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Can atorvastatin with metformin change the natural history of prostate cancer as characterized by molecular, metabolomic, imaging and pathological variables? A randomized controlled trial protocol

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ABSTRACT

Background: Atorvastatin and metformin are known energy restricting mimetic agents that act synergistically to produce molecular and metabolic changes in advanced prostate cancer (PCa). This trial seeks to determine whether these drugs favourably alter selected parameters in men with clinically-localized, aggressive PCa.
Methods/design: This prospective phase II randomized, controlled window trial is recruiting men with clinically significant PCa, confirmed by biopsy following multiparametric MRI and intending to undergo radical prostatectomy. Ethical approval was granted by the Royal Brisbane and Women's Hospital Human and The University of Queensland Medical Research Ethics Committees.
Participants are being randomized into four groups: metformin with placebo; atorvastatin with placebo; metformin with atorvastatin; or placebo alone. Capsules are consumed for 8 weeks, a duration selected as the most appropriate period in which histological and biochemical changes may be observed while allowing prompt treatment with curative intent of clinically significant PCa. At recruitment and prior to RP, participants provide blood, urine and seminal fluid. A subset of participants will undergo 7Tesla magnetic resonance spectroscopy to compare metabolites *in-vivo* with those in seminal fluid and biopsied tissue.
The primary end point is biochemical evolution, defined using biomarkers (serum prostate specific antigen; PCA3 and citrate in seminal fluid and prostatic tissue). Standard pathological assessment will be undertaken.
Discussion: This study is designed to assess the potential synergistic action of metformin and atorvastatin on PCa tumour biology. The results may determine simple methods of tumour modulation to reduce disease progression.

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1. Introduction

Aggressive prostate cancer (PCa)[1] cells increase glucose uptake and glycolysis under normoxic conditions (the Warburg effect [1]) producing glycolytic intermediates that also feed biosynthesis and PCa proliferation [2,3]. Metformin reduces glucose oxidation to increase glutamine metabolism and cell death while inhibiting metastatic behaviour. Epidemiological evidence suggests metformin use is associated with reduced risks of many cancers, including PCa [4,5] with reduced hyperinsulinaemia by metformin in advanced PCa potentially improving androgen deprivation therapy (ADT) response [6]. When statins are combined with metformin, further reduction in PCa progression and improved clinical outcomes have been reported, indicating a potential additive or synergistic effect to this medication combination [7–9]. Statins reduce cholesterol and mevalonic acid biosynthesis, with *in vitro* evidence that statins slow testosterone synthesis by inhibiting pre-cursor molecule transport, improving ADT response [10]. Hypercholesterolaemia is associated with high risk PCa [11] and androgen-independent PCa metastasis [12] with statin use associated with lower prostate specific antigen (PSA) levels, percentage positive biopsies and fewer cases of advanced and fatal disease [8]. Lipophilic statins such as atorvastatin also inhibit PCa cell migration to bone marrow stroma [13], however benefit in reducing biochemical recurrence, remains uncertain [14].

Medication safety profiles of metformin and atorvastatin are favourable, with significant side effects rarely observed. Concern for metformin regarding lactic acidosis is reserved for patients with significant comorbidities (chronic renal failure, congestive cardiac failure) [15]. Large cohorts consuming statins report rhabdomyolysis in up to 11 per 100,000 person-years [16]. The use of metformin as a neoadjuvant agent for 4–12 weeks by Joshua and colleagues was well tolerated and demonstrated a 10% reduction in PSA, 6.5% reduction in IGF-1 and 5% reduction in BMI [17]. Such ideal drug tolerability and favourable clinical effects support their adjunctive use in localized prostate cancer without need for a phase I controlled trial in this context.

Metformin and atorvastatin may influence malignant metabolic transformation in the prostate, known to favour ATP production and fatty acid synthesis, by shifting citrate, detectable in seminal fluid (SF) [18–20]. Markers, such as prostate cancer antigen 3 (PCA3), improve PCa detection and disease monitoring but may vary with epigenetic and exogenous stimuli [21,22].

Initially promising findings by Joshua and colleagues demonstrated significant changes in molecular markers following neoadjuvant metformin therapy prior to RP [17]. These medications are also being explored in Metformin Active Surveillance Trial (MAST) Study (NCT01864096) in delaying pathologic disease progression. Thus, exploring the role of energy restriction mimetic agents (ERMAs) represents an exciting development in managing men with PCa. However, before atorvastatin and metformin can be entertained for use in patients with early PCa, their potential demonstrable beneficial effects with respect to tumour parameters need to be evaluated objectively.

