Individualized Strategy for Dosing Luteinizing Hormone–Releasing Hormone Agonists for Androgen-Independent Prostate Cancer: Identification of Outcomes and Costs

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Abstract

Purpose: Continuing androgen suppression is the current standard in men with androgen-independent prostate cancer (AIPC). An individualized strategy, wherein luteinizing hormone–releasing hormone agonists (LH-RHAs) are redosed when serum testosterone approaches a non-castrate level, may decrease costs without worsening outcomes. To understand possible outcomes, we performed a cost-utility analysis comparing individualized and fixed LH-RHA dosing strategies in men with AIPC.

Methods: The model used a societal perspective, a 5-year time horizon, and 3% annual cost discounting. The model accounted for direct costs of androgen suppression. Utilities were varied in accordance with published preference data.

Results: Under base-case assumptions, individualized LH-RHA dosing yielded 1.089 expected quality-adjusted life years

(QALYs), compared with 1.094 expected QALYs for fixed LH-RHA dosing. In cost analysis, lifetime per-patient costs for androgen suppression were estimated to be \$5,694 for individualized LH-RHA dosing and \$9,157 for fixed LH-RHA dosing. Applied to the total population, a strategy of individualized LH-RHA dosing would cost \$170 million for androgen suppression, compared with \$274 million for fixed LH-RHA dosing. Under these assumptions, adopting the individualized strategy resulted in \$692,600 gained from a societal perspective for each QALY lost (the decremental cost utility).

Conclusion: The results suggest that an individualized LH-RHA dosing strategy would be associated with moderate savings on an individual basis but substantial savings on a population basis, and would not adversely affect quality of life or life expectancy. Further research is needed to establish the effects of this strategy on symptoms and survival, as well as patient satisfaction and true costs.

Introduction

Prostate cancer is a common cancer in American men, with 230,110 new cases and 29,900 deaths estimated for 2004.¹ Costs for the last year of life are estimated at \$24,660.² Early in its natural cycle, prostate cancer is androgen dependent. Late in the clinical course, it is androgen independent, and is refractory to hormonal therapy. However, even in the androgen-independent state, prostate cancer is likely to contain subpopulations of cells that are androgen dependent. This hypothesis is supported by a retrospective analysis demonstrating a 2- to 6-month prolongation in median survival for men who continued androgen suppression.³ On the basis of these limited data, continued androgen suppression in men with androgen-independent prostate cancer (AIPC) is the current standard of care. In the past, testosterone suppression was achieved by bilateral orchiectomy (surgical castration). For the last two decades, injection of long-acting luteinizing hormone-releasing hormone agonists (LH-RHAs) has been used to achieve androgen ablation.

Although LH-RHAs have the advantages of reversibility and patient acceptance,⁴ they are expensive. Approximately 75% of men treated with androgen suppression for prostate cancer elect for LH-RHA.⁵ The two commonly used formulations, goserelin and leuprolide, are typically administered in doses that have a recommended redosing interval of 3 months and have average wholesale prices of \$1,409.98 and \$1,796.51, respectively.⁶

LH-RHAs are typically administered at a fixed dose and schedule without adjustment for patient or response characteristics, which distinguishes these agents from other hormonal agents such as insulin or levothyroxine.

Testosterone suppression by LH-RHA can last longer than the standard dosing interval,⁷ particularly in men with a long history of LH-RHA use.⁸ Individualized dosing regimens for LH-RHA, in which serum testosterone is monitored serially and LH-RHA redosed only after testosterone begins to approach the noncastrate range, offer a potential strategy for minimizing costs without worsening outcomes. Two feasibility trials, enrolling 22 and 32 men each, have already found this to be possible in diverse patient populations.^{7,9} If there is equal survival and symptom control with individualized dosing of LH-RHA, there could be savings in health care costs without compromising outcome.

Individualized androgen suppression appears to be a safe alternative on the basis of general observations in prostate cancer clinical trials. In a randomized trial in stage D2 disease, orchiectomy was not found to be inferior to goserelin,¹⁰ suggesting that the direct antitumor effects of LH-RHA were minimal, if any. A meta-analysis of androgen suppression in advanced prostate cancer found no significant difference in the odds of surviving to 2 years for LH-RHA as compared with orchiectomy.¹¹

Figure 1. Possible androgen-suppression strategies.

Our research aims were to determine which factors could nullify our hypothesis that outcomes were equivalent, and to what degree costs could be reduced by individualized treatment. We chose to evaluate life expectancy (LE) with adjustment for quality of life. Quality-adjusted life years (QALYs) were determined by weighting LE for the preference patients have for the health state, primarily based on possible symptoms. We modeled the effects of individualized and fixed LH-RHa dosing strategies on QALYs for a base case using the best estimates of relevant variables and performed sensitivity analysis over a wide range of values. We determined the cost of an individualized LH-RHa dosing strategy for men with AIPC and compared these costs to other strategies.

Methods

Study Design

This analysis uses a Markov process decision analytic model to estimate the costs and outcomes of four strategies for androgen suppression in men with AIPC. The four strategies shown in Figure 1 include individualized LH-RHa dosing, fixed LH-RHa dosing, discontinuing androgen suppression, and orchiectomy.

We considered parameters required for the actual administration of each strategy (drug costs, laboratory testing, health care provider costs, surgical costs), characteristics of the patients (LE, preferences for treatment), and parameters necessary for evaluation of a palliative therapy (adverse effects of medication, quality of life). Values for these parameters were obtained from the published literature and the Centers for Medicare & Medicaid Services database, and are described in Tables 1 and 2. Where values were not well described in the literature, estimates were used.

We performed a base analysis that measured costs and utilities using the estimate thought to be the most accurate for each parameter in the model. We performed one-way sensitivity

analyses, which evaluated the impact of using more extreme estimates of each parameter on outcomes and costs. Through sensitivity analyses, model parameters that are influential in determining the outcomes and cost of each strategy were identified. Finally, we performed multiway sensitivity analyses, which vary estimates across more than one parameter. These analyses depict consequences across a range of favorable and unfavorable circumstances.

Perspective, Time Horizon, and Discounting

We used a societal perspective, a 60-month time horizon, and 3% annual cost discounting. We terminated the analysis at 60 months, the point at which less than 5% of the base analysis cohort would still be alive.

Study Population

Our model described possible LH-RHa dosing strategies for a man with prostate cancer at the time that he is clinically recognized to have developed androgen-independent disease (i.e., continued disease progression after antiandrogen withdrawal). Typically, palliative chemotherapy would be offered at this time. We assumed that the prevalence of AIPC would equal the annual death rate from prostate cancer (29,900).¹

Model and Transition Probabilities

General model assumptions. We used a Markov model with 1-month cycles to analyze the costs and effects of two LH-RHa dosing strategies for men with AIPC. The details of the individualized strategy are represented in Figure 2. We considered all men to have entered at the time that they were clinically recognized to have developed androgen-independent disease. We fixed their date due for LH-RHa to be the same date. Because of the short time horizon (60 months), monthly interventions, and high monthly mortality rate, we reassessed the QALYs and costs at monthly intervals.

Mortality and castrate duration probabilities. We used mortality rates from a combined analysis of 760 men with AIPC in six Cancer and Leukemia Group B (CALGB) trials to estimate the monthly mortality, which includes death from prostate cancer as well as other causes.¹² The median age at enrollment for these CALGB studies was 71 years. The monthly mortality rate was approximately 0.053, and remained fairly constant over 60 months. We assumed that this would be the monthly mortality rate with any form of complete castration (≤ 20 ng/dL), such as orchiectomy or LH-RHa administration with resultant serum testosterone of less than 20 ng/dL.¹³ Based on findings of a 2- to 6-month survival benefit in a retrospective analysis of men with AIPC who continued castration,³ we increased the monthly mortality rate in the base analysis for men who

