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Clinical Trial Results

A Phase II Trial Evaluating the Efficacy and Safety of Efavirenz in Metastatic Castration-Resistant Prostate Cancer

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Author Summary

Abstract

Background. Preclinical studies demonstrated that non-nucleoside reverse transcriptase inhibitors used for the treatment of HIV could antagonize tumor development. This led us to assess the efficacy of efavirenz in patients with metastatic castration-resistant prostate cancer (mCRPC) in a multicenter phase II study.

Methods. We used a Simon two-stage design and a 3-month prostate-specific antigen (PSA) nonprogression rate of 40% as a primary objective. Patients received 600 mg efavirenz daily with the possibility of a dose increase in case of PSA progression. Exploratory analyses included pharmacokinetics of efavirenz plasma concentrations and correlations with clinical outcomes.

Results. Among 53 assessable patients, we observed 15 instances of PSA nonprogression at 3 months, corresponding to a nonprogression rate of 28.3% (95% confidence interval: 16.8%–42.3%). The exploratory analysis revealed that for the 7 patients in whom optimal plasma concentration of efavirenz was achieved, PSA progression was observed in only 28.6% compared with 81.8% of patients with suboptimal plasma concentrations of efavirenz.

Conclusion. Although 600 mg efavirenz did not statistically improve the PSA nonprogression rate, our exploratory analysis suggests that higher plasma concentrations of this drug (i.e., use of increased dosages) may be of potential benefit for the treatment of mCRPC. ***The Oncologist*** 2014;19:1227–1228

Discussion

Efavirenz is a noncompetitive inhibitor of the HIV reverse transcriptase currently prescribed for the treatment of HIV infections. Efavirenz also acts on the endogenous reverse transcriptase

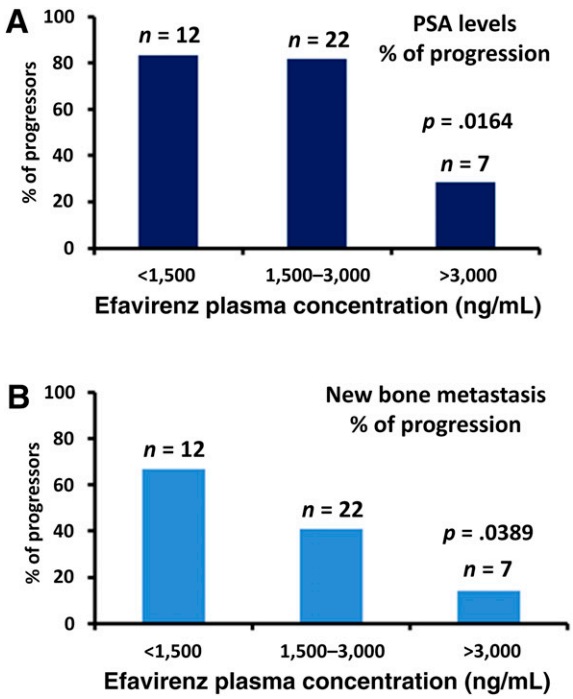

Figure 1. Endpoints at 3 months. The patients with the highest plasma concentrations of efavirenz (>3,000 ng/mL) had the lowest PSA progression (>3,000 vs. <1,500: $p = .0449$ [two-tailed] and $p = .029$ [one-tailed]; >3,000 vs. 1,500–3,000: $p = .0164$ [two-tailed and one-tailed], Fisher's exact test) **(A)** and showed the lowest number of new bone metastases (>3,000 vs. <1,500: $p = .0572$ [two-tailed] and $p = .0389$ [one-tailed], Fisher's exact test) **(B)**.

Abbreviation: PSA, prostate-specific antigen.

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encoded by the retrotransposable element LINE-1. Efavirenz appears to be efficient in preventing tumor growth in mouse xenograft models [1] and has been shown to induce the expression of differentiation markers such as prostate-specific antigen (PSA) or androgen receptor in prostate cancer PC3 cells [1]. We designed a phase II, open label trial to evaluate the efficacy of efavirenz to delay tumor progression. For this purpose, we chose a target population of patients with metastatic castration-resistant prostate cancer (mCRPC) without any clinical symptoms related to disease progression. With only 28% of patients with PSA nonprogression at 3 months, the primary endpoint was not met; however, a potential beneficial effect of efavirenz was suggested by an exploratory analysis that evaluated PSA nonprogression and new bone metastasis as functions of efavirenz plasma concentrations. In patients with plasma concentrations of efavirenz >3,000 ng/mL, corresponding to the concentration needed to obtain a cytostatic effect in vitro, we observed that the percentage that experienced PSA progression was lower than in patients with lower concentrations of efavirenz. A similar trend was observed in terms of radiological response: new bone metastasis appeared in only 14.3% of the subjects with plasma efavirenz concentrations >3,000 ng/mL and in 66.7% and 40.9% of the subjects in the groups with <1,500 ng/mL and 1,500–3,000 ng/mL, respectively (Fig. 1).

Before efavirenz was approved for HIV treatment, a phase I study established the safety of a 1,800-mg/day single dosage and a 1,200-mg/day repeated dosage in healthy patients [2]. These results indicate that higher dosages of efavirenz could be used in prostate cancer patients.

In conclusion, our data indicate that although the dosage of 600 mg/day of efavirenz, which is recommended for AIDS treatment, did not achieve the desired plasma concentration in our cohort of patients with prostate cancer, a higher dosage of efavirenz may offer possible benefit for the treatment of mCRPC patients. A new phase II randomized trial with a larger number of patients, a higher dosage of efavirenz, and a placebo control group is needed to assess the efficacy of efavirenz for the treatment of metastatic castration-resistant prostate cancer.

Author disclosures and references available online.

For Further Reading:

Emmanuel S. Antonarakis, Elisabeth I. Heath, David C. Smith et al. Repurposing Itraconazole as a Treatment for Advanced Prostate Cancer: A Noncomparative Randomized Phase II Trial in Men With Metastatic Castration-Resistant Prostate Cancer. ***The Oncologist*** 2013;18:163–173.

Implications for Practice:

This study investigated two doses of an oral antifungal drug, itraconazole, to determine whether it has antitumor activity in men with metastatic castration-resistant prostate cancer. The results showed that while low-dose itraconazole (200 mg/day) did not have significant antitumor effects, high-dose itraconazole (600 mg/day) did have some activity in these patients. Moreover, the effects of itraconazole appeared to be associated with inhibition of Hedgehog signaling in skin biopsies, and were not caused by testosterone suppression. Therefore, itraconazole may be a non-hormonal treatment option for patients with castration-resistant prostate cancer who wish to prevent or delay the use of chemotherapy. While itraconazole is not as effective as other novel agents for advanced prostate cancer (e.g. abiraterone, enzalutamide), it is a generic drug that may be considered if the cost of these newer agents is prohibitive, or in parts of the world where abiraterone and enzalutamide may not be available.