A Prediction Model of Tumor Progression and Survival in HER2 Positive Metastatic Gastric Cancer Patients treated with Trastuzumab and Chemotherapy

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The effects of different patient factors and dose levels of chemotherapeutic agents on clinical outcomes in advanced gastric cancer are not as yet fully characterized. We aimed at developing an integrative model that incorporates dose and covariate information to predict tumor growth and patient survival in advanced gastric cancer patients treated with trastuzumab(T), 5-FU(F)/capecitabine(X) (F or X), and cisplatin(P). 69 patients (index dataset) were used for model building and separate 86 patients (test dataset) for model validation. Fraction of tumor cells sensitive to each drug was incorporated as a model parameter and T was assumed as cytostatic and X/F and P as cytotoxic. Cox proportional hazards analyses were performed on model parameters and patient covariates. The model well described the time course of observed tumor size changes, and revealed that pre-treatment tumor growth rate constant k_g , which was formulated as a function of pretreatment disease duration and baseline tumor size, was positively correlated with baseline tumor size ($p=0.0084$) and histologic grade ($p=0.034$), and efficacy of 5-FU with body weight ($p<2e-16$) and that of cisplatin with histologic grade ($p=0.00013$). Prior gastrectomy and ECOG score were significant prognostic factors for PFS. For hazards analysis, unit increase of k_g was associated with relative risk of 3.19 for PFS ($p=0.00055$) and 4.45 for OS ($p=2e-04$) in test dataset, with similar trend observed in index dataset. Dose-response simulations showed that, for small baseline tumor size or low histologic grade, maximum cytotoxic effect was attainable with a dose smaller than the current recommended dose.