Table 1. Population Estimates and Costs (in 2003 U.S. dollars)

Variable	Base-Case Analysis	Sensitivity Analysis		Source
		Favors Individualized	Against Individualized	
Estimated No. of prostate cancer deaths in 2004	29,900	40,000	10,000	American Cancer Society, ¹ CMS
Costs (2003 U.S. dollars)				
Orchiectomy	\$2,000	\$1,000	\$3,000	Estimate
LH-RHa	\$1,410	\$1,797	\$705	Drug Topics Red Book ⁶
LH-RHa administration	\$81	\$162	\$40	CMS
Antiandrogen	\$196	\$90	\$393	Drug Topics Red Book ⁶
Cost of serum testosterone test	\$36	—	\$72	CMS

Abbreviations: CMS, the Centers for Medicare & Medicaid Services Web site (www.cms.hhs.gov); LH-RHa, luteinizing hormone–releasing hormone agonist.

stopped androgen suppression such that their median survival in the base case was 2 months shorter than for those patients with complete castration.

Six studies were identified with data addressing duration of castrate testosterone after withdrawal of LH-RHa, with a total of 115 patients with heterogeneous characteristics (Table 3).

Table 2. Probabilities and Utilities

Probabilities	Base-Case Analysis	Sensitivity Analysis		Timeframe
		Low	High	
Monthly mortality rate*				
Not castrate†	0.063	0.039	0.077	
Incomplete castration (fixed or individualized)†	0.058	0.039	0.077	
Castrate (medical or surgical)†	0.053	0.039	NA	
True castrate on LH-RHa‡	0.95	0.9	0.99	
Elect orchiectomy§	0.75	0.5	0.9	
Quality-of-life weights				
Utility				
Not castrate	0.800	0.7	0.9	Life
Incomplete castration	0.750	0.65	0.85	Life
Castrate	0.750	0.65	n/a	Life
Surgical absence of testes	0.700	0.6	0.8	Life
Disutility				
Oral antiandrogen treatment	−0.025	−0.05	0	1 month, repeating
Orchiectomy	−0.200	−0.4	0	1 month
LH-RHa administration	0	−0.025		1 month, repeating
Testosterone monitoring	0	−0.025		1 month, repeating

Abbreviations: LH-RHa, luteinizing hormone–releasing hormone agonist; NA, not applicable.

* More than one variable was adjusted when necessary (i.e., ordered or ranked health states were modified together if needed to preserve their order or rank).

† Taylor, Elson, and Trump³; Halabi et al¹²; Petrylak et al²⁹; Tannock et al³⁰; and Hussain et al.³⁵

‡ Oefelein and Cornum.¹⁹

§ Estimate.

|| Chon, Jacobs, and Naslund⁴; Oefelein⁷; Mariani, Glover, and Arita²³; Krahn et al³⁶; Nygard, Norum, and Due³⁷; and M. Krahn (personal communication, November 2004).

Figure 2. Model for individualized androgen suppression strategy. LH-RHa, luteinizing hormone-releasing hormone agonist.

Taken together, these studies suggest that in many men treated with LH-RHa, testosterone remains in the castrate range beyond the expected effective period of the drug (e.g., 3 months in a 3-month depot formulation). This range is quite variable, from less than the expected duration to beyond 36 months.

Patient and treatment factors associated with longer duration of androgen suppression are shown in Table 3. Older age was positively associated with the duration of castrate testosterone in one study,⁹ but not in another.¹⁴ Longer duration of prior androgen suppression was identified in two studies to be associated with delays to noncastrate⁹ and healthy¹⁴ levels. Although there is an association of the effect of age on duration of use and vice versa, the assumption that these factors are independent is physiologically plausible, given the well-known decline in serum testosterone with normal aging and studies demonstrating damage to the testes and impaired testosterone production after LH-RHa.¹⁵⁻¹⁷

It appears that the duration of LH-RHa therapy is correlated with the duration for which testosterone remains in castrate range after discontinuation of therapy.¹⁸ In the study by Hall et al,¹⁸ wherein the median duration of treatment with LH-RHa was 38.6 months, four of the 14 men had castrate-level testosterone at 12 months after discontinuing therapy. In the study by Pedraza and Kwart,⁸ the median duration of LH-RHa treatment was 108 months, and all four patients' testosterone levels remained in the castrate range for more than 36 months.

