Title: Metformin Prostate Cancer Adjuvant Trial

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PURPOSE OF STUDY AND BACKGROUND

Purpose

This is a Phase II clinical study to determine if Metformin can increase Prostate Specific Antigen (PSA) doubling time for patients with Prostate Cancer who have failed primary treatment with radiation, or surgical patients that are at high risk for recurrence based on surgical pathology. Men with confirmed prostate cancer and rising serum PSA levels will receive Metformin and will be monitored for PSA response and disease progression.

Background

Recent population studies have identified Metformin as a drug which could potentially halt the progression of several cancers, including Prostate Cancer[1]. The specific effect of Metformin on cancer cells is still unclear, but several studies have shown that its mechanism of action may be related to regulation of cellular metabolism. *In vitro* studies have demonstrated that Metformin reduces cell viability and causes cell cycle arrest in prostate cancer cells[2], reduces proliferation of breast cancer cells[3], and induces programmed cell death in p53 deficient colon cancer cells[4].

A large scale population study of 3,837 patients showed that cumulative Metformin use among men with diabetes was associated with a significant decrease in the risk of Prostate Cancer related death in a dose-dependent fashion. For every additional 6 months of treatment with Metformin, the risk of prostate cancer specific mortality decreased by 24%.[5] The study

[1] (Margel, et al., 2013)
[2] (Sahra, et al., 2010)
[3] (Zakikhani, Dowling, Fantus, Sonenberg, & Pollack, 2006)
[4] (Buzzai, et al., 2007)
[5] (Margel, et al., 2013)

also demonstrated that Metformin treatment produced this survival benefit independent of any other cancer treatment. A Phase II trial of Metformin in men with progressive castration-resistant Prostate cancer observed a prolongation of PSA Doubling Time in 52.3% of patients, and two patients had a confirmed ≥50% PSA decline after 12 weeks of Metformin treatment.[6]

Works Cited

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Study Design

This study will have three arms:

1. High Risk Surgical Cohort: Radical prostatectomy patients with high risk surgical pathology (≥Gleason 8, positive surgical margins, evidence of extra capsular extension or seminal vesicle invasion) and undetectable PSA
2. Rising PSA Surgical Cohort: Radical prostatectomy patients with rising PSA defined as any rise in PSA over three successive PSA serum tests at least one month apart
3. Radiation Cohort: Radiation patients with rising PSA meeting Phoenix criteria for Biochemical Recurrence (nadir PSA level plus 2ng/mL, occurring at least 2 years since the last radiation treatment)

After receiving informed consent but prior to beginning the treatment, patients will be asked to complete the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) to determine baseline of

[6] (Rothermundt, et al., 2014)

disease-related patient anxiety, and the Expanded Prostate Cancer Index Composite (EPIC) to determine baseline disease-related quality of life. Participants will be asked to complete these questionnaires every 3 months while enrolled in the study.

Statistical methods (rising PSA surgical and radiation cohorts): At least three PSA data points (pre and post treatment initiation) will be collected for each patient. Prior to enrollment, a minimum of three PSA measurements at least 1 month apart within 1 year of enrollment will be obtained. Post-enrollment, PSA will be measured every 3 months until month 9, for a total of 3 measurements.

PSA kinetics: The relationship between the log of PSA and time of PSA measurement will be estimated from a piecewise linear regression model: $log(PSA) = \alpha_1 + \alpha_2(POST) + \beta_1(Time) + \beta_2(Time \times POST)$, where POST=1 if post treatment initiation, and 0 if pre-enrollment. Pre- and Post-treatment PSA slope will be estimated for each patient (β_1 and $\beta_1 + \beta_2$, respectively). PSA-DT will be computed as the natural log of 2 divided by the estimated slope.

Response: The primary end point is changes in PSA doubling time (PSA-DT) computed at 9 months compared to pre-treatment PSA-DT. Response to treatment will be defined as the lengthening of PSA-DT at 9 months from pre-treatment PSA-DT by > 3 months. Secondary outcomes include safety and other measures of response such as the proportion of patients achieving a PSA decline of ≥ 50% in the highest measured pre-treatment PSA.

Statistical methods (High Risk surgical cohort):

PSA kinetics: The patients in the surgical cohort all have non-detectable pre-treatment PSA levels however are considered at a higher risk for relapse based on surgical parameters such as surgical margins, age, and Gleason scores.

Response: The primary end point is the maintenance of undetectable PSA levels achieved post-surgery for a minimum of 9 months. Response to treatment will be defined as a PSA of < 0.20 at 9 months. Secondary outcomes include safety and PSA slope (if rising PSA levels observed).

