Joint modeling of overall survival and circulating biomarker dynamics in melanoma patients treated with IFN-α2b

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Objectives: To establish a semi-mechanistic model describing the time course of several circulating biomarkers (LDH, S100B, and MIA) in advanced melanoma patients treated with adjuvant high-dose interferon-α2b and to evaluate their dynamics as prognostic factors of overall survival (OS).

Methods: Data related to different biomarker levels in plasma were obtained from 48 melanoma patients treated with adjuvant high-dose interferon-α2b (IFN-α2b) at the University Clinic of Navarra (Pamplona, Spain). The high-dose regimen followed the Kirkwood scheme [1]. Biomarker values and survival versus time data were linked and described using a joint modeling population approach with NONMEM 7.3. Due to the lack of pharmacokinetic data of IFN-α2b, the K-PD approach was used [2].

Results: The semi-mechanistic model combines indirect response-based models to represent synthesis and degradation processes of serologic biomarkers driven by an unobserved variable [Tumoral activity (TA)] which represents tumor progression dynamics. The estimate for the proliferation rate of TA was $2.8 \cdot 10^{-3}$ weeks$^{-1}$. Drug effects were incorporated into the model with two transit compartments which generate a cytotoxic effect on TA. Information about the toxicity was also incorporated using a logistic model. Predicted biomarker dynamics over time were linked to the probability of survival as an argument of the hazard function, which was best described using an exponential model (BASE=0.0023). The predictive checks suggested that the model adequately describes survival and biomarker dynamics over time.

Conclusions: A joint model for the dynamics of circulating biomarkers and overall survival has been established and evaluated in patients with melanoma during treatment with IFN-α2b. The model enables to convert the individual biomarker levels into personalized predictions of survival.

References: