Confounding mitigation for the exposure-response relationship of bevacizumab in colorectal cancer patients

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Abstract

Aims. The exposure-response relationship of bevacizumab may be confounded by various factors, i.e. baseline characteristics, time-dependent target engagement and recursive relationships between exposure and response. This work aimed at investigating the exposure-response relationships of bevacizumab in mCRC patients while mitigating potential sources of bias. Methods. Bevacizumab pharmacokinetics was described using target-mediated drug disposition (TMDD) modeling. The relationships between target kinetics, and progression-free (PFS) and overall (OS) survivals were assessed using joint pharmacokinetic and parametric hazard function models. Both potential biases due to prognostic-driven and response-driven of the concentration-effect relationship were mitigated. These models were used to evaluate the effect of increased antigen target levels and clearance, as well as intensified dosing regimen, on survival. Results. Estimated target-mediated pharmacokinetic parameters in 130 assessed patients were: baseline target levels (R0=8.4 nM), steady-state dissociation constant (KSS=10 nM) and antibody-target complexes elimination constant (kint=0.52 day-1). Distribution of R0 was significantly associated with an increased baseline CEA and circulating VEGF levels, and the presence of extra-hepatic metastases. Unbound target levels (R) significantly influenced both progression and death hazard functions. Increased R0 or CL values led to decreased bevacizumab unbound concentrations, increased R levels, and shortened PFS and OS, whereas increasing bevacizumab dose led to decreased R and longer survival. Conclusion. This study is the first to show the relationship between bevacizumab concentrations, target involvement and clinical efficacy by mitigating potential sources of bias. Most of target amount may be tumoral in mCRC. A more in-depth description of this relationship should be made in future studies.

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