Trial Design and sample size considerations: For each patient group (surgical, rising PSA surgical, radiation), a single arm Phase II trial of the same treatment regimen will be conducted in parallel. For each, Simon's two-stage optimal design will be used with the following assumptions: an ineffectiveness cutoff of 10%; a clinically relevant response rate of at least 30%; type I error rate of 0.05; type II error rate of 0.10. Given these parameters, **a total of 18 patients will be enrolled at the first stage of the trial**. Based response defined as a PSA-DT change > 3 months, if 2 or fewer responses are observed, the study will be terminated at the first stage. However if at least 3 responses are observed in the set of 18 patients, an additional 17 patients will be enrolled in the second stage, for **a total of 35 patients enrolled**. At the end

of the second stage, if 6 or fewer responses are observed then the treatment will be declared ineffective. Otherwise, the study is considered to have achieved the targeted response rate. Under this optimal design, the probability of early stopping given an ineffective treatment is 0.73.

Primary Endpoints

- Increase PSA Doubling Time
- Decrease PSA Levels (% PSA decline)

Secondary Endpoints:

- Determine time to secondary therapy for prostate cancer upon PSA recurrence
- Time to Cancer Progression
- Salvage therapy outcomes after treatment with Metformin
- Determine the safety and incidence of serious adverse events from the administration of 9 months of metformin to men with high risk prostate cancer and prostate cancer with rising PSA post-treatment.

Number of Subjects

Stage 1: 18 High Risk Surgical patients, 18 Rising PSA Surgical Patients, 18 Radiation patients

Stage 2 (if Stage 1 deemed successful): 17 High Risk Surgical Patients, 17 Rising PSA Surgical patients, 17 Radiation patients

Gender of Subjects

All subjects included in this study will be male.

Age of Subjects

Subjects will be at least 18 years or older.

Racial and Ethnic Origin

Subjects will be recruited from all racial and ethnic groups.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Must be male > 18 years of age
2) Biopsy confirmed adenocarcinoma of the prostate.
3) Radiation Patients: Rising serum PSA for on ≥3 time points at least 1 month apart, after Nadir has been reached. Must be at least 18 months since last radiation treatment. PSA-DT must be >6 months.
4) High Risk Surgical Patients: patients who have had radical prostatectomy and:
   a) High Risk based on Surgical Pathology (Patients have any of the following: ≥Gleason 8 or higher, Extra-capsular extension, positive surgical margins, or seminal vesicle invasion)
   b) Undetectable PSA
5) Rising PSA Surgical Patients: Patients who have had radical prostatectomy and:
   a) Rising serum PSA for ≥3 time points at least 1 month apart
   b) Unwilling or medically unfit for salvage Radiation Therapy
6) Able to swallow and retain oral medication
7) Hemoglobin A1c ≤ 7.0%
8) Able and willing to participate in the full 12 months of the study
9) Able to understand instructions related to study procedures
10) Able to read and write (health outcome questionnaires are self-administered), understand instructions related to study procedures and give written informed consent

Exclusion Criteria:

1. Metastatic Disease

2. PSADT < 6 months
3. Subject that has ever been treated for prostate cancer with any of the following:
    - Chemotherapy
    - Hormonal therapy (e.g., megestrol, medoxyprogesterone, cyproterone)
    - Oral glucocorticoids
    - GnRH analogues (e.g., leuprolide, goserelin, degarelix)
        - Previous treatment with GnRH analogues is allowed after a wash out of at least one month and a return to normal serum Testosterone levels
4. Current and/or previous use of the following medications:
    - Use of 5α-reductase inhibitors (eg. Finasteride, Dutasteride) within the past 6 months of screening
    - Drugs with antiandrogenic properties (e.g., flutamide, bicalutamide, ketoconazole, progestational agents) within 6 months prior to screening
    - Diagnosis of Type 1 Diabetes Mellitus
    - Exposure to metformin within 12 months of screening
    - Planned or concurrent use of any oral or injectable diabetes drug
    - Known hypersensitivity or intolerance to metformin hydrochloride
5. Any condition associated with increased risk of metformin hydrochloride-associated lactic acidosis
6. Participation in any investigational or marketed drug trial within 30 days prior to screening or anytime during the study period. This includes any interventional or exercise trials.
7. Any unstable serious co-existing medical condition(s) including, but not limited to, myocardial infarction, coronary bypass surgery, unstable angina, cardiac arrhythmias, clinically evident congestive heart failure, or cerebrovascular accident within 6 months prior to Screening visit.
8. History of megaloblastic anemia.
9. Abnormal liver function test:
        - Total bilirubin > institutional upper limit of normal (ULN)
        - Aspartate aminotransferase (AST) > institutional ULN
        - Alanine aminotransferase (ALT) > institutional ULN
        - Alkaline phosphatase (ALP) > institutional ULN

- Serum creatinine > institutional ULN

10. History of other malignancies, with the exception of adequately treated nonmelanoma skin cancer, stage I melanoma, NMIBC or other solid tumors curatively treated with no evidence of disease for at least 5 years
11. History or current evidence of substance abuse, as defined in DSM-IV, within 12 months of screening
12. History of any illness (including psychiatric) that, in the opinion of the investigator, might confound the results of the study or pose additional risk to the subject

Vulnerable Subjects

No subjects from vulnerable populations (children, pregnant women, incarcerated persons) will be recruited for this study.

