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Economic Evaluation

Cost-Effectiveness Assessment of Monitoring Abiraterone Levels in Metastatic Castration-Resistant Prostate Cancer Patients

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ABSTRACT

Objectives: Abiraterone acetate is registered for the treatment of metastatic castration-sensitive and resistant prostate cancer (mCRPC). Treatment outcome is associated with plasma trough concentrations (C_{min}) of abiraterone. Patients with a plasma C_{min} below the target of 8.4 ng/mL may benefit from treatment optimization by dose increase or concomitant intake with food. This study aims to investigate the cost-effectiveness of monitoring abiraterone C_{min} in patients with mCRPC.

Methods: A Markov model was built with health states progression-free survival, progressed disease, and death. The benefits of monitoring abiraterone C_{min} followed by a dose increase or food intervention were modeled via a difference in the percentage of patients achieving adequate C_{min} taking a healthcare payer perspective. Deterministic and probabilistic sensitivity analyses were performed to assess uncertainties and their impac to the incremental cost-effectiveness ratio (ICER).

Results: Monitoring abiraterone followed by a dose increase resulted in 0.149 incremental quality-adjusted life-years (QALYs) with €22 145 incremental costs and an ICER of €177 821/QALY. The food intervention assumed equal effects and estimated incremental costs of €7599, resulting in an ICER of €61 019/QALY. The likelihoods of therapeutic drug monitoring (TDM) with a dose increase or food intervention being cost-effective were 8.04%and 81.9%, respectively.

Conclusions: Monitoring abiraterone followed by a dose increase is not cost-effective in patients with mCRPC from a healthcare payer perspective. Monitoring in combination with a food intervention is likely to be cost-effective. This cost-effectiveness assessment may assist decision making in future integration of abiraterone TDM followed by a food intervention into standard abiraterone acetate treatment practices of mCRPC patients.

Keywords: abiraterone, cost-effectiveness, food, prostate cancer, therapeutic drug monitoring.

VALUE HEALTH. 2021; 24(1):121–128

Introduction

Abiraterone acetate (AA) is approved for the treatment of metastatic castration-sensitive and resistant prostate cancer (mCRPC) because it improves overall survival (OS) and progression-free survival (PFS) in these patient populations.[1–3] Since the launch of abiraterone in 2012, few cost-effectiveness analyses (CEAs) have been performed that quantify the costs of abiraterone treatment versus its benefits.[4–8] Although these CEAs use different comparators, such as androgen deprivation therapy, docetaxel, or radium-223, and are performed in different countries applying local treatment guidelines, the available CEAs conclude that treatment of mCRPC with abiraterone is not cost-effective, mainly driven by high drug costs. Yet, because of the added clinical benefit for this patient population AA is reimbursed in The Netherlands.[9]

A prospective observational study in patients with mCRPC showed a correlation between abiraterone trough concentrations (C_{min})_the lowest plasma concentration reached before next dose administration—and prostate specific antigen (PSA) response, an accepted prostate cancer-specific biomarker.[10] An optimal abiraterone plasma C_{min} threshold of 8.4 ng/mL was defined, above which patients have longer PFS compared with patients with lower C_{min} (12.2 vs 7.4 months, HR: 0.55).[11] Approximately 65% of patients treated with a fixed dose of AA (1000 mg once daily) reach the target concentration of 8.4 ng/mL,[11] which means treatment optimization may improve clinical outcomes for the remaining 35%. The 8.4 ng/mL threshold was confirmed in a second exposure-response analysis, in which patients with adequate high C_{min} performed better in terms of PSA-PFS compared to patients with a low C_{min} (19.8 vs 3.7 months, HR: 0.52). Measuring concentrations of a drug to personalize treatment is known as therapeutic drug monitoring (TDM) and can be applied in clinical practice for agents with known high interpatient variability.[12] There is potential to optimize treatment for the 35% of mCRPC patients with an abiraterone C_{min} <8.4 ng/mL by implementation of TDM. TDM of this drug, however, is not yet common in clinical practice.

It is known that food has a clinically significant effect on the bioavailability and pharmacokinetics of abiraterone.[13,14] According to the label, abiraterone should be administered in a modified fasting state.[1] In a dedicated food-effect study, exposure (area under the plasma concentration-time curve) increased 5-fold with a low-fat meal and 10-fold with a high-fat meal compared with overnight fasting. Furthermore, the maximum plasma concentration (C_{max}) increased 7-fold and 17-fold when taken with a low-fat and high-fat meal, respectively.[14,15] A milder food-effect was seen in mCRPC patients when compared to modified fasting, with a similar exposure when taken with a low-fat meal and a 2-fold increase with a high-fat meal. Based on this information, concomitant intake of abiraterone with food may increase C_{min} for patients with a low C_{min} (< 8.4 ng/mL).[14,15]

The goal of this study is to assess the cost-effectiveness of monitoring abiraterone C_{min} and subsequently dose increase to 1500 mg once daily in patients with mCRPC in the Netherlands. In an additional scenario, the cost-effectiveness of monitoring abiraterone C_{min} and subsequently advising intake of AA with a low-fat meal is explored.