In our base case, we assumed that 95% of men would become castrate with administration of LH-RHa, given findings in a single study estimating that 5% to 13% of men do not achieve

castrate testosterone levels with LH-RHa.¹⁹ For the men who do become castrate, we assumed that the median duration of castrate level testosterone after stopping administration of LH-RHa would be 6 months, with a distribution between 3 and 8 months. This was based on durations reported for 32 men who had been receiving LH-RHa therapy for a median of 7.5 months (range 3 to 49 months) before stopping LH-RHa treatment.⁹ The monthly monitoring reported in this article made it possible to model month-to-month changes and accurately account for costs over time. The actual duration of castrate level testosterone in the population is likely to be longer because of prolonged previous use of LH-RHa.

Strategy Descriptions and Transition Probabilities

Strategy 1: Individualized LH-RHa dosing. Men who have individualized LH-RHa dosing will receive an LH-RHa injection. At the

3-month follow-up, they will have a serum testosterone determination. If the first testosterone level is found to be noncastrate, those patients will be offered orchiectomy. For the men who are castrate at 3 months, testosterone will continue to be checked monthly; when their serum testosterone is found to be noncastrate, they will receive another LH-RHa injection. If there were more than a 3-month interval since the last injection, they would receive a 2-week course of an antiandrogen to prevent flare reaction because of transient rise in serum testosterone²⁰ that can occur soon after receiving LH-RHa. However, there is evidence when an LH-RHa is administered to patients who have near-castrate levels of testosterone, this transient rise does not occur.^{7,9} The interval to first noncastrate testosterone level is assumed for model purposes to be stable from cycle to cycle.⁹

Strategy 2: Fixed-schedule LH-RHa dosing. Men who continue fixed-schedule LH-RHa dosing will receive it every 3 months, without serial testosterone determination or antiandrogen. However, some men will not be castrate and thus may potentially be undertreated.

Strategy 3: Stopping androgen suppression. Men who are found to be noncastrate and elect to stop androgen suppression can only transition to continue suffering from AIPC without castration or to death. They may choose this to avoid surgery itself or the adverse effects of castration.

Strategy 4: Orchiectomy cohort. Men who are found to be noncastrate may elect to have orchiectomy. They will have the procedure in month 1 and subsequently will not require serial testosterone determinations, LH-RHa dosing, or antiandrogen.

Table 3. Castrate Duration After LH-RHa Cessation

	Dijkman et al ⁹⁸ (1990)	Oefelein ⁹⁹ (1998)	Oefelein ⁹ (1999)	Hall et al ¹⁸ (1999)	Oefelein ⁷ (2003)	Pedraza and Kwart ⁸ (2003)
Study features						
No. of patients	30*	13	32	14	22	4
Design	Consecutive patients	Prospective	Prospective, phase I	Prospective pilot	Prospective, control-crossover	Case reports
Setting	First cancer treatment	Neoadjuvant	Changing to individualized	Discontinuing LH-RHa	Individualized, long term	Discontinuing LH-RHa
Extent of disease	Locally advanced or metastatic	Clinically localized	Locally advanced or metastatic	Locally advanced or metastatic	NCR	Relapsed or metastatic
Participant features						
Mean or median age, years	72.5	65	71	70	73	79
Duration of treatment	1 dose	1 dose	7.5 months† (range, 3-49 months)	38.6 months‡ (25-82 months)	Variable§	108 months‡ (range, 94-120 months)
Drug and dose	Goserelin 10.8 mg	3-month depot	Leuprolide 22.5 mg	3-month depot¶	Goserelin 10.8 mg	4-month depot
Castrate features						
Castrate threshold (ng/dL)	58	20	50	20	20	50
Correlates/findings	NR	NR	Increased with age; increased with duration of therapy; "flare" seemed suppressed	NR	Increased with lower prior testosterone; increased with lower BMI; duration of prior androgen suppression NS; "flare" seemed suppressed; short term improvement in QOL	
Castrate duration after stopping treatment	14 weeks	6 months† (range, < 3-8 months)	6 months† (range, 3-7.5 months)	9 months#	5.5 months† (range, 3.5-10 months)	36 months; all castrate at end of follow-up