The primary aim of this study is to determine whether these drugs by themselves and together, favourably alter selected parameters in a group of clinically-localized, aggressive PCas.

[1] Abbreviations: ADT — androgen deprivation therapy; bEvo — biochemical evolution; DSS — 4.4-dimethyl-4-silapentane-1-sulfonic acid-d_6; DFTMP — difluorotrimethylsilanylphosphonic acid; ERMA — energy restriction mimetic agents; FID — free induction decay; GPC — glycerophosphocholine; ISUP — International Society of Urological Pathology; mpMRI — multiparametric magnetic resonance imaging; MRS — magnetic resonance spectroscopy; NMR — nuclear magnetic resonance; OPLS — orthogonal projections to latent structures; PBS — phosphate buffered saline; PCa — prostate cancer; PCA3 — prostate cancer antigen 3; PLS — partial least squares; PSA — prostate specific antigen; RBWH — Royal Brisbane and Women's Hospital; RP — radical prostatectomy; SF — seminal fluid, SF-36 — Short Form Health Survey 36.

2. Materials and methods

2.1. Study design

This is a prospective randomized, double-blinded controlled phase II window trial designed to determine the efficacy on biochemical evolution of atorvastatin and metformin, in isolation and together, in a population of men with early, clinically significant PCa. In addition, the effect of these drugs on PCa biology will be assessed in a population not previously studied in this respect while these men await definitive treatment by radical prostatectomy (RP), in accordance with a phase II window trial design [23]. Men with an elevated PSA who have a multiparametric magnetic resonance imaging (mpMRI) examination that demonstrates a PI-RADS 4 or 5 lesion and who, at consultation, express an intention to proceed to RP should biopsy confirm the suspicion of high-risk PCa, will be approached to enter the study. Our current practice includes in depth counselling prior to biopsy in order to ascertain the benefits to the patient in investigating for PCa. This includes outlining the biopsy and treatment process, with treatment options of surgery, radiotherapy, active surveillance or watchful waiting all discussed. Following written informed consent and randomisation by the manufacturing pharmacy (QPharm) to ensure clinician and participant blinding, four study groups are being examined, as outlined in Fig. 1.

The protocol is designed and reported according to the SPIRIT guidelines [24]. Participants will provide blood, urine and SF after 48 h abstinence of sexual activity. Blood and SF samples will be used to determine biomarkers of interest as defined by the primary and secondary endpoints. Further exploratory analyses will be conducted as outlined in order to determine biochemical effects of these medications in this patient cohort. Prior to giving specimens, a subset of participants, selected by a sub-randomisation process, will opportunistically undergo a further mpMRI with MRS using a 7 Tesla machine at the University of Queensland Centre for Advanced Imaging. Here, we will assess the metabolic profile of participants prostates *in-vivo*, for comparison with those seen in seminal fluid *in vitro*, and ascertain if superior imaging is provided by this machine. Participants will then undergo transperineal prostate biopsy targeting lesions of interest (cognitive biopsies) detected by pre-trial mpMRI, in addition to systematic whole gland biopsies using a template as per the local department protocol. Biopsy samples from index lesions and from non-index lesion areas will be taken for research purposes and stored for subsequent molecular and nuclear magnetic resonance (NMR) analysis.

Participants will undergo 8 weeks of capsule consumption, as this duration was determined to be most appropriate in which histological and biochemical changes may be observed while allowing prompt treatment with curative intent of clinically significant PCa. Non-invasively obtained participant samples will be collected again and mpMRI with magnetic resonance spectroscopy (MRS) will be repeated (for those previously randomized to have these investigations). The reason for allocating only a limited number of participants for mpMRI and MRS with the 7 Tesla machine is cost. The biomarker kinetic changes following biopsy are poorly described, however we expect these will be minimally affected by biopsy artefacts with 8 weeks of treatment and healing. Latifoltojar and colleagues examined changes in mpMRI parameters following biopsy and described a return to baseline apparent diffusion coefficient (ADC) parameters 1 month post biopsy [25]. The effects of biopsy on MRS parameters are currently unknown and will be examined in this study.

Ethical approval has been obtained from the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (Approval no. HREC/14/QRBW/153 together with HREC/09/QRBW/320, HREC/09/QRBW/305 and 1995/088B) and The University of Queensland Medical Research Ethics Committee (Approval no. 2014000944 together with 2006000262) using the National Ethical Application Form. Specialist clinicians are overseeing all aspects of management through our established team. This trial has been registered in the