

# The value of anticancer drugs in metastatic castrate-resistant prostate cancer: economic tools for the community oncologist

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**Background** Community oncologists need a simplified methodology for assessing the value of anticancer drugs. In the United States and Europe, costs of anticancer drug were previously estimated at US\$50,000 to >US\$100,000 per quality adjusted life-year (QALY). The National Institute for Health and Care Excellence in the United Kingdom states that the average cost-effectiveness ratios intervention of >US\$50,000 per QALY must be questioned.

**Objectives** To design a drug model to estimate the amount in United States dollars (US\$) paid for life-year gain (LYG) and QALY, and to apply that model in the treatment of chemo-naïve and chemo-treated patients with castrate-resistant metastatic prostate cancer (mCRPC).

**Methods** Cost per LYG (cost/LYG) was compared with cost per probability of survival (cost/PoS) calculated as [1.0 minus HR]. Results were expressed in relative values (RV) calculated as US\$50,000 or US\$100,000 per cost/outcome.

**Results** In patients with mCRPC, generic docetaxel demonstrated the lowest cost/LYG (US\$26,330), lowest cost/ PoS (US\$21,942), and the highest RV (3.80-4.56). Cost/LYG of sipuleucel-T was US\$272,195, with an RV of 0.37. Significant variation between cost/LYG and cost/ PoS was noted among drugs with borderline survival and HR. In previously treated patients, the cost/LYG of cabazitaxel was US\$207,240; of abiraterone, US\$194,087; enzalutamide, US\$223,500; and radium-223 dichloride, US\$230,000, all with RVs <0.5.

**Conclusions** A simplified drug model to weigh cost, survival, and HR with imposed limits on cost/outcome was proposed and applied to patients with mCRPC. The results among that patient population suggested that generic docetaxel had the lowest costs, cost/outcome and the highest RV. Sipuleucel-T, abiraterone, enzalutamide, radium-223 dichloride, and cabazitaxel were overpriced for their values. Drugs with RVs of <0.5 should be scrutinized, costs negotiated, or other drugs considered, and those with RVs of <0.25, rejected.

Docetaxel has been the gold standard for the treatment of patients with castrate-resistant metastatic prostate cancer (mCRPC) since 2004.<sup>1-3</sup> Since then, 5 more drugs have since been added to the therapeutic armamentarium: cabazitaxel,<sup>4</sup> sipuleucel-T,<sup>5-7</sup> abiraterone,<sup>8-10</sup> enzalutamide,<sup>11,12</sup> and radium-223 dichloride.<sup>13-15</sup> Costs of anticancer drugs continue to raise concerns about their approval<sup>16-18</sup> and restrict their use.<sup>19,20</sup> In the US and Europe, costs of anticancer drugs were previously estimated at US\$50,000-US\$100,000 per life-year gain (LYG) and significantly higher for quality adjusted life-year (QALY).<sup>21-23</sup> In the United Kingdom, the National Institute for Health and Care Excellence (NICE) states that an average cost-effectiveness ratio (ACER) intervention should be £20,000-£30,000 per QALY gained. This is equivalent in the United States to US\$30,000-US\$45,000

per QALY. From the NICE's perspective, a value of >US\$50,000/QALY ought to be questioned. A scoring methodology was recently described to estimate how much a patient would pay for each additional day of survival resulting from the use of the prescribed drug.<sup>24-25</sup> The current cost evaluation methods are based on survival.<sup>26</sup> Hazard ratios (HR) have not been directly integrated in the cost/outcome evaluation. At the closure of some studies, survival data were not mature for the final analysis. In the present investigation, we constructed a model to assess drug value based on parallel use of survival and HR. We proposed limits on cost/outcome and expressed the results as relative values (RVs). Differences between US and UK policies were outlined. We evaluated docetaxel, sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223 dichloride in chemo-naïve and chemo-treated mCRPC patients.

