

Phase I/II dose finding interval design for Immunotherapy

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Abstract: Immunotherapeutics have revolutionized the treatment of metastatic cancers and are expected to play an increasingly dominant role in the treatment of cancer patients. Recent advances in checkpoint inhibition show promising early results in a number of malignancies, and several treatments have been approved for use. However, the immunotherapeutic agents have revealed to have different toxicity profiles and mechanism of antitumor activity from the cytotoxic agents, and many limitations and challenges encountered in the traditional paradigm were recently pointed out for immunotherapy. Our methods address the difficulty to identify the relationship between immunotherapeutic exposure and clinical outcomes and determine optimal biological dose of immunotherapeutics by effectively utilizing toxicity, immune response, and tumor response. Moreover, we propose an algorithm to allocate the dose for next cohort which makes dose transition safer and more appropriate by prioritizing the safety over efficacy outcomes, which is analogous to the rationale of phase-I-and-then-II. Simulation studies show that the proposed design has desirable operating characteristics compared to existing dose-finding designs. It also inherits strengths of interval designs to have superior performance with the simplicity of the algorithm based on multiple outcomes.