TCP Transl Clin Pharmacol
2016;24(4):189-193
http://dx.doi.org/10.12793/tcp.2016.24.4.189

An imputation-based method to reduce bias in model parameter estimates due to non-random censoring in oncology trials

Dongwoo Chae[1,2] and Kyungsoo Park[1]*

[1]Department of Pharmacology, Yonsei University College of Medicine, Seoul 03722, Korea, [2]Brain Korea 21 Plus Project for Medical Science, Yonsei University, Seoul 03722, Korea

*Correspondence: K. S. Park; Tel: +82-2-2228-1735, Fax: +82-2-313-1894, E-mail: kspark@yuhs.ac

ORIGINAL ARTICLE

Received 3 Oct 2016
Revised 29 Nov 2016
Accepted 30 Nov 2016

Keywords
Tumor size model,
Non-random censoring,
Oncology trials,
Biased parameter estimates

pISSN: 2289-0882
eISSN: 2383-5427

In oncology trials, patients are withdrawn from study at the time when progressive disease (PD) is diagnosed, which is defined as 20% increase of tumor size from the minimum. Such informative censoring can lead to biased parameter estimates when nonlinear mixed effects models are fitted using NONMEM. In this work, we investigated how empirical Bayes estimates (EBE) could be exploited to impute missing tumor size observations and partially correct biases in the parameter estimates. 50 simulated datasets, each consisting of 100 patients, were generated based on the published model. From the simulated dataset, censoring due to PD diagnosis has been implemented. Using the post-hoc EBEs acquired from fitting the censored datasets using NONMEM, imputed values were generated from the tumor size model. Model fitting was carried out using censored and imputed datasets. Parameter estimates using both datasets were compared with true values. Tumor growth rate and cell kill rate were approximately 28% and 16% underestimated when fitted using the censored dataset, respectively. With the imputed datasets, relative biases of tumor growth rate and cell kill rate decreased to about 6% and 0%, respectively. Our work demonstrates that using EBEs acquired from fitting the model to the censored dataset and imputing the unknown tumor size observations with individual predictions beyond the PD time point is a viable option to solve the bias associated with structural parameter estimates. This approach, however, would not be helpful in getting better estimates of variance parameters.

Introduction

In solid tumors, there is recently growing interest in more precisely modeling tumor size to better assess drug efficacy and resistance development. Tumor size is usually expressed as the sum of the longest diameter (SLD), acquired as part of Response Evaluation Criteria in Solid Tumors (RECIST)[1] evaluation. Although changes in the size of measurable lesions often fail to correlate with clinical outcome, they nevertheless constitute the current standard of treatment assessment. In the field of pharmacometrics, there are several published tumor size models for different cancer types, including colorectal cancer and nonsmall cell lung cancer.[2] These models use SLD as a continuous scale measure, to describe the time course of tumor response in relation to drug exposure. Such endeavors began with the criticisms of the traditional approach of classifying tumor responses into four categories – namely, complete response, partial response, stable disease, and progressive disease (PD) – since such an approach results in the loss of information, posing an obvious limit to what can be possibly learnt.[3]

However, fitting tumor size observations acquired from RECIST evaluation all suffer from problems related to non-random censoring. In oncology trials, patients are withdrawn from study at the time of PD diagnosis. Based on RECIST version 1.1, target lesion PD is diagnosed when tumor size increases by more than 20% relative to the minimum size. Hence, patients who are diagnosed with PD early in the trial are under-represented in terms of tumor size observations. Regarding such non-random censoring, Bjornsson et al. (2015)[4] reported the effect of informative dropout on parameter estimation in nonlinear mixed

effects models and found that failure to account for dropout in the analysis resulted in bias of up to 21% in parameter estimates. Recently, a method using NONMEM's capability of estimating empirical Bayes estimates (EBEs) has been suggested for imputation of missing covariates.[5] The method used a four-step multiple imputation, carried out by (1) estimation of model parameters and EBEs using a basic model without missing covariates, (2) creation of a regression model for the covariate values given the EBEs from subjects with covariate information, (3) imputation of missing covariates using the regression model, and (4) re-estimation of model parameters using a basic model with imputed covariates.

With this background, this work aimed to extend the aforementioned method to investigating how EBEs could be exploited to impute missing tumor size observations. We sought to assess the magnitude of bias that results from ignoring informative censoring and test how the use of EBEs of individual parameters to impute for missing values can partially correct for such biases.

