Evolutionary game theory and optimal control for integrated metastatic management of prostate cancer

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While overall survival of early stage prostate cancer is increasing due to early detection and improving therapy for local and regionally confined disease, the 5-year overall survival for metastatic prostate cancer patients has actually dropped by 3.1% (from 31.8% to 28.7%) since 1977. This is despite the increasing number of agents available for treating metastatic prostate cancer. Why, then, do all of these therapies, which have been shown to provide some level of therapeutic effect, fail to result in a higher survival rate of metastatic prostate cancer? It is now known that metastatic cancer populations possess the ability to evolve resistance to all currently available therapies, rendering them ineffective even after an initial strong response.

When a therapy is initially applied to a tumor, a majority of the cancer cells will be sensitive to the treatment, but there may be a small subset of cells that are already resistant or can quickly evolve resistance to the treatment due to their evolutionary history. In this way, when treatment is applied, a strong initial response is generally observed, as the treatment is effective against the abundant sensitive cells. Just as antibiotics kill 99.99% of bacteria, this initial therapy may kill 99.99% of the cancer cells, resulting in a clinical remission of disease. Unfortunately, as therapy is continued, the resistant cells initially present or cells that evolved a novel resistance mechanism in direct response to therapy can continue to proliferate causing disease relapse.

This ability of cancer cells to evolve resistance to therapy is arguably the leading problem in cancer therapy today. Even with this new understanding of cancer as a Darwinian disease, evolutionary principles are generally not considered in the design of clinical treatment. Instead, the conventional treatment strategy used universally in the clinic in an attempt to eradicate every cancer cell is known as maximum tolerated dose (MTD). Decades of clinical observation have clearly demonstrated that a cure using MTD is rarely possible. For example, this thesis focuses on the use of the drug abiraterone in patients with metastatic castrate-resistant prostate cancer (mCRPC). When given continuously at MTD, abiraterone provides a strong initial response, but invariably, the cancer progresses within a median time of 16 months. This failure is rooted in the very design of MTD which precipitates a “resistance crisis.” MTD strongly selects for already present resistant cell types by eliminating the sensitive cell population and by enforcing strong selection pressures for evolution of novel resistance mechanisms during treatment.

In Chapter 2, this “resistance crisis” of metastatic disease is compared to the “resistance crisis” that occurred during the initial attempts of the agriculture industry to eradicate major pests. The development of a large variety of synthetic pesticides and their subsequent widespread high dose usage began in the 1940s. While the impact on the pest population was initially dramatically successful, use of pesticides in high doses resulted in maximal selection pressure for resistance and eliminated competing populations, actually accelerating the proliferation of resistant pest populations. In 2015, Barzman et al., on the basis of 50 years of agricultural experience, formalized the fundamental principles of integrated pest management that proved most successful in obtaining long-term control of pest populations. This chapter discusses these eight principles within the context of cancer biology and provides a novel qualitative framework to build and develop a long-term management paradigm for
metastatic disease, essentially abandoning the idea of a cure.

In Chapter 3, a mathematical model utilizing evolutionary game theory is developed to quantitatively frame the cancer eco-evolutionary dynamics of mCRPC under abiraterone treatment. The mathematical model developed here does not attempt to fully describe every underlying biological process of mCRPC, but instead focuses on the sensitive and resistant clinically known cell types and their interaction with the drug abiraterone. In this way, this mathematical model is not intended to exactly recreate clinical data. Instead, the mathematical model is used to identify critical parameters that affect system dynamics, generate experimentally testable hypotheses, and generally provide an increased understanding of the first principles of evolution of resistance to treatment with abiraterone. This model is the foundation for the remaining chapters where alternative treatment strategies with the goal of, not curing, but managing mCRPC as a chronic condition are developed, tested, and discussed.