Abbreviations: LH-RHa, luteinizing hormone–releasing hormone agonist; NR, not reported; NCR, not completely reported; BMI, body mass index; NS, not statistically significant; QOL, quality of life.

* Nine patients metastatic, 16 newly undergoing androgen suppression.

† Median.

‡ Mean.

§ Sixteen patients newly undergoing androgen suppression.

|| Twelve patients receiving leuprolide 22.3 mg; one receiving goserelin 10.8 mg.

¶ Leuprolide 22.3 mg or goserelin 10.8 mg.

Median testosterone still in castrate range at 9 months.

Costs

All costs are in 2003 U.S. dollars. Costs were discounted 3% annually.

Direct medical costs. The direct medical costs we have accounted for are listed in Table 1. We assigned all of the costs by 1-month

intervals. All of the costs of the LH-RHa were assigned to the month in which it was administered. For base case, we chose goserelin because of its lower average wholesale price and bicalutamide because it is a once-a-day drug, which we assume would be preferable for most patients even though it does not represent the lowest possible cost for the individualized strategy.

Flutamide, which is administered three times a day, is less expensive, but it is unlikely to be favored by patients. For administration costs, we used 2003 values for injection of a therapeutic agent (HCPC 90782) from the Centers for Medicare & Medicaid Services Web site (www.cms.hhs.gov/). For the base case, we used the median value for the nationwide estimates of cost.

Other costs. We have chosen not to include indirect medical costs or direct nonmedical costs. Because these patients have advanced cancer and may receive chemotherapy, they are likely to be in contact with the medical system at least as frequently as would be needed by any of our androgen-suppression strategies.

We have chosen not to include productivity costs. We do not expect significant variation in cost or lost time from work lost among strategies.

Quality of Life

We found few published studies that provide information on patient preferences (“utilities”) for men with AIPC. Utilities here are measured relative to a hypothetical perfect health state whose utility is defined as 1.0. In the single study in which utilities were obtained from patients themselves, the utility was relatively high, from .72 to .83 (M. Krahn, personal communication, November 2004), as opposed to those obtained from physicians, ranging from .45 to .65.²¹ Additionally, we found no utilities to compare AIPC treated with orchiectomy as opposed to medical androgen suppression. On the basis of a study²² that found that quality of life and sex-role identity were unaffected by orchiectomy, it is unlikely that there is a lower utility for the postorchiectomy health state as compared with medical castration. Two studies addressing the willingness of men with prostate cancer to pay out of pocket for medical androgen suppression as opposed to orchiectomy had conflicting findings. When 42 men with prostate cancer were asked about a hypothetical situation requiring additional payment for medical androgen suppression (estimated at \$386 per month), all 42 men felt this cost was worth the benefit of avoiding orchiectomy, although 20 men said they would in fact be unable to pay this amount.⁴ However, a report of men’s actual decisions when required to pay a monthly copayment of approximately \$100 to avoid orchiectomy²³ found that only roughly one third of men elected medical androgen suppression. It is not known whether men would find individualized or fixed-schedule LH-RHa dosing preferable and to what extent either would affect utilities. Men treated with individualized LH-RHa dosing reported satisfaction with the treatment,⁷ suggesting that the burden of additional blood tests is either insignificant or that it was outweighed by the decrease in the number of injections. However, these men were not treated with an oral antiandrogen, which can cause adverse effects, such as diarrhea and constipation, that may decrease utility in this health state.

