The evaluation of finasteride as an intervention in localized prostate cancer

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A. Purpose and Rationale

Finasteride is an anti-androgen that inhibits the conversion of testosterone to DHT – the primary androgen stimulating growth in the prostate. Currently the drug is prescribed to treat benign prostatic hypertrophy. Its potential use as an anti-neoplastic agent, however, still requires elucidation. A randomized multi-center control trial of its efficacy as a treatment for localized prostate cancer could establish evidence that would advance the medical management of the disease.

Prostate cancer is the most common form of cancer in American men – experts expect 189,000 new diagnoses (and 30,200 deaths) in 2002. As age represents the primary risk factor of the disease, its ever-increasing prevalence reflects the growth of the geriatric population. Paradoxically, the continued successes of modern medicine in other areas will inevitably lead to further increased presentations of prostate cancer. The need to establish effective treatments to curtail the progression of the disease, then, will only grow more pressing with time.

The present standard-of-care treatment modalities of localized prostate cancer include radical prostatectomy, irradiation, and conservative management. Each of these approaches carries particular benefits and risks. A recent randomized controlled trial demonstrated, for instance, a mortality benefit accruing to those patients who underwent prostatectomy compared to those who received conservative management. In addition, patients in the conservative management arm of the study were more likely to suffer obstruction. Those patients undergoing the more aggressive surgery or radiation based treatments, however, may incur side-effects including impotence and incontinence. Secondary to the indolent course of localized prostate cancer, then, many patients will refuse aggressive intervention despite the demonstrated and putative benefits of surgery and radiation. In effect, they choose to gamble that their disease will not progress in a timeframe that would justify the morbidity of an intervention. In cases of advanced patient age or significant co-morbidities, especially, the medical establishment often agrees with this risk-benefit analysis and recommends conservative management.

At present, such management consists merely of "watchful waiting" – that is, doing nothing until the disease manifests itself in a way that forces action. No evidence exists, however, that outcomes may be improved by simply deferring intervention: neither monitoring PSA levels, conducting serial biopsies, observing obstructive symptoms, nor performing radiological screens have demonstrable use in identifying optimal moments for action. While continuing present efforts to establish a meaningful early warning system is appropriate, however, the scope of conservative management should be expanded to include treatment of the disease itself. Reliable detection of disease progression would reduce the risk of opting for conservative management; an effective pharmaceutical intervention would increase its benefit. Advancing the role of the medical management of localized prostate will require both.

B. Design and Statistical Analysis

The Finasteride Reduction of Incidence of Neoplastic Growth to Extracapsular Disease (the FRINGE study) has been designed as a randomized double-blind comparison of finasteride versus placebo as a treatment for localized prostate cancer. Patients will be randomly assigned to receive either finasteride or placebo through a telephone call to a centralized assignment center. The patients will receive either the finasteride or the placebo pills prepared at the pharmacy of the central clinical trial center; the preparations will appear identical. Neither the patient nor his local health care provider will know whether he is receiving the study agent or the placebo. The primary endpoint of the study will

compare the proportions of each group that progresses to either metastatic disease, radical prostatectomy, or irradiation. Progression to metastatic disease will be monitored by standard clinical parameters as established under the current "watchful waiting" guidelines – following PSA levels, development of symptoms, and radiologic findings. Progression of the two groups to the combined endpoint of metastatic disease, radical prostatectomy, or irradiation will be charted as Kaplan-Meier curves at three-month intervals for a follow-up period of eight years; the significance of the difference between the two curves will be calculated using standard Chi-square tests.

Three thousand seven hundred participants will be enrolled in each arm of the study. These numbers reflect the sample sizes required to detect an absolute risk reduction of twenty percent at five years of follow-up and of ten percent at eight years of follow-up. The calculations are based figures reported in the clinical trial comparing outcomes of localized prostate cancer treated with radical prostatectomy versus watchful waiting: rate of development of distal metastases were approximately 11% at 5 years and 27% at 8 years for the watchful waiting control group. Assuming similar event rates in the FRING placebo group, sample sizes adequate for Chi-square testing at 80% power testing at P=0.05 were determined.

