Principal Investigator

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General Information

Key Personnel (in addition to PI):

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/coi-dc_0.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

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

Research Proposal

Project Title

The blood pressure increases related to ibrutinib treatment: post-hoc analysis of an RCT.

Narrative Summary:

B-cell malignancies are estimated to be diagnosed in more than 20700 people in US and will be responsible for

more than 4000 deaths in this year. Ibrutinib has been shown to be effective in various B?cell malignancies, such as chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and Waldenström's macroglobulinemia (WM).

However, it increases the risk of atrial fibrillation and hypertension. Besides this association, there is a gap in the knowledge regarding the magnitude of blood pressure increase with this treatment.

We intend to fulfill this gap in the knowledge, by quantifying the magnitude of increase in blood pressure in patients using ibrutinib

Scientific Abstract:

Background: the safety data from ibrutinib 's trials regarding reported adverse events of hypertension is heterogenous. Our previous systematic review and meta-analysis focusing on RCT on ibrutinib showed that this drug was associated with an increased risk of hypertension (RR 2.82; 95%CI 1.52-5.23).

Objective: Quantify the magnitude of increase in blood pressure in patients using ibrutinib in RCT and characterize blood pressure pattern during treatment.

Study design: Post-hoc retrospective analysis of an RCT.

Participants: patients with CLL included in the randomized controlled trial evaluating ibrutinib.

Main outcome measures: comparing ibrutining and control regarding blood pressure (systolic, diastolic and mean blood pressure); previous diagnosis of hypertension (BP > 140/90 mmHg), use of previous antihypertensive medication (drug class: beta-blockers, thiazide diuretics, angiotensin-receptor blockers, calcium antagonists, ACE inhibitors, renin inhibitors, alpha1-receptor blockers; dose and posology). Evaluate the blood pressure according to the initiation, discontinuation or titration of antihypertensive treatment,

Statistical analysis: Descriptive and inferential analysis will be performed with STATA/R software.

Brief Project Background and Statement of Project Significance:

B-cell malignancies are estimated to be diagnosed in more than 20700 people in US and will be responsible for more than 4000 deaths in this year. Ibrutinib has been shown to be effective in various B?cell malignancies, such as chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and Waldenström's macroglobulinemia (WM). 1

However, previous systematic review analyzing safe data of 8 RCT (2580 patients) showed an association with significant increase in the risk of hypertension with a RR 2.82 (95% ci 1.52 – 5.23) with moderate quality evidence.2 Besides this association, there is a gap in the knowledge regarding the magnitude of blood pressure increase with this treatment.

We intend to fulfil this gap by analyzing retrospectively the data of this randomized controlled trial to retrieved further details regarding ibrutinib treatment.

The results of this analysis will be useful to measure the risks of ibrutinib and increase the awareness to this increased risk of blood pressure. Additionally, a better understanding of the blood pressure pattern with different pharmacological classes of antihypertensive drugs could be useful for a better management of blood pressure in these patients.

Specific Aims of the Project:

1) Quantify the magnitude (mmHg) of increase in blood pressure in patients on ibrutinib treatment
2) Characterize blood pressure evolution during follow up time and the need to change antihypertensive medication
3) Characterize the blood pressure profile with the introduction of different classes of antihypertensive drugs
4) Evaluate whether new-onset hypertension worsens the prognosis.

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

New research question to examine treatment safety

Confirm or validate previously conducted research on treatment effectiveness
Confirm or validate previously conducted research on treatment safety

Research Methods

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

All the data from RCT respecting their inclusion and exclusion critreios

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

Blood pressure at baseline and in all visits – continuous variable; also as a cathegorical variable according to the increase
Overall survival (dichotomic)
Progression-free survival (dichotomic)

• Hypertension defined as Systolic blood pressure>140 mmHg or Diastolic blood pressure>90 mmHg, or the increased doses / use of novel of antihypertensive drugs (Categorical)
• Increase in 20 mmHg in systolic blood pressure (Categorical)
• Increase in 10 mmhg in diastolic blood pressure (Categorical)
• Increase in 40 mmHg in systolic blood pressure (Categorical)
• Increase in 20 mmHg in diastolic blood pressure (Categorical)

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

Previous hypertension / baseline blood pressure;
Use of antihypertensive drugs

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

Age (continuous), gender (categorical), ECOG performance score (categorical), Cytopenias at baseline [Hb<11; Platelets<100000; neutrophils<1500] (categorical); Clerance Creatinine<60 mL/min (categorical), Previous history of hypertension or antihypertensive drugs use. Previous history of diabetes. Previous history of other cardiac diseases.

Statistical Analysis Plan:

Statistical summary measures such as arithmetic mean and proportions were used to characterize the population and to derive the mean change of blood pressure (systolic, diastolic and mean blood pressure). Inferential test were made according to the type of outcome – Chi-square test for categorical/dichotomic data; T-Test for continuous data. The results were statistically significant at a p-value <0.05. Chi-square test and T-test were also used to compare the population that reached the categorical primary outcome. Logistic multivariable regression analysis and/or Cox-regression models are intended to be used to derive the independent predictors of developing/worsening the hypertension. In those cases, the estimates will be reported as Odds ratio (OR) or Hazard ratio (HR) with their 95% confidence intervals. The sample will be split in those who developed hypertension de novo and those who did not and the risk of Overall survival
and Progression-free survival will be evaluated among the groups. Kaplan-Meier curves will also be plotted for each of the two subgroups, using log-rak test for inferential comparative analyses.
Software Used:
R
Project Timeline:

anticipated project start date: May 2020
analysis completion date: January 2021
Date manuscript drafted: March 2021
first submitted for publication, and date results reported back to the YODA Project: May2021

Dissemination Plan:

One national congress presentation (Portuguese Cardiolgy Congress); One international congress presentation (ESC Congress 2021).
Submission of 1 or 2 manuscripts for peer-review journals [Possible target - Hypertension Or Eur Heart J Cardiovasc Pharmacother]

Bibliography:

1. Siegel RL, Miller KD. Cancer Statistics , 2019. 2019;69(1):7-34. doi:10.3322/caac.21551
2. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: Systematic review and meta-analysis. PLoS One. 2019;14(2):e0211228. doi:10.1371/journal.pone.0211228