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## Methods

We used average wholesale prices (AWP) and/or third-party payments in United States dollars (US\$). The overall survival gain over control in days (OSg) and HR of death were extracted from previously published data. Cost/OSg and cost/LYG were calculated. The results were compared with cost/probability of survival (PoS) computed as [1.0 minus HR]. We estimated the costs of docetaxel 75 mg/m<sup>2</sup> IV q3w x10 cycles (cy) and of cabazitaxel 25 mg/m<sup>2</sup> IV q3w x6-10 cy for patients weighing 70 kg or 1.7/m<sup>2</sup> of body size. Sipuleucel-T and radium-223 dichloride costs were based on the entire treatment course. The costs for abiraterone and enzalutamide were based on the recommended daily dose for 3, 6, and 12 months. Outdated and unused drug portions were not included. Expenses covering intravenous (IV) administration, oral medications (po) and bone-marrow growth factors were added to the costs of docetaxel and cabazitaxel. Expenditures associated with professional fees, including for doctors, pharmacists, and nurses, hospitalizations, and radiology were excluded. Drug dosages, recommendations, and number of cycles were followed as closely as possible. The results were tabulated as cost/OSg, cost/LYG, cost/PoS, and cost/QALY. A limit of US\$50,000 was imposed on cost/QALY as per NICE recommendations. In the US, a limit of US\$50,000 was used for drugs that had a negative effect on patient quality of life (QoL) and of US\$100,000 for drugs with reported improvement in patient QoL. Relative values (RVs) were calculated as US\$50,000 or US\$100,000 per cost/outcome.

## Results

A survey of 39 approved and widely used anticancer drugs and combinations in 8 types of metastatic cancer demonstrated a median OSg of 108 days. In the US, the negotiated highest drug cost for the entire treatment course was US\$120,000. The costs of >90% of the drugs that were evaluated were <US\$100,000, with a median cost of US\$27,859 and a cost/OSg of US\$367. The median OS in mCRPC was 90 days, with an HR of 0.74, cost/OSg of US\$521, cost/LYG of US\$187,333, and cost/PoS of US\$126,330.

## Survival and HR

A wide variation between cost/LYG and cost/PoS was noted among drugs with borderline survival or HR. In chemo-naïve patients, abiraterone demonstrated an OSg of 132 days and a cost/LYG of US\$202,910, compared with an HR of 0.80 and a cost/PoS of US\$372,000 (Table 1). In chemo-treated patients, cabazitaxel x6 cycles (cy) with ancillary treatment showed an OSg of 72 days and a cost/LYG of US\$207,240, compared with an HR of 0.70 and a cost/PoS of US\$138,160 (Table 2).

## Chemotherapy

In chemo-naïve mCRPC patients, docetaxel, a taxane inhibitor of microtubule depolymerization,<sup>1,3</sup> demonstrated OSg of 72 days and an HR of 0.76. The cost of 10 cy of generic docetaxel was US\$3,508, compared with US\$33,357 for its trade counterpart. The generic docetaxel demonstrated a cost/OSg of US\$49, a cost/LYG of US\$17,540, and a cost/PoS of US\$14,617 (Table 1). The ancillary costs of IV administration, oral medications, and bone marrow growth factors resulted in a modest increase of the cost/outcome and a decrease in the RV. Cabazitaxel, a newer generation semisynthetic taxane, was designed to overcome docetaxel resistance and was approved in second-line treatment<sup>4</sup> (Table 3). Docetaxel and cabazitaxel increased the OS by 72 days. Increasing the number of cycles raised the cost/outcome and lowered the RV. The changes were more noted with cabazitaxel than with docetaxel.

## Sipuleucel-T<sup>7</sup>

This novel immunotherapeutic agent is indicated at an earlier stage of the disease for asymptomatic or minimally symptomatic patients.<sup>5,6</sup> The US\$93,000 price tag included the entire treatment course and the complex preparation procedure. The cost/OSg, cost/LYG, and cost/PoS were excessive and the RV was low despite the strong 4-month gain in OS (Table 1).

## Androgen receptor signaling targeted therapy

Abiraterone is a potent and selective small-molecule inhibitor of testosterone synthesis.<sup>8-10</sup> The cost of 1 year of treatment was US\$74,400. Enzalutamide, formerly called MDV3100, targets multiple steps in the androgen receptor signaling pathway with a higher receptor-affinity than that of the first-generation drugs.<sup>11,12</sup> The acquisition cost of enzalutamide was estimated at US\$89,400, about 15% higher than the cost of abiraterone. Ancillary treatment costs of abiraterone and enzalutamide were estimated at <US\$1,000, an insignificant amount compared with drug cost. Costs for both drugs steadily increased and RVs decreased by extending the duration of treatment from 3 to 12 months.

## Radium-223 dichloride

This alpha-emitting particle was approved in patients with CRPC with bone metastasis.<sup>13-15</sup> The cost of the 6-dose course was US\$69,000, compared with US\$74,400 for 12-month treatment with abiraterone and US\$89,400 for 12-month treatment with enzalutamide (Table 3). The cost/LYG and cost/PoS were superimposed at US\$230,000. The RV of radium-223 dichloride was 0.22 and 0.43 from NICE and US perspectives.

