VA PRACTICE Matters

JANUARY 2001 VOL. 6 ISSUE 1

Use of Androgen Supression Therapy for Advanced Prostate Cancer

- *Prostate cancer is the most common cancer and the second leading cause of cancer deaths among men.*
- *It is estimated that each year nearly 200,000 new cases of prostate cancer will be diagnosed and 40,000 men will die of prostate cancer.*
- *The total Medicare expenditure for treatment of prostate cancer exceeds $1.5 billion annually. Of that total, $500 million was for hormone therapy with androgen suppression using LHRH agonists.*
- *VA's annual expenditure for LHRH agonists is about $40 million.*
- *Hormone therapy delays clinical progression and palliates prostate cancer symptoms in the majority of men but has not been clearly shown to improve survival.*
- *The prevalence and morbidity of prostate cancer are likely to increase with the aging of the population, as are expenditures for treatment due to earlier detection of the disease.*
- *VA research has improved our understanding of the relative effectiveness, safety and cost effectiveness of different forms of hormone therapy for prostate cancer.*

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BACKGROUND:

Prostate cancer is the most common malignancy in men and is second only to lung cancer in cancer related deaths. Androgen suppression, or hormonal therapy, is the mainstay of treatment for recurrent or advanced (non-localized) prostate cancer.

Androgen suppression, while not curing prostate cancer, provides temporary palliation of symptoms and reduction in tumor size and Prostate Specific Antigen (PSA) levels in the vast majority of men. Androgen suppression can result in adverse effects including: fatigue, nausea, breast tenderness, hot flashes, osteoporosis, erectile dysfunction, liver function abnormalities, thromboembolic events, diarrhea and loss of muscle mass and libido. Determining the potential risks and benefits of different methods for androgen suppression therapy, including their effects on length and quality of life, are of great importance in delivering evidence based health care to male veterans.

TREATMENT GOALS AND THERAPIES:

Recent systematic reviews and technology assessment reports have evaluated the evidence regarding efficacy, safety and cost-effectiveness of different methods of androgen suppression in men with advanced prostate. Three questions were addressed:

1. What are the best methods for monotherapy (orchiectomy (removal of both testes), diethylstilbestrol (DES) luteinizing hormone releasing hormone agonists (LHRHa), or nonsteroidal antiandrogens (NSAA))?
2. Are there survival and quality of life differences if using combined androgen blockade (CAB) compared to monotherapy? and
3. Is there a difference in outcome between implementing immediate androgen suppression versus deferring androgen suppression until signs or symptoms of clinical progression?

The findings are highlighted in this issue of VA Practice Matters.

Monotherapy (see Figure 1)

Monotherapy uses a single drug or surgical procedure for androgen suppression. Evidence indicates no overall survival difference for men treated with LHRH agonists compared to orchiectomy or DES, nor a survival difference among men treated with different LHRH agonists. There is a trend toward lower survival rates for men treated with nonsteroidal antiandrogens compared to orchiectomy, DES, or LHRH agonists. While LHRH agonists, DES and nonsteroidal antiandrogens differ in their adverse effects, the evidence does not suggest that one agent is superior to the others with regards to adverse effects. There is insufficient evidence to compare the effects of monotherapies on quality of life.

Combined Androgen Blockage (CAB) vs Monotherapy (see Figure 2)

There is no survival difference at 2 years between men treated with CAB or monotherapy. The difference in survival at 5 years is 3% (28% vs. 25%) and at 10 years is 2% (9% vs. 7%) in favor of CAB. The difference in median survival is 3.4 months (33.3 months vs. 29.9 months). Survival differences between CAB and monotherapy did not vary by patient age or disease stage. Among men given CAB, survival is similar regardless of the type of nonsteroidal antiandrogen used. The evidence comparing adverse effects is limited, but favors monotherapy. Evidence comparing quality of life was available from only one study with 6 month follow-up and favored monotherapy.

Immediate compared to deferred androgen suppression (see Figure 3)

The evidence is insufficient to determine whether androgen suppression initiated immediately at diagnosis improves survival compared to androgen suppression deferred until clinical signs or symptoms of progression. However, initiating androgen suppression immediately delays development of symptomatic disease progression and complications compared to deferring androgen suppression.

