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Impact of chemo-immunotherapy on tumour-immune interactions: a non-autonomous model of tumor necrosis factor and T cell dynamics

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This study explores the interaction between cancer cells, helper T cells, cytotoxic T cells, and tumour necrosis factors in chemotherapy and immunotherapy treatment in the microenvironment [1]. The goal is to analyze the connection of helper and cytotoxic T-cell levels with the anti-tumour immune response and the impact of various dosing regimens when combined with immunotherapy and chemotherapy. These protocols aim to shorten the interval between treatment cycles from three to two weeks or less to prevent tumour regrowth and maximize its cell elimination by treatment. Motivated by clinical trials, we thoroughly compare procedures involving two medications supplied sequentially or simultaneously in a non-autonomous system. We discussed the positivity and boundedness of the model. Further, we analyze the biologically valid equilibria and investigate their local stability properties, examining transcritical, saddle-node, Hopf, and Bogdanov-Takens bifurcations numerically and analytically [2]. Furthermore, direction and stability conditions for periodic solutions are determined.

Since cancer treatments are administered in phases or cycles (periodically), the choice of therapy, whether sequential or simultaneous, often depends on the patient's critical condition. Thus, the model examines the impact of periodic treatment fluctuations. This study demonstrates that administering chemotherapy before immunotherapy yields better outcomes compared to starting with immunotherapy followed by chemotherapy. A theoretical analysis is conducted on

periodic solutions, global stability, and the persistence of the non-autonomous system. Chaos is extensively demonstrated, and chaotic attractors are depicted through the periodicity of parameters S_1 (TNF immunotherapy), S_2 (Cytotoxic T cells immunotherapy), and σ (chemotherapy concentration). When periodicity is introduced in S_1 and S_2, the non-autonomous system also displays bursting oscillations, indicating both the expeditious growth of the tumour (relapse) and the swift elimination of tumours through treatment remission.

Additionally, a sensitivity analysis follows a Latin hypercube sampling-based uncertainty analysis and an eFAST sensitivity analysis to evaluate how parameter uncertainties influence tumour growth. Numerical simulations illustrate how the model's dynamic behaviour changes with system parameter alterations. The findings highlight the critical role of helper, cytotoxic T cells and immunotherapy in tumour elimination. Additionally, the study explores the efficacy of cycle-specific drug administration at lower doses between treatment courses to prevent tumour relapse, suggesting this approach may be superior to shortening treatment intervals. Periodic treatment results indicate that the concurrent use of chemo-immunotherapy rapidly reduces tumour cells and maintains patients' overall health more effectively than sequential use (immunotherapy first, then chemotherapy). However, starting with chemotherapy followed by immunotherapy produces the best results compared to other treatment combinations.

Keywords: autonomous model, non-autonomous model, chaos, sensitivity

References

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