Cost Utility of Prostate Cancer Chemoprevention with Dutasteride in Men with an Elevated PSA

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Running Head: Cost Utility of Prostate Cancer Chemoprevention in Men with an Elevated PSA

Key Words: Chemoprevention, Prostate Cancer, Quality of Life, Decision Analysis Model, REDUCE, Dutasteride

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ABSTRACT

Background
In the REDUCE trial, dutasteride reduced the relative risk of prostate cancer (CaP) diagnosis over a 4 year period by 22.8% but questions remain regarding the cost-effectiveness of widespread utilization. We evaluated the cost-utility of chemoprevention using dutasteride in men at elevated risk for CaP.

Methods
A Markov decision analysis model with probabilistic sensitivity analysis was designed to determine the lifetime prostate-health-related costs, beginning at age 50, for men treated with dutasteride compared with placebo who are at elevated risk for CaP. Model assumptions were based on data in REDUCE; Surveillance, Epidemiology, and End-Results program; literature review of costs, utilities, and transition rates among various prostate cancer health states; and local institutional cost data.

Results
Under the assumptions of the base case analysis, dutasteride chemoprevention is associated with a gain of 108 QALYs per 1000 men and the quality-adjusted cost-effectiveness ratio for dutasteride compared to men not receiving chemoprevention was $140,240 per QALYs. At a cost of $626 per year, down from the current cost of $1400, the model predicts a cost benefit from dutasteride with a willingness to pay threshold lower than $50K. Assuming a 15% period prevalence renders an incremental cost-effectiveness ratio of $576,630 per QALYs and a 30% period prevalence would yield a $98,059 per QALYs.

Conclusions
Dutasteride is unlikely to be cost-effective when considering the impact on survival differences among treated versus untreated groups. However, chemoprevention may be cost-effective in high risk populations when taking into consideration adjustments for the impact on quality of life.
INTRODUCTION

The Prostate Cancer Prevention Trial (PCPT) used the 5 alpha-reductase inhibitor finasteride to prevent prostate cancer in a prospective randomized trial.(1) The trial demonstrated a nearly 25% reduction in the prevalence of prostate cancer compared with placebo. Finasteride is a type 2-specific 5 alpha-reductase inhibitor, whereas dutasteride is an inhibitor of both type 1 and type 2 5 alpha-reductase.(2) Evidence indicating that there may be increased expression of the type 1 5 alpha-reductase in prostate cancer versus benign prostate tissue prompted the REDUCE trial which evaluated the impact of chemoprevention using the dual 5 alpha-reductase inhibitor dutasteride in a group of men identified at increased risk of developing prostate cancer.(3) The REDUCE trial recruited patients with an elevated PSA and a previous negative biopsy. Among men who underwent a biopsy or prostate surgery, dutasteride conferred a 22.8% relative risk reduction in the prevalence of prostate cancer over the 4-year study period. Dutasteride therapy, as compared with placebo, also resulted in a reduction in the rate of acute urinary retention and need for surgery for benign prostatic hypertrophy. While the risk reduction in prostate cancer incidence was significant, the reductions were limited to patients with Gleason 6 prostate cancer and there was no survival benefit demonstrated.

Prior to instituting a chemoprevention strategy to a large population, the utility and cost need to be well understood. How will a drug improve survival, quality of life and the financial implications are all critical issues especially when the population numbers in the millions. Studies such as the PCPT and REDUCE did not evaluate these outcomes so they need to be extrapolated from the data using cost-utility modeling. We previously created a markov model based on the results of PCPT to predict the cost-effectiveness and quality adjusted cost-effectiveness of chemoprevention using finasteride to prevent prostate cancer.(4;5) The REDUCE trial utilized dutasteride in men with higher risk for prostate cancer as compared with the PCPT. In this study, we evaluated the cost utility of using Dutasteride in prevention of prostate cancer in this population taking into consideration cost, survival and quality of life implications.
METHODS