Androgen suppression initiated at the time of identification of positive lymph nodes during prostatectomy improves survival compared to deferral until symptomatic metastasis. In men with

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CLINICAL VIEWPOINT

Physicians are faced with uncertainty regarding hormonal therapy for metastatic prostate cancer. In the VA medical system, the decision is related to two issues:

1. how often is hormonal therapy the primary reason why patients transfer care to the VA medical system, and
2. do the clinical findings reported from randomized phase III clinical trials support the use of hormonal therapies and if so, which ones, how often, and when should the treatment be started.

Two sources of data provide relevant information:

1. A recent survey of Veterans found that among prostate cancer patients who transferred to the VA, most did so because of the VA's pharmaceutical benefit program.
2. Three recent overviews of the entirety of phase III randomized clinical trials for metastatic prostate cancer indicate that:
   - early hormonal therapy is associated with longer cancer-free survival times, but not longer overall survival;
   - survival is similar with the alternative medical and surgical therapies for castration (orchiectomy, LHRH agonists, and diethylstilbestrol), but patient preferences and costs vary; and
   - combined androgen blockade with an oral nonsteroidal antiandrogen in conjunction with medical or surgical castration is associated with an estimated 3% improvement in 5-year survival rates, although quality of life and toxicity that may occur during the first few months of treatment may be worse.

Many Veterans with prostate cancer transfer their medical care to the VA because of gaps in pharmaceutical benefit coverage in the non-VA setting. The data indicate that VA patients should be counseled on the expected benefits and toxicities of early versus late initiation of hormonal therapy, alternative approaches to castration, and the potential benefits and toxicities of oral nonsteroidal antiandrogens when used in conjunction with castration. VA physicians should be reminded that hormonal therapy of prostate cancer should be based on a shared decision making approach between patients and physicians.

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IMPLICATIONS FOR PRACTICE

1. There is no difference in survival among different forms of monotherapy. The choice of monotherapy should be based on patient preference but will be associated with marked differences in cost. Additionally, the availability of DES within the VA or at outside pharmacies is limited.
2. The small benefit in median (3.3 months) and 5 year survival (3%) with CAB compared to monotherapy must be balanced against the cost and adverse events associated with CAB.
3. Men who undergo immediate hormonal treatment for advanced prostate cancer should be informed that they have a longer duration of therapy in which they may experience adverse effects and costs of androgen suppression. However, complications due to disease progression may be decreased by immediate treatment. There is no clear evidence whether immediate or deferred treatment provides the longest survival except in men who have also received radiotherapy.
4. There is no evidence from randomized trials to support or refute the use of immediate hormone therapy upon PSA rise or recurrence. Men should be informed about potential, but unproven, risks and benefits.

VA Practice Matters is a publication for VA decision makers and practitioners that summarizes the results of important research to help inform policy and to promote the application of research for improved health care delivery and decision making within VA. It is produced by HSR&D's Information Dissemination Program in collaboration with topic experts in the field. For more information or to provide us with your suggestions, please contact:

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TREATMENT GOALS AND THERAPIES

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advanced prostate cancer treated with radiotherapy, immediate addition of androgen suppression continued for several years improves survival compared to radiotherapy alone with androgen suppression delayed until disease progression. There is little data on duration of androgen therapy, adverse effects and effect on quality of life.

Cost Effectiveness (see Figure 4)

The least expensive androgen suppression option is DES. Orchiectomy is the most cost effective with an incremental cost-effectiveness ratio of $8100 per quality adjusted life year relative to DES. All other strategies — LHRHa, NSAA, and both combined androgen blockade strategies — had higher costs and lower quality adjusted survival than orchiectomy. The cost-effectiveness is sensitive to the patients' perceptions regarding the effect of orchiectomy on the quality of their life. CAB is expensive and is, at best, marginally cost-effective. Initiating early androgen suppression therapy may reduce disease related complications. However, it is associated with higher costs and does not improve survival compared to deferring therapy. Therefore, early hormonal therapy may not be beneficial to patients at a time when they are still able to enjoy a good quality of life. The exception to this is for men treated with radical prostatectomy who have positive lymph nodes, or men treated with radiotherapy.

REFERENCES

Kim SP, Moran EM, Bowes ED, Tennant AG, Bennett CL. The anti-androgen transfer. The Prostate Journal. 2000; 2: 88-93.

Aronson N, Seidenfeld J, Samson DJ, et al. Relative Effectiveness and Cost-Effectiveness of Methods of Androgen Suppression in the Treatment of Advanced Prostate Cancer. Evidence Report/Technology Assessment No. 4. (Prepared by Blue Cross/Blue Shield Association Evidence-based Practice Center under Contract No. 290-97-0015. AHCPR Publication No. 99-E0012. Rockville, MD: Agency for Health Care Policy and Research. May. 1999.

