trials.

Background: Because of the low historical prevalence of measurable disease in metastatic castration-resistant prostate cancer (mCRPC), phase II trials have used prostate-specific antigen (PSA) and bone scan changes as primary end points. Frequent whole-body imaging and improved computed tomography technology currently identify measurable disease more frequently, warranting consideration of objective response as a major end point. **Patients and Methods:** Data from reported phase III trials of mCRPC were analyzed. The proportion of patients with measurable disease, setting (pre-docetaxel [D], D-based, post-D), year of starting accrual, PSA, and the requirement for symptoms were collected. The χ^2 test was used to evaluate the association of variables with measurable disease rate. **Results:** Twenty phase III trials totaling 19,276 men with mCRPC were evaluable. Three trials (n = 1289) started accruing before 2000 and 17 trials (n = 17,987) accrued after 2000. The proportion of measurable disease rate for all trials was 47.5%. The measurable disease rate was significantly higher ($P < .001$) in trials that accrued after 2000 versus before 2000 (48.7% vs. 31.1%; $P < .001$), D-based (51.8%) or post-D patients (48.9%) compared with pre-D patients (38.6%) and in trials allowing symptomatic versus asymptomatic/minimally symptomatic patients (50.1% vs. 40.0%). **Conclusion:** The proportion of men with measurable disease was significantly higher in phase III trials of mCRPC that accrued after 2000, in D-based or post-D patients and in trials that allowed symptomatic patients. Because of the association of objective measurable changes with survival, Response Evaluation Criteria in Solid Tumors changes might warrant consideration as a major end point in phase II trials to obtain a firm signal of efficacy before launching phase III trials.

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Introduction

The investigation of new agents for metastatic castration-resistant prostate cancer (mCRPC) is confounded by the frequent presence of nonmeasurable bone metastases and absence of objectively measurable disease. Radiographic progression-free survival has been used as an end point in recent phase II trials to provide a signal of therapeutic activity, which accounts primarily for new lesions on bone scan followed by a component of patients who show Response Evaluation Criteria in Solid Tumors (RECIST) disease progression.[1,2] However, new lesions on bone scan might not always represent tumor progression. Prostate-specific antigen (PSA) response or progression has also been used as a surrogate for clinical activity, but is also plagued by poor association with clinical outcomes.

In contrast, trials of most solid tumors rely exclusively on objective changes in measurable disease by using RECIST 1.0 or 1.1 to screen the activity of new agents.[3,4] We hypothesized that more frequent use of improved computed tomography (CT) technology might be increasing the proportion of men with measurable disease in more recent years and in certain subsets of more heavily pretreated or symptomatic patients. If our hypothesis is proven,

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measurable changes might need to be reconsidered as major end points in phase II trials of mCRPC seeking a signal of activity. Moreover, recent studies have shown the association of changes in measurable disease with survival in men receiving chemotherapy for mCRPC.[5,6] To substantiate our hypothesis, we analyzed phase III trials of mCRPC to systematically quantitate the proportion of mCRPC with measurable disease.

Patients and Methods

Eligible Trials

Trial-level data from both arms of all reported randomized trials of mCRPC were eligible for analysis. Trials were required to report baseline measurable disease according to conventional criteria such as World Health Organization, RECIST 1.0, or RECIST 1.1. The overall number enrolled, the proportion of patients with measurable disease, the years of trial accrual, and year of publication were recorded. Certain eligibility criteria that might affect the proportion of patients with measurable tumors were recorded including the requirement for symptomatic disease or absence of visceral disease. In addition, the baseline key prognostic variables were recorded including PSA, pain, pre- versus post-docetaxel or docetaxel-based therapy.

Statistical Considerations

The study primarily represents a descriptive report of the proportion of patients with measurable disease overall in evaluable phase III trials. The χ^2 test was used to evaluate the difference in measurable disease rate on the basis of the period of starting accrual (before the year 2000 and after 2000), setting (pre-docetaxel, docetaxel-based, post-docetaxel), PSA level, and the presence or absence of symptomatic disease. For proportion of patients with the disease, the 95% confidence intervals (CIs) were also estimated.