Assumptions

The study design is a cost-effectiveness analysis from a societal perspective. Similar to the REDUCE entry criteria, the base case was assumed to have a PSA of 2.5-10.0 mg per milliliter, a normal biopsy within 6 months of study entry, absence of severe lower urinary tract symptoms (IPSS <25 and Qmax ≥5ml/sec), and a prostate volume of ≤80ml.(3) The base case is a 50 year old man who receives daily dutasteride treatment for a total of 25 years or until prostate cancer is diagnosed. Incidence rates for prostate cancer were based on for-cause and end-of-study biopsy detection rates in the REDUCE study. Incidence rates for men age ≥75 were based on 2007 SEER data.(6) Incidence rates among dutasteride-treated and non-treated men were derived from the dutasteride-treated and placebo-arm, respectively, in the REDUCE trial. A yearly relative risk reduction afforded by dutasteride was applied to men taking dutasteride.(3) The Gleason score distribution found in the dutasteride and placebo arms of the REDUCE trial was utilized for the group receiving dutasteride and placebo, respectively, in the model. Because the REDUCE trial observed a disproportionately higher percent of Gleason 7-10 in the Dutasteride arm, the absolute number of high grade cancers (Gleason score 7-10) was similar for the placebo and Dutasteride arms, while reduction in cancer occurred primarily for Gleason 6 cancers like outcomes for REDUCE. The cost of treatment for prostate cancer was estimated based on the assumption that 50% of men would be treated with radical prostatectomy and 50% would be treated with radiation therapy. Men who experience adverse side effects, such as erectile dysfunction, loss of libido, and gynecomastia, as a result of chemoprevention are assumed to discontinue medication within the first year of initiating dutasteride treatment. The incidence of BPH for men was estimated from age-matched community-based population estimates but assumed to be increased slightly due to higher risk among men with elevated PSA (BPH incidence 20% for men less than 75 was 25% for men 75 years of age or older).(7) Men with symptomatic benign prostatic hypertrophy (BPH) were treated with medication (95%) or surgery (5%). Therefore, for...
men with symptomatic BPH, receiving dutasteride chemoprevention, the extra cost for medication treatment of BPH symptoms was equal to the cost of an alpha-blocker. For men not receiving chemoprevention, cost of medication included alpha-blocker therapy (60%), dutasteride (30%), or combination of alpha-blocker therapy and dutasteride (10%). Rates of retention and surgery from REDUCE were not used for the placebo group since those men were not allowed to initiate a 5 alpha-reductase inhibitor during participation in the trial. Such therapy might have prevented retention episodes and surgery.(7) In a “real-world” environment, a man with symptoms and enlarged prostate would usually be initiated on a 5 alpha-reductase inhibitor rather than be allowed to progress to surgery. This is consistent with our assumptions.

The cost per life-year saved is the difference between the lifetime costs for the chemoprevention group and placebo group divided by the gain of life years (LYs). Results for quality adjustment are displayed as cost per quality-adjusted life-years (QALYs) saved. An annual discount rate of 3% was applied to future costs and future years of life.(8;9) Discounting is necessary when the experience of the patient in the near term is valued more than future costs and health outcomes.(8) We assumed 40% of men experiencing biochemical recurrence would incur the additional cost of yearly lupron.(9) Model assumptions are shown in tables 1 and 2.

Health utility states were gathered from the available literature (10). However, for the patient without any complications following a radical prostatectomy for low risk disease, we set the baseline health utility state at 0.97 reflecting a 0.03 disutility form the baseline patient (table 1). Illustration of model structure is shown in the appendix. All costs were updated to 2009 U.S. dollars with the Gross Domestic Product Deflator Inflation Calculator.(11). Markov modeling was designed with TREEAGE PRO HEALTHCARE (Treeage Pro Healthcare. In. Williamstown, MA: Treeage Software; 2004).

The long-term progression and survival rates for patients treated with radical prostatectomy are based on literature regarding the natural history of treated prostate cancer,(12;13) To approximate the likely outcomes of men diagnosed with prostate cancer in a heavily screened population, we utilized publications characterizing outcomes among patients with low stage disease (T1c and T2a-b) in the PSA era when
available. Transition rates for biochemical recurrence at 5, 10, and 15 years from treatment were based on validated nomograms for various cancer grades.(12) Transition rates for metastasis and death were based on data by Pound and associates.(13)

**Health State Utilities**

Estimates of quality of life for various prostate cancer- and treatment-related health states are shown in table 1. These were adapted from prior studies examining outcomes in men with and without prostate cancer.(10;14;15) In these reports, values are assigned to various health states on a scale ranging from 0 (dead) to 1 (perfect health). Disutility for men with symptomatic BPH was estimated to be 0.05 based on a higher disutility of 0.12 in men with untreated BPH(10) since we assumed that all men with symptomatic BPH were treated. For post-prostatectomy NED, asymptomatic metastasis, and symptomatic metastasis health states, a standard deviation of 0.06 was applied the group but the relative impact of worse disease states on QOL were maintained.

