Luteinizing Hormone–Releasing Hormone Agonists in Prostate Cancer

Elimination of Flare Reaction by Pretreatment with Cyproterone Acetate and Low-Dose Diethylstilbestrol

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Background. **In response to the first administration of a luteinizing hormone–releasing hormone (LHRH) agonist, the secretion of pituitary gonadotropin increases sharply and gives rise to a transient surge in the concentration of serum testosterone. This effect reaches a peak 4 to 7 days after the start of therapy and results in the onset of clinical symptoms and signs of tumor flare in 5% to 10% of patients.**

Methods. **To determine whether the effects of the LHRH-induced flare reaction are preventable, cyproterone acetate (100 mg) and low-dose diethylstilbestrol (0.1 mg) were administered daily for 4 weeks to inhibit the pituitary before the initiation of therapy with a depot LHRH agonist, goserelin acetate (3.6 mg every 4 weeks). Diethylstilbestrol was stopped after 8 weeks to eliminate associated minor toxicity while administration of cyproterone acetate was continued to suppress vasomotor symptoms. Twenty-four men with histologically confirmed prostate cancer were enrolled in the study: 6 with Stage C, 2 with Stage D1, and 16 with Stage D2 disease.**

Results. **Lead-in therapy reduced the concentration of serum testosterone into the castrate range within 1 week, and no significant change was observed in the mean level after administration of goserelin acetate. Neither was there an effect on the initial rate of normalization of serum prostate specific antigen (PSA); normal PSA values were obtained in 50% of patients after 10 weeks and in 70% after 32 weeks. In the subgroup of patients with Stage D2 disease, longer median survival was predicted by a normal serum PSA, either stable or decreasing, after 32 weeks of treatment. The regimen was well tolerated with a low incidence of hot flushes.**

Conclusions. **These results imply that in the absence of LHRH-induced tumor flare, prognosis is related to the ability of therapy to maintain a PSA nadir in the normal range.** ***Cancer*** **1993; 72:1685–91.**

Key words: luteinizing hormone–releasing hormone agonists, prostate cancer, flare reaction, antiandrogens, prostate specific antigen.

Androgen suppression is an effective approach to the treatment of advanced prostate cancer and can be accomplished by surgical orchiectomy or by employing agents which inhibit the synthesis and peripheral action of testosterone.[1] Several luteinizing hormone-releasing hormone (LHRH) agonists and antiandrogens are available for this purpose and may be used in combination not only to increase the effectiveness of androgen suppression but also to reduce the incidence of side effects.[1] Of major concern is the risk of a flare reaction associated with the first administration of LHRH agonist. The pituitary normally is stimulated by the pulsatile release of LHRH from the hypothalamus; when this periodicity is effaced by the continuous infusion of exogenous LHRH agonist, the pituitary becomes refractory to hypothalamic regulation. However, in response to the initial dose of LHRH agonist, gonadotropin secretion increases sharply and then tapers off as does the secretion of testosterone by the testis.[2] The surge in plasma testosterone peaks 4 to 7 days after therapy is started and results in the onset of a flare reaction in 5% to 10% of patients.[3] Clinical symptoms and signs may take the form of increased bone pain,[4] urinary retention,[3,5] spinal cord compression,[4] and sudden death.[5] Biochemical manifestations include temporary in-

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creases in the plasma levels of luteinizing hormone, testosterone, prostatic acid phosphatase (PAP), and prostate specific antigen (PSA) lasting 7 to 14 days.[2] Transient prostatic enlargement may occur in 30% to 50% of men[6,7] and presumably tumor growth is temporarily stimulated with similar frequency, thus culminating sporadically in urinary and neurologic complications.

The flare phenomenon has also been implicated in the early treatment-related progression of prostate cancer by the results of the Leuprolide Study Group Trial comparing leuprolide versus diethylstilbestrol[8] and those of the National Cancer Institute (NCI) INT0036 study comparing leuprolide with and without flutamide.[9] In the former clinical trial, treatment was considered to have failed at the 3-month time-point in 10 patients receiving leuprolide compared with 2 receiving diethylstilbestrol because of early progression of disease. In the latter trial, a 2.6-month gain in median time to progression was observed in the group receiving leuprolide and flutamide. This advantage was already evident at the 3-month time-point implying that earlier progression of disease occurred in the leuprolide monotherapy group.