Schmitt B, Seidenfeld J, Wilt TJ, Bennett CB. Combined androgen suppression versus monotherapy for advanced prostate cancer. Cochrane Library. 2000; issue 2.

Schmitt B, Bennett CL, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer. [Cochrane Review]. In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software.

Prostate cancer trialists' collaborative group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Lancet, 2000;355:1491-98.

Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL and Wilt TJ. Single-Therapy Androgen Suppression in Men with Advanced Prostate Cancer: A Systematic Review and Meta-Analysis. Ann Intern Med. 2000;566-577.

Bayoumi AM, Brown AD, Garber AM. Cost-Effectiveness of Androgen Suppression Therapies in Advanced Prostate Cancer. J Natl Cancer Inst 2000;92:1731-9.

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Androgen Suppression Therapy for Advanced Prostate Cancer

Figure 1

Two year overall survival relative to orchiectomy in men with advanced prostate cancer and treated with various forms of monotherapy. Point estimates for hazard ratios (center marks) and 95% CIs (error bars) relative to orchiectomy.

Monotherapy uses a single drug or surgical procedure for androgen suppression. There were no differences in survival for men treated with LHRH agonists compared to orchiectomy or DES, nor survival differences among men treated with different LHRH agonists. There is a trend toward lower survival with NSAA compared to other monotherapies. There is insufficient evidence to evaluate quality of life.

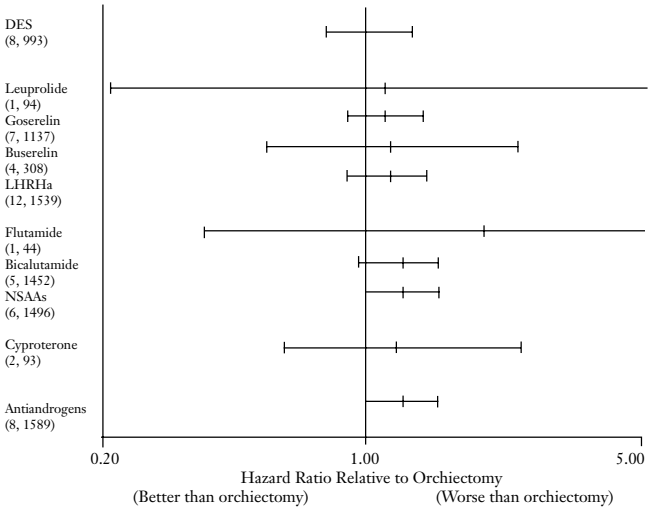

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Figure 2

Overall survival in men treated with Combined Androgen Blockade (CAB) versus androgen suppression monotherapy.

CAB uses the addition of a NSAA to standard androgen suppression monotherapy with orchiectomy, DES or LHRHa. The difference in survival at 5 years is 3% and at 10 years is 2% (9% vs. 7%) in favor of CAB. The difference in median survival is 3 months (33 months vs. 30 months). Survival differences between CAB and monotherapy did not vary by patient age or disease stage. Evidence comparing adverse effects and quality of life is limited but favors monotherapy.