Methods

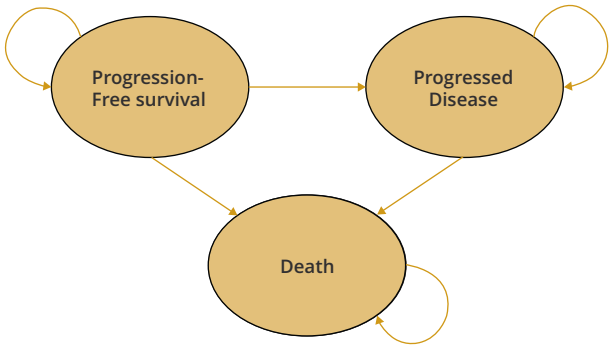
To model benefits and costs in patients with mCRPC treated with abiraterone in the Netherlands, a partitioned survival model was constructed using Microsoft Excel (Microsoft, Redmond, WA). We compared a hypothetical group of patients receiving a fixed dose of 1000 mg of abiraterone once daily without TDM as current standard of care with a hypothetical intervention group. The intervention consisted of TDM, after which patients with a plasma $C_{min} < 8.4$ ng/mL received a dose increase to 1500 mg once daily. Given the evidence of a food-effect relationship for abiraterone, we investigated an alternative scenario in which patients were advised to combine the fixed dose of abiraterone of 1000 mg once daily with a low-fat meal (hereafter called the food intervention). Benefits were expressed as incremental life-years (LYs) and incremental quality-adjusted life-years (QALYs) gained owing to TDM as compared to no TDM, and costs were expressed as incremental costs in 2018 euros.

Model Overview

The Markov model included 3 health states: PFS, progressed disease (PD), and death (see Fig. 1). PFS was defined as the time from treatment initiation to first progression event (measured as PSA or radiologic progression) or death (any cause). PSA progression was defined as a 25% increase from the nadir with an increase in absolute PSA of at least 2 ng/mL. Radiographic progression was defined according to response evaluation criteria in solid tumors or when bone scans showed two or more new lesions.[11]

In accordance with Dutch treatment guidelines, after progression, patients received second-line treatment. Upon entering the PD state, patients were proportionally distributed among the second-line treatment options. Based on a trial by Carton et al, we assumed 35% of patients starting abiraterone treatment do not reach the 8.4 ng/mL threshold.[11] Cycle length was 1 month (30.5 days) with a 5-year time horizon. This time cutoff reflects overall survival in mCRPC patients. A healthcare payer perspective was used. Input parameters and their ranges for sensitivity analyses are specified in Table 1. Reporting of this economic evaluation was done according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline.[16]

Figure 1. Structure of the Markov model. Base case population with progression-free survival is pretreated with doctaxel (21%) or treatment naiive (79%). After disease progression patients are treated with docetaxel (24%), enzalutamide (8%), cabazitaxel (11%), radium-223 (24%), or no treatment (33%).



Modeled Population and Intervention

Mean age of patients in our model was 77 (72-84) years old, based on Carton et al, which was the main source for survival and progression data between intervention groups.[11] We assumed that all patients were monitored during routine visits to an outpatient clinic. Based on previous studies, 21% of the modeled population was treated with docetaxel prior to starting abiraterone treatment,[11] and this was included in the model accordingly. Abiraterone is registered for mCRPC in combination with prednisone or prednisolone 10 mg/day, which is reflected in our model.

Trough levels were considered low when <8.4 ng/mL, and adequate when ≥ 8.4 ng/mL. Patients with low C_{min} received a dose increase from 1000 mg abiraterone once daily to 1500 mg abiraterone once daily to be taken in a fasting state. Fasting state was defined as an overnight fast of at least 8 hours and at least 2 hours before any food intake. The adherence to abiraterone is 92.7%,[17] and, with the assumption that the TDM intervention did not affect adherence rate, the percentage of patients with adequate C_{min} when applying TDM was set at 92.7%.

In the alternative scenario, we modeled the effect and cost of TDM followed by intake of 1000 mg once daily abiraterone with a low-fat continental meal. A low-fat continental meal is defined as 160-320 kilocalories with 25% to 50% fat.[13] Based on a study by Groenland et al, we assumed that 88% of patients receiving the food intervention reached adequate high plasma levels. The same percentage was assumed for patients receiving a dose increase because no data are available on the actual effect of this intervention, and we wanted the ability to compare both strategies.[18]

Patient Survival

PFS and OS were based on Kaplan–Meier curves of a clinical trial directly comparing survival difference between patients with low and high abiraterone C_{min}[11], as no individual patient data were available. The fraction of patients with PD was calculated using the OS and PFS (PD=OS-PFS). To extrapolate patient survival beyond the duration of the clinical trial, different parametric survival curves (exponential, Weibull, log-normal, log-logistic) were fitted on the published survival data of patients with mCRPC. We used methods described by Hoyle, Henley, and Tierney and utilized their proposed Microsoft Excel spreadsheets with incorporated VBA- and R-protocols.[19,20] Best fit was determined through the Akaike Information Criterion and the Bayesian Information Criterion and plausibility of the estimated long-term survival.[19]

Table 1. Patient characteristics and input parameters calculated for a cycle length of 1 month.