It has been found that the risk of precipitating a symptomatic clinical flare reaction can be reduced by one of two methods. The first entails the pretreatment of a patient with cyproterone acetate[10] or diethylstilbestrol[11,12] for 1 week before the initiation of LHRH agonist therapy. The antigonadotropic action of these agents results in partial lowering of plasma testosterone and blunting of the LHRH-induced hormonal flare. The second alternative is to give flutamide,[9] nilutamide,[13] or cyproterone acetate[14] concurrently with the first administration of LHRH agonist to counteract the potential adverse effects of the acute increase in the level of testosterone. Although clinical symptoms and signs are mitigated by these methods, other measurable parameters of the flare reaction are not completely suppressed.[2]

The current study concerns the use of cyproterone acetate (100 mg/d) and low-dose diethylstilbestrol (0.1 mg/d) as a means of suppressing the pituitary before LHRH administration. We have previously demonstrated that the combination of these two agents is characterized by a rapid onset of action significantly lowering the concentration of serum testosterone within 1 day, and down to the castrate range within 1 week.[15] It was thus assumed that lead-in therapy with cyproterone acetate and low-dose diethylstilbestrol for 4 weeks would be sufficient to prevent any manifestations of a flare reaction either clinical or biochemical. Our results indicate that in the absence of tumor flare, survival appears to be related to the ability of therapy to produce a sustained suppression of serum PSA into the normal range.

Materials and Methods

In this Phase II nonrandomized pilot study, treatment with cyproterone acetate, low-dose diethylstilbestrol, and goserelin acetate was offered to eligible patients as an alternative to conventional therapy for advanced prostate cancer. The protocol was approved by the Clinical Investigation Committee of the British Columbia Cancer Agency and the Ethics Committee for Research involving Human Subjects of the University of British Columbia. Informed consent was obtained from all patients before entry into the study.

Enrollment

The eligibility of consecutively referred patients was determined by histologically confirmed prostatic carcinoma requiring systemic therapy; inoperable locally advanced disease or metastatic disease involving bone, lymph nodes, or other soft tissues outside of the pelvis; adequate renal function with a serum creatinine level of less than 176 μmol/l; normal liver function studies; normal hemoglobin, leukocyte count and platelet count; Eastern Cooperative Oncology Group performance status of 2 or less; and life expectancy of more than 3 months. No patient had previously received hormones, cytotoxic drugs, or irradiation of metastatic disease.

Treatment

The regimen used to produce an androgen-withdrawal effect was based on the sequential use of three agents as described before[16] and combined the following steps: (1) lead-in therapy with cyproterone acetate (50 mg orally twice daily) and diethylstilbestrol (0.1 mg once daily) administered for 4 weeks; (2) goserelin acetate (3.6 mg subcutaneously) started after 4 weeks of lead-in therapy and given every 4 weeks thereafter; (3) diethylstilbestrol stopped after 8 weeks with maintenance of cyproterone acetate to prevent vasomotor symptoms.[17]

Clinical and Laboratory Tests

The pretreatment evaluation included a full history and physical examination, and measurement of total serum testosterone, serum PSA by radioimmunoassay (Diagnostic Products Corporation, Los Angeles), PAP by radioimmunoassay,[18] blood urea nitrogen, creatinine, alkaline phosphatase, lactic dehydrogenase, and a complete blood count. Radiologic studies included x-rays of the chest, lumbar spine, and pelvis; and a computed tomography (CT) scan of the abdomen and pelvis to determine the extent of the local disease and lymphade-

nopathy. To complete the evaluation of metastatic disease, a bone scan also was obtained. Follow-up assessments were conducted at monthly intervals after the initiation of treatment. At each visit, the serum testosterone, luteinizing hormone, follicle stimulating hormone, PAP, and PSA were assayed again. The other biochemical tests, radiographs, CT scan, and bone scan generally were repeated every 4 to 6 months. During the initial part of this study, the levels of serum PSA below 2 μg/l were not titrated; this was later altered to 0.2 μg/l so that the normal range became 0.2 to 4.0 μg/l. Patients were questioned about side effects of treatment at each follow-up visit.

