Intermittent Chemotherapy as a Platform for Testing Novel Agents in Patients With Metastatic Castration-Resistant Prostate Cancer: A Department of Defense Prostate Cancer Clinical Trials Consortium Randomized Phase II Trial of Intermittent Docetaxel With Prednisone With or Without Maintenance GM-CSF

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Abstract

Docetaxel improves survival in metastatic castration-resistant prostate cancer (mCRPC) but chemotherapy resistance is universal. In the current study, patients were randomized to intermittent docetaxel with or without maintenance granulocyte-macrophage colony-stimulating factor. The approach was demonstrated to be feasible and suggests a potential benefit of maintenance immunotherapy in mCRPC. Follow-up studies emphasizing radiographic over prostate-specific antigen-based end points will be needed to definitively address the role of maintenance immunotherapy.

Background: Immunotherapy with granulocyte-macrophage colony-stimulating factor (GM-CSF), an agent that previously demonstrated antitumor activity, was evaluated within an intermittent chemotherapy framework of docetaxel with prednisone (D+P) in metastatic castration-resistant prostate cancer (mCRPC). **Patients and Methods:** mCRPC patients with $\geq$ 50% prostate-specific antigen (PSA) decline after 6 cycles of D+P were randomized to either GM-CSF or observation (Obs). At disease progression (PD), D+P was reinitiated for 6 cycles followed by the same "off chemotherapy" regimen in patients eligible for chemotherapy interruption. The sequence was repeated until PD during chemotherapy, lack of PSA response to chemotherapy, or unacceptable toxicity. The primary end point was time to chemotherapy resistance (TTCR). **Results:** Of 125 patients enrolled, 52 (42%) experienced $\geq$ 50% PSA decline on induction D+P and were randomized to GM-CSF (n = 27) or Obs (n = 25). The median time to PD was 3.3 months (95% confidence interval [CI], 2.4-3.5) and 1.5 months (95% CI, 1.5-2.4) during the initial course of GM-CSF and Obs, respectively. Twelve of 26 (46%) patients responded to a second course of D+P. Eleven randomized patients (21%) experienced PD during chemotherapy, precluding accurate assessment of TTCR. The remaining 41 randomized patients discontinued study for lack of PSA response to chemotherapy (n = 8), patient choice to not restart chemotherapy with PSA PD (n = 13), toxicity (n = 7), or study withdrawal (n = 13). **Conclusion:** Conducting a prospective study in mCRPC with maintenance immunotherapy within the framework of

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intermittent chemotherapy was feasible. The use of PSA instead of radiographic end points limited the number of evaluable patients. This study provides important insight into designing contemporary intermittent chemotherapy trials with maintenance immunotherapy in patients with advanced prostate cancer.

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Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is the second leading cause of cancer death in men in the United States, with nearly 30,000 deaths per year.[1] Treatment with every 3-week docetaxel with prednisone prolongs overall survival and is the current standard first-line chemotherapy option in mCRPC.[2] However, this regimen might be associated with cumulative toxicities that can significantly impair quality of life (QOL). Applying chemotherapy on an intermittent basis has the potential clinical advantage of achieving disease control that is comparable with continuous chemotherapy but with less toxicity and improved QOL by minimizing cumulative drug exposure.

Prospective studies in advanced breast and colon cancer have demonstrated similar long-term survival and potentially improved tolerability with intermittent versus continuous chemotherapy.[3-6] However, heterogeneity with respect to study end points chosen and criteria for stopping and starting chemotherapy has limited the ability to form a standardized framework for this approach. Even less is known about applying intermittent chemotherapy in mCRPC. The results of several small prospective studies in which patients were treated with intermittent docetaxel-based chemotherapy have been reported, but no standardized approach exists.[7-9] For example, in a phase III clinical trial in mCRPC of weekly docetaxel with or without high-dose calcitriol, patients who wished to, could suspend therapy if prostate-specific antigen (PSA) declined by $>$ 50% from baseline and was $<$ 4 ng/mL. In this analysis, of the 45 patients who met parameters for and suspended therapy, 45% had a PSA decline of $>$ 50% with reinitiation of docetaxel with a median chemotherapy-free interval of 18 weeks.[7]

To date, no agent combined with front-line docetaxel therapy has been shown to prolong survival in mCRPC patients.[10-17] This might be because of a number of reasons, including limited efficacy of the novel agents tested, difficulty of demonstrating additive benefit while receiving concurrent docetaxel-based therapy, and potentially a high disease burden at the time of treatment initiation. Establishing a framework of intermittent chemotherapy provides the potential to test novel agents as maintenance therapy after induction chemotherapy. This approach is predicated on the hypothesis that the efficacy of noncytotoxic agents in mCRPC might be optimized in settings of minimal or reduced disease burden after effective cytoreductive chemotherapy. Under these circumstances a clinically relevant outcome measure could be a prolongation of the time with no chemotherapy and/or a delayed time to chemotherapy resistance.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was an attractive agent to test in this trial design because of previous evidence of antitumor efficacy and also a favorable safety profile.[18,19] In a previous single-agent study in patients with mCRPC, PSA decline $>$ 50% was observed in nearly a quarter of patients and treatment was well tolerated.[18] GM-CSF has also been shown to stimulate an immune response within localized prostate cancers.[20]

On the basis of these previous clinical studies, a multicenter noncomparative randomized phase II trial of intermittent docetaxel with prednisone with or without maintenance GM-CSF was undertaken within the Department of Defense Prostate Cancer Clinical Trials Consortium.[21]

Patients and Methods

Study Population

Patients had progressive prostate adenocarcinoma despite castrate levels of testosterone ($<$ 50 ng/dL) with evidence of 1 or more metastases. An Eastern Cooperative Oncology Group performance status of $\leq$ 2 was required, as was adequate renal, hepatic, and bone marrow function. Patients could have received up to 3 previous cycles of every 3 weeks docetaxel treatment at standard doses immediately before enrolling in the study without other intervening therapy. Patients without a previous history of bilateral orchiectomy were required to continue taking a luteinizing hormone releasing hormone analogue. Key exclusion criteria included Grade $\geq$ 2 peripheral neuropathy at study entry, and use of previous immunotherapy including systemic GM-CSF or vaccines using GM-CSF (previous use of granulocyte colony stimulating factor for prophylaxis was allowed).

The protocol was approved by the local institutional review board of all participating centers, and written informed consent was obtained from all patients.

Treatment and Study Assessment

At the time of study design, there were no standard criteria for definitions of response or progression based on radiographic criteria. As such, PSA response and progression according to PSA Working Group (PCWG)-1 criteria were used to define eligibility for stopping and starting chemotherapy.[22] Induction chemotherapy consisted of docetaxel 60 to 75 mg/m^2 (per investigator discretion) on day 1 in combination with prednisone 5 mg orally twice daily every 3 weeks for 6 cycles.

After 6 cycles of induction chemotherapy, for patients with a confirmed PSA response according to PCWG1 criteria (PSA decline $\geq$ 50% from baseline), prednisone was tapered over 14 days and patients were randomized to either observation (Obs) or treatment with GM-CSF, dosed at 250 mg/m^2 subcutaneously (maximum dose, 500 mg) daily on days 15 to 28 of an every 28 day cycle as previously described.[18] Obs or GM-CSF treatment was