Methods

Simulation model

The tumor growth model considered for simulation was the published model by Claret et al [6] below.

$$\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D(t) \cdot \text{Exposure}(t) \cdot y(t) \quad (1)$$

$$K_D(t) = K_{D,0} \cdot e^{-\lambda t} \quad (2)$$

$$y(0) = y_0 \quad (3)$$

In the above, y(t) is the tumor size at time t, y_0 is the baseline tumor size, K_L is the tumor growth rate, $K_D(t)$ is the drug-constant cell kill rate that decreases exponentially with time (according to λ) from an initial value of $K_{D,0}$ to account for the progressive development of resistance. Exposure(t) is the drug exposure at time t. For Exposure(t), since no drug concentration or dose information was available in the original work by Claret et al, using the prior knowledge that the usual amount of capecitabine, a drug used in the original work, is 1,000 mg/m^2/day and the mean BSA is about 2 m^2, it was initially assumed as 2 g/day and then finally chosen to be 1 g/day for simplicity. For y_0, based on the median value of 71 mm reported in the original work, an exponential distribution with a mean value of 50 (mm) was used.

However, using an exponential growth model above led to excessively large tumor sizes during simulations, so a logistic growth restriction was imposed as below.

$$\frac{dy(t)}{dt} = (K_L y(t) - K_D(t) \cdot \text{Exposure}(t) \cdot y(t)) \cdot (1 - \frac{y(t)}{1000}) \quad (4)$$

In the above, 1000 is the theoretical maximum tumor size (or called carrying capacity) (mm), which was chosen based on the empirical evidence that the observed maximum tumor size was reported as 100 ~ 300 mm in previous studies[6-7] and 500 mm in ToGA study recently conducted, implying that carrying capacity could be larger than 500 mm. The approach of fixing the maximum tumor size in logistic growth model has been used by other research groups, one of which is Ribba et al.[7]

The inter-individual variance (IIV) was modeled as

$$P = TVP \cdot \exp(SD \cdot \eta) \quad (5)$$

$$CV(P) = SD \quad (6)$$

P and TVP denote individual and typical or population estimates of K_L, K_D,0 and λ, respectively, SD denotes the scale parameter for inter-individual error η assumed to follow the standard normal distribution, and CV denotes coefficient of variation. For residual variance, unlike the original article, a proportional error model was used so that negative tumor sizes do not result during simulations.

Then, with the model chosen as above, 50 simulated datasets, each consisting of 100 patients, were generated, with tumor size measurements being simulated at 0 (baseline) and every 3 weeks thereafter up to 51 weeks from the initiation of treatment. The final parameter estimates reported in the original work, as shown in Table 1, were used for the simulations, except for residual variance which was assumed to be 10% (CV).

Generating censored datasets

From each simulated dataset, censoring due to 20% increase of tumor size from the minimum has been implemented as follows:

Step 1. Acquire minimum tumor size y_{min} from each patient. Denote the time at which y_{min} is attained as t_{min}.
Step 2. Find the minimum t satisfying $y(t) \geq 1.2y_{min}$ for $t > t_{min}$ and denote it as t_{PD}.
Step 3. Discard y(t) for $t > t_{PD}$

Table 1. Estimate (%RSE) of tumor growth model parameters reported in the original publication

Parameter	Estimate (%RSE)
Structural parameters	
Tumor growth rate, K_L /week	0.015 (25.4)
Cell kill rate, K_D /g week	0.058 (17.0)
Resistance appearance, λ/week	0.042 (28.7)
Variance parameters	
IIV (variance) of K_L	0.556 (27.8)
IIV (variance) of K_D	0.540 (43.7)
IIV (variance) of λ	0.450 (55.5)
Sigma, mm	14.9

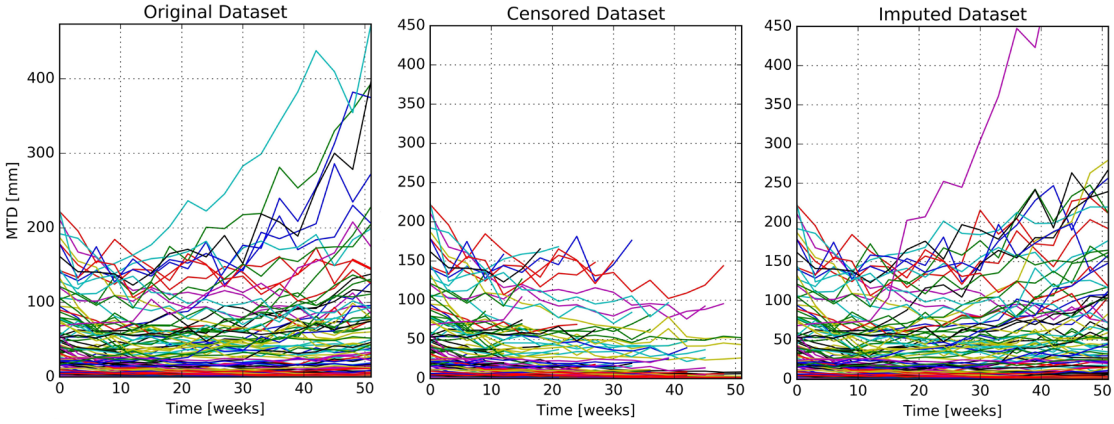

Figure 1. Comparison plots of tumor size observations of original (LEFT), censored (CENTER), and imputed (RIGHT) datasets.