On the basis of these findings, we rated health states for our base case in which men are noncastrate highest (0.8), followed by

health states in which men are castrate (completely or incompletely) on medical management (0.75), and finally orchiectomy (0.70). Disutility for temporary health states was applied on a monthly basis (Table 2).

Outcome Measures

The effect of each scenario on LE after development of androgen-independence until model termination at 60 months was compared. To evaluate whether there was any decrease in quality-adjusted survival, we also modeled the expected QALYs. The cost of each management strategy was determined on an individual as well as societal basis.

Sensitivity Analyses

Sensitivity analysis was performed on all parameters to determine any unexpected influences by model parameters (Tables 1 and 2). Additionally, one-way and multiway sensitivity analysis was performed under seven scenarios (Table 4). These scenarios represented both clinically realistic situations (e.g., that there is not a meaningful decrement in quality of life as a result of oral antiandrogen use), as well as scenarios designed to test dramatic changes in the base-case assumptions. For example, the lower range for the cost of LH-RHa is modeled at 50% of the current average wholesale price of goserelin, a situation very unlikely to be encountered in the future.

Our base-case assumptions are conservative. The values described in the favorable estimates scenario are more likely to be obtained in practice (Table 4).

Results

Effects on Unadjusted Survival

We started by modeling LE without adjustment for quality of life. In this scenario, the individualized androgen-suppression strategy yielded an estimated LE of 1.463 years, whereas the standard androgen-suppression strategy yielded an estimated LE of 1.459 years. This effect is a result of identifying and offering orchiectomy to men who are not castrate after LH-RHa administration.

Effects on QALYs

QALYs were determined by multiplying the estimated LE for each scenario by the average utility for the health states included. The average utility was calculated by weighting the utility for each health state in the scenario proportional to the time the patient would spend in it.²⁴

Under the base-case scenario, individualized LH-RHa dosing resulted in 1.089 expected QALYs, compared with 1.094 expected QALYs from fixed-schedule LH-RHa dosing (Table 4). We found that a strategy of stopping androgen suppression resulted in 1.004 QALYs, and immediate orchiectomy resulted in 1.008 QALYs (data not shown).

Table 4. One-Way and Multiway Sensitivity Analysis of Fixed and Individualized Androgen-Suppression Strategies

Analysis	Fixed Dosing	Individualized Dosing	Difference
Base-case scenario*			
QALY	1.094	1.089	0.005
Lifetime cost per patient	\$9,157	\$5,694	\$3,463
No direct quality-of-life decrement for individualized dosing†			
QALY	1.094	1.093	0.001
Lifetime cost per patient	\$9,157	\$5,694	\$3,463
Survival worse with individualized dosing‡			
QALY	1.094	1.016	0.078
Lifetime cost per patient	\$9,157	\$5,359	\$3,798
Quality of life worse with individualized dosing§			
QALY	1.094	1.069	0.025
Lifetime cost per patient	\$9,157	\$5,694	\$3,463
Unfavorable estimate scenario			
QALY	1.094	1.089	0.005
Lifetime cost per patient	\$4,827	\$4,555	\$272
Favorable estimate scenario¶			
QALY	1.094	1.091	0.003
Lifetime cost per patient	\$12,031	\$5,330	\$6,701
Fixed schedule with check for castrate duration#			
QALY	1.094	1.089	0.005
Lifetime cost per patient	\$8,894	\$5,694	\$3,200
Survival improved for men with AIPC**			
QALY	1.438	1.430	0.008
Lifetime cost per patient	\$11,725	\$7,187	\$4,538

Abbreviations: QALY, quality-adjusted life year; AWP, average wholesale price; AIPC, androgen-independent prostate cancer; LH-RHa, luteinizing hormone–releasing hormone agonist.