METHODS AND PROCEDURES

Pre-Enrollment Evaluation

1. Personal Medical History, including medication history, alcohol and tobacco use
2. Physical Examination including ECOG status, blood pressure, pulse, height, weight and BMI.
3. Hematology and Serum Chemistry, Liver Panel, total and free PSA, Testosterone level, Hemoglobin A1C, Insulin levels.
4. Tumor Characteristics, including Gleason score, tumor grade, MRI results (if available), biopsy results
5. List of previous prostate cancer treatment, any previous radiation treatment (for any disease condition).
6. PSA Kinetics: current PSA doubling time, record of all PSA tests in the year prior to enrollment
7. Completion of two study questionnaires for baseline disease related anxiety and quality of life: MAX-PC and EPIC.

Study Interventions

1. Upon study initiation, patient will receive two weeks of 750mg Metformin Extended Release (ER) to assess any adverse reactions.
2. After two weeks, patient will receive two doses of 750mg Metformin Extended Release (ER) per day for 8 months, two weeks.
3. Patients will receive Metformin Extended Release (ER) from the Principal or Sub-Investigators free of charge.

4. The study drug, 750mg Metformin Extended Release (ER), will be stored in the Principal Investigator's practice in a separate locked safe accessible only to research study personnel.

Study Evaluations

Patients will return to the Principal Investigator's practice every three months for evaluation of study compliance, completion of study questionnaires, and blood draw.

a) Study subjects will be required to bring the medication bottle with them on each study visit and will also be required to sign an attestation that they are taking the medication as per study protocol.
b) Study subjects will also submit a blood sample for evaluation of hematology and serum chemistry, insulin levels, total and free PSA, and Hemoglobin A1C.
c) Study subjects will complete two questionnaires, the Expanded Prostate Cancer Index Composite (EPIC) to evaluate Prostate Cancer specific symptoms, and the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) for evaluation of disease and treatment related anxiety.
d) At the end of the study, at approximately 9 months, subjects will also be tested for insulin and testosterone levels.

Study Exit Procedures

If study participants experience any of the following while receiving Metformin treatment, they will be removed from the study and referred for alternative treatment such as Androgen Deprivation Therapy, Salvage Cryotherapy for radiation patients, or Salvage Radiotherapy:

- High Risk Surgical Patients: PSA level rises 0.6ng/mL from baseline
- Rising PSA and Radiation Patients: PSA Doubling Time accelerates below 6 months

These participants will be removed from the intervention arm of the study, but will continue to be followed for disease outcome and quality of life for three years following removal from the study.

Data Analysis and Data Monitoring

The Winthrop University Hospital Department of Biostatistics has been consulted during the development process of this protocol, and will be consulted for statistical analysis of PSA kinetics, adverse events, and overall outcome.

The research coordinator will review study conduct including informed consent procedures, accrual, drop-outs, protocol deviations and AEs in aggregate on a monthly basis. The principal and sub-investigators review serious adverse events (SAEs), and laboratory results monitoring

in real-time. The research coordinator, research fellow and study investigators will review study subject compliance with study procedures on a three month basis.

Study data are provided to the research coordinator and study investigators prior to each monthly review by the research fellow. Data reports for end of phase analysis are prepared by the study statistician, Melissa J. Fazzari.

The research coordinator provides a written report to the study team with recommendations for study modification, study continuation/discontinuation as relevant. After the report is generated, the coordinator will meet with the study investigators to discuss relevant findings.

The study team is responsible for forwarding the report to the IRB.

Analysis of Adverse Events

Adverse events will be monitored on an ongoing monthly basis throughout the duration of the study, and the rates will be formally analyzed at the end of the first stage of the study as outlined in the statistical methods section of the protocol.

Analysis of Serious Adverse Events

Serious adverse events will be monitored in real time, and the rate of subjects experiencing these events will be analyzed every month as needed as the study progresses.

Analysis of Efficacy

The primary end points for efficacy for each study cohort will be analyzed at the end of the first stage of the study (total accrual 18 patients, 9 months of treatment).

