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Prostate Cancer

Selective Estrogen Receptor Alpha Agonist GTx-758 Decreases Testosterone with Reduced Side Effects of Androgen Deprivation Therapy in Men with Advanced Prostate Cancer

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Abstract

Background: A need remains for new therapeutic approaches for men with advanced prostate cancer, particularly earlier in the disease course.
Objective: To assess the ability of an oral selective estrogen receptor α agonist (GTx-758) to lower testosterone concentrations compared with leuprolide while minimizing estrogen deficiency–related side effects of androgen-deprivation therapy.
Design, setting, and participants: Hormone-naive advanced prostate cancer patients were randomized to oral GTx-758 1000 mg/d, 2000 mg/d, or leuprolide depot.
Intervention: GTx-758 and leuprolide.
Outcome measurements and statistical analysis: The primary end point was the proportion of patients achieving total testosterone ≤50 ng/dl by day 60. Secondary end points included serum free testosterone, prostate-specific antigen (PSA), sex hormone-binding globulin, hot flashes, bone turnover markers, and insulin-like growth factor (IGF)-1 levels.
Results and limitations: Of 159 randomized patients, leuprolide reduced total testosterone to ≤50 ng/dl in a greater proportion of patients than GTx-758 by day 60 (43.4%, 63.6%, and 88.2% of subjects receiving GTx-758 1000 mg [$p < 0.001$], GTx-758 2000 mg [$p = 0.004$], and leuprolide, respectively). GTx-758 reduced free testosterone and PSA earlier and to a greater degree than leuprolide. GTx-758 led to fewer hot flashes, decreases in bone turnover markers, and alterations in IGF-1 compared with leuprolide. A higher incidence of venous thromboembolic events (VTEs) was seen with GTx-758 (4.1%) compared with leuprolide (0.0%).
Conclusions: Although leuprolide reduced total testosterone to ≤50 ng/dl in a greater proportion of patients compared with GTx-758, GTx-758 was superior in lowering free testosterone and PSA. GTx-758 reduced estrogen deficiency side effects of hot flashes, bone loss, and insulin resistance but with a higher incidence of VTEs.
Patient summary: This paper reports findings that leuprolide lowered total testosterone more than GTx-758 but that GTx-758 lowered free testosterone and prostate-specific antigen more than leuprolide. GTx-758 also reduced estrogen deficiency side effects, albeit at a higher rate of vascular events.
Trial registration: Clinicaltrials.gov identifier NCT01615120.

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1. Introduction

Androgen-deprivation therapy (ADT) is the mainstay of treatment for advanced prostate cancer. Although ADT improves disease-free survival in men with advanced disease, patients eventually develop castration-resistant prostate cancer (CRPC). One of the main causes for the development of CRPC is suboptimal androgen suppression by primary ADT, resulting in sustained androgen levels within the tumor [1]. Secondary hormonal strategies to further reduce androgen levels in men with CRPC have resulted in improvement of progression-free and overall survival [2,3].

Surgical castration is the gold standard for lowering serum testosterone levels in the palliative treatment of advanced and metastatic prostate cancer. With the advent of medical agents to lower testosterone, such as luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, "castration" has been defined as a total testosterone level $\leq$50 ng/dl, based on the lower limit of detection of obsolete total testosterone assays [4]. With more sensitive mass spectrometry–based assays, total and free testosterone levels can be determined more accurately [5], revealing that medical castration with LHRH agents often does not result in levels of total testosterone that are similar to those measured in men who underwent surgical orchiectomy [6]. A reevaluation of testosterone levels in men on medical agents suggests that a serum testosterone level $\leq$20 ng/dl may be a more contemporary goal of ADT [7–10]. More important, based on the free hormone tissue hypothesis, measurements of free testosterone, the unbound biologically active form of testosterone, may be a more accurate indicator of the effectiveness of ADT [11,12].

ADT has estrogen deficiency side effects because estradiol is derived from the aromatization of testosterone in men [13]. Estrogen deficiency–related side effects associated with ADT include hot flashes, bone loss and fractures, development of insulin resistance, metabolic syndrome [14], and reduced libido and cognitive function [15].

