Revealing Association between Kinases and Adverse Events for Small-Molecule Tyrosine Kinase Inhibitors using Machine Learning Method

Xiajing (Jean) Gong[1,3], Meng Hu[1], Jinzhong Liu[2], Liang Zhao[1]

[1]Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, CDER, FDA
[2]Division of Oncology Products I, Office of Hematology and Oncology Products, Office of New Drugs, CDER, FDA
[3]ORISE Fellow, Oak Ridge Institute for Science and Education

CONTACT INFORMATION:
Liang.Zhao@fda.hhs.gov; Xiajing.Gong@fda.hhs.gov

INTRODUCTION

- Small molecule tyrosine kinase inhibitors (TKIs) have revolutionized anticancer treatment and can turned rapidly life-threatening illnesses into chronic diseases. Therefore, they are being approved at a fast pace under expedited programs, without sufficiently optimizing dosing and dosing regimen. It has been reported that the rate of dose discontinuation and/or dose reduction of these TKIs can be as high as 80% in the oncology setting [1]. Most of the adverse events (AEs) leading to these dose modifications are related to either on-target or off-target kinase inhibition.
- Although kinase-specific AEs have been described in the clinical setting, there are no published work to systemically model relationship between AEs and kinase targets, as well as to predict AEs caused by on-target and/or off-target effects of TKIs.
- Using data of previously-approved TKIs, a successful model will establish a landscape of association between AEs and kinases, and provide prediction of the safety signals for a new TKI treatment. This effort can potentially be used to guide dose selection and clinical trial design for new TKI applications..

OBJECTIVES

By leveraging an integrated comprehensive dataset of approved TKIs, we developed a novel approach of combining machine learning and pharmacometric modeling to prospectively identify kinase-specific safety signals.

METHODS

➢ Construct comprehensive dataset

- Eight US FDA-approved kinase inhibitors (KIs) covering various kinase targets was included in this study.
- Clinical Information
  - Pharmacokinetics (PK) data, safety data and demographic information were obtained from clinical trials used to support marketing approval.
- Non-clinical Information
  - Selectivity and inhibitory potency of the approved TKIs against hundreds of kinase targets from published literatures.

➢ Exposure of TKI **Mechanism-based**

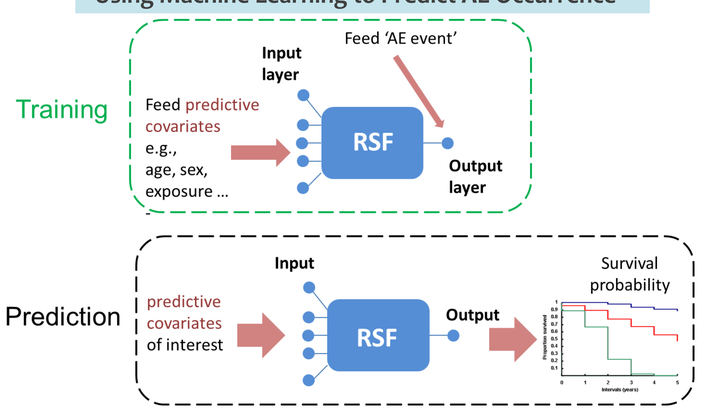
· Population PK model for each TKI was conducted in NONMEM to obtain steady-state plasma concentration (C_{ave}) for each patient.

METHODS

➢ Kinase-related AE prediction **Data-driven**

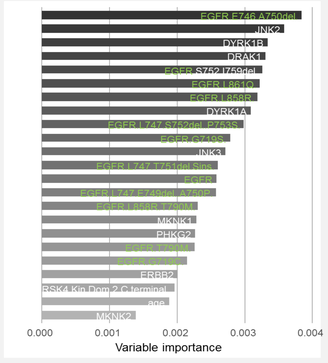
- Comprehensive dataset was integrated by linking individual-level TKI induced AE and kinase target through a proxy variable derived from Cave.
- Considering the large dimensionality and potential nonlinear relationship between covariates in data, a data-driven analysis approach is desirable for identifying the association between kinases and AEs.
- With the time-to-event outcome, safety data are typically investigated by survival analysis. Given the promising results of machine learning (ML) based method simulation study [2], random survival forest (RSF) [3] was applied for AE prediction using R.