Response and Progression

Since this study was primarily concerned with measurable parameters of tumor flare, the effect of treatment was defined mainly in terms of the responses of serum PAP and PSA. Long-term outcome was given by absolute overall survival. Treatment was continued despite a rising serum PSA level and other evidence of progressive disease. In these circumstances, it was assumed that the termination of androgen suppression with resultant recovery of testicular function would stimulate the growth of androgen-sensitive, androgen-independent disease[1] and reduce the length of the symptom-free period. In some patients, attempts were made to extend the useful life of the antiandrogen component of the therapeutic regimen by escalating the dose of cyproterone acetate or substituting an alternative antiandrogen such as flutamide or nilutamide.

Statistics

The probability of survival was determined by the Kaplan–Meier method of nonparametric estimation. The significance of the difference in median survival times was calculated using the log-rank statistic.

Results

Patient Characteristics

Twenty-four patients were enrolled in the trial. Mean patient age at entry was 66 years (range, 41–80 years). Included in this group of men were 6 with Stage C disease, 2 with Stage D1 disease, and 16 with Stage D2 disease. At analysis, nine patients were alive and had been monitored for 30 to 58 months.

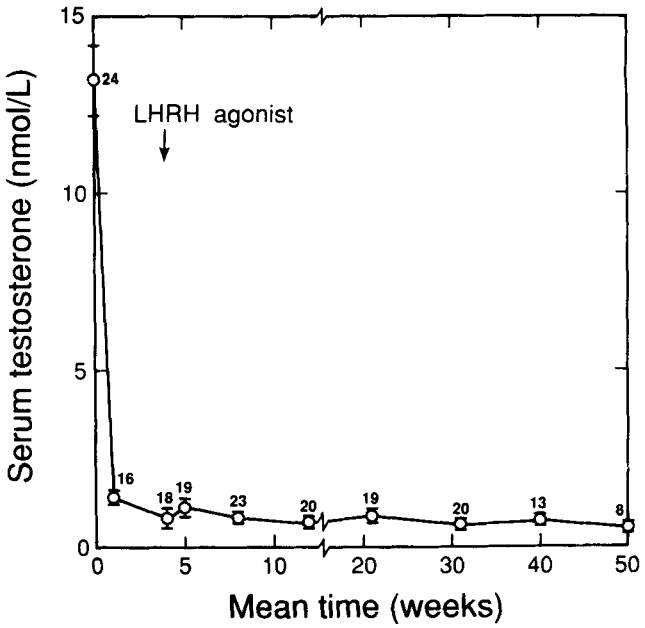

Figure 1. Effects of therapy on serum testosterone. Patients were treated with cyproterone acetate (50 mg twice daily) and low-dose diethylstilbestrol (0.1 mg once daily) for 4 weeks before the first dose of LHRH agonist, goserelin acetate (3.6 mg subcutaneously), was administered at the 4 week time-point. Diethylstilbestrol was discontinued at 8 weeks and the patients were maintained on goserelin acetate given every 4 weeks and cyproterone acetate. Results are expressed as mean ± standard error. Number of patients assessed is shown above each time-point plotted.

Effects of Therapy on Serum Testosterone

The changes which occurred in the concentration of serum testosterone after commencement of therapy are shown in Figure 1. The initial value of 13.3 ± 1.0 nmol/l (mean ± standard error) decreased to 1.4 ± 0.2 nmol/l after 1 week and to 0.8 ± 0.2 nmol/l after 4 weeks, representing decreases of 90% and 94%, respectively. The first administration of the LHRH agonist, goserelin acetate, at 4 weeks resulted in a slight increase in the mean level to 1.2 ± 0.2 nmol/l 1 week later at the 5-week interval but this was not statistically significant when compared with the mean value recorded at 4 weeks (t test, $P > 0.05$). After 8 weeks, the mean value had fallen slightly to 0.9 ± 0.1 nmol/l and remained relatively constant at this concentration throughout the follow-up to 50 weeks. Thus, no fluctuations were observed in the concentration of serum testosterone indicative of a hormonal flare reaction.