Parameter	Base case	Low	High	Distribution	Source
Patient characteristics (Low and high values varied between IQR)					
Age	77.0	-	-	Fixed	[11]
Fraction patients low plasma level (<8.4 ng/mL)	0.35	0.24	0.47	Beta	[11]
Body weight (kg)*	75	70	95	Normal	[11]
Body surface (m^2)	1.9	1.6	2.0	Beta	[39]
Treatment naive fraction (no docetaxel pretreatment)	0.79	0.74	0.84	Beta	[11]
PFS (low and high abiraterone plasma levels)					
Intercept	2.34	2.03	2.65	Loglogistic	[10,11]
Log(scale)	–0.71	–1.04	–0.39	Loglogistic	[11]
PD (enzalutamide)					
Intercept	2.42	2.23	2.60	Weibull	[25]
Log(scale)	–0.56	–0.81	–0.31	Weibull	[25]
PD (docetaxel)					
Intercept	2.33	2.09	2.57	Loglogistic	[26]
Log(scale)	–1.07	–1.41	–0.02	Loglogistic	[26]
PD (cabazitaxel)					
Intercept	2.62	2.44	2.79	Weibull	[27]
Log(scale)	–0.043	–0.27	0.19	Weibull	[27]
PD (RA-223)					
Intercept	2.67	2.42	2.74	Loglogistic	[28]
Log(scale)	–0.56	–0.66	–0.53	Loglogistic	[28]
PD (no treatment)					
Intercept	2.47	2.05	2.67	Loglogistic	[22]
Log(scale)	–0.52	–0.61	–0.49	Loglogistic	[22]
Prostate cancer mortality (treatment naive)					
Intercept	3.42	3.36	3.49	Loglogistic	[21]
Log(scale)	–0.86	–0.94	–0.77	Loglogistic	[21]
Prostate cancer mortality (post docetaxel)					
Intercept	2.47	2.36	2.57	Loglogistic	[22]
Log(scale)	–0.52	0.62	–0.42	Loglogistic	[22]
Utility (low and high values varied ± 25% of base case)					
PFS abiraterone	0.84	0.63	1.00	Beta	[40]
Disutility PD abiraterone First cycle PD	0.052	0.039	0.065	Beta	[2,9,30]
Disutility PD abiraterone > First cycle PD	0.047	0.036	0.059	Beta	[2,9,30]
Costs (low and high values varied ± 25% of base case)					
TDM	€111	€84	€139	Gamma	[31]
Cost abiraterone (monthly)	€3353	€2514	€4191	Gamma	[2,9,23,30,41]
Care used PFS (monthly)	€794	€447	€1241	Gamma	[24,32,42,43]
Care used PD (monthly)	€2570	€1446	€4016	Gamma	[24,32,42,43]
Adverse events Abiraterone first cycle	€51	€38	€64	Gamma	[2,9,24,30]
Adverse event Abiraterone > First cycle	€11	€8	€14	Gamma	[2,9,30]

IQR indicates interquartile range; PD, progressed disease; PFS, progression-free survival; PSA, prostate-specific antigen; RA-223, radium-223.
*Body weight values are derived from source and clinical data. Low and high values are not IQR, but Dutch population data.

Background mortality was assumed equal for patients with low and high abiraterone plasma levels and represents the transition probability from PFS directly to the death state. Background mortality was calculated using a weighted average of placebo arm data from trials with mCRPC patients, adjusting for chemotherapy-naive (79%) and docetaxel pretreated patients (21%).[21,22]

After disease progression, patients were modeled to receive 1 of 5 treatment options in line with Dutch treatment guidelines: docetaxel (24%), enzalutamide (8%), cabazitaxel (11%), radium-223 (24%), or no treatment.[23] Patients were distributed over the 5 treatment options according to Restelli et al, which was found to be generalizable to the Dutch setting based on the clinical validation.[24] Survival curves were modeled separately for each treatment option in the PD state based on clinical studies from the literature.[25–28] Again, survival was extrapolated beyond trial duration by fitting different parametric survival curves (exponential, Weibull, log-normal, log-logistic).[19,20] The model did not allow patients pretreated with docetaxel to receive this drug after disease progression.

Cost and Utility Inputs

Costs were included according to the healthcare payer perspective and are expressed in 2018 euros. Cost based on pre-2018 data was corrected for inflation using the national inflation calculator.[29] Discounting of 4% annually was applied in line with guidelines from the Dutch National Healthcare Institute (Zorginstituut Nederland; ZIN).[9] Treatment-specific cost and frequency of adverse events were extracted from recent clinical studies and available ZIN reports.[2,9,30] We assume that dose increase does not cause additional adverse events, as there is no literature to suggest an exposure-toxicity relationship for abiraterone. Reference prices published by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit) and ZIN were used to establish the costs for drugs and care.[31,32] In the food intervention scenario, we did not include costs of the low-fat meal because this falls outside the healthcare payer perspective. A detailed list of all costs is included in Appendix Tables 1 and 2 (in Supplemental Materials found online at https://doi.org/10.1016/j.jval.2020.04.1838), and a summary is shown in Table 1.

