Integrating Patient Experience Data to Enhance Treatment Benefit Evaluation in Oncology Trials: An Application of Joint Models

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Abstract
Joint models were applied in the randomized, double-blind, phase 3 BRISK-FL trial to examine their utility in improving treatment effect estimation and for dynamic predictions compared to conventional analyses of time-to-event and patient-reported outcome (PRO) data. In Aims 1 and 2, the relationships between treatment arms (sorafenib versus brivanib), PROs (physical function, role function, quality of life [QoL]; abdominal pain, abdominal swelling, fatigue, fever, jaundice, nutrition, pain), and overall survival were quantified using trajectory function models (TFMs) and shared random effects models (SREMs). In Aim 3, joint latent class models (JLCMs) were used to identify latent symptom (fatigue, nutrition, jaundice, pain, symptom cluster) classes and predict class-specific disease progression.

In Aims 1 and 2, PROs were generally associated with survival, though incorporating PROs did not markedly improve model fit. Comparable efficiency was observed between joint models and naïve models for most PRO scales. Joint models confirmed no survival differences between treatments and that both had adverse effects on symptoms, function, and QoL. TFMs and SREMs did not significantly enhance treatment effect estimation, especially considering model fitting complexity. In Aim 3, distinct classes were identified for fatigue, jaundice, pain, and the symptom cluster. Fatigue and symptom clusters were particularly useful in examining differential disease progression and identifying patients more likely to benefit.

TFMs and SREMs may offer a statistically rigorous approach for integrating PROs into treatment efficacy evaluation by adjusting for informative censoring and measurement error, and making optimal use of the available time-to-event and PRO data—when the two outcomes are highly correlated and the relationship is modeled correctly. Finding a practical balance between clinically plausible relationships and parsimony was challenging in this application. These methods may not be fully appreciated in some settings due to potentially strong assumptions, interpretation ambiguity, complicated implementation, and computational demand.

Still, with the push for patient-centered drug development, the ability to integrate patient experience data with efficacy data will be increasingly critical to contextualize patient-relevant benefit as new therapeutic options become available. Accordingly, more robust analysis of PROs alongside traditional efficacy outcomes will help to support enhanced decision-making for regulators, payers, clinicians, and patients.

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