Comparison of Single-Agent Androgen Suppression for Advanced Prostate Cancer

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Gonadotropin-releasing hormone (GnRH) agonists are the agents of choice for achieving androgen suppression in men with advanced prostate cancer. The GnRH agonists that have been developed and marketed for prostate cancer are leuprolide, goserelin, triptorelin, and histrelin. So far, there have been few randomized studies directly comparing these single-agent therapies; however, the literature and the data on file with the Food and Drug Administration suggest that triptorelin may be more reliable than leuprolide in maintaining castration levels of serum testosterone. The clinical significance of this benefit remains to be proven.
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Key words: Androgen suppression • Gonadotropin-releasing hormone agonists • Orchiectomy • Luteinizing hormone–releasing hormone • Prostate cancer

In 1941, Huggins and Hodges[1,2] ushered in the era of hormonal therapy for prostate cancer with a report describing dramatic regression of advanced prostate cancer and improvement in bone pain, lower urinary tract symptoms, and quality of life following surgical or medical castration with estrogens. Over the next 25 years, sporadic uncontrolled reports confirmed the beneficial effects of hormonal therapy for advanced prostate cancer. Estrogen therapy was often

preferred over orchiectomy because of the presumed psychological advantages associated with retaining the testes. Huggins and Hodges were awarded the Nobel Prize in medicine in 1967 for their landmark observations.

The Veterans Administration Cooperative Urological Research Group (VACURG) was established in 1959 with the objective of investigating different treatment strategies for managing bladder and prostate cancer using multicenter randomized placebo-controlled trials. Between 1960 and 1975, more than 4000 men with prostate cancer were randomized into 1 of 3 studies examining the role of hormonal therapy for prostate cancer (Figure 1).[3] The relevance of these studies in the modern era is limited because Gleason scores were not used to stratify risk groups, bone scintigraphy was not available to detect metastasis, and serum prostate-specific antigen (PSA) was not available for ascertaining disease progression. Another important caveat when interpreting these studies is that the majority of men in the placebo-controlled arm crossed over to active treatment at the discretion of the investigator. Therefore, these studies compare early versus delayed endocrine therapy rather than treatment versus placebo.

