



Plasma Levels of Enzalutamide and Its Main Metabolites in a Patient With Metastatic Castration-resistant Prostate Cancer Undergoing Hemodialysis

Merel van Nuland,^{1,2} Steffie Groenland,^{1,2,3} Andre M. Bergman,³ Joris I. Rotmans,⁴ Hilde Rosing,¹ Jos H. Beijnen,^{1,2,5} Alwin D.R. Huitema^{1,2,6}

Clinical Practice Points

- Enzalutamide is a well-established treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC). However, for patients with end-stage renal disease, no pharmacokinetic data is available. Therefore, we present a case of a patient with end-stage renal disease undergoing hemodialysis treated with enzalutamide, including plasma levels of enzalutamide and its main metabolites.
- The pharmacokinetics of enzalutamide were explored in a 79-year-old man diagnosed with mCRPC undergoing hemodialysis. The patient was initially treated with 160 mg enzalutamide daily, but received a dose reduction to 80 mg owing to adverse events.
- Plasma levels of enzalutamide and N-desmethyl enzalutamide were in line with the average values cited in the literature in patients with normal renal function; however, enzalutamide carboxylic acid concentrations were significantly increased compared with literature (34 µg/mL vs. 4.22 µg/mL; 80 mg once daily).
- We are the first to show that the pharmacokinetics of enzalutamide and the active metabolite N-desmethyl enzalutamide are not affected by hemodialysis in a 79-year-old man with end-stage renal disease. Enzalutamide seems a feasible treatment strategy for patients undergoing hemodialysis. However, further studies will be required to confirm these findings.

Clinical Genitourinary Cancer, Vol. 17, No. 2, e383-6 © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Keywords: Enzalutamide, Hemodialysis, Metabolites, Prostate cancer, Renal failure

Introduction

Prostate cancer is the most common malignancy in men in the Western population.¹⁻³ After initial response to androgen deprivation therapy, the disease will eventually progress into metastatic

castration-resistant prostate cancer (mCRPC); a clinical state in which the androgen receptor axis is reactivated, despite testosterone suppression. Treatment options of patients with mCRPC currently consist of docetaxel, cabazitaxel, radium-223, and anti-hormonal treatment with enzalutamide or abiraterone acetate.⁴ Enzalutamide inhibits the androgen signaling pathway by androgen receptor blockage.^{5,6} After gastrointestinal uptake, enzalutamide is converted to the active metabolite *N*-desmethyl enzalutamide by cytochrome P450 2C8/3A4 and to the inactive metabolite enzalutamide carboxylic acid by carboxylesterase 1.⁵ The potency of *N*-desmethyl enzalutamide is similar to that of enzalutamide itself. Median steady-state trough plasma concentrations of enzalutamide, *N*-desmethyl enzalutamide, and enzalutamide carboxylic acid are 11.4 ± 3.0 µg/mL, 13.0 ± 3.8 µg/mL, and 8.44 ± 6.8 µg/mL, respectively.^{5,7} Owing to the long half-life of enzalutamide (~6 days), steady-state concentrations are reached after approximately 1 month. Enzalutamide and

¹Department of Pharmacy and Pharmacology

²Division of Pharmacology

³Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

⁴Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

⁵Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences

⁶Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Submitted: Nov 1, 2018; Revised: Nov 27, 2018; Accepted: Dec 7, 2018; Epub: Dec 19, 2018

Address for correspondence: Dr Merel van Nuland, PharmD, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
E-mail contact: m.v.nuland@nki.nl

Enzalutamide Plasma Concentrations During Hemodialysis

Table 1 Patient Characteristics at Baseline and During Treatment

Parameter	Baseline	2 Weeks	4 Weeks	8 Weeks
Dose, mg (QD)	—	160	80	80
Plasma concentrations, µg/mL				
Enzalutamide	—	6.74	4.94	5.59
<i>N</i> -desmethyl enzalutamide		3.71	5.95	3.83
Enzalutamide carboxylic acid		14.0	34.0	36.4
PSA, µg/L	2.2	14.5	19.5	39.2
Kidney function				
Creatinine, µmol/L	460	654	515	588
eGFR, MDRD-4	11	7	9	8
Liver function				
Bilirubin, µmol/L	5	5	6	7
ASAT, U/L	14	47	19	19
ALAT, U/L	7	11	17	12
γ-GT, U/L	14	15	15	14
Testosterone, ng/mL ^a	<0.5	0.02	0.03	0.02

Abbreviations: ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; γ-GT = gamma glutamyltransferase; MDRD-4 = modification on diet in renal disease; PSA = prostate-specific antigen; QD = once daily.

^aAt baseline, testosterone was determined with an immunoassay (limit of quantification being 0.5 ng/mL), whereas at later time points, testosterone was quantified using liquid-chromatography mass spectrometry (limit of quantification being 0.01 ng/mL).

