Predictors of Pathological Progression among Men with Localized Prostate Cancer Undergoing Active Surveillance: a Sub-Analysis of the REDEEM Study

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Purpose: We identify risk factors for pathological progression among men on active surveillance in the REDEEM (REduction by Dutasteride of clinical progression Events in Expectant Management trial).

Materials and Methods: REDEEM was a 3-year, randomized, double-blind study of patients in 65 North American academic centers. Eligible men were 48 to 82 years old, with low risk prostate cancer (T1c–T2a), Gleason score 6 or less, 3 or fewer cores positive, tumor less than 50% of any 1 core, serum prostate specific antigen 11 ng/ml or less, life expectancy greater than 5 years and undergoing active surveillance. Entry biopsies (10 cores or more) were required. The analysis included 276 patients with 1 biopsy or more after the start of study treatment. Patients received dutasteride 0.5 mg per day or placebo for 3 years. Time to pathological progression (volume [4 or more cores positive or 50% or greater of 1 core] or grade progression [Gleason score 7 or greater]) in a post-baseline biopsy (not preceded by therapeutic intervention), and baseline variables were analyzed using a Cox proportional hazard model.

Results: In total 94 of 276 patients with a post-baseline biopsy (34.1%) had pathological progression, 54 (19.6%) had volume progression only, 19 (6.9%) had grade progression only and 21 (7.6%) had both types of progression. Older age (HR 1.05, 95% CI 1.01–1.08, p = 0.009) and higher prostate specific antigen density (HR 1.06, 95% CI 1.04–1.09, p <0.001) were associated with pathological progression. Post-baseline prostate specific antigen identified grade, but not volume progression in patients treated with placebo and dutasteride.

Conclusions: Older age and higher prostate specific antigen density were independent predictors of pathological progression. Post-baseline measurements as predictors of pathological progression could not be established. Further studies are needed to evaluate the role of dutasteride and establish better markers of pathological progression in active surveillance.

Key Words: watchful waiting, dutasteride, disease progression, prostate-specific antigen, prostatic neoplasms

Abbreviations and Acronyms

5-ARI = 5α-reductase inhibitor

AS = active surveillance

DRE = digital rectal examination

I-PSS = International Prostate symptom Score

PSA = prostate specific antigen

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At present most prostate cancers are detected via PSA screening and, therefore, are early stage, low risk tumors.[1,2] Conventional treatments such as surgery or radiation can negatively affect the quality of life of patients and their families.[3,4] Active surveillance has emerged as

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an attractive alternative since it can reduce the overtreatment of patients with clinically insignificant disease, while offering curative treatment to those in whom disease progresses.[5–7] Although no uniform followup exists for AS, most protocols rely on repeated PSA measurements, DRE and repeated biopsies to identify progression. Numerous cohort studies have demonstrated excellent outcome with this treatment paradigm.[6–8]

Several studies have tried to identify predictors of pathological progression among men on AS.[9–13] However, former studies are either single center cohort studies,[9–12] or only offer short-term followup.[13] REDEEM is the first multicenter, randomized controlled study to be conducted among patients on AS.[14] It was designed to evaluate whether dutasteride, a dual 5-ARI, can increase time to clinical progression among men on AS. The primary outcome of REDEEM was a composite outcome defined as the earliest of either receipt of primary therapy for prostate cancer (eg prostatectomy, radiation, hormonal therapy) or pathological progression (4 or more cores involved, 50% or more of any core involved, or any Gleason score 7 or greater). One of the main criticisms of REDEEM was the inclusion of primary therapy in the composite outcome since this is a patient driven decision and may not represent progression. We now report a sub-analysis of this study and focus on predictors of pathological progression.

MATERIALS AND METHODS

Cohort

The REDEEM study design and data have been reported previously. The trial began screening of patients on July 18, 2006 and ended on March 6, 2007.[14] A total of 302 patients with biopsy proven, low risk, localized prostate cancer from 65 academic centers in North America were randomized to receive 0.5 mg dutasteride daily (147) or placebo (155) for 3 years while on AS. Eligible men were between 48 and 82 years old, had clinical stage T1c–T2a prostate cancer, a Gleason score of 6 or less, 3 or fewer cores positive for prostate cancer, the tumor did not exceed 50% of any single core and serum PSA at study entry was 11 ng/ml or less. An entry biopsy of 10 or more cores was performed within 8 months before screening. In this analysis we included all patients who underwent at least 1 biopsy after the first dose of study drug. All biopsy specimens underwent a central pathology review conducted by one pathologist. The study was approved by institutional review boards at every site and all patients provided written informed consent (www.clinicaltrials.gov/ct2/show/NCT00363311).

Protocol Defined Procedures

PSA measurements and DRE were performed every 3 months for the first year and semiannually thereafter. Protocol mandated prostate biopsies were done at 18 months and 3 years (and at early withdrawal if applicable). For cause biopsies were performed for any clinical suspicion of prostate cancer progression (eg a PSA increase or abnormal DRE) and left to the discretion of the investigator. A standard of 12 cores was required for all study biopsies, including the for cause biopsies. Prostate volume was measured along with biopsy procedure by transrectal ultrasound.

Outcome

Pathological progression was defined as volume progression (either 4 or more cores positive for cancer or a single core involvement of 50% or more) or grade progression (Gleason score 7 or greater) in a post-baseline biopsy that was not preceded by therapeutic intervention for prostate cancer. Time to pathological progression was the number of days between start of study treatment and pathological progression for patients who exhibited pathological progression. For patients with no pathological progression the time to censoring was the number of days from treatment start to the latest biopsy date before any therapeutic intervention for prostate cancer, or to the latest biopsy date if there was no therapeutic intervention for prostate cancer during the study. We further stratified patients without progression as those with no cancer on repeat biopsies and those with favorable risk cancer (ie cancer on biopsy does not meet the criteria for pathological progression).

PSA Definitions

All PSA measurements during the study were performed at a central laboratory. Baseline PSA was defined as the last PSA value on or before study treatment start date. Baseline PSA density = baseline PSA/baseline prostate volume.

Baseline PSA velocity = 365*(baseline PSA − historical PSA)/(baseline PSA date − historical PSA date), where historical PSA is determined in local laboratories and is the earliest one available in the clinical database within 18 months of baseline PSA date.

All post-baseline PSA measurements performed on the day of biopsy or within 42 days after the biopsy were deleted from analysis (since biopsy could potentially increase PSA temporarily). Nadir PSA is the minimum of baseline and post-baseline PSA measurements within this analysis set of PSA values.

Final PSA for patients with pathological progression was defined as the last PSA available before progression. For patients without pathological progression, it is the last PSA before final biopsy at which progression was assessed.

Statistical Analysis

Time to pathological progression has been analyzed with a step-wise, backward elimination method in a Cox proportional hazard model, keeping treatment as a covariate, and exploring baseline covariates of age, ethnicity, family history of prostate cancer, prostate volume, PSA, PSA density, PSA velocity, I-PSS, dihydrotestosterone and testosterone levels and number of cores evaluated in screening biopsy. The significance level for remaining in the model was 0.10. Since post-baseline PSA values are confounded with treatment, these could not be explored in a predictive model. However, we explored sensitivity and