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Cost-effectiveness of docetaxel in high-volume hormone-sensitive metastatic prostate cancer

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See related commentary on page 404

Abstract

Introduction: Three pivotal trials have considered the addition of docetaxel (D) chemotherapy to conventional androgen-deprivation therapy (ADT) for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). While an initial small trial was inconclusive, two larger trials demonstrated significant clinical benefit, including pronounced survival benefits (added 17 months) among patients with high-volume metastatic disease. Given the evolving clinical evidence, the cost-effectiveness of this approach warrants exploration.
Methods: The cost-effectiveness of six cycles of ADT+D compared to ADT alone to treat patients with high-volume mHSPC was assessed from a Canadian public payer perspective. We included three health states: HSPC, metastatic castration-resistant prostate cancer (CRPC), and death. Survival data were obtained from the CHAARTED trial, which reported outcomes specifically for high-volume disease. We used Ontario costs data and utilities from the literature.
Results: In the base case analysis, ADT+D cost an additional $25 757 and produced an extra 1.06 quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of $24 226/QALY gained. Results from one-way sensitivity analysis across wide ranges of estimates and a range of scenarios, including an alternate model structure, produced ICERs below $35 000/QALY gained in all cases.
Conclusions: The use of D with ADT in high-volume mHSPC appears to be an economically attractive treatment approach. The findings were consistent with other studies and robust in sensitivity analysis across a variety of scenarios.

Introduction

Prostate cancer is the most commonly diagnosed cancer among males, representing 23.9% of all cancers diagnosed among men, with an annual incidence of 24 000 in Canada[1] and over 220 800 in the U.S.[2] With an estimated 307 000 deaths in 2012, it is the fifth leading cause of cancer-related death among men worldwide.[3]

The proliferation of prostate cancer is largely mediated through the androgen receptor pathway; therefore, by reducing the level of circulating androgen through androgen-deprivation therapy (ADT), one can impede further proliferation of disease.[4] However, in using ADT alone, patients will eventually develop androgen resistance, becoming castration-resistant.[5]

For metastatic castration-resistant prostate cancer (mCRPC), the results of the TAX 327[6] and SWOG-9916[7] trials using docetaxel showed overall survival (OS) benefit relative to mitoxantrone. These studies raised the question as to whether men with hormone-sensitive prostate cancer (HSPC) could benefit from adding this chemotherapy to improve outcomes.

Three pivotal trials have looked at the addition of docetaxel to first-line ADT for the treatment of metastatic (m)HSPC. In the first reported trial, GETUG-AFU15, 385 men with mHSPC were randomized to ADT alone or ADT plus docetaxel 75 mg/m^2 every three weeks for up to nine cycles.[8] At median followup of 84 months, there was improvement in biochemical progression-free survival (median 22.9 vs. 12.9 months; hazard ratio [HR] 0.67; 95% confidence [CI] 0.54–0.84). There was no statistically significant increase in OS; however, in an unplanned post-hoc analysis, there was a 20% reduction in risk of death in the high-volume disease group that failed to reach statistical significance.[9] In the CHAARTED trial (E3805),[10] 790 men with treatment–naive mHSPC were randomized to ADT alone or ADT plus six cycles of docetaxel at 75 mg/m^2 every three weeks.

OS was significantly increased with ADT plus docetaxel compared to ADT alone (median 57.6 vs. 44 months; HR 0.61; 95% CI 0.47–0.80). This trend was most pronounced among patients with high-volume disease, defined by visceral metastases and/or four or more bone metastases, with median OS of 49.2 vs. 32.2 months favoring the docetaxel group. The median time to biochemical, symptomatic, or radiographic progression was also significantly longer with ADT plus docetaxel (20 vs. 12 months; HR 0.61; 95% CI 0.52–0.72). Long-term results after 53.7 months median followup were consistent with initial reports, including significant increase in OS for ADT plus docetaxel of 51.2 vs. 34.4 months in the high-volume subgroup (HR 0.63; 95% CI 0.50–0.79).[11,12] Finally, the STAMPEDE trial[13] randomized 2962 men to one of four different treatment regimens, including long-term ADT or ADT plus docetaxel 75 mg/m² every three weeks for six cycles. The addition of docetaxel to ADT improved OS (median 81 vs. 71 months; HR 0.78; 95% CI 0.66–0.93) and failure-free survival (median 37 vs. 20 months; HR 0.61; 95% CI 0.53–0.70) compared to ADT alone. This trial included 24% non-metastatic patients, and the OS improvement appeared to be enhanced for patients with metastases (HR 0.76; 95% CI 0.62–0.92). However, unlike the other two trials, the proportion and outcomes for patients with high-volume disease were not reported. Meta-analyses of these trials[14-16] have consistently demonstrated that addition of docetaxel is associated with OS benefit, particularly among those with high-volume metastatic disease.

