Short Communication

Costs and Values of Anticancer Drugs in Prostate Cancer: Drug Innovations versus Generics

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Abstract

**Background:** California and Ohio are considering legislative measures to reduce prescription drug prices.

**Objectives:** 1- Design a grading system to control costs and improve transparency of anticancer drugs. 2- Weigh costs and values in relative values (RV) in metastatic prostate cancer (mPC)

**Methods:** Updated overall survival (OS), hazard ratios (HR) and dosage were utilized. Costs of 1-day of added OS were calculated. The 1-year-cost (yC) were graded (gr) A < 50,000, B $50,000 to $75,000, C > $7,500 to $100,000 and D > $100,000. The yC was divided by (1.0 –HR) and compared with cost/life-year gain (C/LYG). RV were computed as $50,000 or $100,000/C/LYG depending on lack vs. maintenance/improvement of quality of life (qol). Grade D was assigned to <0.20, C: 0.20 - 0.35, B: 0.35- 0.50 and A: > 0.50.

**Results:** Costs, values and RV of generic docetaxel demonstrated A/gr. Cabazitaxel yC was $ 52,734 with B/gr and enzalutamide $108,348 with D/gr. In chemo-treated patients, RV of cabazitaxel was 0.19/D, abiraterone 0.39/B, enzalutamide 0.37/B and radium-223 0.39/B. In chemo-naive, enzalutamide RV was 0.17/D. All drugs demonstrated wide differences between C/(1.0-HR) and C/LYG. The 2 values of radium-223 however were superimposed at the reported OS and HR.

**Conclusions:** Docetaxel remains the most cost-effective drug in mPC management. The lowest values were demonstrated by enzalutamide in chemo-naive patients. Decisions based on costs without value consideration were misleading. Radium-223 demonstrated superimposed C/LYG and C/(1.0-HR). The wide value discrepancy observed with other drugs suggests parallel use of survival and HR and warrants further investigation.

**ABBREVIATIONS**

CRPC: Castrate-Resistant Prostate Cancer; CN: Chemo-Naïve; CT: Chemo-Treated; CI: Confidence Interval; C: Cost; C/LYG: Cost/Life-Year Gain; dC: Cost Of 1-Day Of Added Overall Survival Over Control; D: Day; GR: Grade; HR: Hazard Ratio; HS: Hormone Sensitive; IV: Intravenous; M: Metastatic; MG: Milligram; M: Month; RV: Relative Value; Y: Year

**INTRODUCTION**

Docetaxel has been the backbone of prostate cancer management since 2004 [1]. Over the last 10 years cabazitaxel [2], sipuleucel-T [3,4], abiraterone [5,6], enzalutamide [7,8] and radium-223 dichloride [9] were developed. These drugs demonstrated significant prolongation of overall survival (OS) with documented safety in metastatic castrate-resistant prostate cancer (CRPC). The high costs (C) however restricted affordability [10]. Legislative measures are being contemplated in California and Ohio to reduce prescription drug prices. The American and the European Societies of Medical Oncology recently reported models to score and weigh the clinical benefits of drug treatment. In the United States (US) the average cost-effectiveness ratios (ACER) of $100,000 per quality adjusted life-year (QALY) are considered acceptable. We previously postulated that the American society was willing to pay up to a total sum of $100,000 per year (y) with $50,000 for OS gain and $50,000 for quality of life (QoL) [11]. Our objectives were 1- Design a simplified grading system to control anticancer drug costs, clarify values and improve transparency for patients 2- Weigh costs and values in relative values (RV) in metastatic prostate cancer (mPC)

**METHODS**

Previously reported OS, hazard ratios (HR), dosage and 2015-16 drug prices were utilized. Median OS gain by the drug over
control and costs of 1-day of added OS (dc) were calculated. The 1-year-cost (yc) were graded A/gr < 50,000, B $50,000 to $75,000, C > $75,000 to $100,000 and D > $100,000. The yc was divided by (1.0 -HR) and compared with C/LYG. Relative Values (RV) were calculated as the total sum of $100,000/C/LYG for maintenance or improvement of QoL and $50,000/C/LYG for lack of. A D/gr was assigned to <0.20, C: 0.20 - <0.35, B: 0.35- 0.50 and A: > 0.50.

RESULTS

Docetaxel, a taxane inhibitor of microtubule depolymerization was recently evaluated in hormone-sensitive (HS) [12] and hormone-resistant patients. Costs, C/LYG and RV earned A/gr. Cabazitaxel, a newer generation semi-synthetic taxane was designed to overcome docetaxel resistance in refractory disease. Primary prophylaxis with colony stimulating factors and other ancillary treatment increased the costs to $52,734 with B/gr. Due to lack of QoL improvement, the RV decreased to 0.19/D (Table 1).

Sipuleucel-T, an autologous immunotherapeutic agent demonstrated OS gain of 4 months (m) in asymptomatic or minimally symptomatic CRPC. The OS gain increased at lower PSA levels. There was no reported marker to follow the disease process. The $93,000 costs included the complex preparation and the 3-cycle course. The cost was graded C, the dc 756, C/LYG 272,195 and RV 0.37/B.

Abiraterone is a potent and selective small-molecule inhibitor of testosterone synthesis, possibly more potent and selective than ketoconazole. Enzalutamide targets multiple steps in the androgen receptor–signaling pathway with a higher receptor-affinity than that of the first-generation drugs. The yc of enzalutamide was $108,738/D, approximately 11% higher than abiraterone of $97,920/C. In chemo-naïve (CN), the 1-day cost of added OS (dc) by abiraterone was $742 and enzalutamide $1642. Abiraterone C/LYG was 267,055 compared with C/(1.0 -HR) 489,600. Enzalutamide C/LYG was 590,980 vs. C/(1.0 -HR) 361,160. The RV of enzalutamide in CN patients was low at 0.17/D.

