Predicting Survival of Patients with Advanced Hepatocellular Carcinoma Treated with Bevacizumab: Tracer Kinetic Analysis of Baseline First-pass Perfusion CT

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Purpose: To compare four different tracer kinetic models for the analysis of baseline first-pass perfusion computed tomographic (PCT) data and determine the best early prognostic pharmacokinetic biomarkers in terms of the prediction of 1-year survival (1YS) and the association with overall survival (OS) of patients with advanced hepatocellular carcinomas (HCCs) treated with antiangiogenic agents (bevacizumab).

Materials & Methods: This study was part of a phase II clinical trial approved by the institutional review board. Twenty-two patients (15 men and 7 women; mean age, 61.18 years; median survival, 11.62 months) with advanced HCCs underwent PCT imaging at baseline, and treated with bevacizumab on day 1 of cycle 1 (14 days). For the subsequent 28-day cycle, patient were treated with bevacizumab on days 1 and 15, gemcitabine on days 2 and 16, and oxaliplatin on days 2 and 16 of every cycle (GEMOX-B chemotherapy). Treatment was continued until progression, unacceptable toxicity, or withdrawal of consent. The baseline first-pass PCT data were analyzed retrospectively by using four different tracer kinetic models: the Tofts-Kety (TK), two compartment exchange, adiabatic approximation to the tissue homogeneity (AATH), and distributed parameter models. Pharmacokinetic parameters consisted of blood flow (BF), blood volume (BV), mean transit time, permeability-surface area product, fractional interstitial volume, and extraction fraction (E). For each model, the optimal parameter cut-off values for predicting 1YS were derived from receiver operating characteristic curve analysis, with additional leave-one-out cross validation. Parameters of the different kinetic models were compared in terms of 1YS discrimination using cross-validated Kaplan-Meier analysis, and association with OS using a univariate Cox proportional hazard model, with additional permutation testing.

Results: In terms of 1YS prediction, the TK model-derived E, and the AATH model-derived BF, BV, and E had a statistically significant predictability after cross-validation and permutation testing: the TK model-derived E (P=0.046, cut-off value=0.528), and the AATH model-derived BF (P=0.032, cut-off value=54.888 mL/min/100 g) and BV (P=0.047, cut-off value=17.972 mL/100 g) were all higher in the high-risk group, whereas the AATH model-derived E (P=0.012, cut-off value=0.437) was lower in the high-risk group. In terms of association with OS, only the AATH model-derived E remained statistically significant after permutation testing: the increase of the AATH model-derived E was associated with a statistically significant increase in OS with a hazard ratio of 0.03 (P=0.005), indicating that, as E increases by 0.1 (10%), the risk of death falls by approximately 30%.

Conclusion: The tracer kinetic model applied to generate first-pass liver PCT data influenced its predictability as a prognostic biomarker in HCC. The AATH model-derived E was an only effective prognostic biomarker with respect to association with OS as well as 1YS prediction. Among the models investigated, the AATH model was the most favorable predictor in survival analysis. Additional knowledge of the association of parameters with OS may enable better choice of a prognostic biomarker than only knowledge of the predictability of parameters for landmark survival.

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