Adaptive Therapy: Using Evolutionary Game Theory to Combat Cancer Treatment Resistance

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ABSTRACT

Adaptive therapy is a cancer treatment based upon the principles of evolutionary game theory (EGT) utilized to minimize treatment resistance as a cause of tumor evolution. This treatment strategy incorporates a foundation of Darwinian evolutionary principles with mathematical modeling and clinical data. As a result, adaptive therapy ameliorates the negative effects of traditional cancer treatments such as therapy resistance and a debilitated quality of life. By eliminating the use of maximum tolerated dose (MTD), the hallmark of traditional therapies, the evolutionary properties of tumors to develop drug resistance are circumvented and the probability of a prolonged life for patients is significantly increased. This paper explores the effectiveness of an expanded usage of adaptive therapy through an evaluation of current oncological research.

Introduction

Adaptive therapy is an emerging form of cancer treatment based on evolutionary game theory (EGT), which describes situations where organisms possessing different inherited traits interact with each other. Unlike in classical game theory, where the assumption is that the players act rationally, the strategies employed by these organisms in EGT do not need to be rational, and instead are inherited rather than logically chosen. Some of these strategies, however, might represent a higher fitness and the individuals using them will in the long run dominate the population. Thus, if cancer is seen as a Darwinian, or evolutionary, process, it can be described as an evolutionary leader-follower game, where cancer cells are the players, with their heritable traits corresponding to the strategies, and the payoffs are represented in terms of survival and proliferation. The oncologist "plays" first and makes informed decisions, whereas the tumor cells respond and adapt to the treatment given (Belkhir, Thomas, & Roche, 2021). In addition, this "game" is dynamic, since the frequencies of different strategies can be temporally analyzed (Wölfl et al., 2021).

Geneticist Theodosius Dobzhansky's hypothesis that "nothing in biology makes sense except in the light of evolution" has provided the basis for designing adaptive cancer therapies centered on principles of EGT and ecology that can predict the behavior of a population of cancer cells and maintain treatment sensitivity by lowering the possibility of treatment-resistance (West et al. and Anderson, 2020 and 2021). Continuously applying a large dose of chemotherapy will destroy the fittest tumor cells but will inevitably leave behind chemo-resistant cells. These treatment-resistant cells will then proliferate freely due to the inefficacy of the treatment as a result of a principle called competitive release (Belkhir et al., 2021). The National Cancer Institute, defining AT, has stated, "in adaptive therapy, drugs are given in a way that allows a proportion of the drug-sensitive cells to disproportionately survive, so that they may compete with and block the growth of the drug resistant cells" (National Cancer Institute [NCI], n.d.).
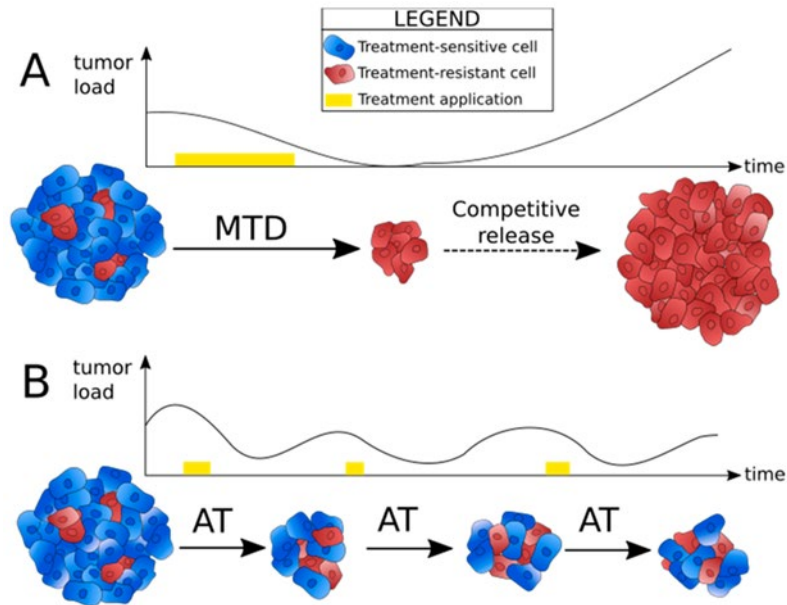
Figure 1. A diagram explaining the principle behind adaptive therapy, comparing the use of AT to the use of maximum tolerated dose (MTD) (Belkhir et al., 2021).

