Role of Perspective and Other Uncertainties in Cost-Effectiveness Assessments in Advanced Prostate Cancer

Bruce E. Hillner, John D. Roberts

Both its natural history and typical age at presentation make prostate cancer a disease for whose treatment the largest third-party payer is the U.S. taxpayer. Medicare payments for prostate cancer treatment were estimated to be $1.4 billion in 1994 (1). Therefore, the cost-effectiveness analysis by Bayoumi et al. (2) in this issue of the Journal, addressing three critical issues in advanced prostate cancer—medical versus surgical castration, the role of total androgen blockade with castration plus nonsteroidal antiandrogens, and the optimal timing of any of these—is timely and appropriate.

Substantial attention has been directed at potential biases in the reporting and funding of cost-effectiveness analyses of pharmaceutical agents (3,4). Identifying such biases has been easier since de facto national standards were established by the 1996 U.S. Public Health Service’s Panel on Cost-effectiveness in Health and Medicine (5). This report, commissioned by a federal agency (the Agency for Healthcare Research and Quality) at the request of the Health Care Finance Administration (Medicare), has an unusual potential bias: It assumes that the government’s perspective is aligned with that of society—i.e., one that incorporates all costs and effects regardless of who incurs them. In this editorial, we highlight a variety of methods, concerns, and clinical issues within (not against) the cost-effectiveness paradigm.

The costs and quality-of-life tradeoffs associated with the form of therapy intended to lower serum testosterone levels lead to completely different conclusions about the optimal form of therapy depending on one’s perspective. The consensus is that medical and surgical castration is equally effective (or ineffective) at prolonging life and delaying disease-specific complications (6). From a societal and Medicare perspective, the obvious preferred strategy is orchietomy based on lower cost. The current choice of 75% of U.S. men is to receive luteinizing hormone releasing-hormone (LHRH) agonists. At least three factors contribute to this choice: a preference for organ preservation, the lack of concern about societal costs on the part of patients, and the financial incentives for prostate cancer physicians.

From a patient’s perspective, there are usually minimal differences between the available choices, since Medicare pays 80%–100% for each type of castration, and other funds often help make up the difference. To date, our society has chosen to insure patient choices for organ preservation. Not only does Medicare pay for LHRH agonists, but it also pays for breast radiation therapy following lumpectomy for breast cancer, despite the fact that breast radiation treatment does not improve survival but only reduces the risk of subsequent local relapse and consequent mastectomy. Bayoumi et al. (2) show that, patient preferences aside, organ preservation in treating prostate cancer is costly and a poor use of societal resources.

How strong is the male patient’s preference for LHRH agonists? A telephone survey by Chon et al. (7) found that 22 of 42 men currently receiving hormonal therapy would be willing to pay an additional monthly discounted expense of $386 for 30 months, based on a formula that determines the net present value of an investment, to avoid orchietomy. Such studies that use hypothetical scenarios, however, are subject to criticism, and the true willingness to pay is, therefore, uncertain. Still, the stated willingness of only about one half of subjects to pay that amount shows that copayments effectively decrease the demand for expensive drugs and that avoiding orchietomy for many men has more monetary value than many would predict.

For the ambivalent patient, the urologist’s recommendation will influence or sway his decision-making. Surgeons are commonly criticized for being quick to cut. So why have so many urologic surgeons shifted to giving hormone injections? From the urologist’s perspective, the financial incentives clearly favor recommending LHRH agonists because of the large difference between the suggested list price and the actual acquisition price. Medicare currently pays hospitals or physician offices 95% of the list price (incorrectly called the “average wholesale price”) of injectable and intravenous therapies. The current average wholesale price of leuprolide and goserelin is about $470 per month. Because of price competition between the two products, the acquisition price is routinely discounted 40% or more. If one urologist had 40 patients over a full year on LHRH agonists, the income from this treatment (before billing expenses) would be about $100,000. An obvious partial solution to address this distortion would be if Medicare began paying prices similar to those negotiated in other Western countries, e.g., the Ontario Drug Benefit plan pays $260 (U.S.) per month (Kroll B: personal communication).

Did the model by Bayoumi et al. (2) start by assuming that all forms of castration were equally effective? Not really. Orchietomy is irreversible, while LHRH agonists are potentially reversible. Only the men taking LHRH agonists can discontinue their therapy, so the statement that LHRH agonists are less effective is inappropriate. The only “what if” analysis explored (of different relative “effectiveness” of LHRH agonists compared with orchietomy) was to use only a single point estimate taken from the meta-analyses where LHRH agonists were 10% less effective, not the 95% confidence interval of the relative effi-

Affiliation of authors: Department of Internal Medicine and the Massey Cancer Center, Virginia Commonwealth University, Richmond, VA.

Correspondence to: Bruce E. Hillner, M.D., Virginia Commonwealth University, Box 980170, Richmond, VA 23298-0170 (e-mail: hillner@hsc.vcu.edu).

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cacy. Therefore, it is an easy and logical step to say that orchitectomy will be the dominant strategy, since it works better and costs less.