**TABLE 1** Cost and outcome in chemotherapy-naïve mCRPC patients<sup>a</sup>

Drug or combination	OSg (HR)	Cost, US\$	Cost/OSg, US\$	Cost/LYG (RV), US\$	Cost/PoS (RV), US\$
Docetaxel, 75mg/m <sup>2</sup> q 3 wk, IV	72 (0.76) [CI not given]				
x10 cy		3,508	49	17,540 (5.70)	14,617 (6.84)
x10 cy + ancillary costs		5,266	73	26,330 (3.80)	21,942 (4.56)
Abiraterone					
1,000 mg po x12 mo (COU-AA-302 trial)	132 (0.80) CI, 0.69-0.93	74,400	64	202,910 (0.49)	372,000 (0.27)
Enzalutamide					
160 mg po x12 mo (PREVAIL trial)	66 (0.70) CI, 0.59-0.83	89,400	1355	487,636 (0.21)	298,000 (0.34)
Sipuleucel-T					
Dose per drug insert, IV x3 doses	123 (0.78) CI, 0.61-0.98	93,000	756	272,195 (0.37)	422,727 (0.24)

CI, confidence interval; cy, cycles; HR, hazard ratio; IV, intravenously; LYG, life-year gain; mCRPC, metastatic castrate-resistant prostate cancer; mo, month; OSg, overall survival gain over control in days; po, orally; PoS, probability of survival; RV, relative value

<sup>a</sup>The drugs were tested in asymptomatic and minimally symptomatic patients. The QoL was unchanged. RV was calculated as 100,000/cost per outcome.

## Discussion

Patients with cancer were reported to be at higher risk of bankruptcy<sup>27</sup> in part because of the run-away costs of their drugs.<sup>28-30</sup> The many efforts to try to bend the cost curve<sup>31</sup> have so far not resulted in meaningful control of the costs of anticancer drugs. Lack of affordability has resulted in low- and some middle-income patients skipping some of their doses, stopping their medications, or failing to buy the prescribed drugs in the first place.<sup>19,20</sup> Attention has recently been focused on drug value defined as the patient's outcome per dollar spent.<sup>32-34</sup> The primary objective of the present investigation was to estimate the fair and equitable amount that a patient and society should pay for a drug to secure an acceptable outcome. It was found necessary to impose limits on values to achieve the desired tight control. The simple and intuitive nature of the model could facilitate transparency and full disclosure of cost information to patients and nonmedical personnel.<sup>36</sup> The RV system would probably lead to easier communication of cost issues with patients. The model was flexible enough to be

able to accommodate changes in number of cycles, prices, and outcome. Each drug was evaluated within a few minutes once the data had been collected. It was fitting to test the applicability and feasibility of the system in patients with mCRPC because all of the evaluated drugs demonstrated a gain in OS. The model could be applied to other survival endpoints.

## Costs

We noted that costs varied with the amount of drug that was purchased and by purchasing agent. During the present study, all of the drugs evaluated with exception of docetaxel had patent protection. The disparity in value between docetaxel and cabazitaxel was partly due to costs, because both of them demonstrated the same OS gain of 72 days.<sup>2-4</sup> Of note, cabazitaxel is presently used when resistance to abiraterone and enzalutamide develops. The costs of generic docetaxel were much lower than those of its trade counterpart, making the case for generic drug use whenever possible.

**TABLE 2** Cost/outcome and RV of cabazitaxel in chemo-treated patients with mCRPC<sup>a</sup>

Cabazitaxel dose and schedule	OSg (HR)	Cost, US\$	Cost/OSg, US\$	Cost/LYG, US\$	RV: \$50,000
25 mg/m <sup>2</sup> , IV	72 (0.70)				
q3w x6 cy	CI, 0.59 & 0.83	34,350	477	171,750	0.29
x6 cy + ancillary costs		41,448	576	207,240	0.24
x10 cy + ancillary costs		46,180	641	230,900	0.22

CI, confidence interval; cy, cycles; HR, hazard ratio; IV, intravenous; LYG, life-year gain; mCRPC, metastatic castrate-resistant prostate cancer; OSg, overall survival gain over control in days; q, every; RV, relative value; w, week

<sup>a</sup>Due to lack of QoL improvement by cabazitaxel, a \$50,000 limit on cost/outcome was imposed.