Utility values were used from the AA assessment report by ZIN.[9] Utilities were proportionally corrected in each cycle depending on frequency and occurrence of adverse events, distinguishing 1-time and chronic adverse events (Appendix Table 2 in Supplemental Materials found online at https://doi.org/10.1016/j.jval.2020.04.1838). QALYs were discounted by 1.5% annually, per the guidelines of ZIN.[32] Utilities and disutilities of health states and adverse events are listed in Table 1. A detailed list of included utilities, disutilities, and adverse event frequency adjustments as applied to each treatment option can be found in Appendix Table 2 (in Supplemental Materials found online at https://doi.org/10.1016/j.jval.2020.04.1838).

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses were performed to determine the impact of the uncertainty in input parameters on the end result. The deterministic analysis shows the influence of each individual parameter on the incremental cost-effectiveness ratio (ICER) by varying parameters between their minimum and maximum values (Table 1 and Appendix Tables 1 and 2 in Supplemental Materials found online at https://doi.org/10.1016/j.jval.2020.04.1838). For survival parameters, the 95% confidence intervals were used from the probabilistic sensitivity analysis. The probabilistic sensitivity analysis consisted of 10 000 iterations with random values according to their individual distributions for all parameters included in the model.[33] The simultaneous random sampling of all input parameters gives a comprehensive estimate of the uncertainty around the model estimations.

To show the correlation of the likelihood of the intervention being cost-effective to different willingness-to-pay (WTP) thresholds, a cost-effectiveness acceptability curve (CEAC) was constructed. Because of the short survival time for mCRPC patients, the threshold related to the highest burden of disease (€80 000 per QALY) was applied.[34] Last, we calculated the incremental net monetary benefit (INMB).[35] A positive INMB implies an intervention is cost-effective, and guidelines advise adoption of such an intervention.

Clinical Validation

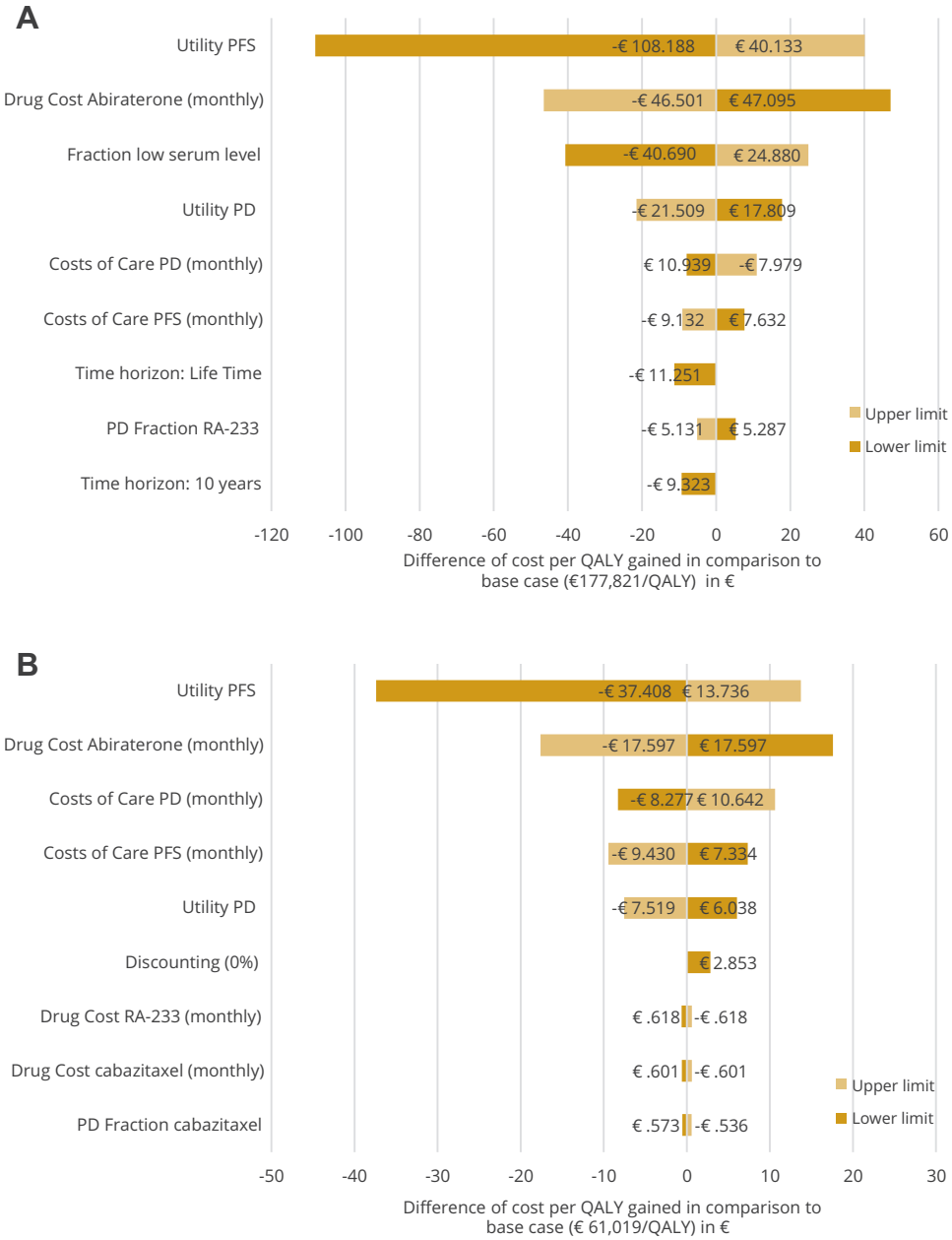
Data from a real-life mCRPC patient cohort treated with AA at the Antoni van Leeuwenhoek/Netherlands Cancer Institute were used retrospectively to validate key model assumptions. Plasma samples of mCRPC patients using abiraterone were obtained as routine clinical care in the period between June 2016 and June 2018. Of 62 included patients, 42% had a low abiraterone C_{min}. The mean age of patients in the clinical population was 72 years. After progression on AA, 18% of patients received docetaxel, 2% received enzalutamide, 8% received cabazitaxel, and 22% received radium treatment, which is similar to data reported by Restelli et al.[24] Furthermore, 41% of patients were treated with AA post docetaxel compared to 21% in the literature. This may be due to the fact that the Antoni van Leeuwenhoek hospital is a tertiary referral center, and patients visiting this hospital are referred for specialized healthcare. In general, the clinical data support the data from the literature, increasing external validity. We chose to implement the more conservative estimates from the literature in our model, such as the 35% of patients with low C_{min} compared to 42% from the real-life cohort.