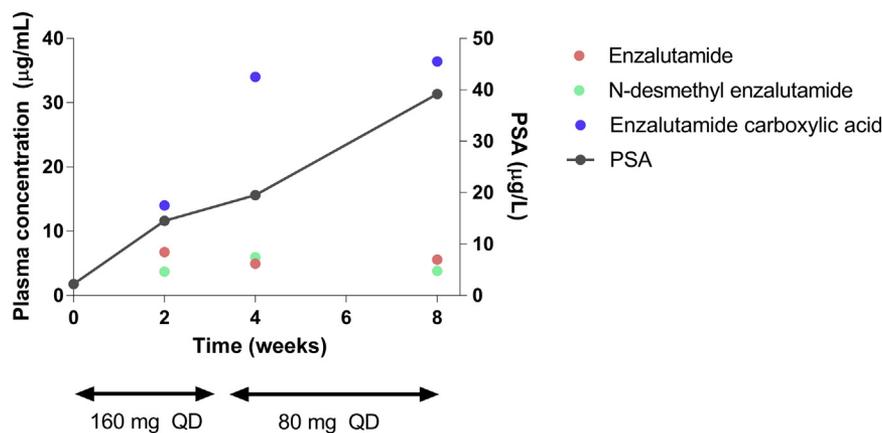
N-desmethyl enzalutamide are cleared hepatically, whereas enzalutamide carboxylic acid clearance mainly depends on renal excretion. Furthermore, enzalutamide is highly protein-bound in plasma (> 95%). Therefore, substantial clearance of enzalutamide by hemodialysis is unlikely.

There is limited evidence to support therapeutic drug monitoring of enzalutamide. However, in a phase I trial, higher androgen receptor binding has been shown with a median plasma trough concentration of 11.4 µg/mL compared with 5.0 µg/mL.⁸

Therefore, a minimum trough concentration of 5.0 µg/mL could be considered as a target for exposure to enzalutamide.⁹

No dose adjustments of enzalutamide are needed for patients with mild or moderate renal impairment. However, no recommendations are available for patients with severe renal impairment or end-stage renal disease, because these patients have not been included in the registration studies.⁵ Two case reports have been published describing the safe use of enzalutamide in this vulnerable patient population, focusing solely on the safety of enzalutamide

Figure 1 Plasma Concentrations of Enzalutamide and Its Main Metabolites, PSA Levels, and Corresponding Enzalutamide Dosages in a Patient With End-stage Renal Disease Undergoing Hemodialysis. Three Weeks After Start of Treatment, Enzalutamide Was Temporarily Withheld Owing to Skeletal Pain, Anorexia, and Dysgeusia. A few Days Later, Enzalutamide Was Resumed After a Dose Reduction to 80 mg QD, Which Was Well-Tolerated. After 2 Months, Further Treatment With Enzalutamide Was Ceased Owing to PSA Progression



Abbreviations: PSA = prostate-specific antigen; QD = once daily.

treatment without pharmacokinetic assessment.^{10,11} We present a case of enzalutamide treatment in a patient with end-stage renal disease undergoing hemodialysis, including plasma levels of enzalutamide, the active metabolite *N*-desmethyl enzalutamide, and the inactive metabolite enzalutamide carboxylic acid.

Case Report

A 79-year-old male presented with a history of mCRPC and end-stage renal disease secondary to chronic post-renal obstruction, for which he started hemodialysis 6 months earlier. Hemodialysis was performed only 2 times per week during 3 hours (Kt/V 1.1 per session) as he had some residual kidney function (creatinine clearance, 5 mL/min).

This patient was initially diagnosed with a cT1cNxM0 prostate carcinoma in 2002, with a Gleason score of 4 + 4, and treated with external beam radiotherapy to the prostate. In 2015, multiple metastases in the bones and lymph nodes were found, after which systemic treatment with cyproterone acetate was started. In 2017, prostate-specific antigen (PSA) progression was seen, and triptorelin was added to the treatment. After 8 months, progression of the bone metastases was observed and enzalutamide treatment was initiated. Treatment was started at the regular dose of 160 mg once daily (QD). Three weeks after the start of treatment, enzalutamide was temporarily withheld owing to skeletal pain, anorexia, and dysgeusia. A few days later, enzalutamide was resumed after a dose reduction to 80 mg QD, which was well-tolerated. After 2 months, further treatment with enzalutamide was ceased owing to PSA progression. Patient characteristics at baseline and during treatment are given in Table 1. Concomitant medication during treatment consisted of alfuzosin (10 mg QD), alfacalcidol (0.25 mg QD), omeprazole (20 mg QD), sodium carbonate (500 mg QD), and triptorelin (11.25 mg once every 3 months).

During treatment, plasma concentrations of enzalutamide, *N*-desmethyl enzalutamide, and enzalutamide carboxylic acid were measured using a validated liquid chromatography with tandem mass spectrometry assay as part of routine clinical care.¹² Minimum plasma concentrations were not calculated for enzalutamide and its metabolites regarding the long elimination half-lives (~6 days). Table 1 shows the plasma concentrations of enzalutamide and both metabolites after 2, 4, and 8 weeks of treatment. Figure 1 visualizes concentrations, PSA levels, and the corresponding enzalutamide dosages.

