Clinical Trial Design
A Placebo Controlled Proof of Principle Study of Hydroxychloroquine (HCQ) in Resectable Prostate Cancer in Patients Undergoing Radical Prostatectomy
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Introduction – Study Objectives

Primary Objective
- To study the effects of hydroxychloroquine (HCQ) on markers of autophagy such as p62 and LC3-II expression in prostate tumors of patients who are undergoing radical prostatectomy

Secondary Objectives
- To evaluate the concentration of HCQ in normal and prostate tumor tissue and to correlate prostate tissue concentrations with the plasma concentrations in these patients.
- To perform tumor genomic analysis for common somatic mutations and to correlate the molecular response to HCQ and presence/absence of mutations.

Eligibility
- Patients undergoing radical prostatectomy for prostate cancer
- Age ≥ 18 years old
- Patients without significant underlying medical illness
- Patients without specific ocular conditions or prolonged QTC interval (HCQ specific toxicities)
- Patients without prior chemotherapy or radiation

Methods – Study Schema

Fig. 1 HCQ blocks autophagy and promotes apoptosis of the prostate after castration in rats1 Urologia Internationalis (2020)
Researchers in this study found that HCQ blocked autophagy and promoted apoptosis and then further promoted atrophy of prostates after castration.

HCQ in Prostate Cancer

Pre-clinical Data

Background
- Prostate cancer is the 3rd most commonly diagnosed malignancy in males, representing 10.6% of all new cancer cases in the US2
- HCQ is a well-established autophagy inhibitor with a low toxicity profile
- However, little is known about serum and tumor tissue distribution of HCQ or its effect on autophagy biomarkers in prostate cancer
- HCQ could be a safe, effective tumor-modulating agent in prostate cancer but needs further analysis3,4

Methods
- Patients with potentially resectable suspected prostate cancer
- Baseline core biopsy
- Randomized 2:1: Placebo vs HCQ
- Placebo PO or HCQ/IV
- Surgical resection of tumor
- Collect tumor tissue & plasma
- Collect tumor tissue & plasma

Clinical Data

Autophagic cell death with HCQ in patients with hormone-dependent prostate-specific antigen progression after local therapy for prostate cancer4 Journal of Clinical Oncology (2019)
- Methods: 52 patients with rising PSA after local therapy treated with HCQ
- Results: 45 of 52 patients demonstrated decreased or negative PSA doubling time

Fig. 2 Model of HCQ Autophagy Modulation
HCQ is thought to accumulate in lysosomes, prevent formation of the autophagosome, and lead to apoptosis, inhibiting autophagy-mediated tumor cell survival and proliferation.5 American Cancer Society (2018)

Conclusion

HCQ appears to induce prostate atrophy via autophagy inhibition and reduce PSA progression after localized therapy. Given that HCQ has limited side effects, the drug has the potential to augment responses to prostate cancer treatment. This highlights the need for further clinical data characterizing HCQ’s tumor tissue and serum distribution, effect on autophagy biomarkers, mutations, and pharmacokinetics.

References
3. Ling et al., Hydroxychloroquine Blocks Autophagy and Promotes Apoptosis of the Prostate after Castration in Rats. (2020) Urologia Internationalis; 104:968-974