* Basic assumptions: castrate interval is 6 months; costs are AWP and best estimate; survival is equal for all androgen suppression; and quality of life is less for orchiectomy and for patients receiving an oral antiandrogen. All other scenarios represent changes from the base-case scenario.

† No disutility for receiving an oral antiandrogen.

‡ Survival with individualized schedule is 1 month less than fixed.

§ Quality of life is worse due to need for testosterone testing.

|| Castrate interval is decreased to 5 months; LH-RHa cost is decreased to \$705 (50% of AWP of goserelin); oral antiandrogen cost is increased to \$393 (200% of AWP of bicalutamide); testosterone testing is increased to \$72 (200% of Medicare reimbursement).

¶ Castrate interval is increased to 9 months; LH-RHa cost is increased to \$1,797 (AWP of leuprolide); LH-RHa administration cost is increased to \$162 (Medicare reimbursement).

Fixed schedule also monitors a single time for effective castration (orchiectomy can be offered).

** Survival for both strategies is 5 months longer.

In sensitivity analysis, the maximum difference between individualized androgen suppression and standard androgen suppression was 0.078 QALYs (Table 4). This occurred when the LE for men on continued androgen suppression was 13 months and individualized LH-RHa dosing results in a survival decrement of 1 month compared with fixed-schedule dosing. We found no evidence in the literature to suggest this decrement would occur, but used this scenario to model effects should there be unanticipated problems.

Effects of Intervention on Costs

Individual case costs. In the base-case scenario, lifetime cost for androgen suppression with an individualized LH-RHa dosing strategy was \$5,694 (Table 4). When compared with the cost for fixed-schedule dosing of \$9,157, this would yield a cost saving of \$3,463 per individual over his lifetime.

In multiway sensitivity analysis, combined unfavorable estimates regarding the castrate interval, LH-RHa cost, antiandro-

Table 5. Per-Patient and Total-Population Lifetime Costs Associated With Androgen Suppression Therapy (in 2003 U.S. dollars)

	Stopping	Orchiectomy	Fixed Dosing	Individualized Dosing	Savings (fixed v individualized dosing)
Per patient	0	2,000	9,157	5,694	3,463
Population (No. of patients)					
10,000	0	20,000,000	91,569,783	56,943,347	34,626,436
29,900	0	59,800,000	273,793,650	170,260,607	103,533,043
40,000	0	80,000,000	366,279,131	227,773,388	138,505,743

gen cost, and the cost of testosterone testing resulted in individual cost savings of only \$272. With combined favorable estimates regarding the castrate interval, LH-RHa cost, and cost of LH-RHa administration, the cost savings were \$6,701 per individual over his lifetime (Table 3).

Population costs. When the base-case scenario findings are applied to the estimated population of men with AIPC, the cost savings for individualized LH-RHa dosing strategy compared with the fixed-schedule dosing would be \$104 million (Table 5). These savings would be less or more depending on the size of the actual population. With sensitivity analysis, we identified no situation in which the societal savings were less than \$34 million when an individualized strategy was used, except if a combination of four unfavorable variables were modeled simultaneously (Table 4); in this case the savings was only \$8 million.

Decremental Cost Utility

The relatively new conceptual framework, called decremental cost utility,²⁵ can be used to compare the individualized dosing strategy with the fixed-schedule in terms of the dollars gained for each QALY lost under the base-case assumptions (Table 6). Under these assumptions, adopting the individualized strategy resulted in a gain of \$692,600 from a societal perspective for each QALY lost.

A review of published cost-utility analyses that adhered to methodological recommendations of the U.S. Public Health Service identified four studies of oncologic interventions.²⁶

These studies had variable interventions (chemotherapeutic, surgical, and stem-cell transplantation), and the incremental cost-utilities ranged from \$5,400/QALY to \$21,000/QALY.

