A Longitudinal Tumor Growth Inhibition Model Based on Serum M-Protein Levels in Patients With Multiple Myeloma Treated by Dexamethasone

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Summary and Conclusions

A model for longitudinal paraprotein data following Dexamethasone treament has been developed

- Drug effect is driven by dose over time
- The model provided a good fit of the data
- No important covariate relationships were found

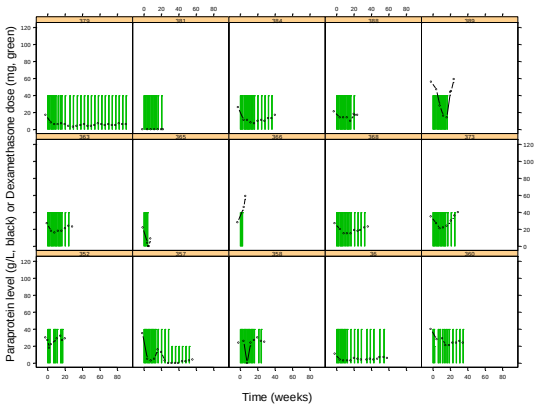
The model is qualified to simulate relative change of paraprotein level at end of cycle 2 (week 8) and is useful in overall modeling framework

Methods

Model development

Data were derived from the dexamethasone arms of two pivotal phase 3 registration studies of lenalidomide plus dexamethasone vs. dexamethasone (MM009 (1), MM010 (2)). The original data set contained 704 patients, of which 351 in the dexamethasone arm. 346 patients had more than one paraprotein measurement . A longitudinal exposure-response tumor growth inhibition model of drug effect on tumor growth dynamics (5) was adapted to predict the paraprotein level (taken as a marker of tumor size) and fit to the data. The model was implemented in NONMEM v6 using FOCE INTER. A GAM check of covariate relationships on individual estimates of random effects was run on the final model.

Example of individual paraprotein levels overlaid with dexamethasone doses (green bars)



Posterior predictive check

The model was used to simulate the relative change from baseline in paraprotein level at the end of cycle 2 (week 8). These simulated changes were subsequently used as predictors in the survival and Progression Free Survival models (3), see flowchart left. 500 replicate studies were simulated and both inter-individual variability and parameter uncertainty were sampled. Given doses and simulated baseline paraprotein levels were used as inputs to the model. The simulated distribution of 25th,50th, and 75th percentiles were recorded and compared to those observed in the studies.

References

1 - Dimopoulos M et al. Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med, 357, 2123-2132, 2007.

2 - Weber DM et al. Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med, 357, 2133-2142, 2007.

3 - Claret L et al. A Drug Independent Tumor Burden Reduction-Survival Model in Patients with Multiple Myeloma to Support Early Clinical Development Decisions. Poster presentation, 6th International Symposium on Measurement and Kinetics of In Vivo Drug Effects, Noordwijkerhout, The Netherlands, April 21-24, 2010.

4 - Bruno R, Claret L. On the use of change in tumor size to predict survival in clinical oncology studies: Toward a new paradigm to design and evaluate Phase II studies. Clin Pharmacol Ther, 86, 136-138, 2009 (invited Commentary).

5 - Claret L et al. Model-based prediction of Phase III overall survival in colorectal cancer based on Phase II tumor dynamics. J Clin Oncol, 27, 4103-4108, 2009.

Objectives

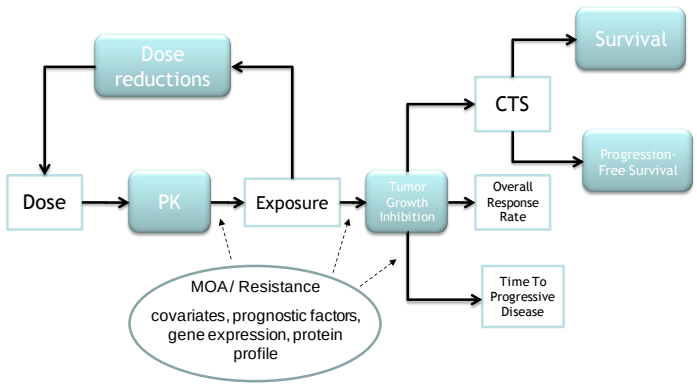
To use serum paraprotein (M protein) level as a marker of tumor burden and develop a modeling framework similar to the one used in solid tumors

Leverage lenalidomide multiple myeloma Phase III data (1, 2)

- To develop a drug-specific tumor growth inhibition model for dexamethasone based on changes in serum M Protein
- To develop drug-independent models linking early change in M protein level (end of cycle 2, week 8) to clinical response (survival and PFS) (3)

To support development of new drug candidates in multiple myeloma

General drug-disease modeling framework to simulate clinical endpoints and support oncology drug development . Modified from Bruno and Claret (4).



Results: Longitudinal Model for Paraprotein

$$\frac{dy\ t}{dt} = K_L \cdot y\ t - K_D\ t \cdot D\ t \cdot y\ t$$

$$K_D(t) = K_{D,0} \cdot e^{-\lambda t}$$

$$\frac{dD\ t}{dt} = -K_P \cdot D\ t$$

$$y\ 0 = y_0$$

y(t) : Paraprotein level at time t (g/l)
D(t) : Dose at time t (mg)
λ : Rate constant of disappearance of drug effect ($week^{-1}$)
K_P : Rate of elimination of drug from virtual biophase compartment ($mg^{-1}.week^{-1}$)
K_L : Rate of paraprotein increase ($week^{-1}$)
K_D : Rate of drug-induced paraprotein decrease ($mg^{-1}.week^{-1}$)

Data did not support estimation of Kp

- Kp fixed to 20 $mg^{-1}.week^{-1}$ after likelihood profiling (not shown)

A mixed residual error model was used

- Error model had one exponentiated (proportional) and one additive component
- Random variability was added to the baseline observation
- Simpler models for residual error also tested

Variability terms included on all three model parameters

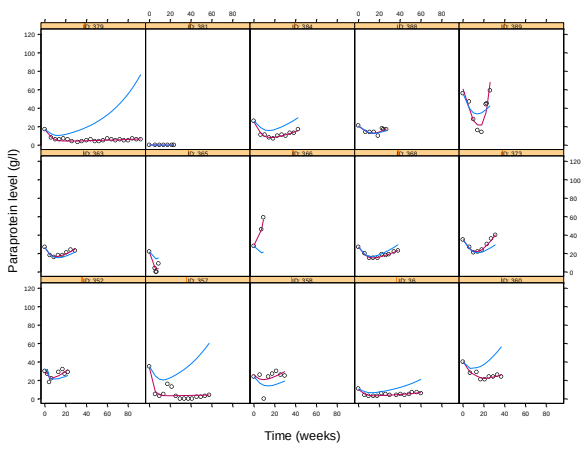
No clinically relevant covariate effects were found.

Results - Model parameters

Parameter	Estimate	RSE(%)*	Interindividual variability (variance)	RSE* (%)
K_L (wk^{-1})	0.0264	8.6	0.76	15
K_D (wk^{-1} per mg dexamethasone)	0.0265	6.0	0.44	13
λ_M (wk^{-1})	0.158	8.9	0.34	34
σ_1 (additive res error, g/l)	1.90	10.6		
σ_2 (proportional res error)	0.102	33.5		

* RSE: relative standard error of parameter estimates

Example of model fit to individual data
(dots=observed, blue= population pred, red= individual predictions)



PPC – predicted relative change in paraprotein level at week 8 (line indicates observed quartiles)