Effects of Therapy on Serum Luteinizing Hormone and Follicle Stimulating Hormone

Goserelin acetate-induced changes in the levels of serum gonadotropin were more apparent, as shown in

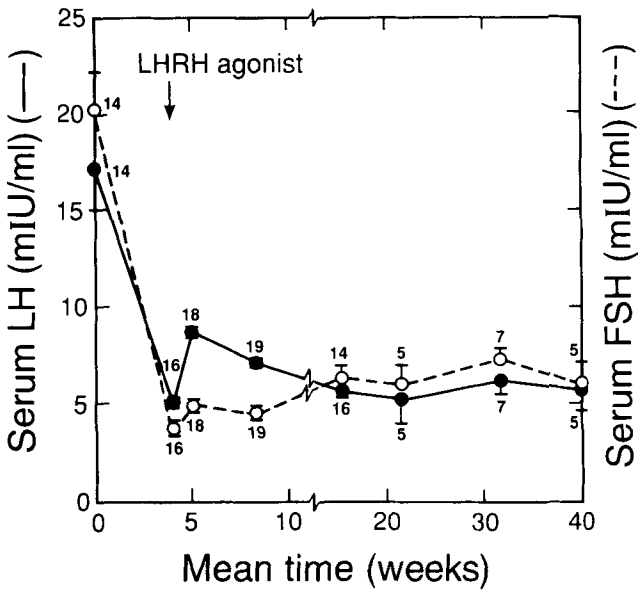

Figure 2. Effects of therapy on serum luteinizing hormone (LH, solid line) and follicle-stimulating hormone (FSH, broken line). Patients were treated as described in the legend to Figure 1. Results are expressed as mean ± standard error. Number of patients assessed is shown above each time-point plotted.

Figure 2. From an initial mean level of 17.3 ± 2.1 mIU/ml, the concentration of serum luteinizing hormone decreased to 5.1 ± 0.6 mIU/ml after 4 weeks. After the first administration of goserelin acetate, there was a statistically significant increase in the level to 8.6 ± 0.8 mIU/ml ($P < 0.05$) representing a 70% rise over the nadir value at 4 weeks; however, relative to the zero time value, the increase was small and not of sufficient magnitude to affect the concentration of serum testosterone (Fig. 1). The mean level had declined slightly to 7.2 ± 0.5 mIU/ml after 8 weeks before falling to a plateau level of about 5.6 ± 0.5 mIU/ml after 15 weeks which was maintained to the end of the observation period. The concentration of serum follicle-stimulating hormone decreased from 20.4 ± 2.7 mIU/ml to 3.8 ± 0.3 mIU/ml after 4 weeks and then underwent a small but statistically significant 30% increase to 4.9 ± 0.3 mIU/ml ($P < 0.05$) in response to goserelin acetate. These results indicate that the concentrations of serum luteinizing hormone and follicle stimulating hormone remain well suppressed below the initial levels even after the administration of goserelin acetate.

Effects of Therapy on Serum PSA and PAP

At the time of entry into the trial, the serum PSA was abnormal in 100% of patients and PAP was abnormal in 76%. The rate of normalization of these tumor markers is shown by the results presented in Figure 3. The percentage of patients with an abnormal PSA value declined over a period of about 32 weeks. The rate of normalization was faster between zero time and 10 weeks than in the succeeding interval between 10 and 32 weeks. From this point onward, the PSA result remained abnormal in about 30% of patients. These results indicate that PSA response is most likely to be observed in the first 32 weeks of therapy with little chance of treatment producing a normal result beyond this time.

An abnormal level of serum PAP was observed in 76% of patients. The initial rate of normalization paralleled that of serum PSA with abnormal values being observed in about 20% of patients after 9, 16, and 24 weeks. At later time-points, abnormal PAP values were recorded in about 30% of patients, similar to the percentage with abnormal serum PSA determinations. Both the PSA and PAP data imply an objective response rate of 70% in this particular group of patients.

Details of the time-course of serum PSA levels obtained in the eight patients in whom the values did not reach a stable nadir in the normal range are shown in Figure 4. In all patients, an initial brief decline occurred in serum PSA followed by an increase. Only in one patient was a nadir observed in the normal range but this was not sustained. The mean of the initial serum PSA value in this group of patients was 135 μg/l (range, 34–360 μg/l).

The time-course of serum PSA levels in the patients in the group whose readings decreased to a prolonged nadir in the normal range during treatment is shown in

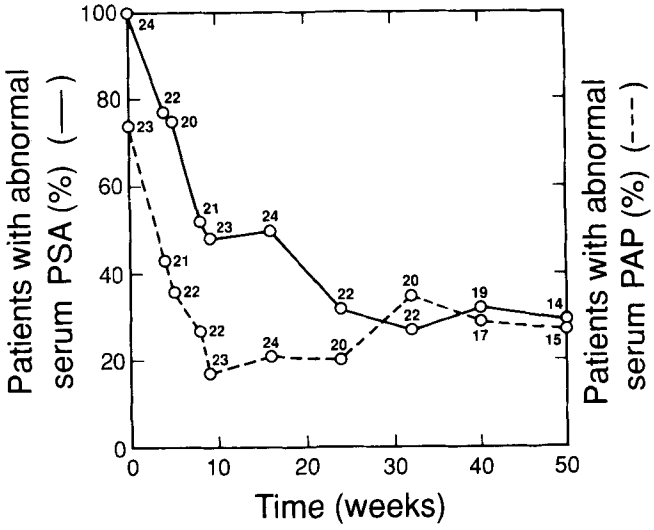

Figure 3. Time-course of normalization of serum prostate specific antigen (PSA, solid line) and prostatic acid phosphatase (PAP, broken line). Patients were treated as described in the legend to Figure 1. Number of patients assessed is shown above each time-point plotted.

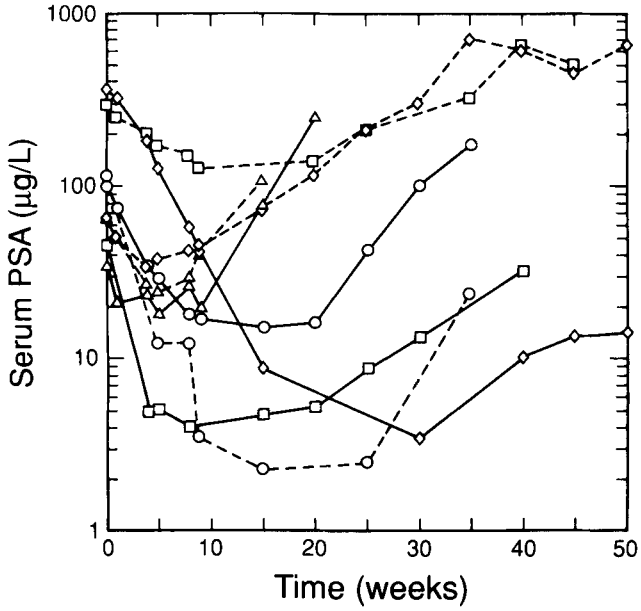

Figure 4. Time-course of serum prostate specific antigen (PSA) in eight patients whose PSA levels did not attain a stable nadir in the normal range during treatment. Patients were treated as described in the legend to Fig. 1.

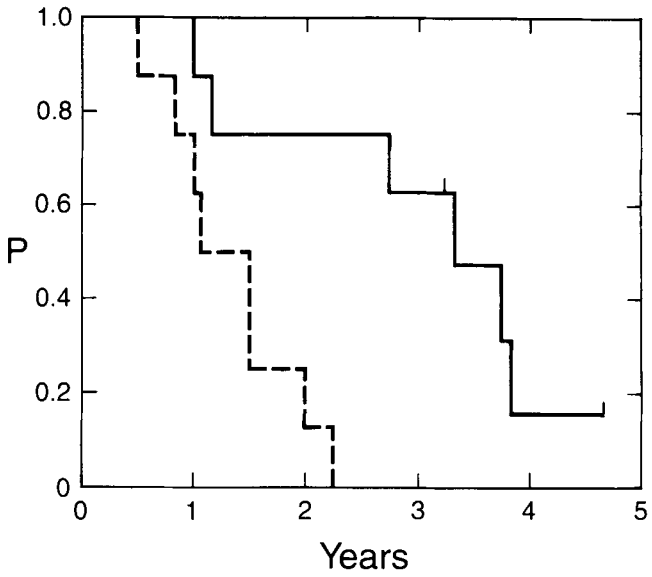

Figure 6. Kaplan–Meier estimation of survival in Stage D2 patients according to a prolonged nadir of serum PSA in the normal range. Vertical markers represent patients alive at last follow-up. P, probability of survival; solid line, PSA levels attained a stable or decreasing nadir in the normal range; broken line, PSA levels did not attain a stable nadir in the normal range.

