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PHARMACODYNAMICS OF A LONG ACTING DEPOT PREPARATION OF AVORELIN IN PATIENTS WITH PROSTATE CANCER

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ABSTRACT

Purpose: We evaluate the pharmacodynamics, pharmacokinetics and tolerability of a sustained release depot formulation of avorelin, a new potent super agonist of luteinizing hormone-releasing hormone receptors, in patients with prostate cancer.

Materials and Methods: A total of 60 patients were randomized to receive a 10 mg. (31) or 15 mg. (29) avorelin subcutaneous depot. Serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and plasma avorelin were measured regularly until depot exhaustion.

Results: Of the 10 mg. group patients 3 withdrew from the study after 31 to 35 weeks due to disease progression. Of the 15 mg. group patients 1 did not complete the study for logistical reasons. After the expected flare in serum testosterone, LH and FSH during week 1, medical castration (testosterone concentration less than 1.735 nmol./l.) was achieved within 4 weeks of depot injection. Median duration of testosterone suppression was 40 weeks in the 10 mg. (95% confidence interval 35 to 42) and 39 in the 15 mg. (37 to 43) group. The reduction in serum LH was similar to that of testosterone, while that of FSH was less pronounced. Plasma avorelin was proportional to the dose and correlated with serum testosterone. Normalization of serum prostate specific (4 ng./ml. or less) at 6 months was achieved in 80 and 88% of the 10 and 15 mg. groups, respectively. During the (7 to 20-month) observation period 94 and 86% of the 10 and 15 mg. groups, respectively, complained of adverse events mainly related to androgen suppression (hot flushes, decreased libido and impotence) or the nature of the disease (skeletal pain). In each group 3 patients had serious adverse events requiring hospitalization for reasons unrelated to avorelin treatment. The depot was well tolerated locally.

Conclusions: Subcutaneous depot formulations of avorelin were well tolerated and had protracted inhibitory effects on pituitary gonadotropin secretion in patients with prostate cancer. Testosterone suppression was maintained for more than 6 months in all patients. Avorelin depots could be the first luteinizing hormone-releasing hormone agonist formulation to be administered at 6-month intervals.

KEY WORDS: gonadorelin, prostatic neoplasms, testosterone

Adenocarcinoma of the prostate is the most commonly diagnosed malignant neoplasm in the United States.[1] Presently, there is no curative treatment for patients with metastatic prostate cancer, who have a progressive and eventually fatal clinical course. Median survival of cohorts of patients with metastatic disease who have entered large prospective randomized trials during the last 3 decades has been relatively stable at 24 to 36 months.[2,3] Initially, the growth of prostate cancer requires androgens, which is the rationale for endocrine manipulations that rely on suppression of testosterone production to control androgen dependent tumor growth.[4,5] Androgen deprivation has substantial palliative effects but in all patients the tumor eventually progresses to an androgen insensitive state and no treatment can prolong survival.[6] Suppression of androgens of testicular origin is part of androgen deprivation therapy, which can be accomplished by surgical castration or medical suppression of testicular function with synthetic analogues of gonadotropin-releasing hormone.[2–5]

Avorelin is a new potent agonist of luteinizing hormone-releasing hormone (LH-RH) receptors.[7] Chemically, avorelin is the acetate salt of 5-oxo-Pro-His-Trp-Ser-Tyr-DTrp(2-Me)-Leu-Arg-NH(Et)-prolinamide. The affinity of avorelin for LH-RH receptors is 100-fold greater than that of natural LH-RH, and 10 times greater than that of buserelin and goserelin.[7] Avorelin is dispersed in a matrix of a high molecular weight copolymer of D,L-lactic and glycolic acid, which is completely biodegradable. The final formulation of cylindrical rods (depots) for subcutaneous administration releases

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avorelin in a continuous manner for at least 6 months.[8] In dogs subcutaneous depots of 7 and 9 mg. avorelin produced suppression of testosterone levels for about 7 and 9 months, respectively.[9] Dosages in dogs (0.6 to 0.9 mg./kg.) are substantially higher than those used in humans (0.1 to 0.2 mg./kg.). We evaluate the pharmacodynamics, pharmacokinetics and tolerability of avorelin depot in patients with prostate cancer.

MATERIALS AND METHODS

Patients. From September 1996 to November 1997, 5 English hospitals consecutively recruited 60 men with carcinoma of the prostate. All patients gave written informed consent to participate in the study and were treated as outpatients. The study protocol was approved by the hospital local ethics committee. At entry all patients had histologically proved, previously untreated adenocarcinoma of the prostate. The Gleason system (score 1 to 5) was used for histological grading of the tumor[10] and TNM staging was used for classification of disease.[11] A life expectancy of more than 6 months, age 40 to 85 years, serum testosterone 8 nmol./l. or greater, bone scan in the previous 8 weeks, and absence of concurrent malignancy and liver or renal function abnormalities were requisites for study entry. The extension of cancer was assessed by endorectal ultrasonography of the prostate, chest x-ray and isotopic bone scan.

Study design and treatment. Patients were randomized to receive a 10 or 15 mg. subcutaneous depot of avorelin, which was loaded in a disposable syringe with a retractable needle. Since antiandrogens cause significant gastrointestinal and hepatic toxicity[12] they were not used in this study to avoid confounding effects on the tolerability profile of avorelin. Chemotherapy also was not given. The end point of the study was depot exhaustion, defined as 2 consecutive serum samples 1 week apart of testosterone greater than 1.735 nmol./l.