Results

Regular abiraterone acetetate treatment, not including TDM, resulted in 1.653 (95% CI: 1.483-1.893) LYs and 1.246 (0.985-1.542) QALYs per treated patient, with a cost of €96 450 (79 469-123 756). The TDM intervention group followed by dose increase resulted in 0.149 (0.044-0.267) incremental LYs and 0.125 (0.033-0.245) incremental QALYs (1.803 [1.582-2.087]) LYs and 1.371 (1.064-1.716) QALYs) against incremental costs of €22 145 (4205-46 273) (total, €118 595 [96 777-133 975]) resulting in an ICER of €177 821 per QALY. The scenario exploring TDM followed by the food intervention resulted in equal incremental QALYs (assumption) and incremental costs of €7598 (2358-15 321) (total, €104 049 [85 415-133 975]), resulting in an ICER of €61 019 (40 919-116 352) per QALY.

Results of the deterministic sensitivity analysis (DSA) for the base case are given in Figure 2(A), showing the 10 most sensitive input parameters. The parameter that influenced the ICER most was monthly abiraterone drug cost. The ICER varied from €17 985 and €286 985 per QALY when varied to extremes (+/-25%). PFS utility was followed by monthly abiraterone drug cost and fraction of patients with a low plasma level. The costs of TDM and change in time horizon from 5 to 7 or 10 years had little influence on the ICER. Figure 2B displays the DSA result for the food-intervention scenario, which shows similar results. Here again, PFS utility is the most sensitive parameter, followed by monthly abiraterone cost and monthly cost of care in PD. The fraction of patients with low plasma C_{min} was not among the 10 most influential

Figure 2. (A) Deterministic sensitivity analysis of TDM with dose increase scenario compared with base case. (B) Deterministic sensitiviy analysis of TDM with food intervention compared with base case. The ten most sensitive parameters are displayed in each figure. Parameters are varied between upper and lower limit, reported in Table 1.



PFS indicates progression-free survival; PD, progressed disease; TDM, therapeutic drug monitoring; low $C_{min,}$ the fraction of patients with abiraterone C_{min} <8.4 ng/mL.

parameters. Results of the probabilistic sensitivity analysis are depicted in Figure 3.

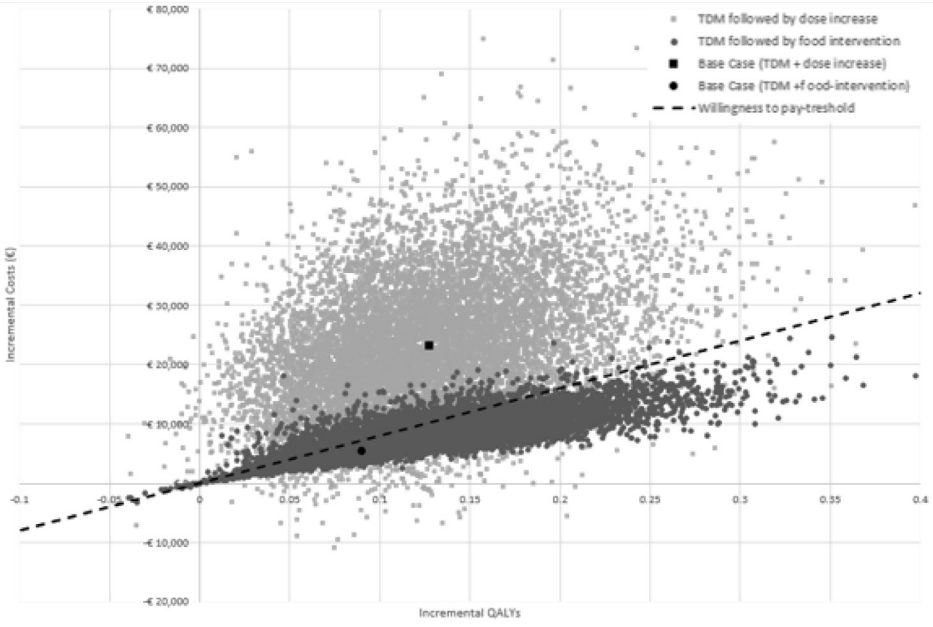
Figure 4 presents the cost-effectiveness acceptability curves (CEAC). The likelihood of TDM with a dose increase being cost-effective, given a WTP of €80 000, was 8.04%. The food-intervention scenario increases the likelihood of cost-effectiveness to 81.9% but does not reach 100% due to negative ICER values in the northwest and southwest quadrant of the cost-effectiveness plane.