**Sensitivity Analysis**

Sensitivity analysis was performed to investigate the effect of adjusting base case assumptions, including the cost of dutasteride, the estimated period prevalence of prostate cancer for the population, and the willingness-to-pay threshold. Uncertainties in values are considered simultaneously using probabilistic sensitivity analysis. The probability distributions for model variables were derived from the literature. (10) For cost estimates, average and standard deviations determined from available cost estimates were used to define normal distributions. For all other cost estimates, baseline values +/- 20% were used to define triangular distributions. 5000 Monte-Carlo samples were used for probabilistic sensitivity analysis. An acceptability curve was created to examine the probability of chemoprevention cost-effectiveness dominating over placebo across various willingness-to-pay thresholds. This was based on evaluating the model over the ranges of values in tables 2 and 3.
RESULTS

Under the assumptions of the base case analysis, the mean (SD) quality-adjusted life years (QALY) after age 50 for men taking dutasteride was 25.54 (0.21) QALYs and this chemoprevention strategy cost $29,293 ($936) per person. This compared to a mean (SD) of 25.43 (0.28) for men not taking dutasteride and a cost of $14,194 ($1,501) per person. Dutasteride chemoprevention is associated with a gain of 108 QALYs per 1000 men and the quality-adjusted cost-effectiveness ratio for dutasteride compared to men not receiving chemoprevention was $140,240 per QALYs.

Probabilistic Sensitivity Analysis

The precision of our ICER estimate is graphically represented in Figure 1. The probability that an incremental cost-effectiveness ratio (ICER) less than $100,000 per QALYs could be realized under model assumptions was 27.2%. On the other hand, the probability that an ICER of more than $100,000 per QALYs could be realized under model assumptions was 72.8%. These estimates were also displayed with an acceptability curve, which relaxes the willingness to pay (WTP) threshold assumption (Figure 2). This figure illustrates the probabilistic sensitivity analysis across various WTP thresholds. Assuming a WTP threshold of $50,000 per QALYs, the probability that chemoprevention is more cost-effective than no chemoprevention is less than 10%. However, assuming a WTP threshold of $200,000 per QALYs, the probability that chemoprevention is more cost-effective than no chemoprevention is 66%.

Sensitivity Analysis for Cost and Prevalence Estimates

A one-way sensitivity analysis relaxing the assumptions regarding the cost of dutasteride is shown in Figure 3. At a cost of $626 per year, down from the current cost of $1400, the model predicts a cost benefit from dutasteride with a willingness to pay (WTP) threshold lower than $50K. For the base case model, we assumed a 25 year period prevalence of 25% based on estimates taken from the REDUCE trial. However, a tornado diagram indicated that the model estimates are particularly sensitive to the period-prevalence (data not shown) and therefore a one-way sensitivity analysis was performed.
performed to examine the influence of this period prevalence on the model estimates. Assuming a 15% period prevalence renders an ICER of $576,630 per QALYs and a 30% period prevalence would yield $98,058 per QALYs. Table 3 demonstrates the cost per QALYs for varying costs and prostate cancer prevalence. With current costs, the QALYs for dutasteride exceed $50,000 even if 30% of men develop prostate cancer. However, reducing the cost to $700 at 30% cancer prevalence would result in less than $50,000 per QALY. With a cost around $350 per year, the prevalence of cancer can decrease to close to 15% while maintaining a QALYs of $84,912.

DISCUSSION

The PCPT and REDUCE trials targeted patients at disparate risk for development of prostate cancer but both found a similar relative risk reduction of approximately 23-24%. (1;3) This study and previous analyses of the PCPT found a modest survival advantage in the chemoprevention arms of the studies. (4)(5;16) The survival advantage of 108 QALYs per 1000 men conferred by Dutasteride is small but not surprising. The risk reduction of prostate cancer was in men with Gleason 6 disease and these men are almost all cured by therapy once diagnosed. (17) When one considers the high cost of $140,240 per QALYs, one must consider the fact that every man in the prevention arm accrues the cost of dutasteride of almost $1400 per year while only a small number of men (5 out of 100) will be prevented from getting a prostate cancer diagnosis and even a smaller percentage will benefit from either QOL benefits (avoidance of anxiety related to cancer, disease progression, incontinence, impotence, etc.) or have a survival benefit. While there are benefits in reducing the impact of benign prostatic hypertrophy (BPH), we assumed that patients who became symptomatic would get appropriate treatment for their BPH. This is unlike the REDUCE trial where patients in the placebo arm were denied a 5-alpha reductase inhibitor and suffered from retention and surgery for BPH at higher than expected rates over a 4-year period.