In addition to the survival benefit, the impact of docetaxel on quality of life (QoL) is an important consideration. Though adverse events were higher with docetaxel in the CHAARTED trial,[10] in the long run, at 12 months from time of treatment, QoL was better in the docetaxel and ADT arm.[17] The implication is that ADT plus docetaxel may be a favorable intervention that provides not only a survival benefit, but also preserves better QoL for mHSPC than ADT alone.

These studies have practice-changing implications and the transition of docetaxel earlier into the hormone-sensitive space needs to be formally evaluated from a cost-effectiveness perspective. The objective of this study was to evaluate, from a Canadian public payer perspective, the cost-effectiveness of six cycles of docetaxel plus ADT compared to ADT alone to treat patients with high-volume mHSPC. The results were used to inform decision-making for the Ontario public healthcare system.

Methods

Model structure

An economic model was constructed to conduct a cost-effectiveness analysis and a cost-utility analysis following the guidelines outlined by CADTH.[18] A partitioned survival model was developed for high-volume metastatic prostate cancer with three health states: HSPC, CRPC, and death (Fig. 1). A partitioned survival model uses area under the curve to determine mean time spent in each state. This approach was chosen because time-to-event survival curves for time to CRPC and OS endpoints were relatively complete for both treatment groups, thus providing good estimation of the time spent in each health state with little need for extrapolation.

Our model assumed all patients begin in the HSPC state, are chemotherapy-naive for metastatic disease, eligible to receive ADT, and have patient characteristics in line with the CHAARTED trial, which was the most recent trial data available at the time of initiation of this analysis and largest reported group of high-volume patients.[10] The time horizon used for the analysis was 15 years based on clinical input. This analysis was conducted in Ontario from the government perspective. Outcomes and costs were discounted at 1.5% per year.[18]

Comparators

We compared six cycles of docetaxel at 75 mg/m² given every three weeks plus ADT (ADT+D) to ADT alone in mHSPC. In accordance with the trial protocol, we considered ADT as a class of therapy using luteinizing hormone-releasing hormone (LHRH) therapy (agonists or antagonists).

Clinical data

In the base case analysis, the survival curves from the high-volume subgroup in the CHAARTED study were used to estimate time to CRPC and OS for each treatment group. The Kaplan-Meier survival curves from the latest followup of 53.7 months[11,12] were digitized using Engauge digitization software and patient-level data were estimated.[19] Survival curves were extrapolated using independently fit parametric curves for each treatment arm according to best practice[20] (Fig. 2, Table 1).

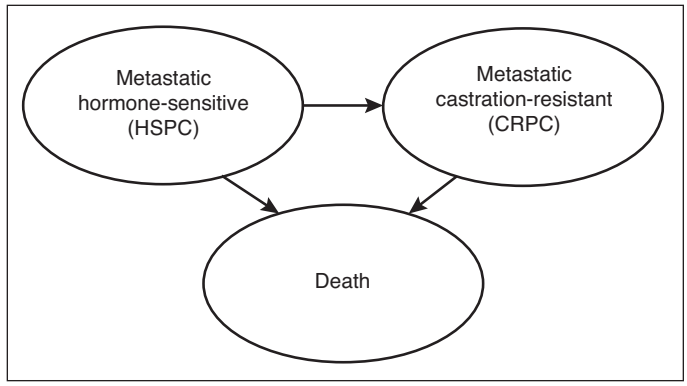

Fig. 1. Model diagram demonstrating health states. CRPC: castration-resistant prostate cancer; HSPC: hormone-sensitive prostate cancer.

