A Modeling and Simulation Framework for Exposure-Response Analysis in Oncology: Comparison and Considerations of Multiple Methodologies

Dan Polhamus[1], Jonathan French[1], Shang-Chiung Chen[2], Bei Wang[2], Chunze Li[2], Dan Lu[2], Sandhya Girish[2], Jin Jin[2], Angelica Quartino[2]
Metrum Research Group[1], Genentech[2]

Abstract

Objectives: There is a need for dose optimization in oncology drug development. Typical M&S framework for this application focuses around exposure-response (ER) analysis with direct or indirect (e.g., via tumor growth inhibition (TGI)) ER for progression free survival (PFS) and overall survival (OS). As typical with many large molecule therapies, ER assessment in our example is confounded by multiple prognostic factors. Additionally, survival analysis with time varying exposure is complicated by the need to integrate the hazard function with respect to time. Here, we propose and discuss a M&S framework for ER analysis in oncology with a case example to compare different aspects of multiple direct ER methodologies.
Methods: The direct ER approaches are exemplified using data from an oncology Phase 3 trial with methods including: 1) stratified Kaplan-Meier (KM) estimates by exposure quartiles, 2) Cox proportional hazards (CPH) analysis with covariate adjustment, 3) case matching (CM) to address confounding effects on ER, and 4) parametric survival modeling (PS) for extrapolation to other dosing regimens.
Results: CPH, while allowing direct ER assesment, relies on assumptions about the relationship of covariates with outcome and exposure. Recent publications from FDA reviewers proposed matching methods easing these assumptions [Yang et al., 2013], but ER assesment is no longer directly addressed as in such approaches as in CPH. A doubly robust ER using CPH within CM on strata of exposure is demonstrated, guarding against either poor matching or model misspecification. In addition to TGI, PS gives another longitudinal approach to evaluate the ER relationship for dose/regimen optimization if deemed desirable based on CPH and/or CM ER.

Conclusions: Universal discussion and adoption of a general ER framework will expedite trial design and analysis. We propose and discuss one possible ER M&S framework that guards against model mispecification, provides a clear strategy for dose optimization if indicated, and to addresses regulatory review questions.

Methods:

Determine the ER relationship and build model fit for simulation

- Kaplan-Meier estimates of $S(t)$ stratified by summary PK (Cycle 1 Ctrough, AUC_{ss}) exposure quartile to assess whether an ER trend exists. R:::survfit was used in our example. This method is naive to covariates, but makes no assumptions about the hazard function between groups.
- Cox proportional hazards models with summary PK measures were used to assess exposure response relationship after correcting for covariates. Summary PK enters into the model by: 1) quartile of exposure for a non-parametric quantification of ER shape, 2) with functional forms to enable simulation (linear, log-linear). Residuals of exposure vs Martingale residuals are used to assess fit of continuous forms of the ER response. Covariate screening is stepwise backward (at $\alpha = 0.05$) from the set identified from a univariate screen at $\alpha = 0.1$. R:::coxph, R:::survreg
- To account for confounding of the ER relationship, case matching (as proposed in [Yang et al., 2013]) is used to compare exposure within overlapping covariate distributions. Optimal matching based on propensity scores is used [Rosenbaum and Rubin, 1983, Stuart, 2010] via R:::MatchIt [Ho et al., 2007] with an emphasis placed upon assessment of balance as measured by standardized differences between comparator groups. Additional care is made to preserve the correlation structure by also assessing the pairwise interactions of covariates between comparator groups. Preference is given to propensity score methods due to their ability to easily deal with mixed variable types [Polhamus and French, 2015].
- To assess a more flexible range of functional forms for the ER relationship, to account for varied dosing history, and to simulate based on varied dosing history, a continuous time-exposure effect on hazard via the plasma compartment or an effect compartment. NONMEM 7.3
- Use model to simulate alternative dosing regimens for patients with low exposure. NONMEM 7.3, R:::mrgsim

Time and concentration varying hazard

$$h(t) = exp\left(\theta_0 + \sum_j \theta_j x_j + \text{DEFF}(t)\right) \text{ (exponential)}$$

$$\text{DEFF} = \begin{cases} \theta^{\text{Eff}} \text{AUC}_{SS} & \text{linear function of exposure} \\ \frac{\theta_1^{\text{Eff}} \text{AUC}_{SS}}{\theta_2^{\text{Eff}} + \text{AUC}_{SS}} & \text{Emax function of exposure} \\ \frac{\theta_1^{\text{Eff}} C(t)}{\theta_2^{\text{Eff}} + C(t)} & \text{Emax function of concentration} \end{cases}$$

