Cost-Effective Models for Flutamide for Prostate Carcinoma Patients

Are They Helpful to Policy Makers?

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BACKGROUND. More than 50,000 male patients received hormonal therapy for metastatic prostate carcinoma in 1995. Nonsteroidal antiandrogens, such as flutamide, when used in conjunction with castration, are effective in prolonging the time to progression of disease and survival. Only one-third of newly diagnosed patients with metastatic prostate carcinoma receive flutamide. Physicians may be reluctant to prescribe flutamide because of quality of life, toxicity, and cost considerations.
METHODS. Physician focus groups evaluated quality of life factors for metastatic prostate cancer.
RESULTS. Using quality of life estimates with the National Cancer Institute's (NCI) 0036 clinical trial results, our revised model of flutamide use predicted that, for minimal disease, survival increased by 4.33 quality adjusted months (QAMs) at an incremental cost of $25,000 per quality adjusted life year (QALY) saved and for severe disease, survival increased by 4.11 QAM at a cost of $18,000 per QALY saved. However, if quality of life estimates are used in conjunction with the Prostate Cancer Trialists' Collaborative Group (PCTCG) meta-analysis estimates, survival increased by 2.1 QAM at an incremental cost of $41,000 per QALY saved for persons with severe disease and increased by 2.6 QAM at an incremental cost of $53,700 per QALY saved for persons with minimal disease.
CONCLUSIONS. Using NCI 0036 trial data, flutamide has an incremental cost-effectiveness more favorable than most therapies, while estimates based on the PCTCG found a less favorable outcome for the drug. Concerns about out-of-pocket expenditures and efficacy limit flutamide utilization; quality of life considerations are less cogent. ***Cancer* 1996; 77:1854–61.**

KEYWORDS: combined androgen blockade, cost-effectiveness, flutamide, metastatic prostate cancer, Medicare.

Because of concern over the high cost of health care for cancer, policy makers are focusing on studies that evaluate cost effectiveness.[1-9] Although the clinical efficacy of new pharmaceutical agents is evaluated extensively prior to approval, it often takes several years to obtain estimates of cost effectiveness. These issues are especially important with respect to prostate carcinoma. Prostate carcinoma is the second most common malignancy in men, accounting for 240,000 new cases in 1995.[10] Over 50,000 men with prostate cancer received therapy for metastatic disease in 1993, even with increasing focus on early diagnosis.[11]

Nonsteroidal antiandrogens, such as flutamide, have been shown in some studies to be effective in prolonging the time to progression of disease and overall survival for men with metastatic prostate carcinoma.[12,13] However, these results are controversial. Some physicians may

be reluctant to prescribe flutamide because of concerns that survival benefits may not be as large as shown in the original National Cancer Institute and European Oncology Research Trial Cooperative (EORTC) studies.[14] A recent metaanalysis of 1,542 patients who participated in Phase III clinical trials found only a 9% benefit with combined androgen blockade.[15] There are concerns that the economic hardship of out-of-pocket costs for patients of approximately $250 per month may be too large to merit use of the drug, given the debate about its effectiveness. In addition, some physicians may be concerned that gastrointestinal toxicity, which occurs in 10–15% of patients, may limit its usefulness.