The INMB of the dose increase scenario was –€13 157 ([95% CI] –€34 104 to 5344), indicating net losses for this intervention. The INMB of the low-fat meal scenario was €1985 ([95% CI] –€2476 to 7378), indicating nonsignificant benefits for this intervention. Results from the PSA were used to inform the INMB and the 95% CI.

Discussion

TDM of abiraterone followed by a dose increase to 1500 mg daily for patients with low C_{min} (< 8.4ng/mL) gives an ICER of €154 393 per QALY and is therefore not cost-effective when using the relevant Dutch WTP of €80 000 per QALY. The scenario in which patients with low plasma concentrations were advised to combine drug intake with a low-fat meal resulted in an ICER of

Figure 3. Cost-effectiveness plane of the results of the probabilistic sensitivity analysis. The scenario in which standard of care (1000 mg abiraterone once daily) is compared to the intervention of TDM followed by a dose increase (1500 mg abiraterone once daily) for a patient with low plasma C_{min} (<8.4 ng/mL) is shown in light grey squares, with the base case shown in black. An alternative treatement scenario of TDM with a food intervention is displayed in dark grey circles, with the base case shown as a bigger black circle. Dutch willingness-to-pay threshold for high burden disease is €80 000/QALY.

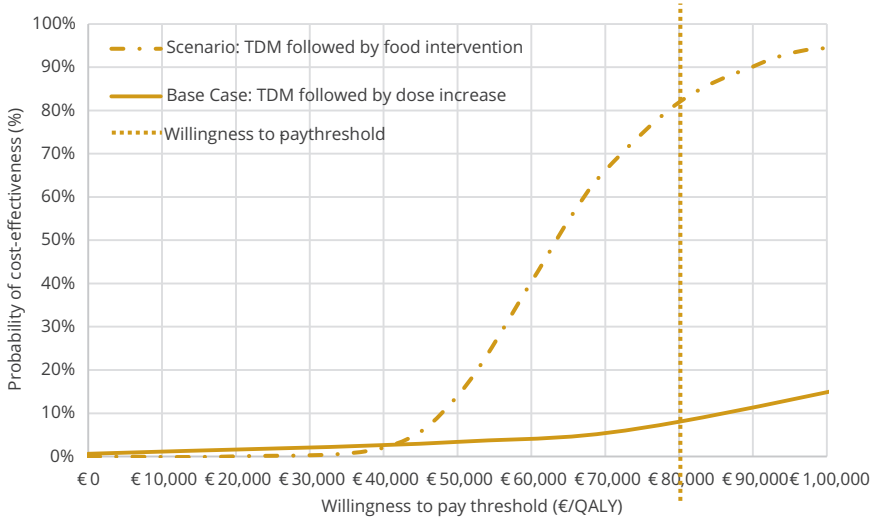


QALY indicates quality-adjusted life-year; TDM, therapeutic drug monitoring.

€60 717. Based on our model, TDM for all patients followed by a food intervention to increase clinical effectiveness of AA in mCRPC patients could be a cost-effective option for clinical practice. Costs are driven solely by prolonged AA treatment, which is favorable from a clinical perspective. Additionally, it is important to realize that the calculated ICER represents the intervention defined as TDM in combination with a low-fat meal. The reported costs and effects are in excess of the effect, cost, and ICER of abiraterone alone.

The ICER was sensitive to some of the assumptions of the model, as shown in the DSAs. TDM of abiraterone followed by dose increase will result in an ICER below the relevant Dutch WTP threshold if a 16% abiraterone cost reduction is applied. A decrease in costs for abiraterone would substantially reduce the ICER in both scenarios. In our model, we used a range of ± 25% to test the sensitivity of the ICER to the costs of abiraterone. If a generic competitor would enter the market, the cost reduction might be more substantial, potentially changing our conclusions. However,

Figure 4. Cost-effectiveness acceptability curve (CEAC) for the base case and alternative treatement scenario.



ICER indicates incremental cost-effectiveness ratio; TDM, therapeutic drug montioring.

the United States patent of AA is set to expire in 2027 and in Europe in 2022; therefore we do not expect a lower drug list price soon,[36] indicating that the finding of cost-ineffectiveness is robust. The robustness of the conclusions is confirmed in the probabilistic analysis and the CEAC, which show a very small likelihood of cost-effectiveness at the WTP threshold of €80 000 per QALY when combining TDM with a dose increase.

Food-drug interactions are often considered undesirable, but examples are available in which drug intake with a specific food can be used to a therapeutic advantage.[37,38] As an alternative to conventional TDM, we show that TDM of abiraterone in mCRPC patients in combination with a low-fat meal is likely to be cost-effective.

