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LETTER TO THE EDITOR

Prolonged biochemical response after discontinuation of orteronel (TAK-700) in a patient with metastasized castration-resistant prostate cancer

Case

A 73-year-old man, was diagnosed with a T3N1M1a adenocarcinoma of the prostate, Gleason 4 + 4, with iliacal and paraaortic lymph node involvement and an initial PSA of 778 ug/l. Other laboratory results including creatinin, hemoglobin level, LDH and alkalic phosphatase were normal and there was no evidence of bone metastasis. Palliative therapy with busereline, a Gonadotropin releasing hormone (GnRH) agonist was initiated. A biochemical response occurred with a PSA nadir of 23, 16 months after the initiation of androgen deprivation therapy. Castrate refractory disease was diagnosed with a consistent rise in PSA 26 months after diagnosis, but the patient was still asymptomatic. After 14 months of watchful waiting during the castrate refractory state, radiological evaluation was performed due to a shortening in PSA doubling time, although he was still asymptomatic. Multiple bone metastases were detected and PSA had risen to 286 ug/l with a normal alkaline phosphatase at that moment. The patient decided to participate in a double blind, placebo-controlled trial of prednisone with or without orteronel. After the study was closed, deblinding of the study learned that he had been randomized to receive 400 mg orteronel twice daily, together with 5 mg of prednisolone twice daily. Three months after the start of therapy a biochemical response was noted with a decline in PSA to 4.8 ug/l, which decreased further below 1.0 ug/l in May 2012, which was nine months after the start of the treatment.

However, after 17 months of orteronel therapy, the patient developed symptoms of severe fatigue (grade 4 CTC AE). The prostate cancer was still in regression (with a PSA of 0.1 ug/l). Thorough physical, laboratory and cardiopulmonary evaluation ruled out non-treatment-related causes for these symptoms. Adrenal insufficiency was ruled out as explanation for the severe fatigue, as ACTH and corticosterone levels were not elevated during the orteronel treatment. The treatment with orteronel and prednisone was interrupted to evaluate whether the symptoms were attributable to the novel agent. Rapidly afterwards recovery started and he fully recovered after two months of drug interruption. In this time frame PSA remained stable on 0.1 ug/l. The orteronel was rechallenged at a 50% dose (200 mg twice daily and prednisone once daily 5 mg), but the symptoms re-occurred within four weeks of treatment. The patient did not want to continue the study medication, therefore the study medication (orteronel and prednisone) was stopped in April 2013 and no other systemic therapy was started. Again after dechallenge, he recovered from the severe fatigue, while PSA levels in the meanwhile became undetectably low (<0.04 ug/l) and remained at that level during a prolonged period of time. A first PSA increase to 0.3 ug/l was seen 14 months after discontinuing orteronel permanently. The PSA levels from time of diagnosis until now are depicted in Figure 1.

Testosterone at baseline was compatible with the castrate refractory state, however, during therapy with orteronel, there was a further decrease from baseline with about 98% (from 0.3207 to 0.006934 nmol/L). At the end of treatment when orteronel was discontinued for several weeks, the testosterone already increased (0.0659 nmol/L). Regretfully, sensitive testosterone measurements beyond the trial are lacking, but most likely it further increased back to baseline. During treatment, there was also a decline in dehydroepiandrosterone sulfate (DHEAS) and cortisol levels, which similar to testosterone levels, increased already after the discontinuation of orteronel for several weeks. An overview of the hormone levels and number of circulating tumor cells during the study is shown in Table 1. Enumeration of circulating tumor cells was performed in 7.5 ml blood and a CTC count of 3 was found at baseline, while in the four follow-up samples after two, four, six and nine months of therapy the CTC count was zero (Table I).

Radiological evaluations were performed at a regular basis during the trial and in comparison to baseline the number of bone metastases declined from six to two on the bone scan two months after initiation of orteronel and no further changes were seen during therapy. Since the initiation of orteronel 39 months have elapsed and the patient is still asymptomatic with no necessity to perform radiological evaluation after discontinuing orteronel. In addition to PSA levels and radiological evaluations, evaluation of hemoglobin, LDH and alkalic phosphatase levels, were normal during the treatment with orteronel and after discontinuation of the study medication indicating no clinical evidence for disease progression.