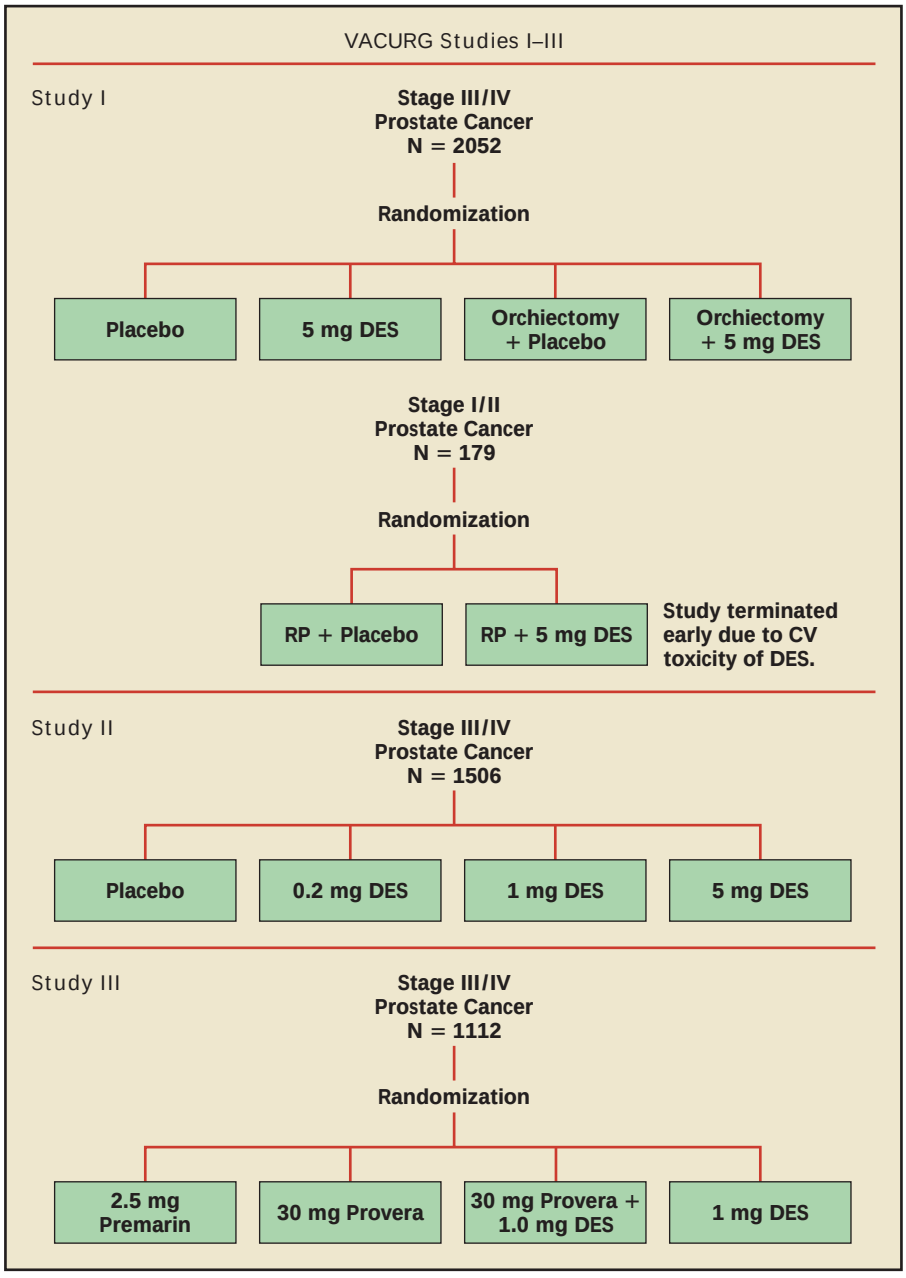

Figure 1. *The study design for the 3 randomized placebo-controlled studies sponsored by the Veterans Administration Cooperative Urological Research Group (VACURG) investigating hormonal therapy for prostate cancer. Premarin is manufactured by Ayerst Laboratories, St. Davids, PA; Provera is a product of Pharmacia and Upjohn Co., Kalamazoo, MI. CV, cardiovascular; DES, diethylstilbestrol; RP, radical prostatectomy. Data from Byar and Corle.*[3]

Several very important observations that influenced the management of prostate cancer were gleaned from the VACURG studies on hormonal therapy. Three important observations were derived from study 1.[4] First, diethylstilbestrol (DES) 5 mg was found to cause problematic cardiovascular morbidity and mortality. Second, orchiectomy and DES 5 mg monotherapies exhibited similar overall survival. DES 5 mg had a greater effect on reducing prostate cancer mortality, which was counterbalanced by its negative effect on cardiovascular mortality. Third, overall survival with a combination of orchiectomy plus DES 5 mg was shown to be no better than with the monotherapies, contradicting a prior report advocating combination therapy.[5]

Study II was designed to evaluate lower doses of DES. This study was terminated prematurely because of the emerging trend confirming the cardiovascular toxicity previously seen with 5 mg DES. DES 1 and 5 mg

Table 1
Structure of GnRH Analogues Approved for the Treatment of Advanced Prostate Cancer

	1	2	3	4	5	6	7	8	9	10
GnRH	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	Gly-	Leu-	Arg-	Pro-	Gly-NH_2
Leuprolide	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-Leu	Leu-	Arg-	Pro-	Ethylamide
Goserelin	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-Ser(tBu)-	Leu-	Arg-	Pro-	Gly-NH_2
Triptorelin	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	D-Trp-	Leu-	Arg-	Pro-	Gly-NH_2
Histrelin	(pyro)Glu-	His-	Trp-	Ser-	Tyr-	d-His(Imbzl)	Leu-	Arg-	Pro-	N-Et-NH_2

GnRH, gonadotropin-releasing hormone.

appeared to have equivalent effects on reducing prostate cancer mortality despite the fact that the 1-mg dose of DES did not reliably achieve castration levels of testosterone. Urologists interpreted these studies to show that DES 5 mg was associated with unacceptable cardiovascular morbidity and mortality whereas 1 mg DES did not adequately suppress serum testosterone to castration levels. Therefore, DES 3 mg emerged as the presumed optimal dose of DES.