Conclusion

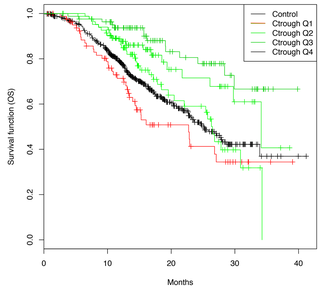
- ER in oncology is complicated by many factors, including limitations in estimation arising from the need to evaluate integrated hazard functions and with large molecule treatments, exposure confounding with key prognostic covariates.
- Models should be developed with both the goal of effect assessment and simulation for dose optimization
- Non-parametric representations of exposure help to assess the true shape with and without the presence of covariates but are limited with respect to simulation
- Causal inference approaches can greatly reduce dependence upon modeling assumptions for assessing exposure response
- We proposed one possible ER M&S framework that guards against model mispecification, provides a clear strategy for dose optimization if indicated, and gives a thorough analysis on which to address regulatory questions

References

Daniel Ho, Kosuke Imai, Gary King, and Elizabeth Stuart. Matchit: Nonparametric preprocessing for parametric causal inference. *Journal of Statistical Software*, 2007.
Daniel G Polhamus and Jonathan L French. Assessment of propensity score and mahalanobis distance matching in mixed outcome data. In *PAGE 24*, 2015.
Paul R. Rosenbaum and Donald B. Rubin. The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70(1):pp. 41–55, 1983. ISSN 00063444. URL http://www.jstor.org/stable/2335942.
Elizabeth A Stuart. Matching methods for causal inference: A review and a look forward. *Stat Sci*, 25(1):1–21, Feb 2010. doi: 10.1214/09-STS313.
Jun Yang, Hong Zhao, Christine Garnett, Atiqur Rahman, Jogarao V Gobburu, William Pierce, Genevieve Schechter, Jeffery Summers, Patricia Keegan, Brian Booth, and Yaning Wang. The combination of exposure-response and case-control analyses in regulatory decision making. *J Clin Pharmacol*, 53(2):160–6, Feb 2013. doi: 10.1177/0091270012445206.

Results:

ER assessment relating non-parametric exposure to the outcome using standard methodology (KM, CoxPH):



- ER (OS) indicated by Kaplan-Meier stratified by exposure quartile
- Low exposure appears to do underperform the control in absence of covariate correction
- A similar trend was seen in PFS

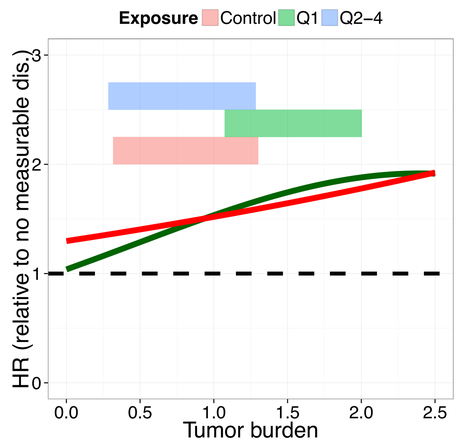
Variable	P-value
Tumor burden	< 0.005
Number of disease sites (>= 3)	< 0.005
SGOT/AST	< 0.005
Liver metastasis (1)	< 0.005
Measurable disease	< 0.005
Visceral disease (yes)	< 0.005
Imputed ECOG score (1)	< 0.005
Baseline HER2/NEU ECD (ng/mL)	< 0.005
Brain metastasis	< 0.005
Study region	0.079
Prior trastuzumab (yes)	0.098
Prior anthracycline (yes)	0.266
Age (years)	0.363
Bone metastasis	0.384
Sex	0.397
Race	0.823

- Univariate screening performed while adjusting for exposure quartile
- Covariates significant at $\alpha = 0.1$ are included in the *full* model