- Efficacy in the Rising PSA Surgical and Radiation Cohorts: Response to treatment is defined as a lengthening of PSA doubling time from pre-treatment PSA doubling time by >3 months at the end of the 9 months of treatment.
- Efficacy in the High Risk Surgical Cohort: Response to treatment is defined as PSA level of <0.20ng/mL at the end of the 9 months of treatment.
- Secondary Efficacy in Rising PSA Surgical and Radiation Cohorts: The proportion of patients achieving a PSA decline of $\geq$ 50% from the highest measured pre-treatment PSA.

Data Storage and Confidentiality

Data will be stored in our HIPAA-compliant case report form database. Only the study investigators, research coordinator, research fellow, and biostatistician will be provided with

access information to the database. A unique non-identifying code will be assigned to each study participant.

RISK/BENEFIT ASSESSMENT

Risk

Expected AEs

Expected AEs associated with Metformin include:

- Hypoglycemia (10% of diabetic patients)
- Diarrhea (9.6% of diabetic patients)
- Nausea/Vomiting (6.5% of diabetic patients)
- Constipation (Between 1-5% of diabetic patients)
- Weight loss (14% of metastatic prostate cancer patients)
- Fatigue (18% of metastatic prostate cancer patients)

Rare but Serious AEs

Rare but serious AEs that may be associated with Metformin include:

- Lactic Acidosis: approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years

AE Management

The rate of expected adverse events cannot be definitively predicted in this population of patients. Adverse events will be recorded and monitored throughout the study, and the rates will be reported as part of the study end points. Subjects who cannot tolerate adverse events will be removed from the study at the request of the subject or at the discretion of the investigators.

Study subjects will be screened for known risk factors of Metformin associated lactic acidosis and will be excluded from enrollment in the study if any risk factors are found. If lactic acidosis occurs in a study subject while on Metformin, the subject will be immediately removed from the study.

ADDENDUM:

Subjects who cannot tolerate the 1500mg per day dose of Metformin will be kept on the study at a lower dosage. They will receive Metformin 750mg, once daily dose for 8 months, 2 weeks.

Protection against Risks

Study subjects will be evaluated for adverse events at every study visit (every 3 months). In the case of unacceptable toxicity or side effects, patients may be removed from the study at the discretion of the Principal Investigator or Sub-Investigators. Patients may also drop out of the study at any time if side effects become intolerable.

Potential Benefits to Subjects

The potential benefits to subjects include reduction of serum PSA levels, prolongation of PSA doubling time, and increased time to disease progression, however, the probability of these benefits are uncertain, and will be evaluated as part of this trial.

INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

All research personnel are required to complete training in the protection of human subjects. In addition, all investigators will submit a copy of their CV through the IRB website.

SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

Subject Identification and Recruitment

Subjects meeting the inclusion criteria will be referred to the Principal Investigator or Sub-investigators by their treating physician. IRB-approved posters will also be posted throughout the community to advertise and recruit patients.

Process of Consent

Patients who have been identified as possible study subjects will meet with the Principal Investigator or one of the Sub-Investigators to review the study protocol details, and review and sign the informed consent form.

Subject Capacity

As this study includes self-administered questionnaires, and self reporting of symptoms, every subject must have full mental capacity, as judged by the Principal Investigator or Sub-Investigators.

Subject/Representative Comprehension

No subjects with reduced mental capacity as judged by the investigators will be enrolled in this study.

Early Withdrawal of Subjects

Study subjects are permitted to leave the trial at any time for any reason. Subjects electing to discontinue the study should contact the Principal Investigator or Research Coordinator. Subjects may also be released from the study in the event of unacceptable adverse effects of the drug under the guidance of the Principal Investigator or Sub-Investigators.

Consent Forms and Documentation of Consent

Consent forms will be reviewed with each study subject with the Principal Investigator or Sub-Investigator to ensure understanding the benefits, risks and all steps of the research study. Consent forms will be signed and stored with the Research Coordinator in a locked file cabinet accessible only to study personnel.

Costs to the Subject

There are no anticipated extra costs for study subjects. Research tests which are outside the standard of care will be paid for by the Department of Urology research fund. Prostate Specific Antigen testing is standard of care for Prostate Cancer patients and will not be included in research costs. Hemoglobin A1C is not a standard of care and will be paid for by the Department of Urology.

Payment for Participation

There will be no payment given to participants in this trial.

STORAGE AND DISPENSING OF STUDY DRUG

Study drug will be stored in the principal investigator's practice at 1300 Franklin Ave Garden City, NY 11530, in a locked storage cabinet accessible only to necessary research personnel. Any unused study drug will be destroyed as per the Medical Waste and Tracking Act of 1989, EPA, New York DOH and New York DEC regulations and standards and WUH Regulated Medical Waste Policy and Procedures.