While the cost per QALYs is high in our baseline scenario, it can be decreased by identifying patients at higher risk of disease based on family history or other factors such as potentially genetic variants. (18) However, the REDUCE trial studied the
chemoprevention properties of dutasteride among a group of men with an elevated PSA and a previously negative biopsy. Identification of a subpopulation within this group that would likely benefit narrows the target population to which this drug may be applied even further. On the other hand, reduction in the cost of Dutasteride will also reduce the cost per QALYs. One should also recognize that the high cost from a societal perspective does not impact an individual’s decision to utilize their own resources to reduce their risk of prostate cancer. In 2007, adults in the United States spent $22 billion out of pocket on complementary and alternative medicine. The vast majority of these products have not been extensively studied in randomized trials that have demonstrated a benefit over placebo. Certainly, one can surmise that men at risk for prostate cancer may be willing to spend of their own money for the possibility of reducing the likelihood of developing prostate cancer especially considering the low toxicity of 5-alpha reductase inhibitors. On the other hand, the implications on society of widespread utilization that is paid for by insurance or the government can result in extremely high costs. Based on the 2010 census there are approximately 34 million men between the ages of 50 and 70. If this population were to initiate a chemopreventive medication at the cost of $1000 per year, the cost to the health care system would be 34 billion dollars per year. As the U.S. population ages this figure could increase further. It is also possible that men under the age of 50 would initiate therapy and that men over the age of 70 might continue the drug. One needs to consider that cost of the drug could be significantly decreased especially if used on a widespread basis. There are other examples of expensive drugs such as those used for treating HIV infection whose costs were dramatically decreased to allow treatment of large populations outside the U.S. At a cost of $350 per year there could be many men with sufficient risk of cancer to justify the use from a financial standpoint using a threshold of $50,000 per QALYs.

There are several potential limitations to our model. The small number of cancers diagnosed for-cause in the REDUCE trial limited our ability to estimate impact of dutasteride without including the cancers diagnosed by the end-of-study biopsy. In addition, the age-specific incidence of prostate cancer, therefore, was not applied to the dutasteride arm. There are concerns regarding the accuracy of cost and transition rates
given the variability of different practice patterns, local costs, and differences in prostate cancer outcome found in published series. In tables 1 and 2, we used a range of values to try to account for variance and in figure 1 it can be seen that over this range, there is not significant variability in the model. It is not known whether chemoprevention results in sustained effects of risk reduction in prostate cancer throughout a person’s life or following discontinuation of the drug. It is possible that utilization of the drug for only a short period of time could confer long-term effects, which would make the drug more cost-effective.

CONCLUSIONS

Dutasteride is unlikely to be cost-effective using a threshold of $50,000 per QALYs when considering the impact on survival differences among treated versus untreated groups. However, chemoprevention may be cost-effective in high-risk populations when taking into consideration adjustments for the impact on quality of life or with significant reductions in the cost of treatment.
Table 1. Health Utilities and Rate Assumptions (10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (SE)</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health States</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Prostatectomy with No Evidence of Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason Score 6</td>
<td>0.97 (0.02)</td>
<td>Normal</td>
</tr>
<tr>
<td>Gleason Score 7</td>
<td>0.91 (0.02)</td>
<td>Normal</td>
</tr>
<tr>
<td>Gleason Score 8-10</td>
<td>0.86 (0.02)</td>
<td>Normal</td>
</tr>
<tr>
<td>Quality of Life with Biochemical Recurrence</td>
<td>0.82 (0.02)</td>
<td>Normal</td>
</tr>
<tr>
<td>Quality of Life with Metastasis</td>
<td>0.60 (0.02)</td>
<td>Normal</td>
</tr>
<tr>
<td>Quality of Life with Erectile Dysfunction</td>
<td>0.89 (0.10)</td>
<td>Normal</td>
</tr>
<tr>
<td>Quality of Life with Incontinence</td>
<td>0.83 (0.10)</td>
<td>Normal</td>
</tr>
<tr>
<td>Quality of Life with Symptomatic Benign Prostatic Hypertrophy Rates</td>
<td>0.90 (0.02)</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Rates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence after Treatment</td>
<td>0.60 (0.1)</td>
<td>Normal</td>
</tr>
<tr>
<td>Incontinence after Treatment</td>
<td>0.20 (0.05)</td>
<td>Normal</td>
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Table 2: Cost estimates