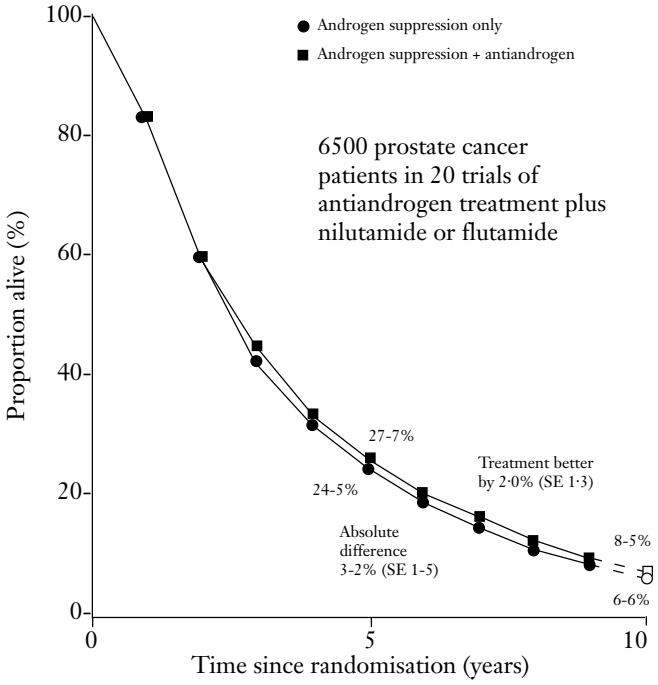

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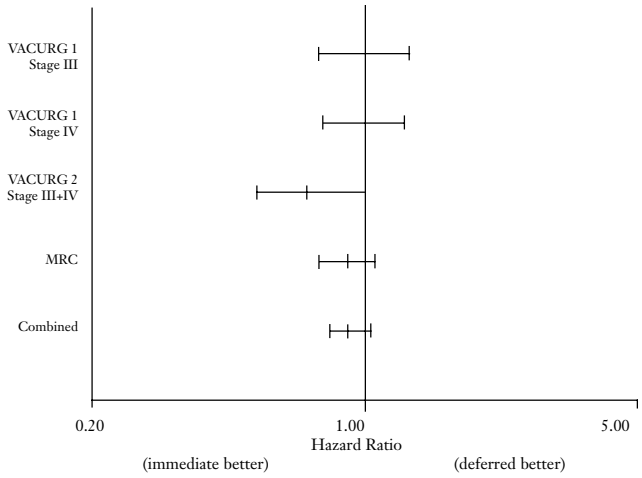
Figure 3

Immediate compared to deferred androgen suppression.*

The evidence is not sufficient to determine whether androgen suppression initiated immediately at diagnosis improves survival compared to androgen suppression deferred until clinical signs or symptoms of progression. Early initiation delays development of symptomatic disease progression and complications. However, it is associated with higher costs of androgen suppression and exposes men to longer treatment periods in which they may experience therapy-related adverse effects.

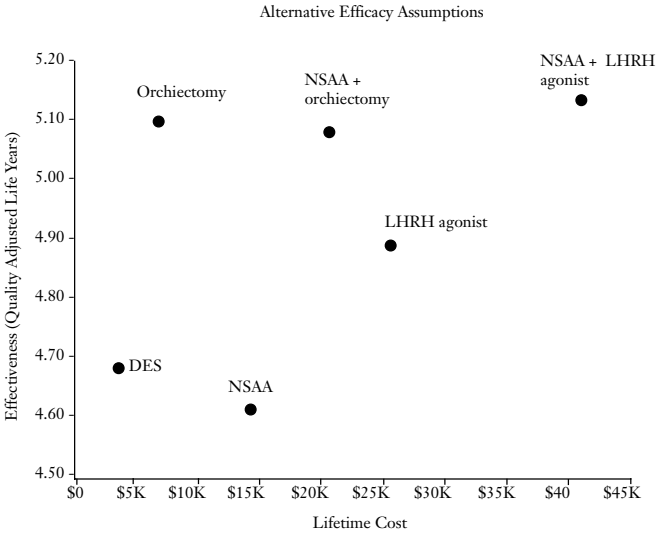


Survival at 5 years, immediate vs deferred primary hormonal therapy for previously untreated patients

Figure 4

Costs and Outcomes with All Monotherapies and Combined Androgen Blockade.*

The least expensive androgen suppression option is DES (lifetime costs = $3600). Orchiectomy is the most cost effective treatment option with an incremental cost-effectiveness ratio of $8100 per quality adjusted life year relative to DES. Other strategies-LHRHa, NSAA and both combined androgen blockade strategies had higher costs and lower or equivalent quality adjusted survival compared to orchiectomy (marginal cost effectiveness ratio of NSAA + LHRH vs. orchiectomy = $1,110,000/QALY). However, the cost effectiveness is sensitive to the patients' perception regarding the effect of orchiectomy on the quality of their life.



Assumptions about efficacy reflected the point estimates from the meta-analysis

Strategy	*Cost*	*Effectiveness (QALYs)*	*Marginal Cost-Effectiveness*
DES	$3,567	4.68	
Orchiectomy	$6,957	5.10	$8,092/QALY
NSAA	$14,382	4.61	Eliminated by strict dominance
NSAA +orchiectomy	$20,857	5.08	Eliminated by strict dominace
LHRH agonist	$25,709	4.89	Elimated by strict dominace
NSAA + LHRH agonist	$41,443	5.13	$1,109,581/QALY

*Relative effectiveness and cost-effectiveness of androgen suppression in the treatment of advanced prostatic cancer. AHCPR Publication No. 99-E0012. Evidence Report/ Technology Assessment Number 4. Rockville: AHCPR. US Department of Health & Human Services, May 1999.