Post hoc analysis of the VACURG studies suggested that DES 1 mg was associated with increased cardiovascular mortality primarily in older men with lower-grade tumors.[3] These older men were at greatest risk for cardiovascular events because of their advanced age and longer disease-free survival due to the favorable Gleason scores.

Development of Gonadotropin-Releasing Hormone Agonists

In 1971, Schally and colleagues[6] discovered and characterized the amino acid sequence of gonadotropin-releasing hormone (GnRH), a decapeptide that is produced by the hypothalamus and stimulates the pituitary cells to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Schally was subsequently awarded the Nobel Prize in medicine for this discovery. Chronic exposure to GnRH desensitized the GnRH receptors of the anterior pituitary cells, thereby resulting in the shutdown of LH and FSH production and the suppression of testosterone production by the testes.[7] Exogenously administered GnRH had limited clinical utility because of its very short half-life.

Substitutions and modifications of the 6 amino acid residue of GnRH yielded analogues with a longer half-life and increased potency (Table 1).[8] Depot or long-acting formulations of these GnRH analogues were subsequently developed to increase the dosing interval up to 4 months.

One of the primary limitations of GnRH agonists for the treatment of advanced prostate cancer is the initial flare phenomenon, which is characterized by an increase in serum testosterone following initial exposure to these drugs.[9,10] The flare phenomenon has been observed with all agonists and may cause life-threatening sequelae in cases with significant metastatic tumor burden. The life-threatening sequelae from the flare phenomenon may be prevented by the coadministration of an antiandrogen.[11] The primary advantage of GnRH antagonists is the absence of the flare phenomenon; however, development of antagonists has been limited primarily because of adverse events, including severe allergic reactions. Abarelix is the only GnRH antagonist currently approved by the Food and Drug Administration (FDA) for the treatment of advanced prostate cancer. Because of its propensity for immediate-onset systemic allergic reactions, some resulting in syncope and hypotension, patients must be observed for 30 minutes following administration of abarelix.[12] Prescribing physicians must be enrolled in the Plenaxis Plus Program (Praecis Pharmaceuticals, Waltham, MA) and must attest that they have access to medication and equipment to treat allergic reaction, including any anaphylaxis. Patients must sign a patient information document outlining risks and benefits of abarelix.

The primary advantage of GnRH antagonists is the absence of the flare phenomenon; however, development of antagonists has been limited primarily because of adverse events, including severe allergic reactions.

GnRH Agonists: Landmark Studies in Drug Development

Owing to the cardiovascular toxicity of DES, there remained a need to develop a safe form of medical castration. The discovery of GnRH in 1971 was made a few years after the VACURG studies reported on the toxicity of DES. The potential clinical advantage of achieving medical castration with GnRH analogues was promptly recognized by the pharmaceutical industry, resulting in major drug discovery programs.

Leuprolide acetate, goserelin acetate, triptorelin pamoate, and histrelin acetate are the four GnRH agonists that have been developed and marketed for the treatment of advanced prostate cancer in the United States (Table 2). Leuprolide[13] and goserelin[14] were initially compared with standard therapy, which at the time was DES 3 mg and orchiectomy, respectively. Triptorelin pamoate was compared with a monthly intramuscular injection of leuprolide acetate for depot suspension.[15]

Table 2
GnRH Agonists Approved for the Treatment of Advanced Prostate Cancer

Generic Names	Trade	Dose (mg)	Route of Administration	Dosing Interval (days)
Leuprolide acetate for depot suspension	Lupron depot*	7.5	IM	28
	Lupron depot	22.5	IM	84
	Lupron depot	30	IM	112
Goserelin acetate implant	Zoladex†	3.6	SC	28
	Zoladex	10.8	SC	84
Triptorelin pamoate injectable suspension	Trelstar depot‡	3.75	IM	28
	Trelstar LA‡	11.25	IM	84
Leuprolide acetate for injectable suspension	Eligard§	7.5	SC	28
	Eligard	22.5	SC	84
	Eligard	30	SC	112
Leuprolide acetate implant	Viadur‖	65	SC	365
Histrelin acetate implant	Vantas¶	50	SC	365

*Abbott Laboratories, Abbott Park, IL.
†AstraZeneca Pharmaceuticals, Wilmington, DE.
‡Watson Pharmaceuticals, Corona, CA.
§Sanofi-Synthelabo, New York, NY.
‖ALZA Corp., Mountain View, CA.
¶Valera Pharmaceuticals, Cranbury, NJ.
GnRH, gonadotropin-releasing hormone; IM, intramuscularly; SC, subcutaneously.