Outcome measures of efficacy. Serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prostate specific antigen (PSA) and plasma avorelin were measured at baseline, on days 1, 2 and 4, at weeks 1, 2, 4, 8, 12, 16, 20, 24, 26, 28 and 30, and then weekly until depot exhaustion. Transrectal digital assessment of prostate width and length was performed at the beginning of the study, at weeks 4, 12 and 24, and at the end point visit. Pain was scored by the patients as 0—none, 1—mild, is easily tolerated; 2—moderate, discomfort enough to cause interference with usual activity; 3—severe, incapacitating with inability to work or do usual activity, or 4—intractable. Analgesia consumption was scored by the patients as 0—none, 1—nonnarcotics occasionally required, 2—nonnarcotics regularly required, 3—narcotics occasionally required or 4—narcotics regularly required. Urinary symptoms of polyuria, difficulty controlling urination, hematuria and dysuria were scored by the patients as 0—absent, 1—a little, 2—quite a bit and 3—very much, yielding a total score ranging from 0 to 12. The World Health Organization (WHO) performance status scale was used to assess patient functionality (score 0 to 4).[13] Patients were evaluated at entry, every 4 weeks after avorelin administration and at the end of the study.

Assays. Serum testosterone, LH, FSH and PSA were measured at a centralized laboratory. Serum testosterone was assayed using a radioimmunoassay with a sensitivity of 0.87 nmol./l. Interassay and intra-assay coefficients of variation were 7.5 to 8.6% and 5.5 to 9.0%, respectively. "Flagged" samples were analyzed by gas chromatography mass spectroscopy. Serum LH and FSH were measured by an enzyme immunoassay with a sensitivity of 0.5 IU/l. Interassay and intra-assay coefficients of variation were 2.4 to 6.2% and 0.6 to 3.8% for LH, and 4.5 to 9.3% and 0.9 to 9.7% for FSH, respectively. Serum PSA was measured by an immunoradiometric assay with a sensitivity of 0.5 ng./ml. Interassay and intra-assay coefficients of variation were 3.7 to 4.8% and 1.4 to 3.7%, respectively.

Plasma avorelin was measured at the Faculty of Pharmacy, University of Montreal, Canada with a sensitive and specific radioimmunoassay.[8] Briefly, 0.5 to 1.5 ml. plasma samples were centrifuged at 10,000 rpm for 15 minutes at 4C. The clear supernatant (350 μl.) was transferred to an Eppendorf tube and aliquots of 100 μl. were used for the direct radioimmunoassay. The quality control samples and blank plasma, used to prepare the standard curve, were treated similarly. The assay was validated in terms of accuracy (recovery 94.0 to 105.4%), precision (inter-assay and intra-assay variations of 10.0 to 12.4% and 8.6 to 11.3%, respectively) and sensitivity (limit of quantitation 78 pg./ml.). All samples were analyzed in triplicate.

Outcome measures of safety. Laboratory surveillance included periodic measurements of hematology, clinical blood chemistry studies and urinalysis. Vital signs included measurement of supine and standing blood pressure, heart rate, body weight and electrocardiogram. Any sign or symptom that began during or after administration of the avorelin depot, or worsened during treatment was considered an adverse event. A decrease in sexual function (libido and/or erections) compared to baseline performance was considered an adverse event. Adverse events were coded and grouped into common terms.[14]

Statistical analysis. The primary variable was the duration of testosterone suppression defined as the time between administration of depot and 2 consecutive serum samples 1 week apart yielding testosterone greater than 1.735 nmol./l. Median duration of testosterone suppression and 95% confidence intervals were calculated using the Kaplan-Meier method. Differences in median duration of testosterone suppression between doses were evaluated by the log rank test. All randomized cases were included in the analysis. Scores for pain, analgesia consumption, urinary symptoms and WHO performance status were analyzed by an analysis of covariance with the last visit score as the dependent variable and the baseline score as the covariant. The statistical model included terms for treatment and site. Statistical significance of the overall differences in scores between the 2 treatment groups was determined using type III sum of squares. When differences existed pairwise comparisons between the 2 groups were performed using Fisher's 2 tailed least significant difference procedure.

RESULTS

Patient demographic and clinical characteristics at study enrollment are summarized in table 1. Patient age and weight, and stage and duration of disease were not different between the 2 groups. The incidence of metastases and PSA levels were also comparable. Of the 10 mg. group patients 3 withdrew from the study between weeks 31 and 35 because of disease progression (unrelieved symptoms and/or high PSA) requiring palliative radiotherapy and antiandrogen treatment. Of the 15 mg. group patients 1 dropped out of the study at week 16 because he moved out of the country. All 4 dropouts had testosterone levels in the castrate range at the time of withdrawal. Patients were observed for a median of 41 weeks in the 10 mg. (range 31 to 84) and 42 in the 15 mg. (range 36 to 71) group.

Pharmacodynamics. After administration of the avorelin depots median serum testosterone increased from 14.3 and 15.3 nmol./l. at baseline to a maximum of 24.8 and 31.1 on days 2 to 3 in the 10 and 15 mg. groups, respectively. Then testosterone concentrations progressively decreased to undetectable levels within 4 weeks in both groups (figs. 1 and 2). Median duration of testosterone suppression (less than 1.735 nmol./l.) was 40 weeks (95% confidence interval 35 to 42, minimum 28 and maximum 84) in the 10 mg. and 39 (37 to

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