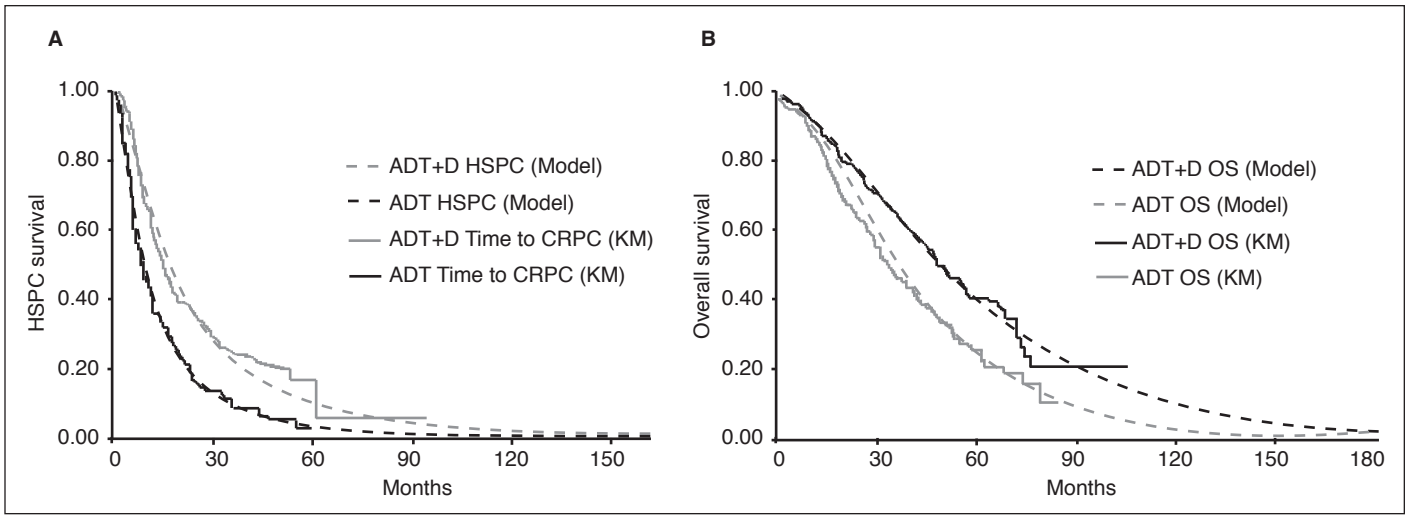

Fig. 2. Model outcomes compared to digitized Kaplan-Meier (KM) data for ***(A)*** survival in the metastatic hormone-sensitive prostate cancer (HSPC) state; and ***(B)*** OS in base case analysis. ADT: androgen-deprivation therapy; CRPC: castration-resistant prostate cancer; D: docetaxel; OS: overall survival.

In sensitivity analyses, we tested alternative extrapolation approaches. In one scenario, a hazard ratio from meta-analysis was applied to the ADT OS curve to explore uncertainty in the relative benefit. We also explored results using alternate parametric distributions (exponential, Weibull, lognormal, log-logistic, Gompertz, and generalized gamma).

A Markov model was also developed to model transitions from HSPC to CRPC and CRPC to death separately. This was conducted as a scenario only because there were no direct data to estimate mortality transition probabilities. The transition probability from HSPC to CRPC was calculated from time-to-CRPC curves, and risk of death from HSPC was assumed to be equal to age-related mortality, given the asymptomatic nature of the disease.[21] Risk of death from CRPC in each arm was estimated by calibrating to the median OS for each treatment group from the trial.[11] When assuming equal risks of death from CRPC regardless of initial treatment group, the average of the estimated risks from each arm were used for both arms. Transition probabilities for the scenario analyses are also summarized in Table 1.

Costs

Costs are reported in 2017 Canadian dollars (Table 1). While the costs for LHRH therapy differ depending on drug and formulation, on average, the monthly costs of these medications are approximately $300–400.[22] We estimated the costs using leuprolide (Lupron Depot®) 22.5 mg three-month formulation injection kit. We also added management costs, including nursing time, administrative support, clerical work, and pharmacy time for preparation (Cancer Care Ontario payment model data) for patients on intravenous (IV) or on non-IV therapy, and we assumed patients would visit the oncology clinic monthly.