Discussion

This patient used orteronel for a period of 18 months, in which there was a biochemical response with PSA levels of around 300 ug/l at the beginning of the study, which became undetectable low after nine months of treatment. However, patient discontinued the use of orteronel due to complaints of severe fatigue. Very interestingly, a prolonged biochemical

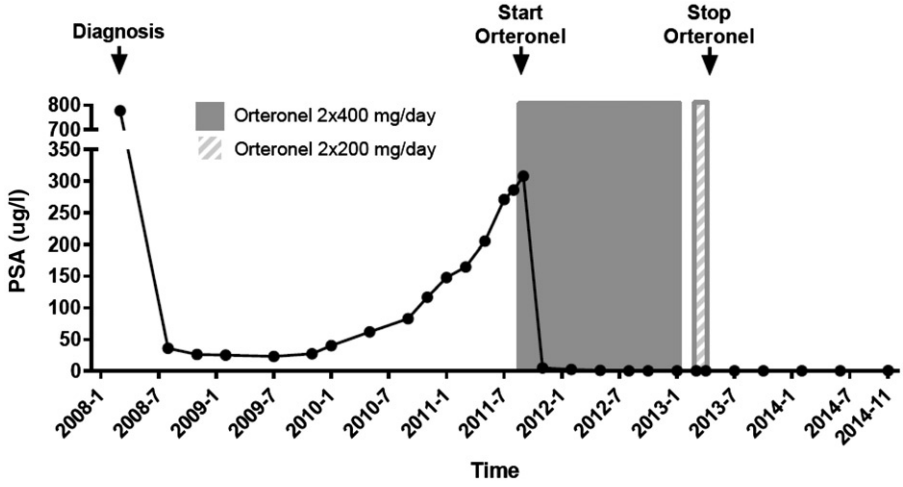

Figure 1. PSA levels before, during and after orteronel use.

Table I. Number of circulating tumor cells and levels of testosterone, dehydroepiandrosterone sulfate and cortisol during the treatment with orteronel.

Date	CTC enumeration (CTC/7.5 ml)	Testosterone (nmol/l)	DHEAS (nmol/l)	Blood cortisol (nmol/l)
2011–08 (Screening)		0.321	4490	281
2011–09	3	0.335	5442	384
2011–09		0.007	44	115
2011–10	0			
2011–11		0.007	24	83
2011–12	0			
2012–02	0	0.007	5	35
2012–05	0		3	36
2012–08		0.007	2.721	32
2012–10			2.721	51
2013–01		0.010	8	177
2013–04 (end of study)		0.066	253	281
2014–11		<0.4	200	270

CTC, circulating tumor cells; DHEAS, dehydroepiandrosterone sulfate.

response was observed consisting of undetectable low PSA and testosterone levels and no clinical signs of disease progression up to 14 months after discontinuation of orteronel.

It has been shown that in patients with CRPC androgen receptors (AR) remain active [1]. This suggests that further diminishing testosterone synthesis could be important in the treatment of CRPC, as is also the mechanism of action of abiraterone, a drug that has shown to be able to prolong overall survival [2]. Orteronel (TAK-700) is a non-steroidal, selective, reversible inhibitor of 17,20-lyase, which is a key enzyme in the production of androgenic hormones. The enzyme 17,20-lyase facilitates the conversion of 17-hydroxy-pregnenolone to dehydroepiandrosterone (DHEA), and therefore the production of testosterone by the adrenal glands and possible metastases, without affecting the production of the other adrenal hormones, such as glucocorticoids and mineralocorticoids by the adrenals. In vitro studies have shown that orteronel is a potent inhibitor of human, rat and monkey 17,20-lyase activity [3,4]. In addition, in vivo studies showed that orteronel potently suppressed serum testosterone and serum DHEA levels and to a lesser extent cortisol levels as was also seen in our patient. However, the effect of orteronel on glucocorticoid levels was dependent on the dosage of orteronel. Dosages of 400 mg BID, such as our patient received, required the coadministration of prednisone.

The first clinical trials have shown that orteronel is capable of lowering PSA and androgen levels, with a minimal effect on glucocorticoid levels. In one of the first phase I/II trials, the median time to PSA progression was estimated at 225 days [5]. Another phase II study showed, that the median time to PSA progression was 13.8 months and the median time of progression-free survival was (PSA progression, metastasis or death) was 14.8 months [6]. The phase III, double blind, placebo-controlled trial of orteronel + placebo in chemotherapy naïve metastatic CRPC patients showed that the median radiologic progression-free survival was increased (+5.1 months) in the orteronel + prednisolone group, however, the overall survival was not significantly different [7]. Due to these results, the development program for orteronel in patients with prostate cancer has been stopped.

The hypothesis behind the use of orteronel and other steroidogenesis enzyme inhibitors is that ARs remain active in CRPC patients due to, e.g. upregulation of the AR or AR gene amplification, activation of the AR by growth factors, increased coactivator expression and AR mutations. Several studies have shown that the AR pathway is amplified in up to 20% of the CRPC tumors [8–11]. Further diminishing the production of androgens might therefore result in decreased activation of the AR, which might be beneficial in the treatment of prostate cancer.