Leuprolide Versus DES

In 1984, the Leuprolide Study Group[13] reported the first large-scale randomized study comparing leuprolide acetate 1 mg subcutaneously daily versus DES 3 mg in men with untreated stage D2 prostate cancer. Ninety-eight men were randomized to leuprolide and 101 to DES. The duration of follow-up ranged from 24 to 120 weeks. Leuprolide produced an initial increase in serum testosterone (flare phenomenon) and required a longer time to achieve castration levels compared with DES. The time-to-progression and survival plots were not significantly different between the two treatment groups. The incidence of hot flushes was significantly higher in the leuprolide group, whereas gynecomastia/breast tenderness, nausea/vomiting, and edema were significantly more common in the DES group. The study was inadequately powered to show clinically significant differences in survival or cardiovascular toxicity. The sevenfold increase in cardiovascular toxicity (thrombosis, phlebitis, pulmonary embolus) was almost statistically significant. The cardiovascular toxicity observed with DES 3 mg in this study sealed the fate of estrogen therapy for prostate cancer. Overall, the 3 mg dose was thought to have unacceptable toxicity, and DES 1 mg failed to reliably achieve castration levels of testosterone.

Orchiectomy Versus Goserelin

One hundred sixty-four men were randomized to orchiectomy versus goserelin 3.6 mg depot administered every 28 days via subcutaneous injection.[14] Median and maximum follow-up was 200 and 462 days, respectively. Serum testosterone levels were measured every 4 weeks; therefore, the flare phenomenon was not directly observed biochemically. Overall, serum testosterone levels were similar between the two groups at the evaluable time points. One subject developed spinal cord compression 4 days after receiving goserelin, presumably because of the flare phenomenon. The Kaplan-Meier plots for time to disease progression were not significantly different between the two groups. The most common side effect was hot flushes, occurring in 53% and 39% of men randomized to goserelin and orchiectomy, respectively. Based on this study, it was concluded that goserelin was an appropriate treatment option

for advanced prostate cancer because the drug was as effective as orchiectomy in achieving castration levels of testosterone.

Triptorelin Versus Leuprolide Acetate

Triptorelin pamoate is a potent GnRH agonist developed for the hormonal therapy of prostate cancer. The registration of triptorelin pamoate required demonstrating the ability to induce and maintain castration levels of testosterone comparable to standard therapy. Two hundred eighty-four men with advanced prostate cancer were randomized to receive triptorelin pamoate 3.75 mg or leuprolide acetate 7.5 mg. Both drugs were administrated by intramuscular injection every 28 days for 253 days (9 injections). The primary endpoints were the percentages of men whose serum testosterone concentration declined to, and were maintained at or below, castration levels (≤ 1.735 nmol/L). Secondary endpoints included adverse events, overall survival, quality of life, PSA levels, bone pain, testosterone pharmacodynamics, and LH levels. In this study, two endpoints were significantly different between the two treatment groups.

Castration levels of serum testosterone were achieved on day 29 in 91.2% of the subjects in the triptorelin pamoate group compared with 99.3% in the leuprolide acetate group. The point estimate and 95% confidence interval for the means was −8.0 (−16.9-1.4), suggesting a significant advantage in favor of leuprolide acetate. The percentage of men achieving castration levels of testosterone in the leuprolide group at 29 days was significantly greater than all other registration trials for the different doses and formulations of leuprolide acetate (Table 3).[13] By day 57, there was no significant difference between the proportions of men achieving castrate levels. In the registration trial of triptorelin pamoate 11.25 mg, 97.7% of men achieved castrate levels of testosterone by day 29. A comparison of all the existing data for leuprolide and triptorelin indicates comparable rates for achieving castration levels of testosterone by day 29.