C. Study Procedure

The protocol will mandate establishment of participant baselines during the first year of enrollment and also follow-up with patient interviews every three months. After one year of enrollment on the study drug or placebo, baseline labs and radiologic studies will be performed. These will include PSA levels; bone scans; and CTs of chest, abdomen, and pelvis. The timing of these baseline studies is necessary to correct for reductions in PSA that are known to occur after one year on finasteride – as such, the cost of baseline studies will be covered by the study. After the establishment of the baseline studies, the only additional studies are those which would have been required for standard clinical management. Note that the preserved utility of following PSA levels for the detection of prostate cancer has been established among patients on finasteride for BPH. The interviews will investigate for presence of new symptoms of obstruction, bone pain, decreased anal tone, and lower extremity weakness and/or numbness. Labs will be drawn to follow levels of PSA. The development of new symptoms or doubling of previous lab levels will prompt repeat imaging studies.

D. Study Drug

The first FDA approved indication of finasteride was for the treatment of benign prostatic hypertrophy (BPH) after researchers demonstrated that its use reduced the obstructive symptoms among patients with the condition. It has since received approval for a second indication: androgenic alopecia. Finasteride prevents the conversion of testosterone to di-hydro-testosterone (DHT) by blocking the action of 5-alpha-reductase. DHT stimulates the development and growth of prostate cells, both *in vivo* and *in vitro*. Furthermore, the use of finasteride among men with BPH is known to reduce serum levels of PSA – a marker for prostate cancer. Animal models of prostate cancer show that inhibition of 5-alpha-reductase prevents or delays development of the disease. Of special note, a separate trial to determine the efficacy of finasteride as a primary prostate cancer prevention agent was launched in 1993; the study will reach its primary endpoint in 2004. Finally, finasteride is extremely well-tolerated in men: a three-year randomized control study of its safety found only that it can rarely cause impotence (6.9%) and decreased libido (8.1%). Other studies have reported weak associations with headaches (around 2%) and rare instances of gynecomastia. The proposed route and dosage of the drug for the study is 5 mg PO qD – the same as was studied in the safety trial.

E. Study Subjects

Eligibility for the study requires patients with previously untreated, biopsy-proven adenocarcinoma of the prostate classified as stage T0d, T1, T1c, or T2 (i.e., confined to the prostate) who have either refused surgery and radiation or are not candidates for surgery or radiation. Patients with a history of other cancers are excluded. Eligibilty for enrollment also requires a bone scan and a chest, abdomen, and pelvis CT scan without evidence of metastases and a PSA level less than 50 ng per milliliter. Note that these eligibility requirements are separate and distinct from the baseline studies to be performed after one year of enrollment in the study.

F. Recruitment of Subjects

Subjects will be identified by referral from their primary physician. Consent for participation will be sought by investigators only at the request of the primary MD. The assistance of primary physicians will be enlisted by the project directors at the various study centers. Only patients who have refused surgery and radiation treatments, or who are not candidates for such treatments, will be consented.

G. Confidentiality of Study Data

Usual precautions will be undertaken to insure the confidentiality of the study data and the identity of the study subjects.

H. Potential Risks

Risks to the participants in the study protocol include exposure to the side effects of the study drug. As previously discussed, while these side effects have been demonstrated in randomized clinical trials to be mild, they include impotence (8.1%) and decreased libido (6.9%). More infrequently, subjects receiving finasteride have complained of headaches and gynecomastia. In addition, as previously noted, an ongoing trial is examining the role of finasteride in the primary prevention of prostate cancer. While off-label use of finasteride for the treatment of localized prostate cancer is currently not common, such practice could start should the primary prevention trial endorse the anti-neoplastic potential of finasteride. In this event, participants in the placebo arm could be considered to incur a risk by remaining in the study.

I. Alternative Therapies

Radical prostatectomy and irradiation are both standard treatments of localized prostate cancer. A recent randomized clinical trial provides evidence that radical prostatectomy provides a mortality benefit compared with watchful waiting. Disadvantages of these standard treatments include the morbidity of the interventions, notably incontinence and impotence. No established medical alternatives exist, but ongoing experiments hypothesize a protective role for selenium and vitamin E. Minimal evidence exists to support that these agents provide an advantage in the setting of known local disease.

J. Compensation and Costs to Subjects

Cost of the study drugs and of those tests required by the protocol, but not covered by insurance, will be paid by the study. Travel expenses and other incidentals incurred by the subject will not be covered by the study.