<table>
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<tr>
<th>Description</th>
<th>Parameters/Info</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha blocker</td>
<td>Mean = 1021.5, Std Dev = 445</td>
<td>Normal</td>
<td>Drugstore.com</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>Mean = 1380, Std Dev = 51</td>
<td>Normal</td>
<td>Drugstore.com,walmart</td>
</tr>
<tr>
<td>Lupron</td>
<td>Mean = 9050, Std Dev = 2068</td>
<td>Normal</td>
<td>Drugstore.com</td>
</tr>
<tr>
<td>Biochemical Recurrence</td>
<td>Likeliest 398, Min = 318, Max=477</td>
<td>Triangular</td>
<td>(20)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Likeliest=497, Min=398, Max=596</td>
<td>Triangular</td>
<td>(20;21)</td>
</tr>
<tr>
<td>Terminal Care</td>
<td>Likeliest=43,720, Min=34976, Max=52464</td>
<td>Triangular</td>
<td>(20;21)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Mean = 27,000, Min=21,600, Max=32,400</td>
<td>Normal</td>
<td>(22;23)</td>
</tr>
<tr>
<td>Early surgical complications</td>
<td>Likeliest=2623, Min=2098, Max=3148</td>
<td>Triangular</td>
<td>(22;23)</td>
</tr>
<tr>
<td>TURP</td>
<td>Likeliest=4933, Min=3946, Max=5920</td>
<td>Triangular</td>
<td>(5)</td>
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<tr>
<td>Chemotherapy</td>
<td>Likeliest=20798, Min=16638, Max=24958</td>
<td>Triangular</td>
<td>(5)</td>
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<tr>
<td>Physician Visit</td>
<td>Likeliest=66, Min=53, Max=79</td>
<td>Triangular</td>
<td>(5)</td>
</tr>
<tr>
<td>PSA</td>
<td>Likeliest=26, Min=20.8 Max=31.2</td>
<td>Triangular</td>
<td>Medicare reimbursement 2009</td>
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<tr>
<td>Late complications after surgery per</td>
<td>Likeliest=104, Min 83.2, Max=124.8</td>
<td>Triangular</td>
<td>(5;24)</td>
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</table>
Table 3: Cost effectiveness of Dutasteride varying cancer prevalence and drug costs

<table>
<thead>
<tr>
<th>Period Prevalence</th>
<th>$350/yr</th>
<th>$700/yr</th>
<th>$1400/yr</th>
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<tr>
<td>15%</td>
<td>$84,912</td>
<td>$252,000</td>
<td>$576,630</td>
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<tr>
<td>20%</td>
<td>$31,178</td>
<td>$97,637</td>
<td>$226,758</td>
</tr>
<tr>
<td>25%</td>
<td>$17,676</td>
<td>$58,683</td>
<td>$138,353</td>
</tr>
<tr>
<td>30%</td>
<td>$11,585</td>
<td>$40,969</td>
<td>$98,059</td>
</tr>
</tbody>
</table>
Figure Legends

Fig 1. Sensitivity analysis. Incremental Cost/Effectiveness per QALYs gained of chemoprevention with dutasteride when relaxing assumptions regarding yearly cost of dutasteride.

Fig 2. Acceptability Curve. Incremental Cost/Effectiveness of chemoprevention versus no chemoprevention as a function of the willingness-to-pay threshold.

Fig 3. Sensitivity analysis. Distribution of Estimated Incremental Cost/Effectiveness using Monte Carlo Probabilistic Sensitivity Analysis (5000 samples). The willingness-to-pay threshold of $50,000 is drawn as a reference line on the y-axis.

Appendix

Illustration of model diagram
Reference List


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Cancer Prevention Research

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