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Requires Data Access? Yes

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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/05/YODA-Cyrus-Hsia-PI-COI-form.pdf
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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. NCT01236391 - PCYC-1104-CA - Multicenter Phase 2 Study of Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Relapsed or Refractory Mantle Cell Lymphoma
3. NCT01105247 - PCYC-1102-CA - A Phase 1b/2 Fixed-dose Study of Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia
4. NCT01578707 - PCYC-1112-CA - A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
5. NCT01611090 - PCI-32765CLL3001 - Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination With Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
6. NCT02165397 - PCYC-1127-CA - iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination With Rituximab in Subjects With Waldenström's Macroglobulinemia
7. NCT02195869 - PCYC-1129-CA - A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease
8. NCT02264574 - PCYC-1130-CA - A Randomized, Multi-center, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Subjects With Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
9. NCT01855750 - PCI-32765DBL3001 - A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma
10. NCT01776840 - PCI-32765MCL3002 - A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination With Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma
11. NCT01646021 - PCI-32765MCL3001 - A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, Versus Temsirolimus in Subjects With Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy
12. NCT01973387 - PCI-32765CLL3002 - A Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 (Ibrutinib) Versus Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
13. NCT02703272 - 54179060LYM3003 - A Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Participants With Relapsed or Refractory Mature B-cell Non-Hodgkin 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

Bleeding outcomes in patients on Bruton's Tyrosine Kinase inhibitors with thrombocytopenia (BLEED-BTKI)

Narrative Summary:

Ibrutinib is an oral medication used to treat chronic lymphocytic leukemia (CLL) and other related cancers by blocking a protein (BTK) that helps cancerous B cells survive. While effective, ibrutinib has been linked to an increased risk of bleeding. Although BTK plays a role in platelet function, the exact cause of bleeding with ibrutinib is not fully understood. Other factors like anemia, blood thinners, and low platelet counts may contribute, but past studies haven't shown a clear link between very low platelet count (thrombocytopenia) and bleeding risk--possibly due to limited data. This study is designed to specifically look at association between thrombocytopenia and risk of bleeding in patients being treated with ibrutinib compared with control groups in pooled data from large randomized studies.

Scientific Abstract:

Background: Ibrutinib is an oral medication used to treat chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders by blocking Bruton's Tyrosine Kinase (BTK). While effective, ibrutinib has been linked to an increased risk of bleeding.

Objective: To assess the association between thrombocytopenia and risk of bleeding in patients being treated with ibrutinib in pooled data from large randomized studies. We will compare these outcomes in patients on ibrutinib regimens with comparator arms in the randomized studies.

Study Design: Individual participant data meta-analysis of ibrutinib trials.

Participants: We will enroll participants with or without thrombocytopenia in all available ibrutinib trials.

Primary and Secondary Outcome Measures: The primary outcome is to assess the risk of major bleeding associated with thrombocytopenia in patients on ibrutinib. We will be comparing rate of bleeding in patients who have platelet counts less than 50 with patients who have platelet count of 50 or more. Secondary outcomes will include assessing all bleeding outcomes based on variables such as age, sex, use of anticoagulants, use of antiplatelet agents, anemia, and/or elevated INR in patients with or without thrombocytopenia.

Statistical Analysis: Descriptive statistics will be used to summarize baseline characteristics of patients on the ibrutinib studies.
(Please see Supplementary Materials section.)

Brief Project Background and Statement of Project Significance:

Ibrutinib is an orally active Burton Kinase inhibitor (BTKi) used in the treatment of naive and relapsed/refractory chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders [1-3]. BTK has an important role in the downstream B-Cell signalling pathway and contributes to survival and proliferation of normal and malignant B cells. Early clinical trials of Ibrutinib in CLL have reported increased incidence of major bleeding including subdural hematoma, gastrointestinal bleeding and hematuria [2], this has resulted in exclusion of patients on warfarin from subsequent trials. Increased rate of non-major bleeding has also been reported in several studies, in one study risk of petechia and bruising was 44% in ibrutinib arm compared to 12% in ofatumumab arm [4]. A three year follow up of single agent Ibrutinib in treatment naive or relapsed CLL showed 61% overall rate of bleeding, of these 48% were grade 1 bleeding most commonly petechia and contusion, and major bleeding was reported in 7% of patients [5].

It is established that BTK has a role in collagen and von willebrand factor- dependent platelet functions through its involvement in GP1b and GPVI downstream signaling pathways, respectively [6], however effect of BTK inhibition in increasing bleeding risk is not as clear. Notably patients with congenital agammaglobulinemia associated with absence of functional BTK are not at increased risk

of bleeding [7]. This suggests bleeding related to ibrutinib is more complex than BTK inhibition alone. Ibrutinib is known to impair platelet aggregation and reduce platelet function [8]. However, the risk of bleeding may increase due to anemia, elevated INR, and patients requiring antiplatelet and/or anticoagulation therapy [9]. Considering the proposed mechanism of bleeding related to ibrutinib [10-11], significant thrombocytopenia is another clinical factor that its role in increased risk of bleeding is debatable. However previous studies have not shown a significant association between increased bleeding risk and platelet count [8-9]. This might be related to small number of patients enrolled in these studies to observe such an effect. This study is designed to specifically look at association between thrombocytopenia and risk of bleeding in patients being treated with ibrutinib in pooled data from large randomized studies. We will also compare these outcomes in patients on ibrutinib regimens with the comparator arms in the randomized studies.

