II-09

Joint Modeling of Time-Varying Exposure Data and Progression-Free Survival in Elotuzumab-Treated Patients With Relapsed/Refractory Multiple Myeloma

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Introduction

- Exposure-response (E-R) analyses are commonly used during drug development to provide an efficacious and tolerable dosing regimen for the pivotal registrational trial, and during regulatory review to assess the appropriateness of the proposed dosing regimen
- Often during oncology drug development, the optimization of drug dose and/or dosing regimen is investigated following drug approval[1]
- Elotuzumab is an anti-SLAMF7 (signaling lymphocyte activation molecule family member 7) immunostimulatory monoclonal antibody that has shown activity when combined with lenalidomide and dexamethasone for treatment of patients with relapsed/refractory multiple myeloma (RRMM)[2]
  - Elotuzumab is administered as 10 mg/kg IV, once weekly for the first two 28-day cycles and every 2 weeks thereafter, resulting in exposure changes over time
- Previous E-R analyses with Cox proportional hazards (CPH) models assume that the hazard ratio (HR) relative to a reference subject is constant for a given value of a predictor
  - In this model, static values, such as patient baseline characteristics, are often incorporated as the covariates for progression-free survival (PFS), but may not reflect the dynamic disease/physiological status of patients during treatment[3–5]
  - In prior E-R analyses of elotuzumab, a static measure of exposure metric, ie, the average concentration at steady state ($C_{avg,ss}$), and baseline covariates, were applied to the CPH model, predicting survival outcomes[6]
- Time-varying CPH models incorporate longitudinal data, but due to potentially large intersubject random errors in the longitudinal data, may lead to biased and inefficient estimates[3,5]
- To assess longitudinal exposure of elotuzumab, rather than a static concentration, on PFS, we explored joint models/modeling (JM) to simultaneously link longitudinal pharmacokinetic (PK) exposure data with hazard for disease progression to provide insights into associations between dynamic changes in PK exposure and survival
- A comparison between CPH modeling and JM is shown in **Table 1**

Table 1. General comparison between CPH model and JM characteristics

Assumptions/ functions	CPH model	JM
Baseline hazard function	No need to specify	Parametric dominant Non-specified H_0 JM can be performed (eg, CPH-PH-GH), however with challenges of modeling converging after adding 2–3 covariates
Integration method	Step function in time-varying model	Continuous integration with time
HR	Constant throughout trial	Constant or piecewise
Longitudinal data	Observed values	Random errors for observed values
Computational time	Faster	Intensive, especially for NLME models of longitudinal data or piecewise JM (>10 minutes to hours)

CPH-PH-GH, Cox proportional hazards model with Gauss-Hermite integration; H_0, baseline hazard; NLME, non-linear mixed effect

Objective

- To explore a JM simultaneously integrating longitudinal data and time-to-event data in the Phase 3 ELOQUENT-2 study, thereby improving assessment of longitudinal exposure of elotuzumab on PFS for RRMM

Methods

Patients

- In ELOQUENT-2 (NCT01239797), patients with RRMM were randomized to lenalidomide + dexamethasone, with or without elotuzumab[2]
  - 310 patients had evaluable elotuzumab exposure
- Dose scheduling led to changes in elotuzumab exposure over time

Data analysis

JM development

- JM was developed using a 2-step approach, with 2 sub-models: a longitudinal sub-model and a survival sub-model. The 2 sub-models were joined in the JM to perform simultaneous modeling of both:
  1) Longitudinal exposure data
  2) Time-to-event data, ie, PFS
- A linear mixed-effect model was used for longitudinal data[7]:
  Equation 1:

$$\boldsymbol{y}_i(\boldsymbol{t}) = \boldsymbol{m}_i(\boldsymbol{t}) + \boldsymbol{\epsilon}_i(\boldsymbol{t})$$
$$= \boldsymbol{x}_i^{\top}(\boldsymbol{t})\beta + \boldsymbol{z}_i^{\top}(\boldsymbol{t})\boldsymbol{b}_i + \boldsymbol{\epsilon}_i(\boldsymbol{t}), \qquad \boldsymbol{\epsilon}_i(\boldsymbol{t}) \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{\sigma}^2)$$

where $m_i(t)$ = true and unobserved longitudinal value at time t, $x_i(t)$ and β = fixed-effect part, $\epsilon_i(t) \sim N(0, \sigma^2)$ = error effects, and $z_i(t)$ and b_i = random-effects part