Results

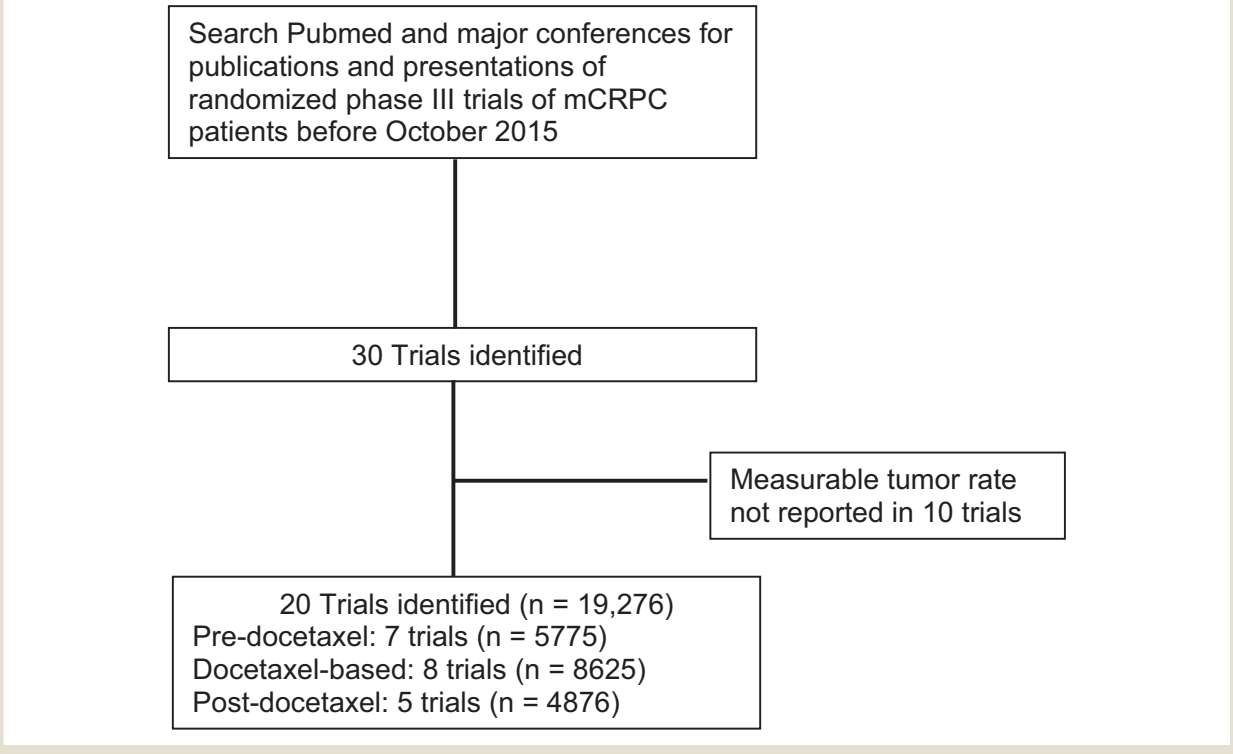
Patient Characteristics

A total of 30 reported randomized phase III trials of mCRPC patients were identified in October 2015. Ten trials were not eligible because of absence of recording of baseline measurable disease or the use of unconventional means to report measurable disease (Figure 1).[7-16] Thus, 20 randomized trials totaling 19,276 men with mCRPC were evaluable: 5775 patients from 7 trials were pre-docetaxel, 8625 patients from 8 trials were docetaxel-based, and 4876 patients from 5 trials were post-docetaxel (Table 1).[1,17-35] The evaluable trials started accrual between 1993 and 2010: 3 trials started accrual before the year 2000, and the remaining 17 trials started in the year 2000 or later (8 trials from 2000-2007, and 7 trials after 2007). Eleven trials used RECIST 1.0, 5 trials used RECIST 1.1, and 4 trials used other criteria.

Proportion of Patients With Measurable Disease and Effect of Year of Accrual

The overall proportion of men with measurable disease was 47.5% (9153 of 19,276 patients). Among patients enrolled in trials

Figure 1 Trial Selection Process



Abbreviation: mCRPC = metastatic castrate-resistant prostate cancer.