Simultaneous administration of pure antiandrogens, a combination necessary for the use of luteinizing hormone-releasing hormone agonists in the treatment of prostate cancer
(testosterone/prostatic acid phosphatase/androgen dependence/medical castration/disease flare)

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Communicated by Choh Hao Li, February 13, 1984

ABSTRACT Although castration levels of serum androgens are consistently achieved after 2–3 weeks of treatment with luteinizing hormone-releasing hormone (LHRH) agonists, the administration of these peptides alone in adult men is always accompanied by a transient increase in plasma testosterone and dihydrotestosterone levels, which lasts for 5–15 days at the beginning of treatment and is accompanied by disease flare-up in some cases, thus seriously limiting the acceptability of this otherwise efficient and well-tolerated treatment. The present data show that the simultaneous administration of a pure antiandrogen neutralizes the influence of the transient increase in serum androgens on prostate cancer, as indicated by the 60% decrease in serum prostatic acid phosphatase observed within 5 days of combined treatment with an LHRH agonist and a pure antiandrogen. The addition of a pure antiandrogen thus makes fully acceptable the use of LHRH agonists as an advantageous substitute for surgical castration and estrogens in the treatment of prostate cancer.

Cancer of the prostate is the second cause of death due to cancer in men, with an estimated minimum of 60,000 newly diagnosed cases annually in the United States. After the pioneering studies of Huggins and Hodges (1), most of the efforts during the last 40 years have been aimed at eliminating the influence of testicular androgens on the growth of the cancer by surgical castration or by treatment with estrogens, which causes a decrease in circulating androgens. Such treatments provide a temporary objective and/or subjective improvement in 60%–70% of cases of advanced prostate cancer (2, 3). However, surgical castration is not always well accepted by patients, and treatment with estrogens causes serious cardiovascular complications, which often offset the benefits (4). There was thus the need for a more acceptable, well-tolerated, and possibly more efficient form of hormonal therapy.

The observation that treatment of experimental animals with luteinizing hormone-releasing hormone (LHRH) agonists causes a marked inhibition of testosterone secretion, accompanied by a decrease in prostate weight (5), offered the possibility of a new approach in the treatment of prostate cancer. Fortunately, among the species studied, man is the most sensitive to the inhibitory action of LHRH agonists on testicular androgen formation, and thus medical castration can be easily achieved (5–10). Although the chronic administration of these peptides in adult men completely blocks testicular androgen formation with no secondary effects other than those related to hypoandrogenicity, a serious limitation pertains to the transient increase in serum androgen levels, which lasts for 5–15 days at the beginning of treatment. This increase in serum androgens is accompanied by disease flare-up in a significant proportion of cases (9), thus seriously limiting the use of LHRH agonists alone in treating prostate cancer, at least during the first 2 weeks of treatment.

The present study shows that the simultaneous administration of a pure antiandrogen neutralizes the influence of increased levels of serum androgens induced by the LHRH agonist during the first days of treatment, as illustrated by the rapid and marked decrease in serum prostatic acid phosphatase, a marker of prostate cancer cell activity.

MATERIALS AND METHODS

Patients. Twenty patients with biopsy-proven prostate adenocarcinoma took part in this study, after written informed consent. Eleven patients had bone metastases (stage D2 disease); nine patients had stage C disease. After the appropriate clinical, urological, biochemical, hematological, and radiological tests (7), the patients received a daily subcutaneous injection at 0800 hours of 500 μg of the LHRH agonist [D-Ser(Bu)6,des-Gly-NH2]-LHRH ethylamide (Buserelin); 100 mg of the antiandrogen (5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2-imidazolidinedione (Anandron; RU-23908) was given orally at 0700, 1500, and 2300 hours. The antiandrogen was given 1 day before first administration of the LHRH agonist (day 0).