- CPH, simplified CPH and Weibull exponential models were developed for PFS; the CPH model was mathematically described as:
  Equation 2:

$$\lambda_i(\boldsymbol{t}|(\boldsymbol{M}_i(\boldsymbol{t})) = \lambda_0(\boldsymbol{t})\boldsymbol{exp}\{\beta_1^{\top}\boldsymbol{w}_{i,1} + \ldots \beta_n^{\top}\boldsymbol{w}_{i,n} + \boldsymbol{\alpha}\boldsymbol{m}_i(\boldsymbol{t})\}$$

where $M_i(t) = \{m_i(s), 0 \leqslant s < t\}$, α = effect of longitudinal data on survival, β = effect of explanatory covariates on probability of survival, λ = hazard at time t for patient i, λ_0 = baseline hazard function, and w_i = baseline covariates for patient i

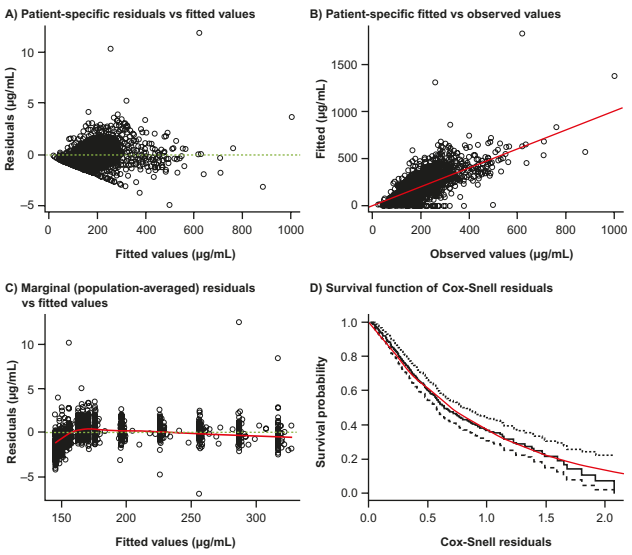
Model selection

- The longitudinal model was selected based on the Bayesian information criterion (BIC)
  - Random intercept/slope with an additional random-effects term gave the lowest BIC value
- PFS model selection evaluated CPH models with log(β_2-microglobulin), lactate dehydrogenase (LDH) ratio (to upper limit of normal), time from diagnosis, prior immunomodulatory drug (IMiD) therapy, prior hematopoietic stem cell transplantation and full-length (FL) CAIR-1 baseline covariates
  - CAIR-1 FL was excluded for the final PFS model
- The final JM was selected using the clinically observed minimum concentration (C_{min}) time profile[6]
  - The piecewise proportional hazards model with Gauss-Hermite integration (CPH-PH-αGH) was used for the final JM
- C_{min} was defined as all evaluable trough concentrations until event (progression or censoring); $C_{min,1}$ as evaluable C_{min} after the first dose
- Sensitivity analysis was performed with $C_{min,1}$ in the CPH model and time-varying C_{min} in the JM
- Additional sensitivity analysis used the clinically observed evaluable C_{min} and population pharmacokinetic (PPK)-simulated C_{min} profiles[6]

Data fitting

- Longitudinal and survival data fitting is shown in **Figure 1**
- Survival dynamic probabilities were predicted using the final JM

Figure 1. JM longitudinal and survival data fitting: A–C) longitudinal model; D) PFS model



Green line represents residual line zero; red line represents (B) identity line, (C) locally weighted smooth line and (D) Cox-Snell survival line

Software

- JM of longitudinal exposure data and PFS was performed using the R package JM (version 1.4-5)[8]

Results

- Compared with the CPH model, the JM found (**Table 2**):
  - Weaker association between elotuzumab exposure and PFS
  - Numerically stronger association between LDH ratio/β_2-microglobulin and PFS
  - Comparable associations for time from diagnosis, prior IMiD therapy and prior stem cell transplantation
- JM results were comparable when using clinically observed or PPK-simulated C_{min} (**Table 2**)