Table 3
Comparison of Time to Achieve Castrate Levels for GnRH Agonists

GnRH Agonist	% Castrate at Days 28–30
Leuprolide acetate for depot suspension	
7.5 mg	94
22.5 mg	95
30 mg	94
Goserelin acetate implant	
3.6 mg	NR
10.8 mg	NR
Triptorelin pamoate	
3.75 mg	91.2
11.25 mg	97.7
Leuprolide acetate for injectable suspension	
7.5 mg	94
22.5 mg	99
30 mg	96
Leuprolide acetate implant	
65 mg	99
Histrelin acetate implant	
50 mg	100

GnRH, gonadotropin-releasing hormone.

The second statistically significant endpoint was the difference in overall survival. The 9-month survival rates for triptorelin pamoate and leuprolide acetate were 97.0% and 90.5%, respectively. This 6.5% difference in mean survival was statistically significant. Although a claim of a survival advantage in favor of triptorelin pamoate can be made based on this comparative study, it is unlikely that a true survival advantage exists in favor of triptorelin pamoate.

Overall, mean serum testosterone levels at all time points throughout the study were comparable between triptorelin pamoate and leuprolide acetate. However, during the 9-month study, 96.4% and 91.2% of men maintained castration levels throughout the study while on triptorelin pamoate and leuprolide acetate, respectively ($P = .092$) (Figure 2). The 5.1% difference was associated with a 95% confidence interval of −0.7 to 10.9. The randomized comparative study suggests that triptorelin pamoate may more reliably maintain castration levels of testosterone. A comparison of the randomized registration study provides further evidence that triptorelin pamoate maintains testosterone levels better than leuprolide acetate for depot suspension (Table 4).

Summary of All GnRH Agonists Registered in the United States for the Treatment of Advanced Prostate Cancer

The last 2 decades have witnessed the approval of many different formulations of the four GnRH agonists:

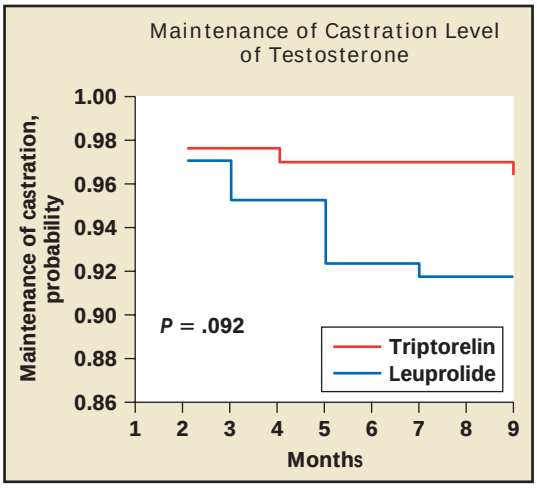

Figure 2. *The percentage of men maintaining castrate levels of testosterone in a randomized study comparing intramuscular injections of triptorelin pamoate 3.75 mg with leuprolide acetate 7.5 mg every 29 days. Reproduced with permission from Heyns CF et al.*[15]

leuprolide acetate, goserelin acetate, triptorelin pamoate, and histrelin acetate (see Table 2). These formulations of GnRH agonists differ in their dosing intervals and routes of injection. Goserelin acetate may be administered subcutaneously every 28 or 84 days; leuprolide acetate for depot suspension may be administered intramuscularly every 28, 84, or 112 days; leuprolide acetate for injectable suspension may be administered subcutaneously every 28, 84, or 112 days. Leuprolide acetate or histrelin acetate may be surgically implanted subcutaneously every 365 days; triptorelin pamoate injectable suspension may be administered intramuscularly every 28 and 84 days.

Comparison of Androgen Suppression Monotherapies for Advanced Prostate Cancer

There have been very few randomized studies directly comparing monotherapies for androgen suppression in men with advanced prostate cancer. Relevant comparisons would be survival, adverse events, pharmacologic properties, maintenance of castration levels of testosterone, injection site reactions, ease of administration, and cost. None of the comparative studies has been adequately powered to demonstrate significant differences among any of these outcomes.