Our patient used orteronel for 18 months and had a good biochemical response to orteronel therapy. Remarkably, although testosterone levels did increase after discontinuation, a prolonged response was observed. In vitro studies have shown that the effect of orteronel is reversible, with restoration of testosterone levels after discontinuation of orteronel [3]. The measurements at the end of the study, measured after a period of two months of discontinuation of orteronel and one month of reduced dosage, show that the effects of orteronel in our patient are reversible as well. DHEAS, testosterone and cortisol levels are increased compared to the measurements during the treatment. Although it seems that the effect of hormone levels is indeed reversible, the malignancy in our patient remained in regression during 14 months. It might be speculated that the use of orteronel during 18 months had resulted in a complete blockade of androgen production in our patient, which might eventually lead to a downregulation of the AR pathway and regression of adrenal tissue and metastasis. The enzymatic

effect might be reversible, however, the target organ might not fully recover, resulting in prolonged remission, even after discontinuation of orteronel.

Another explanation might be the anti-androgen withdrawal effect. This is a remarkable phenomenon that is known in the prostate cancer care. This effect is seen in patients who initially responded to anti-androgen therapy. In these patients, upon disease progression and subsequent discontinuation of the anti-androgen therapy a new response is observed (without the addition of other therapy). Until now, there is no explanation for this phenomenon. It might be that withdrawal from orteronel induced a new response similar as is seen in the anti-androgen withdrawal effect.

Patients participating in the studies, stayed on orteronel until radiographic disease progression occurred or until the occurrence of unacceptable toxicity. There are no results described of patients who stopped using orteronel for other reasons than disease progression and the time to PSA progression after discontinuation of orteronel. Therefore, it is not known if this prolonged biochemical response in our patient is a more frequent phenomenon.

In conclusion, we reported a case of a 73-year-old patient with metastatic CRPC treated with orteronel for 18 months resulting in a dramatic biochemical response with an impressive prolonged response even after discontinuing orteronel. An anti-androgen withdrawal effect has not been previously described as a result of discontinuing orteronel. It might be worthwhile to evaluate this phenomenon in a whole trial population as well as in patients discontinuing abiraterone due to side effects.

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References

1. Attard G, Reid AH, A'hern R, Parker C, Oommen NB, Folkerd E, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol 2009;27:3742–8.
2. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
3. Hara T, Kouno J, Kaku T, Takeuchi T, Kusaka M, Tasaka A, et al. Effect of a novel 17,20-lyase inhibitor, orteronel (TAK-700), on androgen synthesis in male rats. J Steroid Biochem Mol Biol 2013;134:80–91.
4. Yamaoka M, Hara T, Hitaka T, Kaku T, Takeuchi T, Takahashi J, et al. Orteronel (TAK-700), a novel non-steroidal 17,20-lyase inhibitor: effects on steroid synthesis in human and monkey adrenal cells and serum steroid levels in cynomolgus monkeys. J Steroid Biochem Mol Biol 2012;129:115–28.
5. Dreicer R, Maclean D, Suri A, Stadler WM, Shevrin D, Hart L, et al. Phase I/II trial of orteronel (TAK-700)-an investigational 17,20-lyase inhibitor-in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res 2014;20:1335–44.
6. Hussain M, Corn PG, Michaelson MD, Hammers HJ, Alumkal JJ, Ryan CJ, et al. Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. Clin Cancer Res 2014;20:4218–27.
7. De Wit R, Fizazi K, Jinga V, Efstathiou E, Fong PCC, Wirth M, et al. Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trail). J Clin Oncol 2014;32:(suppl; abstr 5008).
8. Holzbeierlein J, Lal P, Latulippe E, Smith A, Satagopan J, Zhang L, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164:217–27.
9. Latulippe E, Satagopan J, Smith A, Scher H, Scardino P, Reuter V, et al. Comprehensive gene expression analysis of prostate cancer reveals distinct transcriptional programs associated with metastatic disease. Cancer Res 2002;62:4499–506.
10. Mousses S, Bubendorf L, Wagner U, Hostetter G, Kononen J, Cornelison R, et al. Clinical validation of candidate genes associated with prostate cancer progression in the CWR22 model system using tissue microarrays. Cancer Res 2002;62:1256–60.
11. Sharifi N, Farrar WL. Androgen receptor as a therapeutic target for androgen independent prostate cancer. Am J Ther 2006;13:166–70.

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