Evaluation of Tumor Size Metrics to Predict Survival in Advanced Gastric Cancer

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OBJECTIVES

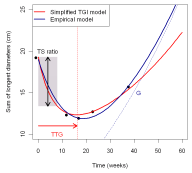
A disease model framework has been successfully applied to predict overall survival (OS) in cancer patients based on observed longitudinal tumor size data (1-4) to support early clinical development decision-making (4-6).

The aim of this project is to evaluate metrics of tumor size response and prognostic factors to predict OS in patients with HER2 positive advanced gastric cancer (AGC).

METHODS

Model-predicted metrics of longitudinal tumor size (TS) response (see Figure, [7]), patients characteristics and drug effect were evaluated as predictors for OS in AGC patients following treatment with trastuzumab plus chemotherapy (n=228) or chemotherapy (n=228) in the Phase III study ToGA.

The survival time distribution was best described by a log-logistic density function. The predictors were explored in multivariate analysis: backward elimination ($p<0.01$) of the covariates significant ($p<0.05$) in univariate non-parametric Cox regression.



TS ratio: baseline TS/TS at week 8 - (Claret, ASCO 2006, JCO 2009)

TTG: time to growth - derived from simplified TGI model (Claret, PAGE 2012 and JCO 2013)

G: tumor growth rate - estimated model parameter in the empirical model (Stein CCR, 2011)

The Simplified Tumor growth Inhibition Model (sTGI)

The sTGI model (7) assumes constant drug exposure for the patients and consist of the tumor size at baseline (TS_0), tumor growth rate (KL) and initial cell kill rate (KD_0), which adjusted by a drug efficacy decay rate parameter (λ).

$$KDE_0 = KD_0 \cdot Exposure$$

$$TS(t) = TS0 \cdot \exp\left[KL\,t - \frac{KDE_0}{\lambda}\cdot\left(1-e^{-\lambda\cdot t}\right)\right]$$

Time to growth (TTG) can be computed: $$TTG_i = \frac{\ln(KDE_i) - \ln(KL_i)}{\lambda_i}$$

The Empirical Tumor Growth Model

The empirical model (8) describes the change in tumor size from baseline (TS_0) by an exponential tumor growth rate (G) and a shrinkage rate (D).

$$TS(t_{ij}) = TS_{i,0}\cdot\left[\exp\left(-D_i\cdot t_{ij}\right) + \exp\left(G_i\cdot t_{ij}\right) - 1\right] + \varepsilon_{ij}$$

Model parameters of are estimated with NONMEM 7.

CONCLUSIONS

The metrics (tumor growth rate [G] and time to tumor growth [TTG]) of longitudinal tumor size response models are good predictors of OS and captured the effect of trastuzumab on survival in AGC patients including the shorter survival seen in patients with low trastuzumab exposure (Cmin) (9) i.e. the shorter survival in this patient cohort could be explained by their tumor response and baseline prognostic factors.

The identified prognostic baseline factors for survival are in line with literature (9,10).

The disease model is drug-independent and thus is a useful tool in design and evaluation of clinical trials of also new investigational agents under development for treatment of HER2 positive AGC and allows early prediction of OS.

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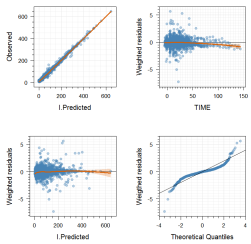
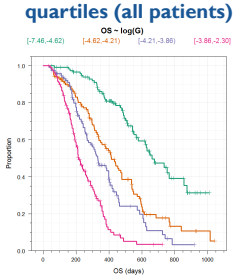
RESULTS

Model diagnostic plots Empirical model



Overall Survival per log(G) quartiles (all patients)



The sTGI model fit the TS data better than the Empirical model according to the objective function (OFV 16551 vs 16728). However the best predictor for OS was G, followed by TTG (ΔAIC 7.5). Both survival models i.e. log(G) and log(TTG) yielded same significant baseline prognostic factors and equally well simulated OS and hazard rations as determined by PPC.

The trastuzumab effect on the tumor growth rate (G) captured the trastuzumab effect on survival i.e. the trastuzumab treatment was no longer significant in the final mulitvariate OS model when tumor response was accounted for.

Good prognostic baseline factors are (in order of significance):

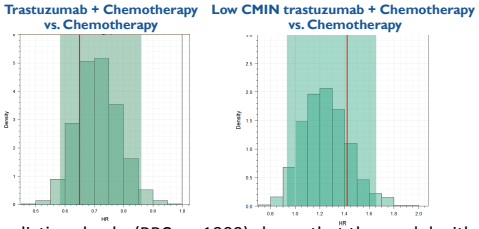
- ✧ High albumin
- ✧ Asian patients vs. others
- ✧ ECOG 0-1 vs. 2
- ✧ 1 or 2 metastatic sites vs. more
- ✧ HER IHC=3

OS model parameter estimates for log(G)

	Value	Std. Error	z	p
(Intercept)	1.6411	0.29608	5.54	2.98e-08
log(G), (G in week^{-1})	-0.5980	0.04555	-13.13	2.24e-39
Albumin (g/L)	0.0296	0.00599	4.94	7.71e-07
ASIAN (Yes/No)	0.2398	0.05954	4.03	5.66e-05
ECOG (0-1 vs 2)	0.3627	0.11151	3.25	1.14e-03
Number of metastatic sites (1-2 vs >2)	0.1774	0.05985	2.96	3.03e-03
HER2 FISH+/IHC3+ (Yes/No)	0.1457	0.05998	2.43	1.51e-02
Log(scale)	-1.1414	0.04892	-23.33	2.08e-120

Note: HER2 3+ had $p<0.01$ in the backward elimination step of the 441 patients with full covariate set. Overall survival (OS) was analyzed in days.

Posterior Predictive Checks of Trastuzumab Hazard Ratio



Posterior predictive checks (PPC, n=1000) shows that the model with logG accurately predicted the OS distribution in each study arm and subpopulation as well as trastuzumab HRs (e.g. model prediction [95% prediction interval]: 0.71 [0.58 - 0.86] vs. 0.65 for OS in trastuzumab plus chemotherapy).

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