Figure 5. In 15 of 16 patients, the serum PSA reached the lowest points within the normal range after 30 weeks; in the one exception, the minimum value was reached after 40 weeks. The mean of the initial serum PSA value was 334 µg/l (range, 5–4600 µg/l) in this group of patients.

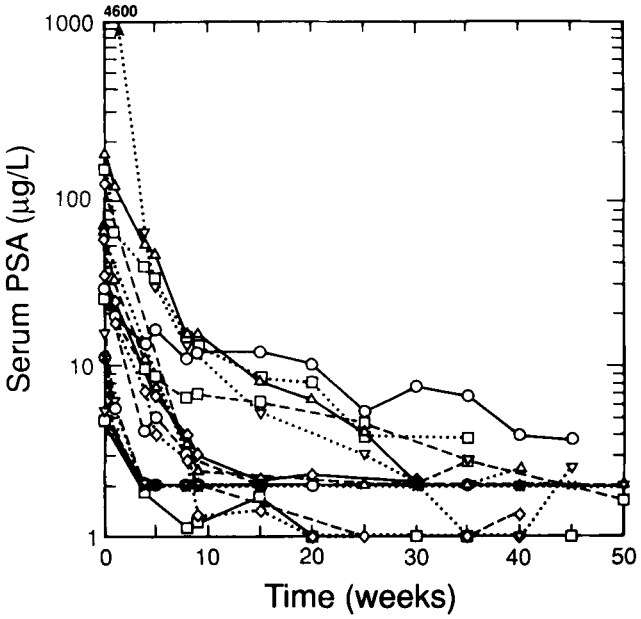

Figure 5. Time-course of serum prostate specific antigen (PSA) in 16 patients whose PSA levels attained a prolonged nadir in the normal range during treatment. Patients were treated as described in the legend to Figure 1.

Survival

The relationship between serum PSA concentration and survival in the 16 patients with Stage D2 prostate cancer is shown in Figure 6. In this group of patients, 14 deaths occurred; the median survival time was 24 months. Subclassification of patients into those whose PSA level did and did not reach a prolonged nadir in the normal range revealed a statistically significant difference in survival ($P < 0.05$). In the group of eight patients in whom the PSA level failed to drop to a sustained nadir in the normal range, eight deaths occurred with a median survival time of 18 months. In contrast, in the group of eight patients in whom the serum PSA did plateau in the normal range, six deaths occurred with a median survival time of 40 months.

Side Effects

The types and incidence of side effects are summarized in Table 1. Impotence occurred in all previously potent men. Mild dyspnea on exertion which occurred in three patients was transient. Nipple tenderness was reported infrequently and disappeared after 3 to 4 months of therapy. Night sweats and hot flushes occurred in two

Table 1. Side Effects in Patients Pretreated With Cyproterone Acetate and Low-Dose Diethylstilbestrol Followed by Goserelin Acetate

	No. of patients (%)
Impotence (19 previously potent)	19 (100)
Mild dyspnea	3 (13)
Nipple tenderness	3 (13)
Hot flushes, night sweats	2 (8)
Loss of energy	2 (8)
Breast swelling	2 (8)
Pulmonary embolus	1 (4)
Depression	1 (4)

men. The observed breast swelling in two men was minimal.

Discussion

This study confirms that pretreatment of patients with cyproterone acetate (100 mg/d) and low-dose diethylstilbestrol (0.1 mg/d) for 4 weeks eliminates the acute increase in serum testosterone associated with the initial administration of LHRH agonist. Consistent with previous results,[15,19] lead-in therapy with these agents reduced the concentration of serum testosterone into the castrate range within 1 week (Fig. 1). When the LHRH agonist, goserelin acetate, was administered at 4 weeks, no significant change in testosterone levels was observed at 5 weeks, the approximate time at which the testosterone surge reaches a peak.[2,6] Baseline levels of serum testosterone remained constant in the castrate range to the end of the observation period at 50 weeks.