The laws in US prohibit discussion of anticancer drug costs during the approval process. California is contemplating legislation of The Drug Relief Act to reduce prescription drug prices. Ohio is considering a similar measure. In the present work, a grading system was proposed to control costs, disclose expenditure and improve transparency for patients [13,14]. Assessment of values relative to an acceptable standardized reference was presented as a reasonable compromise over unpopular and contentious policies of imposing limits. Drugs for adjuvant and curable intent were excluded from analysis. Overall survival data were exclusively used. All drugs evaluated had patent protection with the exception of decetaxel.

Generic docetaxel proved to be the most cost-effective drug in all settings of prostate cancer deserving A/gr in cost, values and RV. The value disparity between docetaxel and cabazitaxel was mostly due to costs, since both drugs demonstrated the same OS gain of 72 days [1,2]. The lack of QoL improvement by cabazitaxel in refractory disease decreased the RV to D/gr, despite its relatively low cost and B/gr. The finding of AR-V7 in circulating tumor cells as predictive of resistance to abiraterone and enzalutamide [15] could lead to timely and earlier use of cabazitaxel.

Enzalutamide reduced the risk of radiological progression and delays initiation of chemotherapy [8]. However, the OS gain in CN patients was limited to 66 days. The dc was excessive at $1,642 with RV 0.17/D. In contrast, enzalutamide, abiraterone

### Table 1: Costs, values, RV and Grades (/gr) of Taxotere in Hormone-resistant and Hormone-sensitive (HS).

<table>
<thead>
<tr>
<th>Drug</th>
<th>OSg &amp; HR</th>
<th>yc &amp; gr</th>
<th>yC/LYG &amp; RV/gr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 75mg/m² iv q 3 weeks, Hormone-resistant [1] + ancillary C</td>
<td>72 (0.76)</td>
<td>7,500 A/gr</td>
<td>37,500 2.67/A</td>
</tr>
<tr>
<td>Docetaxel 75mg/m² iv q 3 weeks HS [22] + ancillary C</td>
<td>408 &amp; 0.61 CI: 0.47- 0.80</td>
<td>7,500 A/gr</td>
<td>6,618 15.10/A</td>
</tr>
</tbody>
</table>

### Table 2: Costs, Values, RV and Grades (gr) in Chemotherapy-treated (CT) mCRPC.

<table>
<thead>
<tr>
<th>Drug</th>
<th>OSg &amp; HR</th>
<th>yc/gr</th>
<th>yC/(1.0-HR)</th>
<th>yC/LYG &amp; RV/gr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone 1000mg po x12 m (COU-AA-301)</td>
<td>138 &amp; 0.74 CI: 0.64 – 0.86</td>
<td>97,920 C/gr</td>
<td>37,615</td>
<td>255,443 0.39/B</td>
</tr>
<tr>
<td>Enzalutamide, 60mg po x12 m, AFFIRM</td>
<td>144 &amp; 0.63 CI: 0.53 – 0.75</td>
<td>108,348 D/gr</td>
<td>292,832</td>
<td>270,870 0.37/B</td>
</tr>
<tr>
<td>Radium-223 iv x 6 doses, ALYSPMCA</td>
<td>108 &amp; 0.70 CI: 0.55–0.88</td>
<td>76,000 C/gr</td>
<td>253,333</td>
<td>253,333 0.39/B</td>
</tr>
<tr>
<td>Cabazitaxel 25mg/m² iv q3w x 6 cy [4] + ancillary costs</td>
<td>72 &amp; 0.70 CI: 0.59 &amp; 0.83</td>
<td>52,734 B/gr</td>
<td>174,780</td>
<td>263,670* 0.19/D</td>
</tr>
</tbody>
</table>

*Due to lack of QoL improvement by cabazitaxel, RV was calculated as $50,000/C/LYG.
and radium-223 in CT patients demonstrated RV ranging from 0.37/B to 0.39/B. The C/LYG and C/(1.0 – HR) of radium-223 were similar at OS gain of 108 days and HR of 0.70. All other drugs demonstrated wide value variations.

LIMITATIONS

Head to head comparative studies of drug costs and values are scarce. The $100,000 reference was higher than that adopted by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK). NICE does not approve ACER of >20,000-30,000 pound per QALY gained. It is rather difficult to put price tags on the quantity and quality of life since they vary between one patient or physician and another. Differences in populations, biology of CRPC, magnitude of hormone-resistance, extent of patients’ symptomatology preclude fair drug comparison. In addition, there are distinct differences between the various drugs. Abiraterone and enzalutamide are administered orally with saving over IV administration. Treatment costs of AEs of chemotherapeutic drugs could be and were expensive than that of other drugs. Nonetheless, each drug accounted for its own values as exemplified in the weight of RV.

The present investigation has illustrated the high cost of innovations in drug development. The highest costs and lowest values were demonstrated by enzalutamide in chemo-naive CRPC patients partly due to limited OS gain. Docetaxel still remains the most valuable drug in mPC management. Its low costs and high values encourage widespread use of generics making it difficult for new drugs to compete. However, the power of generics to curtail drug costs ought to be tempered and balanced against their limitations. The generic ketoconazole, flutamide and bicalutamide may not be as potent, selective or safe as abiraterone or enzalutamide.

Decisions based on costs without value consideration were misleading. The wide discrepancy between C/LYG and C/(1.0 – HR) observed with drugs other than radium-223 suggests parallel use of survival and HR and warrants further investigation. New laws are needed to secure a fair drug price for an equitable value. Meanwhile, drug costs need to be negotiated, litigations minimized and innovations rewarded.

REFERENCES


Cite this article