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Highlights

- Model enables investigation of individualized effects of anti-PD1 immunotherapies
- Analysis of tumor burden, treatment times and T-cell loss by cytostatic treatments
- Model-based design of treatment schedules: initiation, duration and repetition
- Classes of patient trajectories including fixed steady states and cyclic attractors
- Combination of targeted and immunotherapy has better effect than mono-immunotherapy

Modelling of killer T-cell and cancer cell subpopulation dynamics under immuno- and chemotherapies

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Abstract

Each patient's cancer has a unique molecular makeup, often comprised of distinct cancer cell subpopulations. Improved understanding of dynamic processes between cancer cell populations is therefore critical for making treatment more e□ective and personalized. It has been shown that immunotherapy increases the survival of melanoma patients. However, there remain critical open questions, such as timing and duration of immunotherapy and its added benefits when combined with other types of treatments. We introduce a model for the dynamics of active killer T-cells and cancer cell subpopulations. Rather than defining the cancer cell populations based on their genetic makeup alone, we consider also other, non-genetic di□erences that make the cell populations either sensitive or resistant to a therapy. Using the model, we make predictions of possible outcomes of the various treatment strategies in virtual melanoma patients, providing hypotheses regarding therapeutic e□cacy and side-e□ects. It is shown, for instance, that starting immunotherapy with a denser treatment schedule may enable changing to a sparser schedule later during the treatment. Furthermore, combination of targeted and immunotherapy results in a better treatment e□ect, compared to mono-immunotherapy, and a stable disease can be reached with a patient-tailored combination. These results o□er better understanding of the competition between T-cells and cancer cells, toward personalized immunotherapy regimens.

Keywords: combination therapy, immunotherapy, personalized medicine, killer T-cells, side-e□ects

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1. Introduction

Each patient's cancer has a unique molecular makeup, often comprised of populations of genetically, functionally or epigenetically distinct cancer cell subpopulations that undergo dynamic evolutionary processes throughout the disease course and treatment periods. The goal of making cancer treatment more effective and personalized therefore requires an improved understanding of such dynamic processes, including evolutionary competition of space, glucose and other resources between cell populations that lead to the survival of fitter populations (Gillies et al., 2012; Glauche et al., 2018; Greaves, 2015). Mathematical modelling of heterogeneous cell population dynamics and treatment responses has shown great promise as a means to suggest mono- or combination therapies that can theoretically control or even inhibit distinct cancer cell populations, as well as provide mechanistic insights into treatment sensitivity and resistance for adaptive intervention designs (Bozic et al., 2013; Bozic and Nowak, 2014; Fischer et al., 2015; Louzoun et al., 2014; Michor and Beal, 2015; Zhang et al., 2017; Zhao et al., 2016). However, most of the modelling works have focused on genetic differences and architecture of sub-clones and their evolution, even though also non-genetic differences between or within tumors are known to contribute to the individual disease course and personalized responses to therapies in various hematological cancers and solid tumors, including patients with advanced malignant melanomas.

Melanoma is initiated by DNA mutations in melanocytes with major risk from exposure to ultraviolet light. Melanomas typically occurs in skin, where it forms lesions of irregular size, shape and color. In localized disease, common treatment is removal by surgery. However, in the case of advanced malignant melanoma where the disease has metastasized, multidisciplinary treatments, such as radiation therapy, targeted therapy (e.g., BRAF inhibitors such as vemurafinib), chemotherapy (e.g., dacarbazine) or immunotherapy (e.g., anti-PD-1 such as nivolumab and pembrolizumab) are recommended (Bhatia et al., 2009; Garbe et al., 2016; Maverakis et al., 2015). Novel immunotherapies have greatly improved the response rate, duration and tumor stability in patients with advanced melanoma even after treatment discontinuation (Huang et al., 2019; Topalian et al., 2014). However, varying treatment outcomes persist (Gauci et al., 2019), and despite the improved clinical benefit, a proportion of patients remain non-responsive leading to progressive disease (Robert et al., 2015). In some cases, the treatment has to be repeated periodically to control the cancer, leading to a chronic disease (Lipson et al., 2013). However, dormant cancer can also be reached (Aguirre-Ghiso, 2007; Ossowski and Aguirre-Ghiso, 2010; Schreiber et al., 2011; Senft and Ronai, 2016), where undetectable cancer persists after treatment.

Immune-checkpoint inhibitors are revolutionizing the treatment of patients with advanced-stage cancers. In particular, the blockade of programmed cell death protein 1 (PD-1) increases the survival of patients with metastatic melanoma and other solid tumors. Despite encouraging results, however, clinical outcomes of anti-PD-1 therapy remain highly variable and durable treatment benefit is limited to a minority of patients (Keenan et al., 2019). Immune-checkpoint inhibitors reactivate patient's immune system to defeat cancer, especially antigen-specific killer T-cells (or CD8+ T-cells). Approximately 20–50% of human cancers express programmed death-ligand (PD-L1) that inhibits the killer T-cell function by binding to its receptor PD-1 on the T-cell surface (Chen and Mellman, 2013). Monoclonal antibodies, such as anti-PD-1, block the inactivating binding of PD-L1 to its receptor protein PD-1 on killer T-cell surface, enabling the T-cell to attack the tumor (Pardoll, 2012) (see Supplementary Figure 1). Additionally, antigen delivery from dying cancer cells leads to increased activation of killer T-cells that elevates the regulation of T-cells also by other mechanisms, for example T-cell self-regulation. To understand the patient-specific responses to immunotherapies, one needs to take into account the dynamics and competition between active killer T-cells and cancer cells. Some of the currently unaddressed questions in melanoma therapy concern the timing of checkpoint blockage, respective benefits of targeted versus checkpoint inhibitors, and how to optimize the benefit-risk ratio of these regimens (Robert, 2018).

Immunotherapies are also being tested in combination with other cancer therapies, including targeted or cytotoxic chemotherapies, where the former inhibits the growth of cancer cells by interfering with specific

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CRediT author statement:

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Kalle Parvinen: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Supervision.

Henna Kasanen: Writing – Review & Editing

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