Conclusion

A relatively simple practice modification to individualized dosing of LH-RHa in men with AIPC has the potential to offer considerable cost savings on a societal basis with very little, if any, decrement in quality-adjusted survival. Even under the conservative assumptions of our model, the decrement in QALYs with individualized LH-RHa dosing appears to be minimal. Our findings of a 0.005-QALY loss with individualized dosing represents a loss of 1.83 quality-adjusted days. We chose to limit our analysis to men with AIPC because, as a group, they are more likely to have been receiving LH-RHa longer and to be older. These two factors are associated with longer castrate duration after LH-RHa treatment withdrawal.⁹

These savings should be obtained even with new LH-RHa formulations with dosing intervals of 6 months²⁷ or 1 year²⁸ because the duration of androgen suppression is likely to be prolonged after discontinuation of these formulations. The population to which individualized dosing may be applied is likely larger, both on the basis of our conservative estimate of the number of men with AIPC and the other populations who may be treated in this manner, such as men undergoing intermittent androgen ablation. Additionally, recent phase III trials of taxanes have reported median survivals of approximately 18 months in men with AIPC.^{29,30} A recent retrospective analysis

Table 6. Results of a Cost-Utility Analysis of the Choice Between Individualized LH-RHa Fixed-Schedule LH-RHa Dosing for AIPC

Treatment Choice	Cost (2003 U.S. dollars)	Cost Savings for Individualized Dosing (2003 U.S. dollars)	QALYs	Decrement in Utility of Individualized	Decremental Cost:Utility Ratio for Individualized Dosing (2003 U.S. dollars)*
Individualized	5,694	3,463	1.089	0.005	692,600
Fixed-schedule	9,157		1.094		

Abbreviation: QALY, quality-adjusted life year.

*Dollars gained per QALY lost.

of men with AIPC from a single institution revealed a median survival of 40 months in men with skeletal metastasis at initial staging and 68 months in men without metastases at initial staging.³¹ These reported data suggest that our assumptions about survival in the base model are conservative; thus, the cost savings in this population may be larger than we estimated.

Our analysis is limited in that some of the measures used are not available in the literature. In our base case, we assumed that LE would be equal because we assumed that suppression of testosterone would be equal. However, *in vitro* studies suggest that LH-RHa may have direct inhibitory effects on androgen-independent DU 145 prostate cancer cell lines by preventing epidermal growth factor receptor-mediated tumor growth through a protein kinase C pathway³² or insulin-like growth

The population to which individualized dosing may be applied is likely larger, both on the basis of our conservative estimate of the number of men with AIPC and the other populations who may be treated in this manner, such as men undergoing intermittent androgen ablation.

factor system.³³ Additionally, there is a case report of an apparent response to LH-RHa in an orchiectomized AIPC patient.³⁴ Another possible area of concern is the small period of time in which serum testosterone may have begun to rise and may stimulate tumor cells. Evidence from two small clinical trials of 22 and 32 patients suggests that symptoms and prostate-specific antigen do not rise during these intervals.^{7,9} Additionally, the utility analysis we have chosen, although able to

model multiple influencing variables, is not able to provide an estimate of variability in outcomes.

On the basis of available data, the strategy of individualized dosing of LH-RHa is feasible and should be safe. To some men it may even be preferable for reasons such as limitation of seemingly unnecessary medications and associated injections. The results presented in this article suggest that a strategy of individualized LH-RHa dosing would not adversely affect QALYs and would be associated with moderate savings on an individual basis and substantial savings on a societal basis. Our findings persisted over the wide range of assumptions tested in sensitivity analysis. A randomized clinical trial will be required to determine the clinical outcomes and cost of individualized LH-RHa dosing strategy as compared with standard fixed-dose therapy. The ethical and methodologic questions for research are still being developed,²⁵ but we believe this work illustrates the value in pursuing them.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict existed for drugs or devices used in a study if they are not being evaluated as part of the investigation.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Jennifer J. Griggs					Aventis (A) Lilly (A) Novartis (A)			
Dollar Amount Codes (A) < \$10,000 (B) \$10,000-99,999 (C) ≥ \$100,000 (N/R) Not Required								

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