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A model for effects of adaptive immunity on tumor response to chemotherapy and chemoimmunotherapy

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■ **Abstract** Complete clinical regressions of solid tumors in response to chemotherapy are difficult to explain by direct cytotoxicity alone, because of low growth fractions and obstacles to drug delivery. A plausible indirect mechanism that might reconcile this is the action of the immune system. A model for interaction between tumors and the adaptive immune system is presented here, and used to examine controllability of tumors through the interplay of cytotoxic, cytostatic and immunogenic effects of chemotherapy and the adaptive immune response. The model includes cytotoxic and helper T cells, T regulatory cells (Tregs), dendritic cells, memory cells, and several key cytokines. Nearly all parameter estimates are derived from experimental and clinical data. Individual tumors are characterized by two parameters: growth rate and antigenicity, and regions of tumor control are identified in this parameter space. The model predicts that inclusion of the immune response significantly expands the region of tumor control for both cytostatic and cytotoxic chemotherapy. Moreover, outside the control zone, tumor growth is delayed significantly. An optimal fractionation schedule is predicted, for a fixed cumulative dose. The model further predicts expanded regions of tumor control when several forms of immunotherapy (adoptive T cell transfer, Treg depletion, and dendritic cell vaccination) are combined with chemotherapy. Outcomes depend greatly on tumor characteristics, the schedule of administration, and the type of immunotherapy chosen, suggesting promising opportunities for personalized medicine. Overall, the model provides insight into the role of the adaptive immune system in chemotherapy, and how scheduling and immunotherapeutic interventions might improve efficacy.