Limitations

Our study has some limitations. First, the relationship between abiraterone C_{min} and the response has been established in a prospective trial with only 61 participants.[11] This threshold was recently validated in a retrospective trial in 62 patients, in which similar PFS and response data were found. Data from the study of Carton et al were included in this model because these estimates were more conservative. Additionally, an assumption in the model is that 88% of patients with C_{min} <8.4 ng/mL will have adequate C_{min} after a dose increase. This was based on a prospective trial in which it was shown that 88% of patients with an initial C_{min} < 8.4 ng/mL had adequate high levels after the food intervention.[18] Owing to the large variability in bioavailability, the percentage of patients reaching adequate C_{min} after dose increase may be slightly lower than after the food intervention, resulting in conservative cost-effectiveness estimates.

Multiple sources were used for input parameters to approximate the cost-effectiveness of monitoring abiraterone C_{min} in mCRPC patients. Furthermore, the clinical validation was done at the Antoni van Leeuwenhoek hospital, which is a tertiary referral center. Patients visiting this hospital are referred for specialized treatment and may therefore have a different life expectancy. Although this might introduce bias, data from the real-life cohort are in line with data from the literature. Therefore, we believe that our clinical validation adequately represents the clinical setting.

Conclusion

Based on this model, monitoring of abiraterone in mCRPC patients followed by a dose increase is not cost-effective from a healthcare payer perspective, given a WTP of €80 000. TDM combined with a food intervention, however, is likely to be cost-effective. This cost-effectiveness assessment may assist decision making in future integration of abiraterone TDM followed by a food intervention into standard AA treatment practices of mCRPC patients.

Supplemental Material

Supplementary data associated withthis article can be found in the online version at https://doi.org/10.1016/j.jval.2020.04.1838.

Article and Author Information

Accepted for Publication: April 26, 2020

Published Online: September 11, 2020

doi: https://doi.org/10.1016/j.jval.2020.04.1838

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Critical revision of the paper for important intellectual content: ten Ham, Vreman, Bergman, Huitema, Beijnen, Hovels
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Provision of study materials or patients: ten Ham, Rosing, Bergman, Beijnen
Administrative, technical, or logistic support: ten Ham, Rosing, Beijnen
Supervision: ten Ham, Vreman, Huitema, Beijnen, Hovels

Conflict of Interest Disclosures: Dr Beijnen is a part-time employee, stockholder, and patent holder of Modra Pharmaceuticals (a spinout company developing oral taxane formulations). No other disclosures were reported.

Source of financial support: The authors received no financial support for this research.

REFERENCES

1. US Food and Drug Administration. Center for Drug Evaluation and Research. *Clinical Pharmacology and Biopharmaceutics Review(s): Zytiga (Abiraterone Acetate)*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202379Orig1s000ClinPharmR.pdf. Accessed August 15, 2020; 2010.
2. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995–2005.
3. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138–148.
4. Koninckx M, Marco JL, Pérez I, Faus MT, Alcolea V, Gómez F. Effectiveness, safety and cost of abiraterone acetate in patients with metastatic castration-resistant prostate cancer: a real-world data analysis. *Clin Transl Oncol*. 2019;21(3):314–323.
5. Pollard ME, Moskowitz AJ, Diefenbach MA, Hall SJ. Cost-effectiveness analysis of treatments for metastatic castration resistant prostate cancer. *Asian J Urol*. 2017;4(1):37–43.
6. Chiang CL, So TH, Lam TC, Choi HCW. Cost-effectiveness analysis of abiraterone acetate versus docetaxel in the management of metastatic castration-sensitive prostate cancer: Hong Kong's perspective. *Prostate Cancer Prostatic Dis*. 2020;23(1):108–115.
7. Peters ML, de Meijer C, Wyndaele D, et al. Dutch economic value of radium-223 in metastatic castration-resistant prostate cancer. *Appl Health Econ Health Policy*. 2018;16(1):133–143.
8. Aguiar PN, Tan PS, Simko S, et al. Cost-effectiveness analysis of abiraterone, docetaxel or placebo plus androgen deprivation therapy for hormone-sensitive advanced prostate cancer. *Heal Econ Manag*. 2018;16(4):1–10.
9. van der Graaff M. Farmacotherapeutic Report Abirateron (Zytiga) bij gemetastaseerd castratieresistent prostaatcarcinoom mCRPC [in Dutch]. Vol. 1. Diemen, The Netherlands: 2011. https://www.zorginstituutnederland.nl/publicaties/rapport/2012/01/23/abirateron-zytiga-bij-gemetastaseerd-castratieresistent-prostaatcarcinoom-mcrpc. Accessed August 15, 2020.
10. Lojanapiwat B, Anutrakulchai W, Chongruksut W, Udomphot C. Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice. *Prostate Int*. 2014;2(3):133–139.
11. Carton E, Noe G, Huillard O, et al. Relation between plasma trough concentration of abiraterone and prostate-specific antigen response in metastatic castration-resistant prostate cancer patients. *Eur J Cancer*. 2017;72:54–61.
12. Groenland SL, van Nuland M, Verheijen RB, et al. Therapeutic drug monitoring of oral anti-hormonal drugs in oncology. *Clin Pharmacokinet*. 2019;58(3):299–308.

13. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized Phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol*. 2018;36(14):1389–1395.
14. Chi KN, Spratlin J, Kollmannsberger C, et al. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. *J Clin Pharmacol*. 2015;55(12):1406–1414.
15. Groenland SL, van Nuland M, Bergman AM, et al. Concomitant intake of abiraterone and food to increase pharmacokinetic exposure: real life data from a therapeutic drug monitoring programme. *Eur J Cancer*. 2020;130:32–38.
16. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*. 2013;16(2):231–250.
17. Behl AS, Ellis LA, Pilon D, Xiao Y, Lefebvre P. Medication adherence, treatment patterns, and dose reduction in patients with metastatic castration-resistant prostate cancer receiving abiraterone acetate or enzalutamide. *Am Heal Drug Benefits*. 2017;10(6):296–302.
18. Groenland SL, Bergman AM, Huitema A, et al. Concomitant intake of abiraterone and food to increase pharmacokinetic exposure: real-life data from a therapeutic drug monitoring program. *J Clin Oncol*. 2019;37(15_suppl). abstr 3117. https://abstracts.asco.org/239/AbstView_239_256435.html.
19. Hoyle M, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol*. 2011;11:139.
20. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8(16):1–16.
21. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152–160. https://doi.org/10.1016/S1470-2045(14)71205-7.
22. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983–992.
23. Nederlandse Vereniging voor Urologie. Landelijke Richtlijn: Prostaatcarcinoom. Version 2.1. https://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=980. Published 2016. Accessed April 1, 2019.
24. Restelli U, Ceresoli GL, Croce D, et al. Economic burden of the management of metastatic castrate-resistant prostate cancer in Italy: a cost of illness study. *Cancer Manag Res*. 2017;9:789–800.
25. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *Eur Urol*. 2015;67(1):23–29.
26. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Ann Oncol*. 2012;23(11):2943–2947.
27. Al Nakouzi N, Le Moulec S, Albigès L, et al. Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. *Eur Urol*. 2015;68(2):228–235. https://doi.org/10.1016/j.eururo.2014.04.015.
28. Taneja SS, Parker C, Nilsson S, et al. Re: Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2014;369(3):657.
29. Centraal burea voor Statistiek. Statistics Netherlands. https://opendata.cbs.nl/#/CBS/nl/dataset/83131NED/table. Published 2018. Accessed January 1, 2019.
30. Boer A. *Abirateron (Zytiga) bij gemetastaseerd castratieresistent prostaatcarcinoom mCRPC [in Dutch]*. Zorginstituut Nederland; 2011. https://www.zorginstituutnederland.nl/publicaties/rapport/2012/01/23/abirateron-zytiga-bij-gemetastaseerd-castratieresistent-prostaatcarcinoom-mcrpc. Accessed August 20, 2020.
31. Dutch Healthcare Authority (NZa). *DBC product-finder for tariffs*. Utrecht, The Netherlands: Nederlandse Zorg Autoriteiten; 2018. https://puc.overheid.nl/nza/doc/PUC_13274_22/1/. Accessed August 15, 2020.
32. Kanters TA, Bouwmans CAM, Linden N van der, Tan SS, Hakkaart-Van Roijen L. Update of the Dutch manual for costing in economic evaluations. *PLoS One*. 2017;12(11):11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5679627/pdf/pone.0187477.pdf. Accessed August 20, 2020.
33. Drummond MF, Sculpher MJ, Torrance GW, O'Brien, Stoddart BJ, GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. 3. Oxford, England: Oxford University Press; 2005.
34. Dutch National Health Institute (Zorginstituut Nederland). Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg [Guideline for economic evaluation in health care]. Published 2016. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg. Accessed August 15, 2020.
35. Trippoli S. Incremental cost-effectiveness ratio and net monetary benefit: current use in pharmacoeconomics and future perspectives. *Eur J Intern Med*. 2017;43(May):e36.
36. US Food and Drug Administration. Product details for NDA 202379: Zytiga: abiraterone acetate. 2011. https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=202379. Accessed August 15, 2020.
37. Bushra R, Aslam N, Khan AY. Food-drug interactions. *Oman Med J*. 2011;26(2):77–83.
38. Segal EM, Flood MR, Mancini RS, et al. Oral chemotherapy food and drug interactions: a comprehensive review of the literature. *J Oncol Pract*. 2014;10(4):e255–e268.
39. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height weight formula validated in infants, children and adults. *J Pediatr*. 1978;93(1):62–66.
40. Committee for Medicinal Product for Human Use (CHMP). Assessment report Zytiga (abiraterone acetate). *Eur Med Agency*. 2017;44(July):1–81.
41. Dutch National Health Institute (Zorginstituut Nederland). Drug costs in the Netherlands [Dutch]. https://www.medicijnkosten.nl/. Published 2018. Accessed July 1, 2019.
42. Mehra M, Wu Y, Dhawan R. Healthcare resource use in advanced prostate cancer patients treated with docetaxel. *J Med Econ*. 2012;15(5):836–843.
43. Ter Heine R, Frederix GW, Geenen JW, et al. Cost of illness of metastatic prostate cancer: a perspective of costs for new treatment options in The Netherlands. *J Comp Eff Res*. 2017;6(7):575–581.