Like many oral anticancer medications, flutamide is not reimbursed by Medicare. Recently, we reported that flutamide therapy had a favorable cost-effectiveness profile, with an estimated cost of $20,000–25,300 per year of life saved, when based on survival benefits observed in the National Cancer Institute Phase III randomized trial (study 0036), or an unfavorable cost-effectiveness profile with an estimated cost of $47,500–60,900 per year of life saved, when based on survival estimates from the Overview study.[12,15,16] These models, however, did not take into consideration decreases in quality of life that occur when flutamide toxicity occurs and benefits in quality of life when time with stable disease is prolonged. There is concern that, even using the favorable estimates from the NCI study, the survival benefits of flutamide may not be "worth it" when one takes into consideration all aspects of quality of life associated with flutamide therapy. In contrast, when using the less favorable estimates from the Overview report, quality of life benefits may improve the cost-effectiveness profile of flutamide. In terms of health policy, a cost-effectiveness estimate of $40,000 per quality adjusted life year (QALY) saved has frequently been used as a cut point for policy makers. This is the estimated cost of renal dialysis to save one QALY for persons with renal failure.[7] This figure can also be compared with the cost per QALY for mammography screening for women over 50 years of age, with a favorable cost-effectiveness profile currently estimated at $20,000–50,000.[7] Therefore, after adjustment for changes in quality of life, if flutamide therapy has an incremental cost of more than $40,000 to save one QALY, then it is likely to be viewed as being too expensive for society. In this study, we developed cost-effectiveness estimates for flutamide therapy that take into consideration quality of life issues. We used two sources of data in these analyses: 1) the results of the National Cancer Institute Intergroup 0036 trial[13] and the Prostate Cancer Trialists' Collaborative Group metaanalysis to model clinical efficacy and 2) focus group results from urologists and oncologists to model concerns over toxicities and quality of life. In sensitivity analyses, we considered cost-effectiveness ratios based on the focus group quality of life estimates. Our objective was to illustrate the strengths and weaknesses of economic models that included quality of life adjustments for evaluating combined androgen blockade (CAB) with flutamide.

METHODS

Quality of Life Assessments

Quality of life estimates for the cost-effectiveness models were based on assessments from convenience groups of physicians who treated large numbers of prostate carcinoma patients. Four focus groups, consisting of 25 urologists and 18 oncologists, were convened at the 1994 American Society of Clinical Oncology meeting in Dallas, Texas, and at the 1994 American Urologic Association meeting in San Francisco, California. Physicians were excluded if they typically saw fewer than five patients per year.

The focus groups probed issues of quality of life for metastatic prostate carcinoma patients, with concentration on regular disease-related symptoms and treatment-related toxicities. After discussing these issues for 1 hour, physicians participated in an exercise to assess trade offs between living a long life with symptoms related to prostate cancer and its therapy or living for a shorter period of time, but without these symptoms. Similar focus group efforts with physicians have been used previously to evaluate quality of life concerns for persons with other malignancies and other nonmalignant diseases.[17,18]

After listing the major concerns related to prostate cancer and flutamide toxicity, physicians were asked time trade-off questions. Specifically, four major states were investigated in this exercise: A) asymptomatic (stable disease); B) stable disease with gastrointestinal side effects from flutamide not severe enough to require discontinuation; C) moderate pain and fatigue (early progression); and D) severe pain and fatigue (late progression). Physician responses were converted from length of life traded off from a presumed 1 year survival to scores from 0 to 1 (utility scores). For example, if a physician felt that prostate carcinoma patients would have equal preference for 12 months of life with stable prostate carcinoma and minimal side effects vs. 11 months of life in perfect health, then the utility score would be 0.92 (11 months/12 months).

Quality of life adjustments to survival estimates were derived by multiplying the quality of life scores with expected time in each health state. For example, a 1 year period of time for a man with stable disease would be adjusted to represent 0.92 QALYs when adjusted by the utility score of 0.92 that is associated with state A. QALYs for stable-disease patients who received flutamide were derived by taking a weighted average for persons with stable disease and no flutamide-related toxicities and QALYs for persons with stable disease and who experienced flutamide-related toxicities, such as gastrointestinal dis-

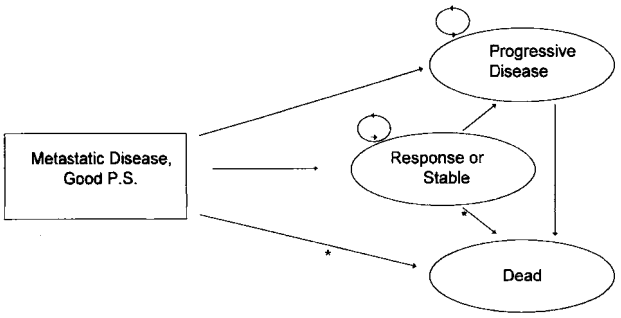

FIGURE 1. Decision-analysis model of prognosis of prostate carcinoma patients over time.

comfort. Similar calculations were used to derive quality of life estimates for progressive-disease patients who received flutamide. Weights were derived from the toxicity results from the National Cancer Institute Intergroup 0036 trial, in which between 13 and 20% of patients experienced gastrointestinal side effects with flutamide.