Using the above procedure, 50 censored datasets were generated from 50 simulated datasets. Then, model fitting using these censored datasets has been carried out.

Generating imputed datasets

The post-hoc EBEs acquired from fitting the tumor size model to censored datasets were used to predict the values to be imputed for censored tumor sizes. The resultant dataset would be a mixture of the original observations and imputed observations before and beyond the PD time point, respectively. That is, observation($t \leq t_{PD}$) = DV(t), observation($t > t_{PD}$) = IPRED(t), where DV(t) and IPRED(t) denote true tumor sizes and individual predicted tumor sizes using EBEs, respectively.

Figure 1 compares the original dataset with censored and imputed datasets. Model fitting using the imputed dataset was then carried out.

Bias assessment of population parameter estimates

Relative bias of the population parameter estimates from the censored and imputed datasets was calculated as follows:

$$\text{Bias of population parameter estimate} = \frac{TVP - \widehat{TVP}}{TVP} \times 100\ (\%) \quad (7)$$

(TVP: true population parameter value used in simulation, $\widehat{TVP}$: estimated population parameter value using the censored or imputed dataset)

The mean bias was then calculated from 50 relative bias estimates. It was then seen whether the estimates from the imputed dataset resulted in reduced biases.

Bias assessment of individual parameter estimates

To assess the bias of individual parameter estimates or EBEs, the individual differences of ETAs acquired from fitting the model to the true and imputed datasets were calculated. Then, the mean difference was calculated for each dataset. Finally, the grand mean difference was calculated for entire datasets. Mathematically,

$$\Delta ETA_{ij} = ETA_{ij}(\text{true}) - ETA_{ij}(\text{imputed}) \quad (8)$$
$$\Delta META_{j} = \text{Mean}(\Delta ETA_{ij}) \quad (9)$$
$$\Delta GMETA = \text{Mean}(\Delta META_{j}) \quad (10)$$

ΔETA_{ij}, $\Delta META_j$ and $\Delta GMETA$ represent the individual differences of ETAs of individual i for dataset j, the mean difference of ETAs for dataset j, and the grand mean difference of ETAs for the entire datasets, respectively.

Software

Parameter estimations were done using NONMEM 7.3 and simulations were performed using Python 2.7.

RESULTS

Table 2 shows the population parameter estimates acquired from fitting the model to original, censored, and imputed datasets and relative biases of the population parameter estimates obtained from fitting the model to the censored and imputed datasets. Tumor growth rate and cell kill rate were underestimated when fitted from censored datasets. Fitting from imputed datasets resulted in tumor growth rate and cell kill rate estimates that were closer to those fitted from the original datasets. For true parameter values used to calculate the bias, parameters estimates obtained from fitting the model to the original dataset reported in Table 2 were used. Tumor growth rate and cell kill rate were approximately 28% and 16% underestimated when fitted using the censored dataset, respectively. When imputed dataset was used for refitting, relative biases of tumor growth rate and cell kill rate decreased to about 6% and 0%, respectively. The estimate of resistance appearance was not particularly biased in the censored dataset, and the relative bias of the estimates using the imputed dataset was similar. The relative biases of the IIV of tumor growth rate and cell kill rate were reduced when imputed dataset was used, but standard error of the former was relatively

Table 2. Estimate (%RSE) and relative bias (%RSE) of tumor growth model parameters obtained from fitting the model to the original, censored and imputed datasets

Parameter	Original Dataset	Censored Dataset	Imputed Dataset
Structural parameters			
Tumor growth rate, K_L /week			
Estimate (%RSE)	0.015 (17.43)	0.011 (35.79)	0.014 (41.21)
Relative Bias (%RSE)	-	28.17 (21.73)	6.06 (35.07)
Cell kill rate, K_D /g week			
Estimate (%RSE)	0.056 (8.85)	0.047 (13.58)	0.056 (16.47)
Relative Bias (%RSE)	-	15.71 (8.62)	0.098 (14.00)
Resistance appearance, λ/week			
Estimate (%RSE)	0.042 (13.86)	0.041 (15.90)	0.044 (17.77)
Relative Bias (%RSE)	-	3.12 (9.27)	-3.38 (14.99)
Variance parameters			
IIV (variance) of K_L			
Estimate (%RSE)	0.52 (35.54)	0.26 (187.3)	0.77 (185.05)
Relative Bias (%RSE)	-	58.17 (49.27)	-29.77 (124.68)
IIV (variance) of K_D			
Estimate (%RSE)	0.62 (17.14)	0.85 (27.82)	0.69 (32.72)
Relative Bias (%RSE)	-	-37.81 (27.72)	-11.66 (28.47)
IIV (variance) of λ			
Estimate (%RSE)	0.40 (27.91)	0.41 (28.96)	0.54 (35.44)
Relative Bias (%RSE)	-	-1.75 (13.12)	-37.99 (47.22)
Sigma (variance)			
Estimate (%RSE)	0.0096 (5.83)	0.01 (8.51)	0.012 (11.76)
Relative Bias (%RSE)	-	-3.61 (3.67)	-19.55 (12.78)