Specific Aims of the Project:

To assess the risk of bleeding associated with thrombocytopenia in patients on ibrutinib containing regimens versus comparator arms and for treatment of lymphoproliferative disorders. We will be comparing rate of bleeding in patients who have significant thrombocytopenia defined by platelets < 50 x 10^9/L compated with patients who don't.
All bleeding events will include the number and severity of bleeding. Severity of bleeding are often categorized as major bleeding, non-major clinically relevant bleeding, and minor bleeding.
Specific Hypotheses:
1. Bleeding in patients on ibrutinib containing regimens are similar to patients on comparator arms.
2. Bleeding on ibrutinib containing regimens are similar between patients with or without significant thrombocytopenia.
3. Bleeding on ibrutinib are higher in patients on anticoagulation with or without significant thrombocytopenia.
4. Bleeding on ibrutinib are higher in patients on antiplatelet agents with or without significant thrombocytopenia.
5. Bleeding on ibrutinib are higher in anemic patients with or without significant thrombocytopenia.
6. Bleeding on ibrutinib are higher in patients with elevated INR with or without significant thrombocytopenia.
7. Bleeding on ibrutinib are higher in older patients with or without significant thrombocytopenia.
8. Bleeding on ibrutinib are higher with more than one risk factor of age, anticoagulation, antiplatelet, anemia, or increased INR with or without significant thrombocytopenia.

Study Design:

Methodological research

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research Methods

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

We will perform pooled data analysis using individual participant data from the 13 trials using ibrutinib.

Inclusion criteria of trial: We will include trials that have patients on ibrutinib compared to placebo or other non BTK inhibitor therapies. The trials must contain a minimum of platelet count, hemoglobin, and bleeding outcomes. Other variables such as age, sex, race, weight, height, smoking, anticoagulant, antiplatelet, full CBC (WBC, ERC, Hb, Hct, Plts, ANC), CRP, ESR, INR, ferritin, CLL Rai stage, molecular, cytogenetics will be beneficial to assess secondary objectives but are optional.
Exclusion criteria of trial: We will exclude trials that do not measure at least the platelet count, hemoglobin, and bleeding outcomes

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary Outcome Measure:
The primary outcome measure will be all bleeding events. This will be defined as any documented bleeding or bruising of any grade from 0 to 5 from the time a patient is enrolled in the included study throughout the duration of that study.

Secondary Outcome Measures:
- Incidence of major bleeding events as defined by the International Society on Thrombosis and Haemostasis (ISTH), is a critical type of bleeding characterized by being either fatal, or occurring in a critical area or organ (like the brain, spine, or eye), or causing a significant drop in hemoglobin levels (20 g/L or more) or requiring a transfusion of two or more units of blood.
- Incidence of clinically relevant non-major bleeding (CRNMB), defined by bleeding events that are not severe enough to be classified as major bleeding, but still require medical intervention or have a notable impact on a patient's health.

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

The main independent variables will be use of ibrutinib or not and thrombocytopenia (platelets < 50 x 10^9/L or not; also will be assessed as a continuous variable).

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

Other variables of interest will be age, sex, platelet count, hemoglobin, INR and use of anticoagulants or antiplatelet agents. Age will be a continuous variable with older age likely predicting higher risk of bleeding. Other variables will be defined as biologic sex (male or female), hemoglobin (low, normal, or high if less than, within, or greater than reference interval 115-160 g/L or 135-170 g/L for male or female respectively), INR (within normal 0.9-1.1 or elevated; will also assess as a continuous variable), and use of anticoagulants or antiplatelet agents (yes or no).

Statistical Analysis Plan:

We plan to use individual participant data from the 13 ibrutinib trials. Descriptive statistics will be performed for the baseline characteristics of the participants and laboratory values in the trials and the subgroups of patients with abnormal laboratory parameters. We will use the chi-square test for categorical variables and Mann--Whitney test for continuous variables to compare populations. We will use paired t-tests or Wilcoxon signed-rank tests to assess within-group changes and ANOVA or mixed-effects models to assess between-group differences over time. We will use Pearson or Spearman correlation for continuous outcomes (e.g., change in age vs. number of bleeding events) and multivariate regression models to adjust for confounders (age, hemoglobin, INR, use of anticoagulants or antiplatelet agents). All statistical tests will be two-tailed, and p-values <0.05 will be considered statistically significant.

Software Used:

STATA

Project Timeline:

The proposed research will begin once approved. Data analyses will be completed within 6 months. Manuscript drafting will take a further 6 months and we will prepare for manuscript submission. Once manuscript submitted, results will be reported back to the YODA Project.

Dissemination Plan:

These results will be impactful and expected to be shared with healthcare providers to inform the impact of ibrutinib and thrombocytopenia on bleeding outcomes. We plan to submit to top Hematology or Oncology journals, such as Blood Advances, Blood Neoplasia, Lancet Hematology, American Journal of Hematology, Annals of Hematology, or Journal of Clinical Oncology.

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Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2025/05/Scientific-Abstract-2.docx