Many cancer researchers support the use of adaptive therapy. According to Moffitt Cancer Center researcher Dr. Robert Gatenby, "there's always been this sense that if we just kill a few more cells, if we could use nine chemo drugs instead of three - we could get the cancer. But all you do is increase the toxicity for the patient. You don't increase the probability of a cure" (Baker, 2017). Therefore, adaptive therapy use should expand in cases where cancer is incurable, or quality of life is compromised. One clinical trial designed by Brady-Nicholls et al. (2021) observed promising results for adaptive therapy, proving a drug called abiraterone acetate (AA) is effective for treating metastatic castration-resistant prostate cancer (mCRPC), which is known for not responding well to treatments. In this trial, it was proposed that adaptive use of AA may reduce toxicity and improve lifespan when compared to continuous use of AA. The heterogeneity of cancer cells, one of the biggest difficulties faced during cancer treatment, means that a tumor can find ways to resist cancer drugs and continue to metastasize.

This treatment resistance can also cause tumors to transform into different subtypes of cancer. For example, some epidermal growth factor receptor positive (EGFR+) non-small cell lung cancers may develop to small cell lung cancer, a much more difficult type of cancer to treat due to its rarity (Eldridge, 2023). While there are many types of successful systemic treatments for common cancers, many cancers can have temporary tumor responses to treatment and reemerge quickly due to the continued existence of treatment-resistant populations of cancer cells remaining in the body. Cancer cells have been proven to be very dynamic, yet therapies are usually fixed and administered following a strict, linear schedule. In contrast, research that was conducted by Gatenby, Silva, Gillies, & Frieden, (2009) demonstrated that adaptive therapy evolves in response to changes in the cancer microenvironment and disturbances to homeostasis as a result of the treatment.

Consequently, an equilibrium should be sought between the treatment and the opposing treatment resistance when implementing adaptive therapy in order to optimize to reduce the size of the tumor. In a paper in the journal *Cancers,* Belkhir, Thomas, & Roche, (2021) highlighted the importance of in-silico or computer-simulation based models, where they wrote:

When designing, testing, and implementing evolution-based strategies, we cannot fully rely on experimental approaches: In vitro experiments are not sufficient to predict exactly what will happen when a treatment

is applied in vivo, and the complexity of interactions and phenomena that occur in vivo is hard to understand. Besides, it is impossible to conduct too many preclinical or clinical studies, for obvious practical and ethical reasons. With mathematical models, the modeler controls all the conditions relative to the tumor modeled and can extract features that are not easily revealed experimentally. For example, in the case of adaptive therapy, it is difficult to assess the actual role of competition between tumor cells in vivo, because of the potential effects of adaptive therapy on the immune system or on vasculature, which could be confounding factors. Using in silico models is a relevant solution to understand the dynamics of cancer, and rethink the conventional approach for therapy.
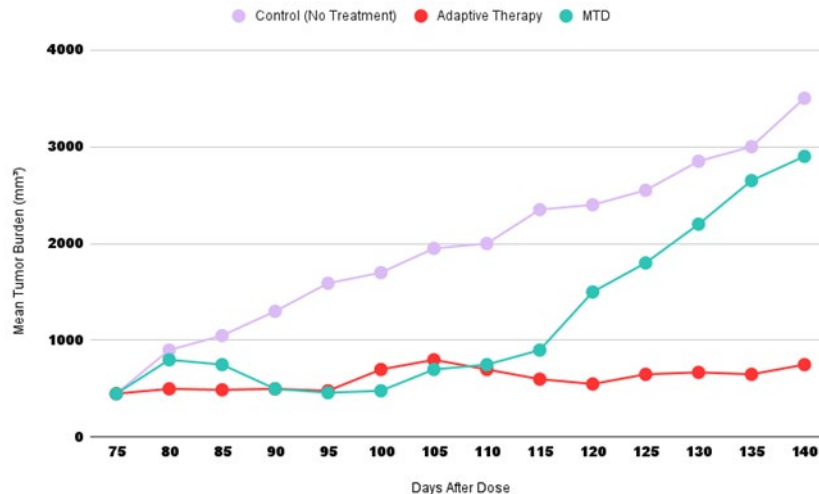

Figure 2. A graph showing results gathered from an in-silico experiment conducted by Gatenby et al. (2009) comparing MTD, AT, and a control trial.