Structure of the Model

The details of the modeling process have been described previously.[16] In brief, clinical strategies were modeled for patients with metastatic prostate carcinoma based on hypothetical cohorts of 70-year-old men with newly diagnosed, untreated metastatic prostate carcinoma with good performance status and belonging to one of two cohorts, one with severe disease and one with minimal disease (based on the definition used in the NCI Intergroup 0036 trial).[13] Should these men receive first-line hormonal therapy alone (surgical orchiectomy or LhRH analogues) or first-line hormonal therapy plus flutamide (CAB)? A decision-analysis model using a Markov process to model the prognosis of these men followed, as a large cohort over time was developed (Fig. 1).[19,20] The Markov model used a 3-month cycle. After the initial 3 months, patients move to one of three health states (Fig. 1): response with therapy (combined or partial remission); and/or no progression (stable); progression (progressive disease); or death from disease progression or other causes. Patients beginning a cycle with progressive disease were assumed to have a constant risk of dying independent of an earlier therapy response. Nonprostate cancer deaths were based on standard age-adjusted mortality tables. Data reported as rates were converted to probabilities.

Probabilities

The primary source of transition probabilities was the survival curve from the National Cancer Institute Intergroup 0036 study (Table 1). We made the conservative assumption that the survival after progression was the same, independent of flutamide. For the initial cycle, response was defined as any improvement in subjective or objective findings. Because defining a response can be difficult, we assigned the same probability of progression from response or stable disease. The relative efficacy of flutamide in reducing deaths was estimated from Intergroup 0036 to be 25%. Because the model separately considers the probability of death from nonprostate cancer, we used the cancer death hazard rate (efficacy = 1-hazard rate) when available.

TABLE 1
Probabilities and Costs Used in the Model

	Baseline	Range
Probabilities per 3 mos. (%)		
Response to death	0	0–5
Response or stable to progression		
Severe disease	12 (36/year)	7–20 (24–52/year)
Minimal disease	6 (20/year)	3–10 (10–35/year)
Progression or death	19 (50/year)	15–30 (43–65/year)
Relative efficacy of flutamide	25	0–50
Costs per 3 mos. ($)		
Depot Goserelin	1000	600–1500
Depot Leuprolide	1400	900–1800
Flutamide, if used	800	600–1000
Response or stable disease	300	100–1000
Progressive disease	3600	1800–10,000
Death	10,000	3000–25,000
Discount rate	5	0–10

In the sensitivity analyses, we varied utility estimates of quality of life for patients with metastatic disease from 1.0 (perfect health despite having prostate carcinoma) to 0.41 (the focus group estimate for severe metastatic prostate carcinoma). Sensitivity analyses based on different estimates of effectiveness and quality of life estimates were explored. In the earlier modeling effort, sensitivity analyses were based on varying estimates of costs, clinical effectiveness, toxicity, and arbitrary estimates of quality of life, and costs were found of less than $35,000 per year of life saved in every case.[16] Since then, the Prostate Cancer Trialists' Collaborative Group overview has been published, indicating an overall benefit of 9% for flutamide, and is included in our sensitivity analyses.[15]

Cost of treatment.

Costs varied with a patient's health state (Table 1). Costs were considered from a global payer perspective, specifically, all direct health care costs paid by Medicare or the Department of Veterans' Affairs, and have been described in detail previously.[16]

Cost effectiveness.

Cost-effectiveness models estimate the amount of money that is required to gain a certain benefit in both quantity

and quality of life. It is usually expressed as dollars per QALY saved. The aggregate costs and quality of life estimates were used to calculate the incremental cost utility of CAB with flutamide, which are defined as the cost per QALY gained from a societal perspective defined as:

$$\text{cost effectiveness} = \frac{\text{costs (CAB-orchiectomy)}}{\text{quality-adjusted survival (CAB-orchiectomy)}}.$$

Time horizon.

The baseline analysis used a 7 year period for severe disease and a 10 year period for minimal disease to have 95% of untreated patients die.

Assumptions.

The model used in this study included five assumptions that have been described in the previous model: 1) flutamide alters the probability or movement between response and stable disease to progressive disease; 2) after progression, flutamide is stopped; 3) after progression, the probability of death is constant per unit time for both arms; 4) all patients dying from prostate cancer live at least 3 months with progressive disease; 5) orchiectomy and LhRH analogs are equally effective and differ only in cost. In addition, two new assumptions that relate to quality of life were added to this model: 1) quality of life considerations allow for positive benefits to occur by extending the time one has with stable or responsive disease, and 2) 15% of patients taking flutamide were estimated to experience gastrointestinal side effects within 3 months of beginning the therapy; therefore, they accrued 3 months of drug costs and a decline in quality of life, and flutamide was discontinued at this point. Subsequently, these patients were modeled to have no subsequent benefit in their risk of recurrence, no drug costs related to flutamide, and quality of life estimates similar to the monotherapy subgroup. We also explored a scenario where no patients withdrew due to flutamide toxicity, but these patients had a persistent drug-related decrease in quality of life and a persistent potential benefit in survival.

RESULTS

Quality of Life Assessments

The 43 physicians varied with respect to demographic/practice characteristics. Most physicians had been in practice for at least 12 years, and over 90% were board certified or board eligible in oncology or urology. About one-third were in private practice, one-third were in academic practices, and the remainder were in other settings. At least half of the physicians treated more than 55 patients per week and more than 10 new prostate carcinoma patients per month. The mean age of the physicians was 40 years. About half of the patients seen by these physicians in the average practice were over 55 years of age.

The four physician focus groups felt that quality of life considerations were the most important factors associated with metastatic prostate carcinoma. Weight loss, anorexia, and pain were the major aspects of quality of life identified by all four groups; three groups highlighted depression and urinary obstruction; and two groups identified reduced functional status, urinary incontinence, impotence and hot flashes with LhRH agonists or orchiectomy, and fear of death as major concerns. Because a major aim of this study was to evaluate the cost effectiveness of flutamide therapy, specific questions about flutamide were probed. Two groups felt that cost and diarrhea were major areas of concern, and only one group focused on inconvenience related to dosing.

For the four scenarios associated with metastatic prostate carcinoma, the median utility values (and interquartile ranges) were: A (stable disease), 0.92 (0.88, 0.96); B (stable disease with gastrointestinal toxicity), 0.84 (0.75, 0.88); C (early progressive disease), 0.83 (0.67, 0.88); and D (late progressive disease), 0.42 (0.25, 0.59). Responses were similar for urologists and oncologists across different age groups and practice settings.

Baseline Cost-Effectiveness Analysis

We have previously published cost-effectiveness analyses based on the NCI Intergroup 0036 trial and the Prostate Cancer Trialists' Collaborative Group metaanalysis, but we did not include quality of life adjustment.[16] By using a baseline relative efficacy of 25% from the NCI trial, the flutamide plus orchiectomy cohort had an average survival benefit of 5.2 months for men with minimal disease and 4.0 months for men with severe disease (Table 2). The incremental cost to gain this benefit was $25,300 for minimal disease and $20,000 for severe disease per additional life year gained. By using the overview estimates with a relative efficacy, the flutamide plus orchiectomy cohort had an average survival benefit of 1.9 months for minimal disease and 1.5 months for severe disease. The incremental cost to gain this benefit was $60,900 for minimal disease patients and $47,500 for severe disease patients.

Quality of Life Adjustments of Previously Derived Cost-Effectiveness Estimates

Quality of life effects on the previously derived cost-effectiveness profiles of flutamide plus orchiectomy vs. orchiectomy alone can be derived.[16] The quality of life estimates are based on the utility scores from the physician focus groups and take into consideration two opposite effects: 1) decrements to quality of life associated with gastrointestinal toxicity that occurs within 3 months in

TABLE 2
Quality Adjusted Cost-Effective Estimates[a]

	Utility score estimate for early progressive disease	Quality adjusted months benefit	Costs per quality adjusted life year saved
Minimal disease	1	5.2	25,300
	0.83	4.3	27,000
	0.42	4.9	24,000
Severe disease	1	4	20,000
	0.83	4.1	18,840
	0.42	4.5	17,200

[a] Flutamide plus orchiectomy versus orchiectomy alone.