Methods. Blood samples were taken at days −2, −1, 0, 1, 2, 5, 14, and 30 for measurement of serum levels of testosterone, dihydrotestosterone, and prostatic acid phosphatase by double-antibody radioimmunoassays (7, 11). Radioimmunoassay data were analyzed using a program based on model II of Rodbard and Lewald (12). Statistical significance was measured according to the multiple-range test of Duncan-Kramer (13). Results are shown as the means ± SEM of duplicate determinations of individual samples. A series of laboratory analyses, including complete and differential blood count, sequential multiple analyzer (SMA-12), and urinalysis, were performed. No side-effects that could be attributed to Buserelin or Anandron were noticed, except for those related to hypoandrogenicity.

Materials. The LHRH agonist Buserelin was supplied by the Medical Department, Hoechst Canada (Montreal), through the courtesy of A. T. A. Fazeckas; the antiandrogen Anandron was supplied by J. Gareau (Roussel Canada, Montreal). Material obtained from New England Nuclear was used for measurement of prostatic acid phosphatase by double-antibody radioimmunoassay.

RESULTS AND DISCUSSION

As illustrated in Fig. 1, increased levels of serum testosterone up to 200% above control are observed during the first days of daily subcutaneous treatment in four representative

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Abbreviation: LHRH, luteinizing hormone-releasing hormone.
patients receiving 500 µg of the LHRH agonist. A maximal increase in serum androgen levels is usually found 3–5 days after starting treatment. After this initial increase in serum testosterone, near-castration levels are then achieved 2–4 weeks after treatment. At time intervals >4 weeks, castration levels of serum testosterone and dihydrotestosterone are maintained for up to 3 years, the longest time interval studied.

The important finding in the present study is that the serum prostatic acid phosphatase concentration, which was elevated before treatment in these 20 patients showed a very rapid and marked decrease after initiation of the combined therapy. In fact, serum prostatic acid phosphatase levels are decreased by 60% as early as 5 days after starting treatment, at a time when serum testosterone levels are maximally increased (Figs. 1 and 2).

It is now well recognized that chronic treatment with LHRH agonists is an efficient and extremely well-tolerated way to achieve medical castration, thus offering an advantageous alternative to surgical castration and estrogens. The rationale for treatment of prostatic carcinoma with LHRH agonists is to mimic the effects of castration or DES on serum androgen levels. However, it was observed in an adult man treated with a high dose of an LHRH agonist (6), and confirmed in subsequent studies (7–10), that increased levels of serum testosterone and dihydrotestosterone are always found during the first days of treatment. Unfortunately, these high levels of serum androgens can cause disease flare-up in a significant proportion of patients having advanced prostate cancer (9). The well-known high androgen sensitivity of prostate cancer and the risk of a disease flare-up at the

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**Fig. 1.** Representative changes in serum testosterone (---) and prostatic acid phosphatase (-----) concentrations during the first month of combined treatment with an LHRH agonist and a pure antiandrogen. Blood samples were obtained at 0800 hours, 24 hr after last administration of the LHRH agonist.

**Fig. 2.** Time course of changes of serum testosterone and prostatic acid phosphatase levels in 20 patients with advanced prostate cancer receiving the combined therapy with an LHRH agonist and a pure antiandrogen. Data are presented as means ± SEM of duplicate determinations of 20 individual samples. No disease flare-up was observed in any of the patients and subjective improvement, especially decrease of pain, was observed within the first 2–5 days of treatment.
initiation of treatment seriously limit the use of LHRH agonists alone in patients with advanced prostate cancer, at least during the first 2 weeks of treatment.

A solution is offered by the present study, which clearly demonstrates that simultaneous administration of a pure antiandrogen at a relatively low dose completely blocks the influence of the transient increase in serum androgens on the activity of prostate cancer, as reflected by serum prostatic acid phosphatase levels as well as by parallel changes of the clinical response. No secondary effects other than those related to hypoandrogenicity (loss of libido and hot flashes in 50% of cases) were noted. The rapid and marked decrease in serum prostatic acid phosphatase observed during the first days of combined therapy with the antiandrogen and the LHRH agonist clearly indicates that the antiandrogen efficiently neutralizes the elevated levels of serum testosterone and dihydrotestosterone induced by the LHRH agonist on the cancer.