Seidenfeld and colleagues[16] recently reported the only meta-analysis of trials comparing monotherapies for androgen suppression in men with advanced prostate cancer. A total of 1477 studies published between 1966 and 1998 were reviewed. Of these studies, only 24 were randomized and controlled and, therefore, included in the meta-analysis.

Twenty-one of these trials reported overall survival rates. Overall survival was reported as the percentage of subjects alive 2 years after initiation of treatment. The hazard ratios and 95% confidence intervals relative to orchiectomy are shown in Figure 3 for DES, GnRH agonists, and antiandrogens. The meta-analysis demonstrated no significant differences between orchiectomy versus DES or GnRH agonists. There was also no significant difference among the different GnRH agonists. Although confidence intervals were very large because of the small sample sizes, the meta-analysis

Table 4
Maintenance of Castration Levels of Testosterone

GnRH Agonist	Patients, n	Duration of Study (wks)	% T > 50 ng/dL
Leuprolide acetate for depot suspension			
7.5 mg	56	24	9%
22.5 mg	92	24	3%
30 mg	49	48	8%
Goserelin acetate implant			
3.6 mg	160	48	9%
Triptorelin pamoate			
3.75 mg	140	36	3%
11.25 mg	174	36	4/0%
Leuprolide acetate for injectable suspension			
7.5 mg	117	28	0%
22.5 mg	117	28	1%
30 mg	90	28	3%
Leuprolide acetate implant			
65 mg	80	52	0%
Histrelin acetate implant			
50 mg	—	52	3%

GnRH, gonadotropin-releasing hormone; T, testosterone.

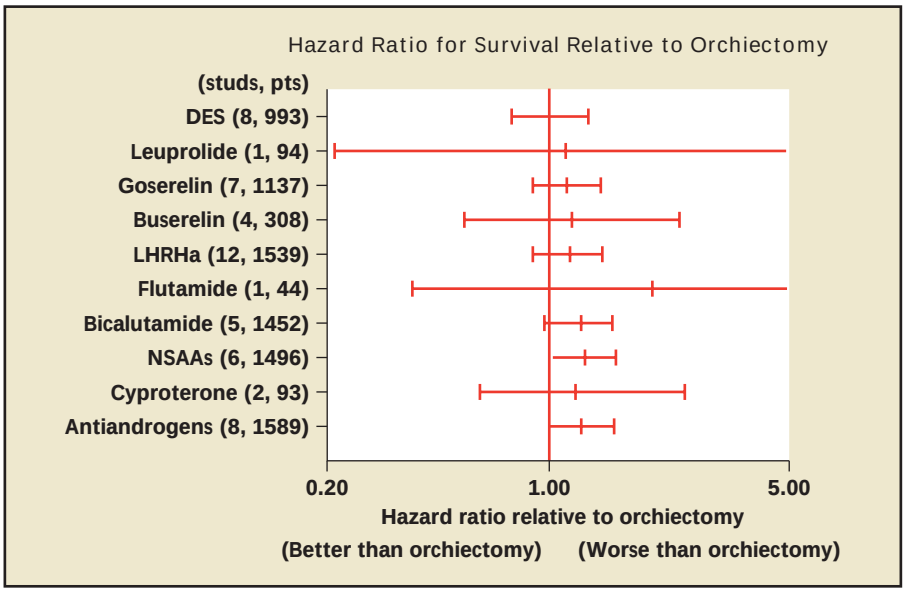

Figure 3. *The hazard ratio for survival relative to orchiectomy at 2 years based on a meta-analysis of randomized studies comparing androgen suppression monotherapies in men with advanced prostate cancer. DES, diethylstilbestrol; LHRHa, luteinizing hormone–releasing hormone agonist; NSAAs, nonsteroidal antiandrogens; studs, number of studies; pts, pooled number of patients. Reproduced with permission from Seidenfeld J et al.*[16]

confirmed other reports indicating that antiandrogens were not as effective as orchiectomy for survival in men with advanced disease.

It is difficult to compare toxicity because adverse events were not captured in a uniform manner and there were no placebo controls. A meta-analysis was performed examining the percentage of men withdrawing because of adverse events (Table 5). Overall, GnRH antagonists were shown to have superior tolerability compared with antiandrogens.