Using Machine Learning to Predict AE Occurrence



RESULTS

➢ Identification of kinase-AE association



Example of top covariates contributing to **diarrhea** occurrence, identified by VIMP ranking using RSF

Significant association between kinase and AE identified by the proposed approach

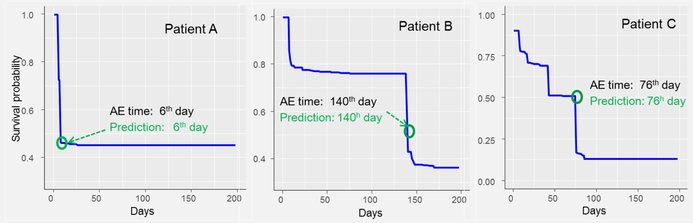
AE	Kinase*
diarrhea	EGFR
hypertension	FLT, VEGFR2
conjunctivitis	EGFR
proteinuria	FLT, VEGFR
...	

*EGFR, epidermal growth factor receptor; FLT, fms-like tyrosine kinase; VEGFR, vascular endothelial growth factor receptor.

The association can be confirmed by well-established kinase-AE association summarized from clinical practices [4], as well as being consistent with previous analysis using association scores [5].

➢ Prediction of AE occurrence

Patient-level AE prediction



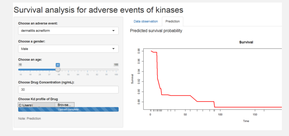
Example of AE occurrence prediction for individual patient A, B and C. Exact AE time prediction is based on setting threshold P(survival) =0.5

Prediction performance

AE (number of events)	C-index (mean ± SD)
Diarrhea (n=323)	0.69 ± 0.01
Hypertension (n=88)	0.78 ± 0.01
Conjunctive (n=25)	0.59 ± 0.02
Proteinuria (n=22)	0.74 ± 0.03

Prediction performance for patient population data was evaluated using C-index (concordance index) as the metric.

➢ AE Prediction Shiny App



A Shiny App is developed for users to import their own data, make AE predictions, and visualize prediction results.

CONCLUSION(S)

The proposed combined method of machine learning and pharmacometric modelling can be a powerful tool to identify association between kinases and AEs, which can inform individual-level AE management and novel TKI development.

REFERENCES

1. Prasad, V., et al. Oral Anticancer Drugs: How Limited Dosing Options and Dose Reductions May Affect Outcomes in Comparative Trials and Efficacy in Patients. J Clin Oncol. 32:1620-1629 (2014)
2. Gong, X., et al. Big Data Toolsets to Pharmacometrics: Application of Machine Learning for Time-to-Event Analysis. Clin. Trans. Sci. 00:1-7 (2018)
3. Ishwaran, H., et al. Random Survival Forests. Ann. Appl. Stat. 841-860 (2008).
4. Dy, G., et al. Understanding, Recognizing, and Managing Toxicities of Targeted Anticancer Therapies. CA Cancer J. Clin. 63:249-279 (2013)
5. J. Liu, et al. Combined Population PK Modeling and Disproportionality Analyses to Assess the Association between Kinase Inhibition and Adverse Reactions. ASCPT, March 8, 2016, San Diego, CA.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Geoffrey Kim, Dr. James Xu, Dr. Amy McKee, Dr. Todd Palmby and Dr. Angelo DeClaro from the Office of Hematology and Oncology Products, Office of New Drugs, CDER, FDA, and Dr. Luning Zhuang from the Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDA for their valuable contributions to the project. This work was supported in part by FDA Critical Path Initiative. Dr. Gong was supported by an appointment to the ORISE Research Participation Program at CDER. This poster presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.