TABLE 3
Sensitivity Analysis[a]

	Efficacy	Quality-adjusted months of survival benefit	Cost per quality-adjusted life year saved
Flutamide efficacy			
Minimal disease	50%	9	$15,600
Severe disease	10%	2.1	$41,000
Persistent gastrointestina l toxicity[b]	25%	3.5	$23,000
Price reduction to $400 per 3 months of flutamide	25%	4.1	$9,160

[a] Based on utility estimate of 0.92 for stable disease and 0.83 for early progressive disease.
[b] Fifteen percent of patients have gastrointestinal toxicity but stay on flutamide with a decrease in quality of life until disease progression.

15% of patients (from the NCI 0036 Intergroup study) and 2) improvement in overall quality of life associated with extension of time spent in a high quality of life state (scenario A) when compared with a low quality of life state associated with progressive disease [scenario C (early progression) or scenario D (late progression)].

If the utility score for progressive disease is 0.83 (associated with scenario C), then the average benefit of CAB decreases to 4.33 months, at a cost of $27,000 per QALY saved for minimal disease patients, and increases to 4.11 months, at a cost of $18,840 per QALY saved for severe disease patients (Table 2). However, if the utility score for progressive disease is as low as 0.42 (associated with scenario D), then the average benefit of CAB decreases to 4.89 quality-adjusted months (QAMs), at a cost of $24,000 per QALY saved for minimal disease patients, and increases to 4.51 QAMs at a cost of $17,200 per QALY saved for severe disease patients. In addition, if severe hepatic failure occurs at a rate of 1 in 200,000 cases and requires hepatic transplantation (at a cost of $200,000), then the quality of life benefit decreases by 0.01–0.02 QAMs, at an additional cost of $10 per QALY saved.

Additional analyses of the QALY estimates for CAB can also be derived that include medical castration with an LhRH agonist rather than orchiectomy. For example, if goserlin plus flutamide is used instead of an orchiectomy plus flutamide, then the cost per QALY gained increases by $5,500 for minimal disease patients and by $5,260 for severe disease patients (based on a utility score of 0.83 for the progressive disease state). Similarly, if leuprolide plus flutamide is used instead of an orchiectomy plus flutamide, then the cost per QALY gained increases by $7,700 for minimal disease patients and $7,360 for severe disease patients.

Sensitivity Analyses

Single variable changes were done for all clinical and cost variables, and selected results are shown in Table 3. The most important analysis assessed a range of flutamide efficacy. For minimal disease, by using a relative efficacy of 50% found in the Intergroup subset analysis, which is prospectively being evaluated, and a utility score of 0.83 for progressive disease, the benefit was 9.0 QAMs at a cost of $15,600 per QALY gained. By using the conservative estimate of 10% efficacy from the Prostate Cancer Trialists' Collaborative Group overview and the progressive disease utility score of 0.83, the benefit is 2.1 QAMs for severe disease and 2.6 QAMs for minimal disease, at an incremental cost ranging from $41,000 for severe disease to $53,700 for minimal disease per QALY saved.

Changes in the cost of flutamide use greatly affected the cost-effectiveness ratios, whereas continuing to use flutamide despite some mild gastrointestinal side effects had little effect. Reducing the cost of flutamide by 50% (presumably through volume purchasing) resulted in an incremental cost per QALY gained that decreased to between $9,160 and 12,500. If all patients with severe disease stay on flutamide, with 15% having a persistent decrease in quality of life due to gastrointestinal side effects, the benefit is 3.5 QAMs at a cost of about $23,000 per QALY saved.

DISCUSSION

In 1993, 50,000 men in the United States began hormonal therapy for metastatic prostate cancer.[11] We estimated the effects of alternative therapeutic strategies on quality-adjusted survival estimates and costs of care for 70-year-old men with newly diagnosed prostate cancer. Our model, which was based on clinical estimates of efficacy from the NCI Intergroup 0036 Trial, indicated that, whereas flutamide and castration are more expensive than castration alone, the QALY estimates are about $18,040 per QALY for men with severe disease and

$27,000 per QALY for men with minimal disease, estimates that are lower than many other generally accepted cancer therapies, such as chemotherapy for elderly women with breast cancer or for persons with acute nonlymphocytic leukemia.[7] In contrast, estimates based on the Prostate Cancer Trialists' Collaborative Group overview indicate that average survival increased by 2.1 QAMs, at an incremental cost of $41,000 per QALY saved for persons with severe disease, and by 2.6 QAMs, at an incremental cost of $53,700 per QALY saved for persons with minimal disease, estimates that are higher than many other generally accepted cancer therapies.