**TABLE 3** Cost/QALY in chemo-treated patients with mCRPC: UK and US perspectives<sup>a</sup>

Drug/combination	OSg (HR)	Cost, US\$	Cost/OSg, US\$	Cost/LYG, US\$	Cost/QALY, US\$	
					UK RV, \$50,000	US RV, \$100,000
Abiraterone 1,000 mg po x12 mo (COU-AA-301 trial)	138 (0.74) CI, 0.64-0.86	74,400	539	194,087	0.26	0.52
Enzalutamide 160 mg po x12 mo (AFFIRM trial)	144 (0.63) CI, 0.53-0.75	89,400	621	223,500	0.22	0.45
Radium-223 dichloride dose per drug insert, IV x6 doses (ALYSMPA updated analysis)	108 (0.695) CI, 0.55-0.88	69,000	639	230,000	0.22	0.43

CI, confidence interval; HR, hazard ratio; IV, intravenously; LYG, life-year gain; mCRPC, metastatic castrate-resistant prostate cancer; mo, month; OSg, overall survival gain over control in days; po, oral; QALY, quality adjusted life-year; QoL, quality of life; RV, relative value

<sup>a</sup>The drugs were reported to improve patient QoL.

## Value

The present work clearly demonstrated that docetaxel offered the best value for the money spent with highest RV irrespective of HR or survival used. All of the other drugs evaluated, including sipuleucel-T, abiraterone, enzalutamide, and radium-223 dichloride, were overpriced for their values. The cost/LYG of cabazitaxel in a refractory and incurable disease was excessive at US\$207,240 and with an RV of 0.29. The drug at lower dose and/or earlier lines of treatment might be more cost effective. Sipuleucel-T's cost/LYG ranged from US\$272,195 to US\$422,727 at an RV of 0.24-0.37. The cost was too high for a drug indicated in asymptomatic or minimally symptomatic patients with no marker to follow the disease process. Payment of >US\$200,000 per year-life gained should automatically trigger serious reconsideration on drug values. Drugs with an RV of <0.5 should be scrutinized, costs negotiated, or other options considered, and those of < 0.25, rejected.

## Cost/outcome, HR, and survival data

Results of costs/QALY are more open to authors' interpretations than are those for cost/LYG. Cost/QALY seemed to be inflated in contrast to the raw data of cost/LYG. Survival data are usually more susceptible to variation along the time curve than are those for the HR. Survival was not reached at the closure of some studies. Incorporation of the HR could improve the interpretation of outcome with less room for errors. The present work demonstrated that the median OS gain in mCRPC was 90 days. Some patients do not respond, cannot tolerate treatment, or succumb to their disease in few weeks or few months. Cost/OS gain in days would relate better than cost/LYG to patients with limited survival expectancy. The impact of communicating the HR of death and recurrence could be frightening to patients in contrast to the softer and more promising probability of survival (PoS).

## Limitations

The amount of limits on cost/outcome are open to debate and criticism. However, these limits could be scaled downward or adjusted upward to suit various patients, budgets, and societies. Nonetheless, drugs with RVs of <0.5 should be suspect and their costs negotiated. The proposed model was not designed to compare one drug with another unless their values were clearly separated. The wide variations in populations, the biology of CRPC, magnitude of hormone-resistance, and extent of symptomatology of patients precluded drug comparison. In addition, there are distinct differences between the various drugs evaluated. Abiraterone and enzalutamide are administered orally with saving over the IV administration and/or the elaborate drug preparation of sipuleucel-T. Oral administration of capecitabine resulted in cost savings.<sup>38</sup> Prednisone was recommended with abiraterone but not with enzalutamide. Ancillary treatments of cabazitaxel and to a lesser extent of docetaxel were costly, in contrast to those of abiraterone and enzalutamide. Cabazitaxel, abiraterone, and enzalutamide were priced per cycle over a certain time period. The cost of radium-223 dichloride and sipuleucel-T were based on the total treatment course. The different pricing systems rendered economic drug comparison challenging.

## Conclusions

A simplified drug model to weigh cost, survival, and HR with imposed limits on costs was proposed and applied to patients with mCRPC. The results among that patient population suggested that generic docetaxel had the lowest costs and cost/outcome, and the highest RV. Sipuleucel-T, abiraterone, enzalutamide, radium-223 dichloride, and cabazitaxel were overpriced for their values. Drugs with RVs of <0.5 should be scrutinized, their costs negotiated, or other drugs considered, and those with RVs of <0.25 should be rejected.

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