Docetaxel costs were estimated using the trial dosing, unit cost of docetaxel at the time of the analysis ($0.54/mg) (Cancer Care Ontario price list) and BSA 1.8 mg/m^2, without dose modifications for up to six cycles, as long as patients remained in the HSPC state. In the CHAARTED trial, 74% of the patients received all six cycles of docetaxel without dose modifications or delays in therapy; patients received an average 5.65 cycles of docetaxel.[10]

Treatment for CRPC includes abiraterone and docetaxel, as well as enzalutamide or cabazitaxel. According to clinical opinion, patients who use docetaxel in the HSPC setting could still potentially benefit from docetaxel in CRPC. Thus, we assumed no differences in the treatment pathway beyond the development of castration resistance, i.e., both groups could receive the same basket of therapies, including retreatment with docetaxel. We assumed an average monthly cost for treatment and management in the metastatic CRPC state as one progressive health state combined. To be conservative, we estimated the average monthly cost based on first-line abiraterone ($3602)[23] plus (non-IV) disease management costs to encompass regular clinic visits and nursing support. Abiraterone and enzalutamide are similarly priced,[23] most widely used for mCRPC, and were the most commonly used of the available therapies after progression in the CHAARTED trial.[10] Thus, we represented costs for the CRPC state using monthly costs for these two expensive therapies. We assumed all other costs are the same between treatment groups (e.g., physician visits). In this model, it is assumed patients are always on ADT or CRPC therapies, and longer survival produces added costs.

Adverse events

In the CHAARTED trial, 6% of patients on ADT+D had febrile neutropenia and 2% had grade 3/4 neutropenia with

Table 1. Inputs used in the model base case and scenario analysis

	ADT+D	ADT alone	Source
Survival distributions			
Time-to CRPC	Lognormal μ=2.827 σ=0.992	Lognormal μ=2.231 σ=1.023	Based on CHAARTED, Guyot et al 2012[11,12,19]
OS	Weibull λ=0.015 γ=1.474	Weibull λ=0.021 γ=1.421	Based on CHAARTED, Guyot et al 2012[11,12,19]
Sensitivity analysis: OS hazard ratio for high-volume disease	0.67 (95% CI 0.51–0.88)		Tucci et al 2016[14]
Probabilities			
Febrile neutropenia risk	8%	0%	Sweeney et al 2015[10]
Sensitivity analysis: Markov model – HSPC to CRPC or death	Lognormal μ=2.827 σ=0.992	Lognormal μ=2.231 σ=1.023	Based on CHAARTED, Guyot et al 2012[11,12,19]
Sensitivity analysis: Markov model - CRPC to death	0.027	0.035	Calculated based on calibration to median OS from CHAARTED[11,12]
Sensitivity analysis: Markov model - HSPC to death	Age-related mortality		Statistics Canada life tables[21]
Costs			
Docetaxel monthly cost ($0.54/mg)	$103	n/a	Cancer Care Ontario
ADT monthly cost (based on leuprolide 22.5 mg every 3 months)	$357	$357	ODB formulary[22]
CRPC therapies (based on abirateratone/enzalutamide monthly)	$3602	$3602	pCODR Economic Guidance Report[23]
Monthly monitoring and administration for non-IV therapy (ADT, abiraterone/enzalutamide)	$92	$92	Cancer Care Ontario costing
Monthly monitoring and administration cost for IV therapy (docetaxel)	$455	n/a	Cancer Care Ontario costing
FN hospitalization	$7326	n/a	Lathia et al 2010[24], Statistics Canada CPI[25]
Utilities			
Metastatic HSPC	0.90	0.90	Bayoumi et al 2000[26]
Metastatic CRPC	0.77	0.77	National Centre for Pharmacoeconomics 2012[29]
Disutility for docetaxel	-0.13	–	Collins et al 2007[32]

ADT: androgen-deprivation therapy CI: confidence interval; CRPC: castration-resistant prostate cancer; D: docetaxel; FN: febrile neutropenia; HSPC: hormone-sensitive prostate cancer; IV: intravenous; OS: overall survival.

infection.[10] We included the cost of hospitalization to treat febrile neutropenia[24] (adjusted to 2017 dollars)[25] for all 8% of patients. We did not include other adverse events, as all other grade 3/4 adverse events occurred in less than 4% of patients in the CHAARTED trial. We assumed no differences in adverse event rates from CRPC therapies.

Utilities

A literature review of previous economic analyses was conducted to capture estimates of health state utility (Table 1). Patients in the HSPC state were assumed to have a utility value of 0.9, consistent with estimates in previous economic evaluations for patients with asymptomatic metastatic prostate cancer.[26-28] Patients in the CRPC state were assigned a utility value of 0.77, consistent with estimates used in an evaluation of abiraterone for patients with mCRPC.[29]

Analysis

Base case

We conducted probabilistic analysis to account for uncertainty in parameters. Beta distributions were used for utilities and probabilities, gamma distributions for costs, and lognormal distributions for the utility decrement and median durations. For the correlated uncertainty in the extrapolation parameters, we used normal distributions and the Cholesky decomposition. For the probabilistic analysis, 5000 simulations were conducted. The average costs and effects for each treatment group were used to estimate incremental costs, incremental effects, and the incremental cost-effectiveness ratio (ICER).

Sensitivity analysis

One-way sensitivity analysis (OWSA) was performed on the survival estimates, costs, and utilities used in the model. We tested scenarios with an estimate of relative treatment benefit from meta-analysis, alternate utility values, alternate distri-

butions for survival extrapolation, and we explored structural model assumptions using a Markov model.

Results

In the base case probabilistic analysis, ADT+D had an incremental cost of $25 757 and produced an extra 1.063 quality-adjusted life years (QALYs), resulting in an ICER of $24 226/QALY gained (Table 2). Longer survival in both health states were each associated with higher costs for the ADT+D arm. A scatterplot of the probabilistic analysis showed all iterations produced added benefits, and nearly all also resulted in added costs (Fig. 3A). Over 99% of iterations were considered cost-effective at a willingness-to-pay threshold of $50 000/QALY gained (Fig. 3B).

We conducted a series of OWSA to evaluate each model parameter. Overall, the model was most sensitive to the cost of treatment and management in the CRPC health state, with lower costs improving the cost-effectiveness of the initial intervention, as well as the survival distributions chosen for CRPC and OS curves. However, no scenario nor parameter change increased the ICER by more than $10 000/QALY gained, i.e., all scenarios and OWSA produced ICERS below $35 000/QALY gained (Fig. 4).

As the impact of the use of initial docetaxel in mHSPC on the outcomes from the downstream CRPC period is uncertain, we also explored uncertainty in the time horizon and the model structure. Using the observed survival outcomes only, i.e., a time horizon of 7.5 years, survival was truncated early, resulting in 0.93 discounted life years (LYs), and the ICER was lowered ($17 056/QALY gained) due to lower CRPC costs. Using the HR from the meta-analysis of trials[14] also produced a lower ICER of $16 966/QALY gained.

A Markov model was used to model the transition from metastatic HSPC to CRPC and CRPC to death separately. As no data are available to inform the effect of initial mHSPC therapy on the risks after developing CRPC, two assumptions were possible. First, assuming no differences in risk of death from CRPC between treatment strategies resulted in a lower ICER than the base case ($3985/QALY gained). This scenario predicted 0.80 discounted LYs, smaller than the survival difference observed in the trial data between the strategies, which also reduced the difference in extra cost arising during the CRPC health state (additional $2 766 discounted costs). To better align the results of the Markov model with the observed data, we calibrated the probability of death from the CRPC health state to the median OS in each arm, thereby assuming a lower risk of death from CRPC from early docetaxel that produces additional benefit in the CRPC period. This produced a larger OS benefit (1.39 discounted LYs) and slightly larger ICER of $27 354/QALY gained, due to the added costs in the CRPC period (additional $31 392 discounted costs).