Mathematical Models

Several mathematical models have been defined that are used to test, design and optimize adaptive therapy schedules. These categories depend on whether the equations are homogeneous or non-homogeneous, and on whether they are deterministic or stochastic. In the homogeneous and deterministic case, the models are based on ordinary differential equations that, in the case of adaptive therapy, resemble the Lotka–Volterra equations, which are used to model predator-prey relationships. The Lotka-Volterra equations are, according to Belkhir et al. (2021), one of the most commonly used systems to design a schedule for administering treatment. To develop the Lotka-Volterra model, the scientist supposes that a predator population, which is the treatment, feeds on a prey population, which are the cancerous cells. In order to conceptualize this in an oncological view, the number of cancerous cells grows exponentially in the absence of treatment, and the amount of treatment will be exponentially decreased by the scientist in the absence of cancer cells (Chasnov, 2016). Therefore, to prevent the emergence of treatment-resistant cells, an equilibrium of treatment versus cancerous cells must be found before administering any type of cancer therapy.

For non-homogeneous cases, there are deterministic models, such as partial differential equation models, and stochastic models, including agent-based models (ABMs) (Belkhir et al., 2021). ABMs are computational approaches to examine how the individual tumor cells interact with each other in relation to the whole tumor (Belkhir et al., 2021). These models consider time and space as factors of the system, as well as other elements such as the behaviors of the independent cancer cells (Belkhir et al., 2021). ABMs can also be used

to explain some assumptions made with adaptive therapy. For example, researchers using an ABM that modeled resistance demonstrated that if some homogeneous tumors mostly composed of treatment-sensitive cells can be cured using maximum tolerated dose (MTD), only adaptive therapy is successful for subduing heterogeneous tumors with treatment resistant cells. Additionally, the same model proved that, in order to keep the tumor at a stable size and avoid competitive release, adaptive therapy would ideally include well-timed treatment vacations, or drug holidays, while also varying the type of drug. To clarify which is the better strategy, the same researchers compared two types of adaptive therapies: one that prioritized drug holidays, and one that focused on varying the drug dose. This ABM experiment showed that, for heterogeneous tumors, taking more drug holidays was a better strategy for keeping control of the tumor. This result aligned with their observations from Lotka-Volterra models that highlighted the benefits of well-timed drug holidays to allow the sensitive cells to regenerate and to suppress any treatment-resistant cells (Belkhir et al., 2021).

Furthermore, many other mathematical methods, in addition to the Lotka-Volterra equations and ABMs, have been developed to optimize equilibrium between the amount of treatment and the number of treatment-resistant cells. Another of these approaches is called the Norton Simon (NS) model, which determines the highest possible dose (not to be confused with MTD) over the shortest period of time, while also suppressing treatment resistance. One important assumption of this model to note is that tumor therapies fail because of the evolution of resistant cells after the therapy has begun. The NS model was designed for the highest rate of cancerous cell death, while also keeping the potential amount of treatment-resistant cells as small as possible (Gatenby et al., 2009). Beyond equilibrium, other factors must be considered before initiating the right cancer therapy.

Quality of Life

Quality of life (QOL) should also definitely be considered when choosing a cancer treatment. QOL can be defined as a state of well-being, and is a very important issue for a cancer patient before and after treatment. The concept of QOL is multifaceted, including physical, psychological, and social perspectives (Jitender et al., 2018) Another type of mathematical model used to structure and design adaptive therapy, with a significance placed on QOL, is called the Markov Decision Process (MDP). In Markovian cancer models, important information regarding the patient is "encoded" in health states, such as a healthy state, various states of disease progression, and a death state. Transitions between these states are illustrated by a stochastic, or randomly determined, process (Bayer et al.). In a 2022 study published in the Journal of Theoretical Biology, Bayer et al. (2022) built a framework based on MDPs in order to include the element of choice for the patient by combining aspects of stochastic processes and decision theory. In their model, the Markovian transition probabilities depend upon both the current state of the patient and the strategy of the doctor to maximize payoffs depending on the wishes of the patient. The patient receives these payoffs, measured in quality adjusted life years (QALY), from spending time in specific states, with more healthy states giving higher payoffs. Problems occur, however, when the decision maker, whether that is the doctor or patient, must make a choice between immediate payoffs or strategies that ultimately fit their goals at the cost of foregoing immediate gains. An example of this is when a patient sacrifices their immediate QOL in favor of undergoing an amputation that, in the long term, increases the chances for a greater life expectancy. These trade-offs are not unique to adaptive therapy and will occur with all cancer therapies (Bayer et al., 2022). Some patients taking therapy will make QALY sacrifices in hopes of a higher probability of cure and greater life expectancy, while others choose the opposite.