high. On the other hand, relative biases of the IIV of resistance appearance and residual error have increased when imputed dataset was used.

When assessing the bias of individual parameter estimates, Δ*GMETA* was 0.0003, -0.0078 and -0.022 for K_L, K_D and λ, respectively, with none of them being significantly different from 0. On the other hand, the mean ETA shrinkage (%) was 69.02, 13.53 and 27.53 for K_L, K_D and λ, respectively.

Discussion

In this report, we have exploited NONMEM's capability to generate post-hoc EBEs of the individual parameters to impute missing values. This idea is based on the fact that although fixed effect parameters (THETAs in NONMEM terminology) are biased when estimated from the censored datasets, post-hoc EBEs might be unbiased, enabling the imputed datasets to produce the unbiased estimates of population and individual parameters.

This indeed seems to be the case (see Table 2). The biases of the structural parameter estimates obtained from the imputed datasets were significantly reduced compared to those estimated from the censored datasets. This approach, however, does not reduce the biases of the variance estimates. For individual parameter estimates, Δ*GMETA* was close to zero, not significantly different from 0 for any of the 3 parameters. The results indicate that the mixed-effect modeling approach used in NONMEM generated unbiased estimates of EBEs. Except for tumor growth rate (K_L) associated with the mean ETA shrinkage of 69.02%, cell kill rate (K_D) and resistance development (λ) were within an acceptable range of the mean ETA shrinkage, supporting the validity of the above assertion.

Our work demonstrates that using EBEs acquired from fitting the model to the censored dataset and imputing the unknown tumor size observations with individual predictions beyond the PD time point is a viable option to solve the bias associated with structural parameter estimates. This approach, however, would not be helpful in getting better estimates of variance parameters.

Further studies would be needed to validate the usefulness of our approach by repeating similar analyses across models of varying complexity and variance structures. The effect of the

type and the magnitude of measurement errors associated with the observations should also be investigated further. Although not tried in this work, other methods for accounting for non-random censoring including M3, jointly modeling tumor size and censored probability and pattern mixture methods are found elsewhere,[8] which might be worth trying and comparing with the proposed method.

Acknowledgements

This study was supported by the Brain Korea 21 Plus Project for Medical Science, Yonsei University

Conflict of interest

The author declared no conflict of interest.

References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247. doi: 10.1016/j.ejca.2008.10.026.
2. Ribba B, Holford NH, Magni P, Trocóniz I, Gueorguieva I, Girard P, et al., A review of mixed-effects models of tumor growth and effects of anticancer drug treatment used in population analysis. CPT Pharmacometrics Syst Pharmacol 2014;3:e113. doi: 10.1038/psp.2014.12.
3. Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, et al., A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. Clin Cancer Res 2008;14:4213-4218.
4. Bjornsson MA, Friberg LE, Simonsson US. Performance of nonlinear mixed effects models in the presence of informative dropout. AAPS J 2015;17:245-255. doi: 10.1208/s12248-014-9700-x.
5. Johansson AM, Karlsson MO. Multiple imputation of missing covariates in NONMEM and evaluation of the method's sensitivity to eta-shrinkage. AAPS J 2013;15:1035-1042. doi: 10.1208/s12248-013-9508-0.
6. Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, et al. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. J Clin Oncol 2009;27:4103-4108. doi: 10.1200/JCO.2008.21.0807.
7. Ribba B, Kaloshi G, Peyre M, Ricard D, Calvez V, Tod M, et al. A tumor growth inhibition model for low-grade glioma treated with chemotherapy or radiotherapy. Clin Cancer Res 2012;18:5071-5080.
8. Martin EC, Aarons L, Yates JW. Accounting for dropout in xenografted tumour efficacy studies: integrated endpoint analysis, reduced bias and better use of animals. Cancer Chemother Pharmacol 2016;78:131-141. doi: 10.1007/s00280-016-3059-x.