Table 2. Base case cost-effectiveness results for ADT+D vs. ADT for patients with mHSPC

	ADT D	ADT alone	Incremental
Costs	**$140 183**	**$114 426**	**$25 757**
HSPC	$14 524	$6873	$7651
CRPC	$125 659	$107 552	$18 106
Life years	**4.767**	**3.489**	**1.278**
HSPC	2.181	1.276	0.905
CRPC	2.585	2.213	0.373
Quality-adjusted life years (QALYs)	**3.915**	**2.852**	**1.063**
HSPC	1.925	1.148	0.776
CRPC	1.990	1.704	0.287
ICER = Incremental cost/incremental LYs gained			$20 154
ICER = Incremental cost/incremental QALYs gained			**$24 226**

ADT: androgen-deprivation therapy; CRPC: castration-resistant prostate cancer; D: docetaxel; mHSPC: metastatic hormone-sensitive prostate cancer; ICER: Incremental cost-effectiveness ratio.

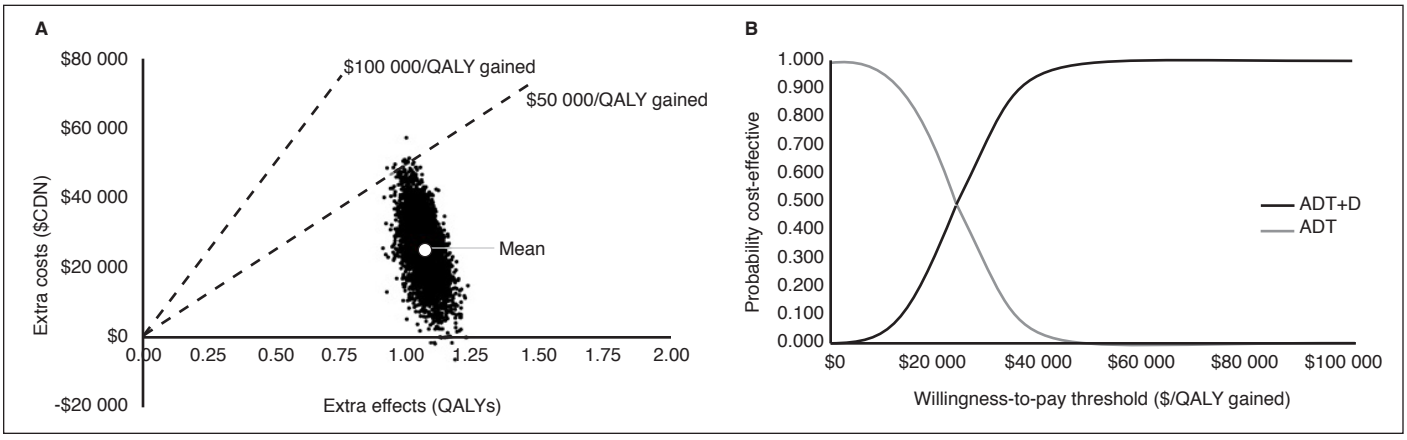

Fig. 3. Results of 5000 Monte Carlo simulations for ADT+D vs. ADT alone to treat patients with high-volume mHSPC presented on ***(A)*** cost-effectiveness plane; and ***(B)*** cost-effectiveness acceptability curve. Willingness-to-pay thresholds of $50 000/QALY gained and $100 000/QALY gained are also displayed on the cost-effectiveness plane for reference. ADT: androgen-deprivation therapy; D: docetaxel; mHSPC: metastatic hormone-sensitive prostate cancer; QALY: quality-adjusted life year.