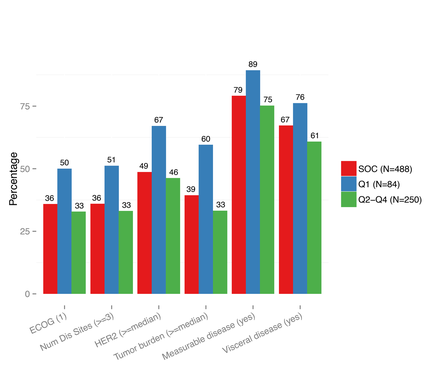
Covariate	HR	P-value	95% CI
Ctrough Q1	0.87	0.47	(0.6, 1.26)
Ctrough Q2	0.79	0.22	(0.54, 1.15)
Ctrough Q3	0.55	0.01	(0.34, 0.88)
Ctrough Q4	0.38	< 0.005	(0.22, 0.67)
Indicators for Measurable Disease (yes)	1.07	0.72	(0.73, 1.58)
Tumor burden	1.35	< 0.005	(1.21, 1.5)
Number of disease sites (>= 3)	1.53	< 0.005	(1.16, 2.02)
SGOT/AST	1.01	< 0.005	(1.01, 1.02)
Brain metastasis	1.74	< 0.005	(1.21, 2.51)
Region (W Europe)	0.85	0.33	(0.62, 1.18)
Region (Other)	1.32	0.06	(0.99, 1.77)

- Final model after stepwise backward elimination ($\alpha = 0.05$) from the full model
- Similar fits using linear and log-linear functions of exposure show residual trends (over/under prediction)
- Low exposure is no worse than control after adjusting for covariates, but are these adjustments made correctly over the range of exposures?

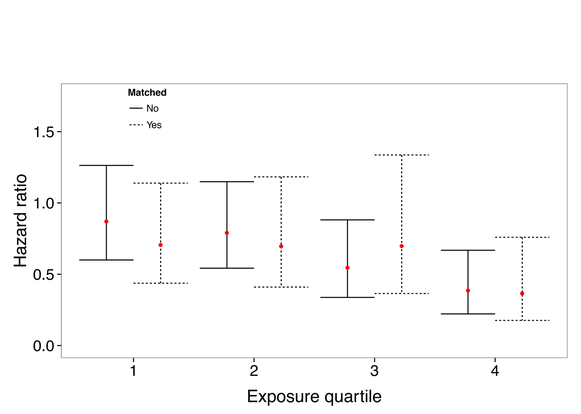
Addressing exposure confounding:



- Covariate correction makes strong assumptions about the covariate effect across the exposure range
- The red line is our covariate effect (linear in tumor burden) while the green line is the true effect (based on a smoothing spline)
- Lack of overlap between Q1 and the control, Q1 and Q2-4 is exaggerated here for demonstrative purposes

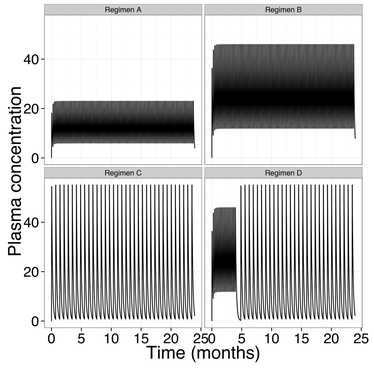


- Several key prognostic covariates are confounded with exposure
- Matching was performed on a large set of covariates determined by ER and clinical input. Three tiers were identified: 1) Likely confounders, stratification variables, and full model covariates; 2) Suspected confounders not identified in tier 1; and 3) not likely to be confounders. Balance criteria were set with the requirement that Tier 1 covariates must be balanced to accept the match, but matching on Tier 2 covariates was also prioritized. The final match balanced (all standardized differences < 0.2) on both Tier 1 and Tier 2 covariates.

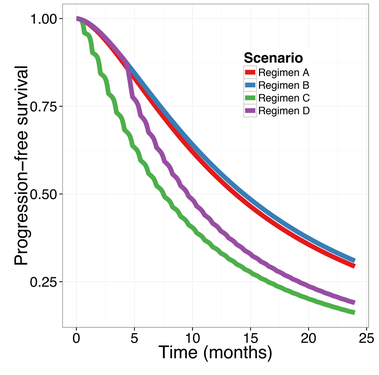


- To investigate the degree to which covariate adjustment addressed confounding, we can compare the hazard ratios from before and after matching to like control patients
- Each quartile is independently matched to the control, and the final CoxPH model is used to assess HR (i.e., the HR estimate is "doubly robust").

Simulating expected survival at different doses:



- To investigate the effect on PFS of modifying the dose for the low exposure patients, different dosing regimens comparing both different doses and different dosing schedules were simulated



- A log-logistic baseline hazard with an Emax function of plasma drug concentration was chosen to describe the exposure response relationship
- Both the baseline hazard and the EC50 were covariate driven using a similar process as outlined for the CoxPH modeling