Cancer patients often face many consequences to their health as a result of treatment, which is one of the main reasons why patients refuse or abandon certain therapies. With each round of therapy, the current health state of the patient often depreciates significantly, with the toxicity level in the body increasing proportionately. Including toxicity in therapy models makes the QOL-cost of the therapy dependent on the effect of the treatment on the patient. Surviving patients have to bear the QALY reduction longer, and patients who are

not cured may have to resort to taking on higher levels of toxicity and end up suffering more QALY reductions from added rounds of therapy. This gives patients an additional option for managing the QALY-cost of therapy. Patients may choose to postpone rather than abandon therapy as a means of allowing their toxicity burden to decrease (Bayer et al., 2022). These periods of postponement can be defined as drug holidays, as mentioned before.

Maximum tolerated dose, as previously referred to when discussing NS models, is scientifically defined as the highest dose a patient can take without experiencing fatal side effects (Banks, 2021). In an interview with *Cancer Today*, Eric P. Winer, a medical oncologist and chief of the Division of Breast Oncology at the Dana-Farber Cancer Institute in Boston, elaborated on MTD, "just because you have cancer and are on treatment doesn't mean you have to be miserable. Oncologists might consider starting with a lower dose and increasing it based on the patient's needs, instead of starting with the highest dose and then laddering down the dosage because of toxicity" (Banks, 2021).

Adaptive therapy has been proven to be much easier on the body than regular treatments and can be evolved to fit the patient's preferences of treatment. Patient choice is especially important to consider, as it is a vital aspect of maintaining an acceptable quality of life during treatment. At each state of the disease, and when starting therapy, the patient's choice of continuing or not is an important component of their well-being, rather than only being conditional on the current level of toxicity. However, in adaptive therapy, the patient is offered a third choice: to take a drug holiday or suspend treatment. If this third choice is selected by the patient, the schedule and models for treatment can be adapted to fit this decision (Bayer et al., 2022).

These physical tolls on the body are also accompanied by the psychological burden of the financial aspects of cancer treatments. These economic strains can be avoided through the use of adaptive therapy. Many patients going through cancer therapies are required to spend countless dollars monthly to continue their treatments. One doctor, from the Moffitt Cancer Center, refers to this phenomenon as "financial toxicity," which is another reason some patients cannot take the continuous therapy that is the standard of care. Patients using adaptive therapy can go on and off treatments as needed, which means they save countless dollars every month. Any opportunity to decrease the amount of drug needed provides an added financial benefit by focusing on optimal dosing rather than MTD (Baker, 2021). In an article published in a supplement in the *Journal of Clinical Oncology* in 2021, Dr. Mark Ratain, a medical oncologist and clinical pharmacologist, and colleagues proved lowering the dosing of Herceptin (trastuzumab), a drug indicated for women with HER2-positive breast cancer, from six milligrams per kilogram of weight, to four milligrams per kilogram of weight every three weeks could reduce annual Medicare spending by as much as $810,000,000 (Banks, 2021). Hence, adaptive therapy can ameliorate many of the issues that are encountered when treating cancer with more common therapies.

Adaptive Therapy is Already Naturally Occurring

The ultimate objective of adaptive therapy in cancer patients is to enhance their survival and quality of life in a manner traditionally implemented today with continuous optimization and intentionality. Interestingly, a model of adaptive therapy is already naturally occurring in many multicellular organisms, including humans. During the growth and maintenance of normal tissue, the human body uses many of the strategies employed in adaptive therapy to deal with the inevitable development of malignant cancer cells as a result of gene mutations. Multicellular organisms, by way of natural selection over many generations, may have evolved forms of what researchers call natural adaptive therapy (NAT) (Thomas et al., 2018). Part of an organism's adaptations to prevent cancer may include containing rather than just eliminating or preemptively inhibiting cancer cells. Through this thinking, NAT could explain why many autopsy studies display small cancers that are present in people and animals who have died from non cancer causes. In a 2018 paper in the *Public Library of Science Journal*, Thomas et al. (2018) observed that "cancer

emerges frequently, but mechanisms like the immune system successfully limit their proliferation in a manner that does not adversely affect host fitness". NAT represents a balance between possible risks and benefits created by the immune system by allowing a response from the body to maintain both a stable small tumor and homeostasis in the body by minimizing the risk of damage to normal tissue (Thomas et al., 2018). Through the concept of NAT, therefore, it can be inferred that the human body has been evolutionarily trending towards adaptive therapy as a treatment for cancer. Thus, whether in terms of oncological or natural means, adaptive therapy has been demonstrated as an effective solution for minimizing the unfortunate consequences of traditional cancer treatments.