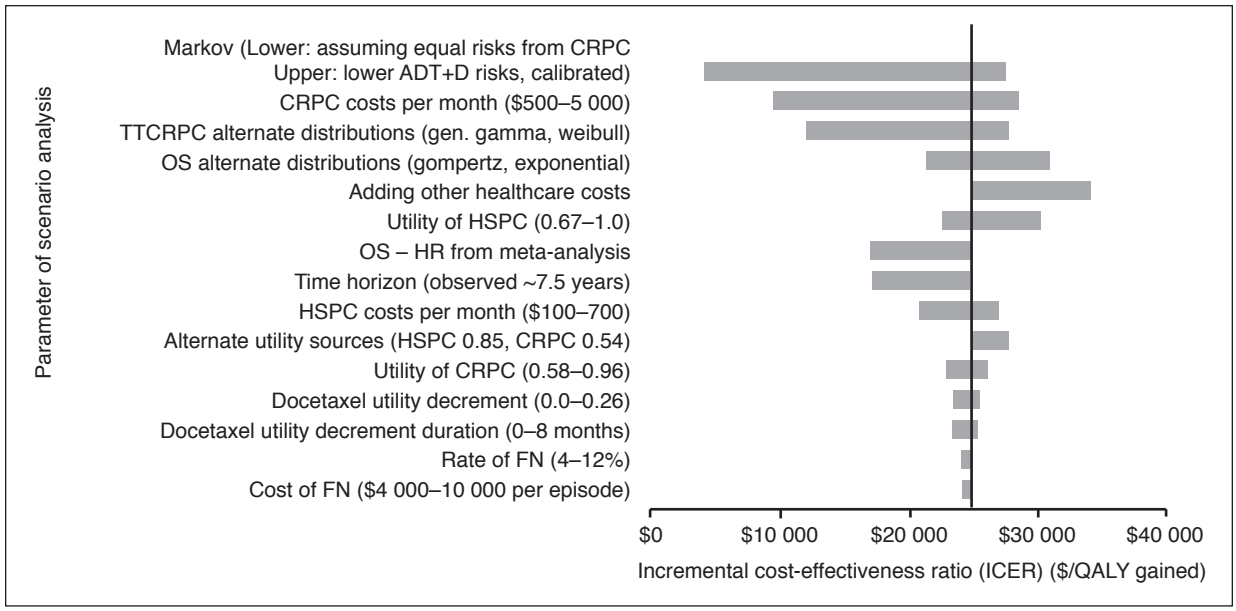

Fig. 4. Tornado diagram for one-way sensitivity and scenario analyses for results of ADT+D vs. ADT alone to treat mHSPC. ADT: androgen-deprivation therapy; CRPC: castration-resistant prostate cancer; D: docetaxel; FN: febrile neutropenia; HR: hazard ratio; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; TTCRPC: time to CRPC.

Discussion

This study, to our knowledge, is the first to attempt to quantify the cost-effectiveness of the addition of docetaxel to ADT in mHSPC from a North American healthcare system perspective. Our study demonstrates that the clinical benefits achieved for patients with high-volume mHSPC also appear to be economically attractive and viable from a public payer approach, with an ICER below commonly accepted willingness-to-pay thresholds of $50 000–100 000/QALY gained. Though this study was conducted using Ontario inputs, treatment patterns and pricing are expected to be similar across Canada, particularly in light of joint negotiations and implementation discussions for new and expensive treatment options through the pan-Canadian Pharmaceutical Alliance (pCPA); thus, we expect these findings are also relevant to other Canadian jurisdictions.

In comparing our findings to other studies, one study in China[30] found that adding docetaxel to ADT among patients with high-volume disease increased cost and effectiveness by US$14 628 and 0.69 QALYs, respectively, producing an ICER of US$21 200/QALY gained. One other study conducted in Brazil reported the combination of docetaxel with ADT produced an additional 0.70 QALYs at added costs in high-volume metastatic disease, resulting in an ICER of US$8417/QALY gained.[31] Both of these studies were conducted using the initial CHAARTED trial data from median followup of 28.9 months.[10]

