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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Swedish Cancer Society
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_lf.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_mk.pdf
https://yoda.yale.edu/system/files/coi_ei.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01722487 - PCYC-1115-CA - Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
2. NCT01105247 - PCYC-1102-CA - A Phase 1b/2 Fixed-dose Study of Bruton's Tyrosine Kinase (Btk)

Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Pharmacometric models on lymphocyte dynamics, lymph node size and blood pressure linked to survival in CLL patients treated with ibrutinib

Narrative Summary:

Chronic lymphocytic leukemia (CLL) a is the most common form of leukemia and for which ibrutinib is an efficient treatment. By application of pharmacometric analysis methods the relationship between dose and response over time for several disease-related variables such as lymphocyte count and lymph node size can be described. The changes in these variables can subsequently be evaluated as predictors of disease progression and survival. Moreover, increased blood pressure is a side-effect of ibrutinib that can be characterized and evaluated as a predictor for drug effect. Both the typical changes in a population and the variability between patients can be described in this type of analysis.

Scientific Abstract:

Background. The phase 1b–2 and 3 (RESONATE-2) studies of ibrutinib include longitudinal data lymphocyte dynamics, lymph node size, blood pressure and survival in CLL patients [5,6].
Objective. Development of an integrated pharmacometric modeling framework to characterize and quantify the relationships between drug exposure, Btk occupancy, lymph node size, lymphocyte dynamics and hypertension and identify functions and predictors related to progression and survival.
Study Design; Based on individual-level data, models will be built using non-linear mixed effects modeling. The submodels describing the effect of ibrutinib treatment on Btk occupancy, lymph node size, lymphocyte dynamics, hypertension and other measured biomarkers of interest (e.g. blood cell count) will subsequently be connected. The inter-individual variability will be quantified and covariates will be explored. Finally, the variables will be evaluated as predictors of progression free and/or overall survival through parametric time-to-event models.
Participants; The CLL patients included in phase 1b–2 and 3 (RESONATE-2) studies. Simulations may be performed to explore the established relationships.
Main Outcome Measure(s): Progression-free and overall survival will be the ultimate outcome in a joint analysis evaluating measures of drug response as predictors.
Statistical analysis: Both typical parameters and between-patient variability will be estimated for each variable. Standard procedures for population analyses will be used in model development and evaluation.

Brief Project Background and Statement of Project Significance:

Chronic lymphocytic leukaemia (CLL) is a slow-growing leukaemia that affects developing B-lymphocytes, and is the most common form of leukemia in the Western world [1]. The median age of diagnosis in the USA, Europe and Australia is approximately 70 years of age1. The disease is highly heterogeneous among the patients. In addition, advances have been made in understanding the biology of CLL which led to the identification of targets like Bruton tyrosine kinase (Btk) [2]. Accordingly, ibrutinib was approved as a first-in-class oral irreversible inhibitor of Btk for treatment of relapsed and refractory CLL2.
In phase 1b–2 and 3 (RESONATE-2) studies of Ibrutinib5,6, the observed lymphocyte dynamics were heterogeneous among CLL patients. In the final analysis of the phase 1b–2 study, patients with lymphocytosis were associated with longer progression free survival than patients without lymphocytosis [3]. In addition, hypertension was observed with rates that increase with time3. Another analysis performed on a separate dataset suggested that ibrutinib results in an increase in the incidence and severity of hypertension and that hypertension development could lead to an increased risk of cardiotoxic events [7]. Thus, a characterization of variability observed in the treatment-related lymphocytosis would be of value to identify predictors of lymphocytosis, the

relationship to progression and survival, as well as any connection to hypertension.
Pharmacometrics is an interdisciplinary science that facilitates translation of complex biologic processes and conveys them in a quantitative manner [4]. This can be done using a set of both differential and algebraic equations that are capable of describing the physiological and pharmacological processes' time course based on longitudinal data measured in the preclinical and clinical studies as well as information obtained from scientific literature. The benefits of applying pharmacometrics in the field of oncology have been demonstrated over the last years in characterizing the pharmacodynamics of different cancer therapies and their relationship to patients' survival [8,9]. Pharmacometric models could increase the information gained from the different measured biomarkers through characterizing quantitatively the relationship between drug exposure, treatment efficacy, toxicity biomarkers and survival. Moreover, the characteristics explaining differences between patients in drug exposures, efficacies, toxicities and survival could be identified through covariate model building. An established relationship can subsequently be used to use changes in biomarker (e.g. lymphocyte) time-course to predict outcomes and evaluated under different scenarios through simulations.
A better understanding of biomarker dynamics using such pharmacometric models may offer an opportunity for a more precise individualization of ibrutinib therapy after treatment initiation. The developed model framework could provide a balance between clinical outcome and side effects to optimize adherence to therapy.