Table 5
Comparison of Treatment Withdrawal for Single-Therapy Androgen Suppression

Hormonal Therapy	% Withdrawal (range)
GnRH agonists	0%-4%
Nonsteroidal anti-androgen	4%-10%

GnRH, gonadotropin-releasing hormone.

Hot flushes are the most common adverse event reported for men on androgen suppression therapy. The incidence of hot flushes reported in the registration trials does not appear to be different among the GnRH agonists (Table 6).

Achieving and Maintaining Castration Levels of Testosterone With GnRH Antagonists

Registration studies for GnRH agonists require the reporting of adverse events as well as time to achieve and ability to maintain castration levels of serum testosterone. A new GnRH agonist is approved if these outcomes are comparable to previously approved drugs in the class. For registration studies, a serum testosterone level of 50 ng/dL (1.73 nmol/L) is considered a castration level of testosterone. The time to achieve castration levels is based on assaying serum testosterone levels on day 29. The percentage of subjects achieving castration levels in the registration trials by day 29 is compared for the GnRH agonists approved by the FDA for the treatment of advanced prostate cancer (see Table 3). There does not appear to be any meaningful difference among the various approved GnRH agonists regarding the time to achieve castration levels of testosterone.

Another requirement of GnRH agonists and other endocrine therapies for prostate cancer is the ability to maintain castration levels of testosterone while on long-term therapy. The transient escape of serum testosterone may cause mini-flares when rechallenged with GnRH antagonists.[17] This effect has been termed acute-on-chronic phenomenon.

The failure of GnRH agonists to consistently maintain castration levels of testosterone has been previously reported.[18] The percentage of men with prostate cancer maintaining castration levels over a defined interval of time is currently required for all drug registration studies of GnRH agonists (see Table 4). These studies suggest a trend favoring triptorelin pamoate over leuprolide acetate for depot suspension.[15] It is important for urologists to note that the package insert for GnRH agonists recommends measuring serum testosterone levels during therapy to ensure that castration levels are maintained.

Following registration, the FDA mandated a phase IV study designed to determine whether men on triptorelin pamoate 11.25 mg experienced the acute-on-chronic phenomenon. The 3-month depot of triptorelin pamoate 11.25 mg was administered every 84 days to 20 men with advanced prostate cancer. None of the subjects rechallenged with triptorelin pamoate was found to have a serum testosterone level above the castration level immediately prior to or 2 days following rechallenge. This is consistent with prior studies showing the effectiveness of triptorelin pamoate for

Table 6
Comparison of Hot Flushes for GnRH Agonists

GnRH Agonist	Hot flushes (%)
Leuprolide acetate for depot suspension	
7.5 mg	57
22.5 mg	59
30 mg	47
Goserelin acetate implant	
3.6 mg	62
10.8 mg	64
Triptorelin pamoate	
3.75 mg	59
11.25 mg	73
Leuprolide acetate for injectable suspension	
7.5 mg	57
22.5 mg	56
30 mg	73
Leuprolide acetate implant	
65 mg	68
Histrelin acetate implant	
50 mg	65

GnRH, gonadotropin-releasing hormone.

maintaining castration levels of testosterone.

Oefelein and Cornum[18] recently reported on the failure to achieve castration levels of testosterone in men with advanced prostate cancer receiving GnRH agonists. In this study of 38 men, 37 received leuprolide 3-month depot and only 1 received goserelin acetate. Serum testosterone levels were measured every 28 days. Overall, 2 men (5.3%) failed to maintain castration levels of testosterone. The level of testosterone considered to achieve a castration level was 1.735 nmol/L (50 ng/dL). Following castration, men routinely achieve testosterone levels < 20 ng/dL.[19] The National Comprehensive Cancer Network has recommended resetting the threshold for serum testosterone levels following medical castration to 20 ng/dL in order to be more consistent with surgical castration.[20] When Oefelein and Cornum[18] reexamined their data using a 20 ng/dL threshold for serum testosterone, 13.1% of the men failed to maintain castrate levels of testosterone on leuprolide acetate.[18]

It is important for urologists to note that the package insert for GnRH agonists recommends measuring serum testosterone levels during therapy to ensure that castration levels are maintained.