When evaluating the cost effectiveness of early docetaxel in mHSPC, it is also useful to put the results in context relative to other interventions in metastatic prostate cancer. The use of docetaxel for mCRPC was associated with an ICER of £28 000–33 000/QALY gained relative to mitoxantrone when it was initially funded in this setting (and prior to becoming generic).[32] Abiraterone, in three separate cost effectiveness analyses[33-35] in mCRPC was found to have an ICER between $94 000/QALY[33] and $389 000/QALY gained.[34] Enzalutamide and cabazitaxel in mCRPC had ICERs of $154 300/QALY gained[35] and $163 200/QALY gained[35] relative to placebo, respectively. In comparing the aforementioned treatment options in metastatic prostate cancer, one can see how older therapeutic drugs that have come off patent can be very economically attractive. From a research development perspective, there may be potential of extracting further cost-effective treatment options by taking established, proven, and inexpensive drugs and applying them in new clinical settings rather than simply searching for new molecule discovery. This is also particularly relevant in light of the findings of the LATITUDE-3 trial studying the addition of abiraterone to ADT for high-risk mHSPC, which appeared to produce similar clinical benefits as docetaxel (OS HR 0.62 compared to ADT alone)[36] but at much higher cost; in the study, patients were treated for a median duration of 24 months at a cost $3600 per month,[23] an over 200-fold increase in costs for the average course of abiraterone compared to docetaxel to achieve these similar benefits. A recent network meta-analysis of five trials with high-risk, mHSPC found no OS differences between abiraterone and docetaxel in this setting, (OS HR 0.84; 95% CI 0.67–1.06).[37] While it would appear from indirect comparison of OS that docetaxel

provides comparable benefits in a more efficient manner, the cost-effectiveness of abiraterone compared to docetaxel in the HSPC setting is another relevant policy question for future funding consideration. Further exploration of treatments in this setting may be of particular interest for those ineligible for chemotherapy and in the future as we anticipate price reductions for abiraterone from generic entrants. From an evaluation perspective, our model can be used in future studies to formally evaluate abiraterone informed by future direct evidence or a network meta-analysis and indirect comparison of all the relevant survival and adverse event endpoints, along with evaluation of other additional therapies that may enter this treatment space in future.

Our analysis had some limitations. As stated above, we did not include all adverse event costs or impact of all specific adverse events on QoL since the frequency of these events was relatively small in the original CHAARTED trial.[11,12] Given the treatment is a short-term add-on therapy in relatively asymptomatic patients fit for ADT, this was unlikely to impact our results; moreover, we incorporated a large utility decrement for the treatment period with docetaxel to account for negative QoL impact of IV chemotherapy. Our analysis, therefore, focused only on the costliest and most frequent of adverse events that could impact the cost-effectiveness of the intervention. We simplified the costing and utilities into two disease states, but tested costs and utilities for each using a wide range in sensitivity analysis in both Markov and partitioned survival model structures. Our model does not explicitly model and test treatment sequences in the CRPC setting, though it makes a conservative assumption that patients receive expensive anti-androgens for the duration of CRPC until death. To conduct our sensitivity analysis with a Markov model, there were no data available to directly estimate death from CRPC specific to patients with high-volume disease, either from the trial or in the literature. On the other hand, the observed data captured near-complete followup for the cohort (survival ~20% and 10% in the ADT+D and ADT arms, respectively), meaning minimal extrapolation was required, reducing the uncertainty typically associated with the partitioned survival model structure. Finally, we did not evaluate the impact of the addition of docetaxel to locally advanced (M0), non-metastatic HSPC as assessed in the subsequent STAMPEDE clinical trial.[13] We felt that the evidence supports the addition of docetaxel to ADT only for those with high-volume metastatic disease, as a recent meta-analysis demonstrated that despite an impact on failure-free survival (HR 0.70; 95% CI0.61–0.81; p<0.0001), no OS benefit was shown among men with locally advanced, non-metastatic disease (HR 0.87; 95% CI 0.69–1.09; p=0.218).[15]

Conclusions

The use of docetaxel with ADT in mHSPC appears to be an economically attractive treatment approach that provides large clinical benefits for a targeted group of patients. The incremental cost-effectiveness ratio for this intervention was less than $25 000/QALY gained in the base case; the findings were similar to those of other studies and robust to a variety of scenarios.

Competing interests: Dr. Hotte has been a national advisory panel member for and has participated in clinical trials supported by Astellas, Bayer, and Janssen. Dr. Loblaw has been an advisor board member for Abbvie, Amgen, Astellas, Janssen, and Sanofi; and has received honoraria from Abbvie, Astellas, Amgen, AstraZeneca, Bayer, Janssen, Sanofi, and TerSera. The remaining authors report no competing personal or financial interests related to this work.

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