In Chapter 4, initial analysis of the mathematical model compares the eco-evolutionary dynamics and subsequent simulated patient outcomes between various treatment strategies of abiraterone including the current standard of care MTD, a common clinical protocol known as intermittent therapy, and a novel strategy known as adaptive therapy which explicitly aims to manage the proliferation of resistant cancer cells. In this adaptive therapy, when a patient is enrolled on trial, their baseline prostate cancer blood marker known as prostate specific antigen (PSA) level is recorded. Abiraterone is then administered and when that patient’s PSA drops to 50% of their personal baseline PSA, abiraterone is discontinued. Off treatment, the PSA levels will rise and abiraterone is re-administered when the patient reaches their original baseline PSA. These results were used to open a first of its kind clinical trial at the Moffitt Cancer Center using this adaptive therapy protocol of abiraterone in 16 men with mCRPC. Adaptive therapy resulted in a median time to progression of 30.4 months for these men, compared to only 14.3 months for a cohort of 16 men receiving MTD abiraterone. Furthermore, this doubling of time to progression was achieved using on average 59% less cumulative abiraterone than MTD.

The initial success of the clinical trial invited an exploration of more sophisticated time-dependent applications of abiraterone. In Chapter 5, the clinical outcome of a patient is framed as an optimal control problem to identify abiraterone dosing schedules using nonlinear constrained optimization. The patient outcomes from standard clinical treatments are compared to those with other treatment objectives, such as maintaining a constant total tumor volume or minimizing the fraction of resistant cancer cells within the tumor. The model showed that continuous high doses of abiraterone as well as other dosing strategies aimed at curing the patient resulted in accelerated competitive release of the resistant cancer cells and rapid subsequent tumor progression. Results suggested that only when a patient is approaching their personal limit of tumor burden should treatment be initiated, and then only the minimum dose required to provide the patient acceptable measures of blood markers and quality of life should be administered.

Finally, in Chapter 6, the mathematical model is used to identify what is coined as an ‘evolutionary stable therapy’ for mCRPC. The objective of this therapy is to maintain a
stable tumor heterogeneity of sensitive and resistant cells to abiraterone in order to prolong treatment efficacy and progression free survival. Surprisingly, optimal control analysis shows that a dose titration protocol, a very common dosing strategy in other medical disciplines, can achieve tumor stabilization for a wide range of potential initial tumor compositions and volumes. Furthermore, larger tumor volumes may, counterintuitively, be more likely to be stabilized if sensitive cells dominate the tumor composition at time of initial treatment, again suggesting a delay of initial treatment could prove beneficial. While it remains uncertain if metastatic disease in humans has the properties that allow it to be truly stabilized, the benefits of a dose titration protocol warrant additional pre-clinical and clinical investigations.

In Chapter 7, the results from this thesis are placed within the context of current clinical and mathematical oncology and future directions are discussed in detail. In particular, a framework for using model predictive control methods are described for implementing evolutionary therapy as a real-time clinical treatment protocol to govern proliferation of resistant cancer cells. Furthermore, a number of clinically available options for measuring the sensitive vs. resistant tumor composition are discussed in detail including blood serum markers, imaging, and liquid biopsy. Lastly, current clinical trials that were inspired by the results in this thesis are presented.

In conclusion, the ultimate goal of treating cancer is for the patient to remain alive. This is not synonymous with eradicating all tumor cells in the body. In this way, clinical success must be redefined as cumulative years of survival with acceptable quality of life regardless of tumor burden. This will require, first and foremost, the discontinuation of the maximum tolerated dose paradigm for available non curative therapies. Instead, each available therapy should be administered using a resistance management plan that judiciously applies therapy guided by the dynamics of each patient’s specific disease. Based on the results from this thesis, it is not unreasonable to assume that the time a drug is effective using MTD can be at least doubled in the clinic using evolutionary enlightened dosing strategies. If overall survival can indeed be doubled for the therapies available, men with metastatic prostate cancer could potentially manage their disease for well over 10 years: an extraordinary clinical achievement.

Associated Publications of Thesis Chapters