A cost-effectiveness analysis, although it is potentially very useful, has several limitations that must be considered. First, the clinical assumptions that are used in economic models are often derived from results of Phase III clinical trials, estimates from literature reviews, opinions of experienced consultants, or metaanalyses of many clinical trials. Each source of information has drawbacks. Estimates based on results of Phase III clinical trials may differ from results observed in routine clinical practice.[2-5] Treatment patterns in a clinical trial may differ from those in clinical practice. Close monitoring with laboratory tests and scans, frequent visits to physicians, and nurse visits add costs that are unlikely to occur in the clinical practice setting. Participation in a clinical trial may affect physician practice patterns. Physicians may be more likely to diagnose toxicity early (and to minimize the costs associated with the treatment of side effects) when a clinical trial is underway, because intensive observation for toxicity is especially important during Phase III licensing trials. Dose and timing also may differ. In the practice setting, physicians may choose to delay CAB therapy until symptoms occur or may opt for cyclical rather than continuous therapy, scenarios that have not yet been evaluated for clinical effectiveness or cost effectiveness. There are inherent tensions that affect the design of Phase III trials and that limit their ability to address cost-effectiveness issues.[4,5] Results from metaanalyses do not take into consideration the heterogeneity of patients and studies.[15] It is possible that the most significant benefit of flutamide therapy will be found in men with minimal prostate cancer, and the most cost-effective therapy may be with schedules and doses that have not been included in trials to date.[12,13]

Second, economic models of pharmaceutical agents may be developed either prematurely or too late.[4] For example, one recent study addressed the cost-effectiveness of a new recombinant pharmaceutical product.[3] This study found that a new drug was associated with significant cost savings when it was used as adjunct therapy for patients who received high-dose chemotherapy and autologous bone marrow transplantation. However, the drug was denied approval for general use by the FDA, thus negating the usefulness of the cost-effectiveness study. In many other cases, cost-effectiveness studies are delayed, often because of the unwillingness of pharmaceutical firms or funding agencies to support cost-effectiveness studies.[21] With respect to flutamide, the drug has been available in clinical practice for several years, most physicians have already made their decision on whether or not to use the drug based on concerns that it is either too expensive or provides benefits that are not worth the out-of-pocket costs incurred by patients, and cost-effectiveness estimates may not influence physician practice at this point in time.[22]

Third, although quality of life adjustments should be included in cost-effectiveness models, they are often methodologically difficult to obtain and may not significantly alter the cost-effectiveness profile.[17,18] In this study, physician estimates of utility estimates for persons with metastatic prostate carcinoma appeared to be consistent with estimates reported for persons with other diseases as well as with utility estimates used in the Patient Outcome Research Team (PORT) studies (Table 4).[18,23] A utility score of 0.92 for stable metastatic disease is similar to that reported for women with stable breast cancer, whereas a score of 0.41 for severe progressive disease is similar to that reported for persons undergoing hemodialysis.[17,18] In addition, quality of life adjustments changed the cost-effectiveness estimates very little. Even though physician focus groups expressed concern over flutamide toxicity, quality-adjusted estimates of its cost-effectiveness are within the range of therapies that are felt to be socially desirable when the NCI data are used and to be above the range when the metaanalysis estimates are used (Table 5).