Discussion

In mCRPC, anti-hormonal therapy is an important treatment modality. Enzalutamide was granted market access in 2011.⁵ However, no data existed for plasma concentrations of enzalutamide and both major metabolites in patients with end-stage renal disease undergoing chronic hemodialysis, which we described in this case report.

Overall, treatment with 160 mg of enzalutamide QD was not well-tolerated by the patient. Therefore, the daily dose was reduced to 80 mg QD. In similar case reports, no significant toxicities were observed.^{10,11} Plasma levels were measured at 2 weeks, 1 month, and 2 months after the start of treatment. Although the first sample was taken while plasma concentrations were not yet at steady-state, the enzalutamide concentration was above the suggested target of 5.0 µg/mL. Thus far, no data on steady-state concentrations after

administration of an 80-mg dose have been reported in previous studies. However, the phase I dose-escalation study showed linear pharmacokinetics over the studied dose range (30-600 mg).⁸ Taking this data into account, estimated plasma concentrations would be one-half of those observed after administration of an 160 mg dose: 5.7 µg/mL, 6.5 µg/mL, and 4.22 µg/mL for enzalutamide, *N*-desmethyl enzalutamide, and enzalutamide carboxylic acid, respectively. Enzalutamide and *N*-desmethyl enzalutamide concentrations after 4 and 8 weeks of therapy are in line with the average values in patients with adequate renal function, considering the 80 mg dose. However, plasma levels of the enzalutamide carboxylic acid metabolite rise far above reported concentrations (34.0 and 36.4 µg/mL vs. 4.22 µg/mL). This can be attributed to the fact that carboxylic acid enzalutamide is excreted renally, whereas enzalutamide and *N*-desmethyl enzalutamide are not detected in urine.^{5,6} Although enzalutamide carboxylic acid is considered inactive at a median concentration of 8.44 µg/mL (160 mg QD), a safety profile of accumulation up to 36.4 µg/mL owing to renal failure has not been evaluated. Therefore, this clinical significance of higher enzalutamide carboxylic acid plasma concentrations is unknown. Although we did not measure enzalutamide levels in the dialysate, our results indicate that hemodialysis does not affect the pharmacokinetics of enzalutamide and its active metabolite, whereas plasma concentrations of the inactive metabolite are increased.

Conclusion

In this case report, we present a patient with mCRPC undergoing hemodialysis. Plasma levels of enzalutamide and the active metabolite *N*-desmethyl enzalutamide were similar to those observed in patients with an adequate renal function, taking into account the 80 mg dose QD, whereas plasma concentrations of the inactive metabolite enzalutamide carboxylic acid were increased up to 8-fold. As the pharmacokinetics of enzalutamide and the active metabolite *N*-desmethyl enzalutamide are rarely affected by hemodialysis, enzalutamide seems to be a feasible treatment strategy for patients with end-stage renal disease undergoing hemodialysis. However, further studies will be required to confirm these findings.

Disclosure

The authors have stated that they have no conflicts of interest.

References

- Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017; 3:524-48.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66: 7-30.
- American Cancer Society. *Global Cancer Facts and Figures*. 3rd edition. Atlanta: American Cancer Society; 2015.
- Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2014; 65:467-79.
- United States Food and Drug Administration. Clinical pharmacology and biopharmaceutics review: xtandi (enzalutamide). Silver Spring (MD). 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203415Orig1s000ClinPharmR.pdf. Accessed: June 28, 2018.
- United States Food and Drug Administration. Prescribing information: xtandi (enzalutamide). Silver Spring (MD). 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf. Accessed: June 28, 2018.
- Gibbons JA, Ouatas T, Krauwinkel W, et al. Clinical pharmacokinetic studies of enzalutamide. *Clin Pharmacokinet* 2015; 54:1043-55.

Enzalutamide Plasma Concentrations During Hemodialysis

8. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* 2010; 375:1437-46.
9. Groenland SL, van Nuland M, Verheijen RB, et al. Therapeutic drug monitoring of oral anti-hormonal drugs in oncology. *Clin Pharmacokinet* 2018 [Epub ahead of print].
10. Simoes J, Augusto I, Meireles S, Vendeira L, Silva C. Metastatic castration-resistant prostate cancer and the challenge of a patient with chronic kidney disease in hemodialysis. *Autops Case Reports* 2018; 8:e2018011.
11. Tsang ES, de Haan M, Egl BJ. A case report of enzalutamide administration in a dialysis-dependent patient with castration-resistant prostate cancer. *J Oncol Pharm Pract* 2018; 24:143-5.
12. van Nuland M, Hillebrand MJ, Rosing H, Schellens JHM, Beijnen JH. Development and validation of an LC-MS/MS method for the simultaneous quantification of abiraterone, enzalutamide, and their major metabolites in human plasma. *Ther Drug Monit* 2017; 39:243-51.