A more pronounced effect of goserelin acetate was apparent on the concentration of serum luteinizing hormone (Fig. 2) with an acute increase from 5.1 ± 0.6 mIU/ml to 8.6 ± 0.8 mIU/ml between 4 and 5 weeks. Since the gonadotropin surge reaches a peak about 4 days after LHRH injection,[2,6] our measurement after 7 days may have underestimated the actual magnitude of the change. Consistent with a below-normal concentration of gonadotropin, however, no significant physiologic effect occurred of the surge on serum testosterone (Fig. 1). These data indicate that if the pituitary is adequately inhibited by lead-in therapy, the acute elevation of serum testosterone produced by LHRH agonist is prevented, and the risk of a flare reaction is eliminated.

In following the effects of treatment on serum PSA, it was observed that the initial rate of normalization of this parameter was not affected by the administration of goserelin acetate (Fig. 3). Normal values were attained in 50% of patients after 10 weeks and in 70% after 32 weeks. Beyond this time-point the proportion of patients with an abnormal serum PSA remained almost constant at 30%.

The rate of normalization of serum PAP paralleled the initial rate observed for PSA; after 10 weeks, only 20% of patients had an abnormal PAP reading. In the interval between 10 and 32 weeks, the proportion of patients with an abnormal result increased to a plateau level of 30%, identical to the final percentage of patients with an abnormal serum PSA.

A striking difference was observed in the response of serum PSA in patients whose level did not reach a stable nadir in the normal range compared with the response observed in patients whose serum PSA attained a protracted normal value. Patients with persistent abnormal values were characterized by serum PSA values which transiently decreased in response to androgen suppression but failed to reach a stable nadir in the normal range (Fig. 4). The median survival of patients who fell into this category was only 18 months (72 weeks) (Fig. 6); none of this group survived.

The time-course of serum PSA levels in 16 patients in whom the PSA levels ultimately became normal (Fig. 5) generally was characterized by an initial rapid decrease followed by a slower decline into the normal range such that an apparent nadir had been reached in most patients after 30 to 40 weeks of treatment. The median survival in the subgroup of eight patients with Stage D2 prostate cancer was 40 months (160 weeks). Thus, in the absence of a flare reaction, it appears that the normalization of serum PSA after androgen ablation is an important indicator of prognosis. An abnormal PSA after 32 weeks strongly suggests androgen independence and progression to Stage D3 disease.

In a longitudinal study of serum PSA in 48 patients with Stage D2 prostate cancer who were treated with orchiectomy, monthly LHRH agonist injection or diethylstilbestrol, Miller et al.[20] observed that the mean time to PSA normalization was 36 ± 4 weeks. For the patients whose posttreatment PSA levels continued to decrease or reached a plateau below 4.0 μg/l, the upper limit of the normal range, the median time in remission was 168 weeks. In contrast, failure to achieve this nadir was associated with a median remission time of only 40 weeks. Our finding of increased median survival, in similarly staged patients who have a normal PSA reading after 32 weeks of androgen suppression, is consistent with these results.

The implications of an LHRH agonist-induced flare in serum PSA concentration include the possibility of an increased risk of nonnormalization of PSA despite further treatment. According to the results of Miller et al.,[20] as well as our findings, this would be associated with a shorter time in remission and reduced survival. The early progression of disease observed in patients

who received leuprolide monotherapy in both the Leuprolide Study Group and the NCI INT0036 trials has been discussed elsewhere on the basis of such concerns.[1,9] Measures to avoid testosterone flare and to adjust for the nonnormalization of serum PSA would certainly strengthen the design of future clinical studies.

In the current study, the combination of cyproterone acetate and low-dose diethylstilbestrol given as lead-in therapy for 4 weeks before injection of goserelin acetate, prevented any acute elevation of serum testosterone which might result in tumor flare. The agents were tolerated well, with symptoms of impotence (100% of patients), mild dyspnea on exertion (13%), nipple tenderness (13%), and loss of energy (8%). Hot flushes (8%) were infrequent and transient; night sweats persisted in the occasional patient. Although cyproterone acetate was used mainly to counteract vasomotor symptoms, the independent antiandrogenic properties of this drug may have added to the benefits derived from the use of goserelin acetate and cyproterone acetate in combination.[21]

We conclude that in the absence of treatment-related tumor flare, enhanced survival is predicted by a normal PSA value, either stable or decreasing, after 32 weeks of androgen suppressive therapy.

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