TABLE 4
Comparative Health Status Utility Scores: Selected Results[a]

Health state	Utility estimate
Tired, sleepless	0.92
Stable, metastatic prostate cancer (this study)	0.92
Colostomy	0.91
Angina, moderate	0.90
Stable, metastatic prostate cancer, Fleming et al.	0.90
Walking stick	0.85
Stable metastatic prostate cancer, with flutamide associated gastrointestinal toxicity	0.83
Early progression of metastatic prostate cancer	0.83
Walking frame	0.81
Limited walking, unable to work	0.75
Hemodialysis	0.62
Breast removed, arm stiff	0.44
Late progression of metastatic prostate cancer	0.42
Breast cancer spread, constant pain, terminal	0.19

[a] Nord E. Methods for quality adjustment of life years. *Soc Sci Med* 1992; 34:560–6.

TABLE 5
Cost-Effectiveness of Other Medical Interventions[a]

Intervention	Costs per qaly saved
Low osmolar contrast media for low risk patients (vs. high contrast media)	220,000
Bone marrow transplant for acute nonlymphocytic leukemia (vs. traditional chemotherapy)	59,300
Dialysis for end-stage renal disease	40,000
Flutamide for early metastatic prostate cancer (minimal disease patient)	24,000–27,000
Flutamide for early metastatic prostate cancer (severe disease patient)	17,200–20,000
Chemotherapy in node negative breast cancer	18,000
Neonatal intensive care unit for 1,000–1,499 gram babies (vs. routine care)	5100

[a] Detsky A, Naglie G. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990; 113:150–8. Hillner BE, McLeod DG, Crawford ED, Bennett CL. Estimating the cost-effectiveness of total androgen blockade with flutamide in M1 prostate cancer. *Urology* 1995:633–40.

Fourth, our results add to the ongoing debate about the usefulness of flutamide therapy. Quality of life considerations do not change the cost-effectiveness profiles of flutamide significantly. For physicians who believe that the drug has significant survival benefits, concern over flutamide-related diarrhea or other gastrointestinal side effects does not dramatically alter the favorable cost-effectiveness profile of flutamide. In contrast, for physicians who are more uncertain about the survival benefits of flutamide, quality of life benefits associated with flutamide are unlikely to dramatically improve a generally unfavorable cost-effectiveness profile. Results from the ongoing Southwest Oncology Group study of combined androgen blockade vs. monotherapy as well as European studies of delayed treatment with flutamide are anxiously awaited, so that physicians can anchor their estimates of the clinical and cost effectiveness of flutamide.

Finally, our study results point out an additional area of concern with respect to Medicare policies and oral medications. After adjusting for changes in quality of life due to drug toxicity and other factors, flutamide therapy has an incremental cost effectiveness that is less favorable than many accepted therapies when clinical estimates are based on the Prostate Cancer Trialists' Collaborative Group overview, and it has an incremental cost-effectiveness profile that is more favorable than many accepted therapies when estimates are based on the clinical trial results from the favorable NCI 0036 trial. Out-of-pocket expenditures have been shown to be significant barriers to cancer screening and palliative care treatment in previous studies.[24–26] Among Medicare beneficiaries, women who lacked supplemental health insurance were the most likely group of individuals to experience financial barriers to care, despite being at high risk for late stage breast cancer diagnosis.[25] For persons with terminal cancer, oral medications are the least expensive form of pain control, costing from one-third to one-twelfth as much as parenteral therapy, but they are often not used because of a Medicare policy that does not cover oral drugs.[26] Because of limited reimbursement for oral morphine, there is a general reluctance of physicians to prescribe oral morphine, despite widespread evidence of both clinical effectiveness and cost savings.[26] Similarly, our study results suggest that the failure of Medicare to reimburse for oral anticancer medications and resultant out-of-pocket expenditures for flutamide present a significant barrier for prostate cancer treatments for those physicians who support the NCI 0036 results. For these physicians, despite support that flutamide is likely to be both clinically effective and cost effective, it is estimated that only 35% of men who are potentially eligible for the drug are estimated to actually receive flutamide.[11] Unless legislation is passed that provides for Medicare reimbursement for oral anticancer drugs, patterns of use of flutamide are unlikely to change.