Acknowledgments

References

Anderson, S. (2021, February 15). *Moffitt researchers identify key factors impacting adaptive therapy* [Press release]. https://moffitt.org/newsroom/press-release-archive/moffitt-researchers-identify-key-factors-impacting-adaptive-therapy

Baker, A. M. (2017). *Adapting for survival* [Press release]. https://moffitt.org/publications/moffitt-momentum/volume-4-issue-2-moffitt-momentum/adapting-for-survival/

Banks, M. A. (2021, July 12). Moving away from the maximum tolerated dose. *Cancer Today Magazine*. https://www.cancertodaymag.org/cancer-talk/moving-away-from-the-maximum-tolerated-dose/

Bayer, P., Brown, J. S., Dubbeldam, J., & Broom, M. (2022). A Markovian decision model of adaptive cancer treatment and quality of life. *Journal of Theoretical Biology*, *551-552*, 111237. https://doi.org/10.1016/j.jtbi.2022.111237

Belkhir, S., Thomas, F., & Roche, B. (2021). Darwinian approaches for cancer treatment: Benefits of mathematical modeling. *Cancers*, *13*(17), 4448. https://doi.org/10.3390/cancers13174448

Brady-Nicholls, R., Zhang, J., Zhang, T., Wang, A. Z., Butler, R., Gatenby, R. A., & Enderling, H. (2021). Predicting patient-specific response to adaptive therapy in metastatic castration-resistant prostate cancer using prostate-specific antigen dynamics. *Neoplasia*, *23*(9), 851-858. https://doi.org/10.1016/j.neo.2021.06.013

Chasnov, J. R. (2016). *The Lotka-Volterra predator-prey model*. Libre Texts Mathematics. Retrieved February 22, 2023, from https://math.libretexts.org/Bookshelves/Applied_Mathematics/Mathematical_Biology_(Chasnov)/01%3A_Population_Dynamics/1.04%3A_The_Lotka-Volterra_Predator-Prey_Model

Eldridge, L. (2023, February 28). *Will cancer ever be cured?* Verywell Health. Retrieved April 22, 2023, from https://www.verywellhealth.com/will-cancer-ever-be-cured-4686392

Gatenby, R. A., Silva, A. S., Gillies, R. J., & Frieden, B. R. (2009). Adaptive therapy. *Cancer Research*, *69*(11), 4894-4903. https://doi.org/10.1158/0008-5472.CAN-08-3658

How adaptive therapy works [Infographic]. (n.d.). National Cancer Institute. https://www.cancer.gov/research/annual-plan/scientific-topics/how-adaptive-cancer-therapy-works-infographic

Jitender, Solanki et al. "Quality of life of cancer patients." *Journal of Experimental Therapeutics & Oncology* vol. 12,3 (2018): 217-221. https://pubmed.ncbi.nlm.nih.gov/29790313/

Thomas, F., Donnadieu, E., Charriere, G. M., Jacqueline, C., Tasiemski, A., Pujol, P., Renaud, F., Roche, B., Hamede, R., Brown, J., Gatenby, R., & Ujvari, B. (2018). Is adaptive therapy natural? *PLOS Biology*, *16*(10), e2007066. https://doi.org/10.1371/journal.pbio.2007066

West, J., You, L., Zhang, J., Gatenby, R. A., Brown, J. S., Newton, P. K., & Anderson, A. R.a. (2020). Towards multidrug adaptive therapy. *Cancer Research*, *80*(7), 1578-1589. https://doi.org/10.1158/0008-5472.CAN-19-2669

Wölfl, B., te Rietmole, H., Salvioli, M., Kaznatcheev, A., Thuijsman, F., Brown, J. S., Burgering, B., & Staňková, K. (2021). The contribution of evolutionary game theory to understanding and treating cancer. *Dynamic Games and Applications*, *12*(2), 313-342. https://doi.org/10.1007/s13235-021-00397-w