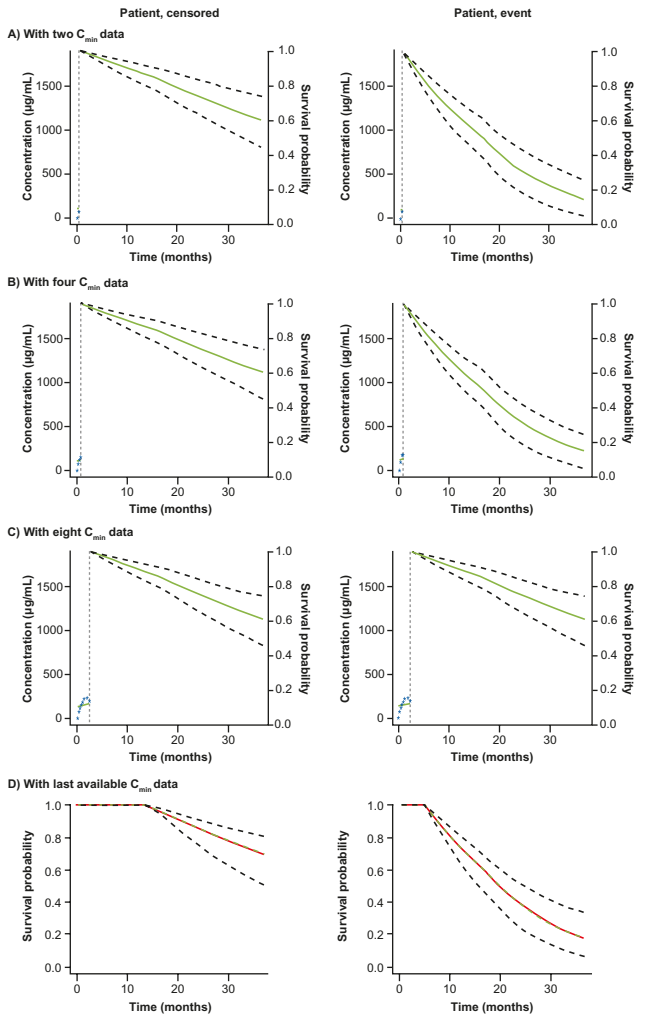
Table 2. PFS HR coefficients for CPH model versus JM

Predictor (reference : comparator)[a]	CPH model with $C_{min,1}$ (n=310, 175 events)	JM with clinically observed C_{min} (n=310, 175 events)	JM with PPK-simulated C_{min} (n=309, 174 events)
Serum elotuzumab concentration (µg/mL)[b]	−0.00752	−0.0002	−0.0006
LogLDH	0.426	0.465	0.452
log(β_2-microglobulin)	1.796	1.788	1.779
Time from disease diagnosis (≥median : <median)	−0.941	−0.905	−0.928
Prior IMiD (yes : no)	0.397	0.298	0.351
Prior stem cell transplantation (yes : no)	0.691	0.653	0.648

[a]For categorical covariates only
[b]HR coefficient represents HR for 1 unit of change in the predictor variable

- Individual dynamic prediction provides dynamic assessment of survival (**Figure 2**)

Figure 2. Individual dynamic prediction of PFS with JM



Green/red plot line: predicted median/mean survival probability of individual, based on 200 Monte Carlo samples; dashed plot line: 95% CI; asterisk: elotuzumab longitudinal concentration data at each time point; vertical grey dashed line: time of last available elotuzumab concentration data

Summary

- JM provides an innovative approach to predict individual patient survival using longitudinal exposure data, rather than one static exposure metric, thus providing insight into the dynamic dependencies between patient exposure and corresponding survival probability
- JM results suggested a weaker dependence of PFS on longitudinal elotuzumab exposure, and stronger association for other covariates compared with the CPH model
- Individual dynamic prediction provides dynamic assessment of survival, as additional longitudinal data become available
- The goal of JM is to use earlier clinical data (including progressive disease biomarkers) to predict individual clinical benefit and reveal the continuous interplay between pharmacokinetics, pharmacodynamics and efficacy to support clinical decisions

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