REFERENCES

1. Weinstein M, Stason WB. Cost-effectiveness of interventions to prevent or treat coronary heart disease. *Annu Rev Public Health* 1985;6:41–63.
2. Welch HG. Valuing clinical strategies early in their development. *Ann Intern Med* 1992;116:263–4.
3. Gulati SC, Bennett CL. Granulocyte-macrophage colony stimulating factor as adjunct therapy in relapsed Hodgkin disease. *Ann Intern Med* 1992;116:177–82.
4. Drummond MF. Cost-effectiveness guidelines for reimbursement of pharmaceuticals: Is economic evaluation ready for its enhanced status? *Health Econ* 1992;1:85–92.
5. Drummond MF, Davies L. Economic analysis alongside clinical trials: Revisiting the methodologies issues. *Int J Technol Assess Health Care* 1991;7:561–3.
6. Hillman AL, Eisenberg JM, Pauly MV, Bloome BS, Glick K, Kinosian B, Schwartz JS. Avoiding bias in the conduct and reporting of cost-effectiveness research sponsored by pharmaceutical companies. *N Engl J Med* 1991;324:1362–5.
7. Bennett CL, Hillner, BE, Smith TJ. Clinical Oncology, 1st Ed. New York: Churchill Livingstone, Inc., 1995:187–200.
8. Bennett CL, Armitage JL, Armitage GO, Schwartz CE, Bierman PJ, Vose JM, et al. Costs and outcome for autologous bone marrow transplantation at the University of Nebraska: 1987–1991. *J Clin Oncol* 1995;13:969–73.
9. Coyle D, Drummond M. Does expenditure on pharmaceuticals give good value for money? current evidence and policy implications. *Health Policy* 1993;26:55–75.
10. Wingo PA, Tong T, Bolden S. Cancer Statistics. *CA—Cancer J* 1995;45:8–31.
11. Gee WF, Holtgrewe HL, Albertson PC. Practice trends in the diagnosis and management of prostate cancer in the United States. *J Urol* 1995;154:207–8.
12. Crawford ED, Eisenberger MA, McLeod DG. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989;321:419–24.

13. Denis LJ, Whelan P, deMoura JL. Goserelin acetate and flutamide vs. orchiectomy: A phase III EORTC trial (30853). *Urology* 1993;42:119–30.
14. Denis L, Murphy GP. Overview of phase III trials on combined androgen treatment in patients with metastatic prostate cancer. *Cancer* 1993;72(Suppl):3888–95.
15. Prostate Cancer Trialists' Overview Group. Maximum androgen blockade in advanced prostate cancer: An overview of 22 randomized trials with 3,283 deaths in 5,710 patients. *Lancet* 1995;346:265–9.
16. Hillner BE, McLeod DG, Crawford ED, Bennett CL. Estimating the cost-effectiveness of total androgen blockade with flutamide in M1 prostate cancer. *Urology* 1995;45:633–40.
17. Ferguson BM, Keown PA. An introduction to utility measurement in health care. *Infect Control Hosp Epidemiol* 1995;16:240–7.
18. Nord E. Methods for quality adjustment of life years. *Soc Sci Med* 1992;34:560–6.
19. Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decision Making* 1983;3:419–28.
20. Pauker SG, Kassierer JP. Decision analysis. *N Engl J Med* 1987;316:250–8.
21. Bennett CL, Smith TJ, George SL, Hillner BE, Fleishman S, Neill HB. Free-riding and the prisoner's dilemma: Problems in funding economic analyses of phase III clinical trials. *J Clin Oncol* 1995;13:969–73.
22. Bennett CL, McCrory DC, Matchar DB. Utility assessments for metastatic prostate cancer vary according to practice composition. *Proc Am Soc Clin Oncol* 1995;1650a.
23. Fleming C, Wasson J, Albertson P. A decision analysis of alternative strategies for clinically localized prostate cancer. *JAMA* 1993;269:2650–8.
24. Antman K. Reimbursement issues facing patients, providers, and payers. *Cancer* 1993;72(Suppl):2842–5.
25. Blustein J. Medicare coverage, supplemental health insurance, and the use of mammography by older women. *N Engl J Med* 1995;332:1138–43.
26. Kolasso M. In Discussion [study published May 1994 in *J Pain Sympt Manag* 1994;12: F-D-C-Reports, Chevy Chase, MD]. Agency for Health Care Policy and Research: Management of Cancer Pain. Clinical Practice Guideline, US Department of Health and Human Services, Public Health Services, 1994.