Cost

Physician reimbursement for GnRH agonists will undergo dramatic changes beginning this year. These changes are reviewed in detail by Dr. Ray Painter in another article in this supplement. Medicare drug payment will be 106% of average sale price, which will be updated quarterly. There will no longer be a significant financial incentive for prescribing a specific GnRH agonist.

Route of Administration

There are no comparative studies that substantiate any claims regarding superiority of the route of administration. The subcutaneous implants require a surgical incision and have greater injection site reactions; however, patients avoid multiple injections. The needle size is one factor likely to be associated with injection site discomfort. Triptorelin pamoate 3.75 mg and 11.25 mg is injected using a small needle. A comparison of data from the registration study suggests subcutaneous injections are associated with a higher incidence of injection site reactions.

There are also important differences regarding storage and reconstitution of the different GnRH agonists. An advantage of triptorelin pamoate is the Clip'n'Ject® device used for its administration. The diluent is a component of the injector apparatus that facilitates the delivery of the drug.

Conclusion

GnRH agonists have become the most common selected option for achieving androgen suppression for prostate cancer. DES is no longer administered because of its unacceptable cardiovascular toxicity, and surgical castration is rarely performed because of the preference of men to retain their testes. GnRH agonists have a demonstrated survival advantage over antiandrogens as monotherapies for advanced prostate cancer. Various formulations of GnRH agonists are available, with dosing schedules

ranging between 1 and 12 months. The 4 different GnRH agonists—leuprolide acetate, goserelin acetate, triptorelin pamoate, and histrelin acetate—appear to have comparable tolerability.

The flare phenomenon can be easily controlled with coadministration of an antiandrogen. All GnRH agonists effectively maintain castrate levels in the overwhelming majority of men on treatment for advanced prostate cancer. It is advisable to measure serum testosterone while patients are on treatment because some men will have serum testosterone above castration levels. The literature and data on file with the FDA suggest that triptorelin pamoate may more reliably maintain castration levels of testosterone compared with leuprolide acetate for depot administration; however, the clinical significance of this apparent ability has yet to be proven. The smaller needle required, the intramuscular route of injection, and the Clip'n'Ject® system for injecting triptorelin pamoate may offer some modest advantages. ■

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Main Points

- Study 1 of the Veterans Administration Cooperative Research Group showed that diethylstilbestrol (DES) 5 mg caused cardiovascular morbidity and mortality, orchiectomy and DES 5 mg monotherapies exhibited similar overall survival, and overall survival with a combination of orchiectomy and DES 5 mg was no better than with the monotherapies. Study 2, which evaluated lower doses of DES, demonstrated that 1- and 5-mg doses appeared to have equivalent effects on reducing prostate cancer mortality despite the fact that the 1-mg dose did not reliably achieve castration levels of testosterone.
- One of the primary limitations of gonadotropin-releasing hormone (GnRH) agonists for the treatment of advanced prostate cancer is the initial flare phenomenon, which is characterized by an increase in serum testosterone following initial exposure to these drugs. The life-threatening sequelae from the flare phenomenon on may be prevented by the coadministration of an antiandrogen. The primary advantage of GnRH antagonists is the absence of the flare phenomenon; however, development of antagonists has been limited primarily because of adverse events, including severe allergic reactions.
- Leuprolide acetate, goserelin acetate, triptorelin pamoate, and histrelin acetate are the four GnRH agonists that have been developed and marketed for the treatment of advanced prostate cancer in the United States.
- Results from a randomized study comparing triptorelin pamoate with leuprolide suggest that triptorelin pamoate may more reliably maintain castration levels of testosterone. A comparison of the registration studies provides further evidence that triptorelin pamoate maintains testosterone levels better than leuprolide acetate for depot suspension.
- Relevant comparisons of monotherapies for androgen suppression in men with advanced prostate cancer would be survival, adverse events, pharmacologic properties, maintenance of castration levels of testosterone, injection site reactions, ease of administration, and cost. None of the comparative studies has been adequately powered to demonstrate significant differences among any of these outcomes.

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