Mathematical Modeling of Combination Therapy with anti-PD-1 as One of the Two Agents

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Abstract

Effective T cells kill cancer cells, but they are inhibited by checkpoints, such as PD-1. When its ligand PD-L1 combines with membrane protein PD-1 on the T cell, the T cell activity is blocked. Recently several anti-PD-1 drugs have been approved by FDA, and they offer exciting opportunities in cancer therapy.

In this talk we first consider a combination therapy of cancer, with one drug, a vaccine, which activates dendritic cells, so that they induce more T cells to infiltrate the tumor, and another drug, a checkpoint inhibitor anti-PD-1, which enables the T cells to remain active against the cancer cells. To address the question of synergy between the two drugs, we develop a mathematical model, by a system of partial differential equations, which includes dendritic and cancer cells, $CD4^+$ and $CD8^+$ T cells, IL-12 and IL-2, CM-CSF produced by the vaccine, and a T cell checkpoint inhibitor associated with PD-1. We use the model to explore the efficacy of the two drugs, separately and in combination, and compare the simulations with data from mouse experiments. We next introduce the concept of synergy between the drugs and develop a synergy map which suggests in what proportion to administer the drugs in order to achieve the maximum efficacy.

In the second example we consider anti-PD-1 with BRAF inhibitor. In this case we find that the two drugs can be antagonistic in some ranges. This suggests that clinical trials with combination therapy should carefully consider the relative amounts of the two drugs before advancing to the next phase in the trial.

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