Estrogenic agents have traditionally been used as a form of ADT in treating prostate cancer with clear antitumor activity [16]. GTx-758 (Capesaris, GTx Inc., Memphis, TN, USA), 3-fluoro-N-(4-fluorophenyl)-4-hydroxy-N-(4-hydroxyphenyl) benzamide, is an oral nonsteroidal selective estrogen receptor (ER)α agonist that binds to the ER with nanomolar affinity [17]. This specificity for ERα provides an opportunity to lower free testosterone levels by increasing sex hormone-binding globulin (SHBG) as its primary mechanism. In a phase 2 clinical study, we compared the effectiveness of GTx-758 versus leuprolide on total and free testosterone and prostate-specific antigen (PSA) levels as well as safety including the estrogen deficiency side effects in men with advanced prostate cancer initiating ADT.

2. Methods

This was a prospective randomized 1:1:1 phase 2 open-label multicenter trial composed of men with advanced prostate cancer (n = 159) initiating either oral daily doses of 1000 mg (two 500-mg tablets) or 2000 mg GTx-758 or leuprolide depot (LUPRON DEPOT 30 mg for 4-mo administration). It was conducted according to the Declaration of Helsinki, approved by appropriate research ethics committees, and each patient provided signed informed consent prior to registration and randomization.

Each subject was to remain on the study for at least 60 d. If a subject failed to reach total testosterone $\leq$50 ng/dl by day 60, he was discontinued from the study. Subjects who achieved castration by day 60 continued for up to 360 d to assess the safety of GTx-758 over this dosing duration and to assess the maintenance of total testosterone levels $\leq$50 ng/dl.

Major inclusion criteria were men between 45 and 80 yr of age; Eastern Cooperative Oncology Group performance score $\leq$2; screening total testosterone $\geq$150 ng/dl; no prior ADT (medical or surgical) unless the subject had been treated with LHRH agent for $\leq$6 mo and that treatment was $\geq$1 yr prior to screening. Key exclusion criteria included history of abnormal blood clotting, factor V Leiden mutation, thrombotic disease, stroke, deep vein thrombosis (DVT), or pulmonary embolus (PE).

The primary end point was the proportion of patients who achieved $\leq$50 ng/dl total testosterone by day 60. Secondary efficacy end points evaluated included serum concentrations of free testosterone, PSA, SHBG, safety and tolerability, incidence and frequency of hot flashes, serum bone turnover markers (bone-specific alkaline phosphatase [BSAP] and c-terminal telopeptide [CTX]), and insulin-like growth factor (IGF)-1 levels, an indicator of insulin resistance.

All serum hormone and PSA measurements were performed by a central laboratory using standard techniques. Serum total testosterone concentrations were determined using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS-MS) method. This platform is currently utilized for total testosterone by most major laboratories and provides values that are more accurate at the lower levels of testosterone found in women, children, hypogonadal men, and men on ADT [18,19]. Percentage free testosterone was determined by equilibrium dialysis. Free testosterone concentrations were calculated as the product of total testosterone (by LC-MS-MS) and free fraction (by equilibrium dialysis). This combination of approaches is considered the gold standard with which to measure free testosterone with excellent accuracy and validity (sensitivity and specificity) [18].

Hot flash assessments were performed utilizing a standard instrument measuring the frequency and severity of hot flashes; data were compiled at baseline, day 28, and day 90 [20]. Men reported as experiencing hot flashes were those indicating any in the period between the respective time point and the prior patient visit. CTX (picograms per milliliter), assayed by an electrochemiluminescent immunoassay and BSAP (units per liter), assayed by immunoenzymatic methodology, were measured as indicators of bone turnover. Serum IGF-1 levels were measured by liquid chromatography/mass spectrometry (LC/MS) at the same time each day (within a $\pm$60-min window).

2.1. Statistical analyses

To determine the appropriate sample size for this trial, bootstrap samples were taken from a trial that included an arm with leuprolide to determine the minimum number of subjects necessary to produce 90% as the lower limit of the 95% confidence interval about the Kaplan-Meier estimate of the proportion castrate at 1 yr [21]. Fifty-two subjects were determined to be the smallest sample size for any one arm. The trial was not powered for comparisons between arms, merely to estimate castration rates and observe safety.

Categorical demographic and presenting features were compared among arms using chi-square tests; continuous features were compared using analysis of variance F tests. The proportion of subjects reaching $\leq$50 ng/dl levels of total testosterone by day 60 were compared between each GTx-758 arm and the leuprolide arm using Fisher exact tests. Fisher