Development of User-friendly Bayesian Predictive Platform for Blood Boron-10 Pharmacokinetics following Intravenous Infusion of [^{10}B] L-4-BORONOPHENYALANINE

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Introduction/Objectives

- Boron neutron capture therapy (BNCT) allows high-precision radiotherapy against tumor using boron-10 (^{10}B) with tumor-localizing characteristics and strong tendency to capture thermal neutrons.
- It is important to accurately predict the blood ^{10}B concentration during the neutron irradiation to deliver the prescribed dose as planned.
- This study was performed to develop user-friendly Bayesian predictive platform for pharmacokinetics (PK) of ^{10}B which is clinically applicable in BNCT.

Methods

- Population PK model for ^{10}B was constructed using blood ^{10}B concentration over time data following intravenous infusion of boronophenylalanine (BPA) which were digitized from previous study results, which was used as a prior distribution model for the Bayesian prediction.
- The predictive model was implemented in NONMEM® 7.4 (ICON Development Solutions, USA), and NONMEM was executed using R (version 4.03) with user-friendly interface provided by Shiny package.
- Simulation and sensitivity analyses were conducted to evaluate the predictive performance of the platform and identify optimal PK sampling time for blood ^{10}B.

Results (PK model)

- Elimination rate constant from central compartment value (k_{10}) was estimated as 0.006(1/min). Volume of distribution of central compartment(V_1) was estimated as 0.252(L).

Conclusion

- This predicted platform has the potential to play a crucial role in clinical trials aiming at evaluating the effect of BNCT, as it assess the treatment effect in a user-friendly and reliable way. By enabling a more precise prediction of the therapeutic effect, the platform can help clinicians tailor treatment plans to individual patients, ultimately improving the overall quality of care in BNCT.

References

[1] Palmer, M. R., Goorley, J. T., Kiger, W. S., Busse, P. M., Riley, K. J., Harling, O. K., & Zamenhof, R. G. (2002). Treatment planning and dosimetry for the Harvard-MIT Phase I clinical trial of cranial neutron capture therapy. International Journal of Radiation Oncology*Biology*Physics, 53(5), 1361–1379.

[2] Chanana, Capala, Chadha, et al. Boron neutron capture therapy for glioblastoma multiforme: interim

results from the phase I/II dose-escalation studies. Neurosurgery. 1999;44(6):1182-1192; discussion

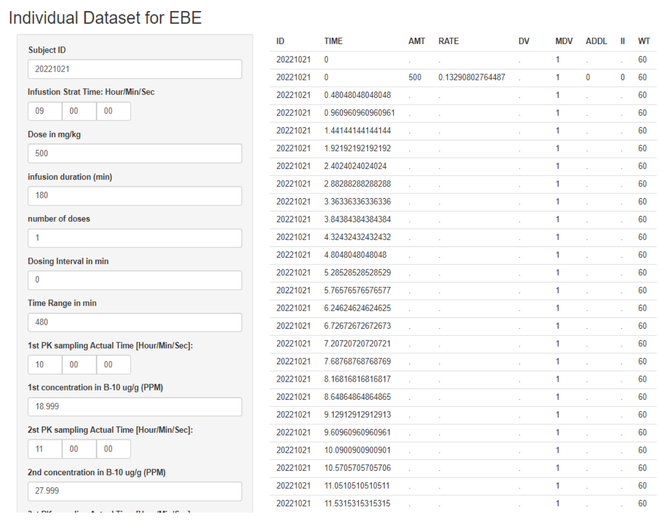
1192-3.

Data processing

R shiny

Import PK Dataset

- Making NONMEM dataset using R shiny
- Input patient's specific information (total dose, rate and also boron concentration acquired from blood samples for its estimation during irradiation)



ID	TIME	AMT	RATE	DV	MDV	ADDL	II	WT
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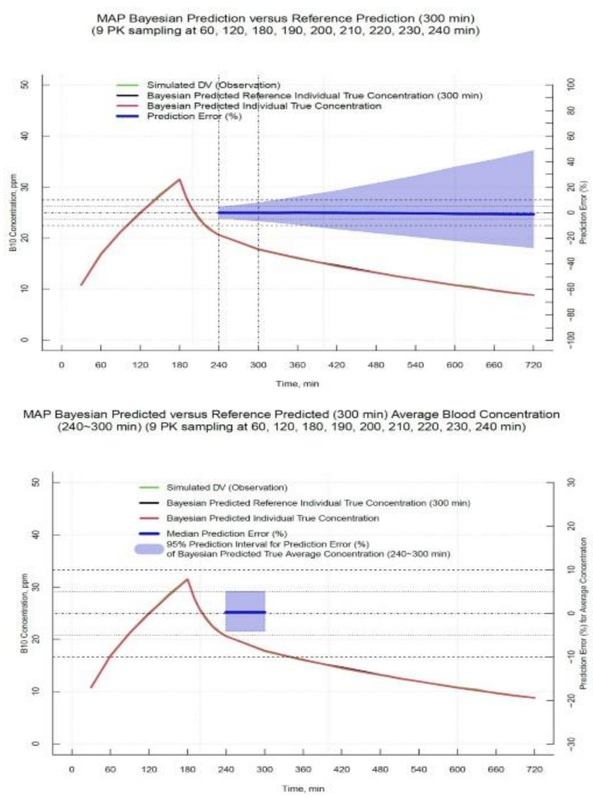
20221021	0	500	0.13290802764487	.	1	0	0	60
20221021	0.480480480480	.	.	.	1	.	.	60
20221021	0.960960960961	.	.	.	1	.	.	60
20221021	1.441441441441	.	.	.	1	.	.	60
20221021	1.92192192192192	.	.	.	1	.	.	60
20221021	2.4024024024024	.	.	.	1	.	.	60
20221021	2.88288288288288	.	.	.	1	.	.	60
20221021	3.36336336336336	.	.	.	1	.	.	60
20221021	3.84384384384384	.	.	.	1	.	.	60
20221021	4.32432432432432	.	.	.	1	.	.	60
20221021	4.8048048048048	.	.	.	1	.	.	60
20221021	5.28528528528529	.	.	.	1	.	.	60
20221021	5.76576576576577	.	.	.	1	.	.	60
20221021	6.24624624624625	.	.	.	1	.	.	60
20221021	6.72672672672673	.	.	.	1	.	.	60
20221021	7.20720720720721	.	.	.	1	.	.	60
20221021	7.68768768768769	.	.	.	1	.	.	60
20221021	8.16816816816817	.	.	.	1	.	.	60
20221021	8.64864864864865	.	.	.	1	.	.	60
20221021	9.12912912912913	.	.	.	1	.	.	60
20221021	9.60960960960961	.	.	.	1	.	.	60
20221021	10.0900900900901	.	.	.	1	.	.	60
20221021	10.5705705705706	.	.	.	1	.	.	60
20221021	11.0510510510511	.	.	.	1	.	.	60
20221021	11.5315315315315	.	.	.	1	.	.	60

Bayesian Estimation

NONMEM

Bayesian Estimation

- Using previous built population PK model for BPA and using patient's blood BPA concentration dataset.
- Bayesian prediction comparison between full dataset (irradiation vs Pre-Irradiation set)
- Figure show real time estimation accuracy and its error.



Output

LATEX

Configure the Draft Report in an Editable Format(PDF)

- Numerical values reported in the main text are automatically updated according to the various input datasets.
- Figure and table captions are automatically generated.

Finalize the Report

- The final report is completed with minimal edits