Specific Aims of the Project:

To build a pharmacometric modelling framework that
• Describes quantitatively the time-courses of changes in the lymph node size and the lymphocyte dynamics in order to investigate factors contributing to the extent and duration of lymphocytosis and the relationships to disease progression. Predicted drug exposure and Btk occupancy may drive the dynamic changes.
• Characterizes the change in the systolic and diastolic blood pressure over time in order to investigate predictors of hypertension for improved management of this side-effect.
• Describes any relationship between the changes in blood pressure and clinical outcomes.
• Quantifies the inter-individual variability in addition to residual unexplained variabilities.
• Defines any significant demographic or measured variables for their predictive value on survival.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project
Research on clinical prediction or risk prediction
Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data sources will be IPD data from the requested clinical trials. All studied CLL patients in those trials will be included, i.e. the inclusion/exclusion criteria will be the same and the patient sample will be the same.

Main Outcome Measure and how it will be categorized/defined for your study:

Main outcome measures are progression free survival and overall survival. The definition of progression free survival and survival will be the same as in the original analyses/publications.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

• The time-course and relative changes in the lymph node size. SPD, sum of the product of perpendicular diameters of lymph nodes.
• The Btk bound by ibrutinib for the time points available. Btk occupancy (%)
• The time-course and relative changes in lymphocyte number. Absolute lymphocyte count (ALC).
• Ibrutinib drug concentrations [unless exposure measures are already available in the dataset (individual clearance, area under the curve (AUC) or steady state ibrutinib concentration)]
• Blood pressure measurements. Diastolic and systolic blood pressure.

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Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

The following variables will be explored as covariates in the analysis:
• Demographics: sex, age and weight.
• Lab values: hemoglobin, absolute neutrophil count, platelets, lactate dehydrogenase, albumin, total proteins and ?2-macroglobulin.
• Treatment-related: Prior treatment for CLL, any concomitant treatment expected to be active against CLL, antihypertensive drug use (time-varying where available)
• History of diabetes or cardiac disease (binary)
• Abnormality existence (ie. no, del(17p), del(11q), del(13q) or trisomy 12)
• CYP status
• Fed status (time-varying, if available)
• Disease related: RAI stage (categorical), ECOG performance score (categorical), FACIT-fatigue score (continuous)
All variables will be defined as in the original database. If there are few patients within a category, that category may be merged with another category.

Statistical Analysis Plan:

This work will be conducted in the Uppsala pharmacometrics group by applying pharmacometric analysis methods to describe the time-courses of SPD, ALC and blood pressures,
1. A dataset suitable for non-linear mixed effects modelling will be prepared.
2. A graphical analysis will be performed that will guide model building
3. The population pharmacokinetic (PK) model developed by Marostica et al will be applied to derive individual estimates of clearance, AUC and/or Css (unless available in the dataset provided).
4. The Btk occupancy model previously published by Jan et al will be applied to derive the predicted time course of Btk occupancy.
5. A model describing the lymphocyte dynamics in blood, will be developed, evaluating treatment, ibrutinib exposure and Btk occupancy as driver.
6. A model describing the dynamic changes in lymph node size (ie. SPD) will be developed, evaluating treatment, ibrutinib exposure and Btk occupancy as driver. Relationship between lymphocyte dynamics and lymph node size will be explored.
7. A model for longitudinal systolic and diastolic blood pressure measurements will be developed.
8. Possible connections between the variables of the PD models described above will be investigated to build a model framework. For example SPD may be related to ALC.
9. Covariates will be explored. The covariate search may constitute an initial graphical exploration (individual differences from population versus covariates). Candidate covariates will be investigated in the models using a stepwise covariate model building approach.
10. Predicted time-courses of SPD, ALC and blood pressures will, together with other covariates be explored for their ability to predict progression free and overall survival using parametric time-to-event models.
The analyses will be performed using the non-linear mixed-effects module nlmixr in R. Models will be developed for each variable and functions connecting the variables will be explored. Various models for between-subject variability and residual variability will be tested. Gold standard approaches for population PKPD analyses will be applied for model building and model evaluation.Comparison of models will be performed throughout the model development using standard pharmacometric methods such as objective function value, goodness-of-fit and visual predictive check plots, and relative standard errors of model parameter estimates.
Software Used:
R

Project Timeline:

After trial data access,
• Anticipated time for data management; one month.
• Anticipated time for model building; eight months.
• Anticipated time to manuscript draft; one month.
• Anticipated time to first manuscript submission for publication; one month.
• Anticipated time to reporting of results to the YODA project; at the end of 11th month.

Dissemination Plan:

• The population approach group in Europe (PAGE) conference (poster or oral presentation)
• Submission as 1 or 2 articles to journals with peer-review (possible choices: Clinical Cancer Research, CPT, CPT: Pharmacometrics & Systems Pharmacology)

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