The key issue is how to represent, in terms of “quality-adjusted effectiveness,” men’s preference for organ preservation. The quality-of-life weighting or utility assigned to a health state should reflect preferences for the state of health during that time. These preferences are related but not necessarily equal to scores on quality-of-life surveys such as the EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 (8). Bayoumi et al. (2) found that, if the absolute quality-of-life benefit of LHRH agonists compared with orchitectomy was either 4% or 10%, then the cost per quality-adjusted life-year benefit associated with LHRH agonists would be $100,000 and $50,000, respectively. Are such differences realistic? At least the 4% advantage for medical compared with surgical castration probably would be. In a study of women who underwent breast-conserving surgery, Hayman et al. (9) found identical utility score differences for women’s utility preferences associated with having had adjuvant radiotherapy (0.92) versus not (0.88) after surgery, where 1.00 represents perfect health.

The second area addressed is whether androgen blockade combined with nonsteroidal antiandrogens (NSAAs) is cost-effective. The impetus for prior cost-effectiveness analyses on the value of NSAAs was the observation that U.S. prostate cancer patients encounter the opposite incentives from those associated with primary androgen therapy (10,11). Medicare does not pay for any NSAAs, since all are oral medications. Currently, therefore, an individual must make his own cost-benefit assessment of the tradeoffs, which may differ from society’s assessment. Medicare only has to pay the deferred costs of subsequent disease complications. The surprising finding in the analysis by Bayoumi et al. (2) was not that adding NSAAs has a high incremental cost but that the base-case analysis found the quality-adjusted benefits for all NSAAs strategies to be lower than those associated with monotherapy. The sensitivity analyses include, but do not clearly identify, the updated findings of another meta-analysis by the Prostate Cancer Trialists’ Collaborative Group (12), where a 5-year survival benefit of 2%–3% was observed for patients taking NSAAs compared with placebo. U.S. sales of all NSAAs have been declining rapidly since the first NSAAs meta-analyses (13). Patients appear to have swiftly made their own cost-effectiveness calculations that are in accord with these findings.

With the widespread use of prostate-specific antigen (PSA) surveillance, the most common management question is not the base-case scenario of clinically evident localized recurrence put forth by Bayoumi et al. (2) but that of a rising PSA level after definitive primary therapy without metastases on imaging studies. It is a classic setting for a decision analysis model: What is the tradeoff between early treatment with known short- and long-term adverse effects with a future survival benefit of uncertain magnitude? The models consistently assumed no benefits in disease progression, its complications, or death associated with early versus late therapy. It should be obvious that they would find that deferring treatment is cheaper and that starting treatment for a rising PSA level without symptoms is the most expensive option.

We disagree with the base-case assumption that there is no benefit to early initiation of hormonal therapy. The meta-analysis included only three studies (1). Two studies (14,15) were from the 1960s (before the era of PSA), used doses of diethylstilbestrol that contributed substantial mortality from thromboembolic events, and included many placebo-group patients who died without receiving androgen blockade. The third trial of more than 900 British men with locally advanced or asymptomatic metastatic prostate cancer found both an absolute survival advantage for early castration compared with deferred therapy of about 4% and a 50% reduction in spinal cord compression and pathologic fracture (16). Since publication of the meta-analysis, a provocative small (n = 98) but randomized trial from the Southwestern Oncology Group (17) found a dramatic improvement in both disease progression and survival in men having early castration for lymph-node positive disease after radical prostatectomy.

On the other hand, in men without imaging evidence of metastases, the long-term nonsexual consequences of androgen deprivation are being increasingly documented (18–20). Anemia, generalized fatigue, muscle wasting, and osteoporosis would be expected to incur a measurable reduction in quality of life. The current model does not explore any tradeoffs in survival versus quality of life.

If the scientific consensus is that early androgen blockade for locally advanced, lymph node-positive, or asymptomatic metastases has no benefit, then the control arm in current randomized trials should include no immediate androgen therapy. However, our review of current clinical trials listed in CancerNet™ (21) found that seven of seven phase III trials for hormone-sensitive, recurrent disease had in the control arm some form of active treatment (two trials of intermittent androgens, four of continuous androgens, and one of local pelvic radiation therapy). This is not the first time that U.S. investigators’ biases have been reflected in the design of trials. Using active treatment in the control arm is inconsistent with the earlier meta-analysis of three trials (1). Fortunately, a large, randomized trial including quality-of-life and cost-effectiveness end points has reached its target 1200 patient accrual and should be reported soon (EORTC 30943) (22).

Estrogens have been laid to rest as a treatment choice for advanced prostate cancer. The choice between orchitectomy and LHRH antagonists is driven by the value of organ preservation and one’s cost perspective. NSAAs appear to offer minimal health benefits at considerable costs (again, a question of cost perspective). The timing of hormonal intervention is probably the most important issue in the clinical management of patients not cured of prostate cancer. Highlighting the cost-utility ranges, where the data foundation is weakest, and the paradoxical role of perspective would maximize the value of this study to policy makers.

REFERENCES


NOTES

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