Multistate modeling and simulation of patient trajectories after allogeneic hematopoietic stem cell transplantation to inform drug development

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Abstract: We present a case study for developing clinical trial scenarios in a complex progressive disease with multiple events of interest. The idea is to first capture the course of the disease in a multistate Markov model, and then to simulate clinical trials from this model, including a variety of hypothesized drug effects. This case study focuses on the prevention of graft-versus-host disease (GvHD) after allogeneic hematopoietic stem cell transplantation (HSCT). The patient trajectory after HSCT is characterized by a complex interplay of various events of interest, and there is no established best method of measuring and/or analyzing treatment benefits. We characterized patient trajectories by means of multistate models that we fitted to a subset of the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Events of interest included acute GvHD of grade III or IV, severe chronic GvHD, relapse of the underlying disease, and death. The transition probability matrix was estimated using the Aalen-Johansen estimator, and patient characteristics were identified that were associated with different transition rates. In a second step, clinical trial scenarios were simulated from the model assuming various drug effects on the background transition rates, and the operating characteristics of different endpoints and analysis strategies were compared in these scenarios. This helped devise a drug development strategy in GvHD prevention after allogeneic HSCT. More generally, multistate models provide a rich framework for exploring complex progressive diseases, and the availability of a corresponding simulation machinery provides great flexibility for clinical trial planning.