Ibrutinib and bleeding REB protocol

**Background and rationale**

Ibrutinib is an orally active Burton Kinase inhibitor (BTK). BTK has an important role in the downstream B-Cell signalling pathway and contributes to survival and proliferation of normal and malignant Bcells. Ibrutinib is an FDA approved medication with significant clinical activity against treatment Naiive and relapsed/refractory CLL and other lymphoproliferative disorders. (Burger JA, NEJM 2015, Byrd JC, NEJM 2013).

Early clinical trials of Ibrutinib in CLL have reported increased incidence of major bleeding including subdural hematoma, gastrointestinal bleeding and hematuria (Byrd JC, NEJM 2013), 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 (Byrd JC, NEJM 2014). A three year follow up of single agent Ibrutinib in treatment Naiive 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 (Byrd JC, Blood 2015).

It is stablished 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. (Queck LS, Current biology 1998, Liu J, Blood 2006), 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 (Oda A, Blood 2009). This suggests bleeding related to ibrutinib is more complex than BTK inhibition alone. Within a phase 2 trial of single agent ibrutinib in patients with CLL, Lipsky et al showed that platelet aggregation was impaired in all patients with CLL compared to healthy controls, treatment with ibrutinib further decreased platelet aggregation, suggesting that both disease and treatment related platelet dysfunction may contribute to increase bleeding risk (Lipsky AH, Haematologica 2015).

Lipsky et al also evaluated platelet function and coagulation factors at baseline and at 4 weeks after initiation of therapy with ibrutinib, reduced platelet function measured by increase epinephrine time as well as lower factor 8 and VWF activity at baseline were significantly associated with increased risk of bleeding with ibrutinib (Lipsky AH, Haematologica 2015). Another retrospective study of patients who were treated with ibrutinib showed that patients with anemia, elevated INR, and patients requiring antiplatelet and/or anticoagulation therapy had significantly increased rates of major bleeding while on ibrutinib (Mock J, Clinical lymphoma, myeloma and leukemia 2018).

Considering the proposed mechanism of bleeding related to ibrutinib, 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 PLT count (Lipsky AH, Haematologica 2015, Mock J, Clinical lymphoma, myeloma and leukemia 2018). 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.

**Objectives:**

*Primary objective*: the primary objective of this study is to investigate the risk of major bleeding associated with thrombocytopenia in patients on ibrutinib for treatment of CLL. We will be comparing rate of major bleeding in patients who have platelet counts 50 or less with patients who have platelet count more than 50.

*Secondary objectives:*

1.To investigate the risk of non-major bleeding associated with significant thrombocytopenia in patients on ibrutinib for treatment of CLL.

2.To investigate the risk of bleeding associated with anticoagulation in patients on ibrutinib.

3.To investigate the risk of bleeding associated with antiplatelets in patients on ibrutinib.

4.To investigate the risk of bleeding associated with invasive procedures in patients on ibrutinib.

**Study Design and Methodology**

*Mode of study*

This is a prospective study of patients 18 years or older with CLL who are on treatment with single agent ibrutinib based on IwCLL 2019 criteria, in regional hematology clinics in a tertiary academic centre in London health sciences centre (LHSC), in London, Ontario Canada.

*Methodology*

Patients will be recruited by study co- investigator who will obtain consent from the study participants at the time of recruitment. Patients will be interviewed at each clinic visit by either the study co-investigator or the staff hematologist for bleeding events based on the ISTH-SCC bleeding assessment tool. All patient will have bloodwork including CBC done prior to their clinic visit. Study participants will be recruited during a one year period from the time of study initiation and followed for at least 6 months after that.

Retrospective data will be also collected form the patients on ibrutinib between Jan 1,2014 to December 31, 2019. Patient’s clinic notes and other health records will be reviewed, and all bleeding events reported by the patient or health care professional will be recorded. Bleeding will be graded based on CTAE criteria in retrospective chart review.

The primary objective is to evaluate the risk of major bleeding associated with significant thrombocytopenia in Patients on ibrutinib. Bleeding events with score 3 or 4 based on ISTH bleeding assessment tool that occurred with associated platelet count 50 or less will be compared to major bleeding events that occurred with associated platelet count more than 50 for primary analysis.

To capture the patients who are on ibrutinib for treatment of CLL we will ask our regional pharmacy for list of patients who filled their prescription in our regional cancer centre pharmacy, we also ask hematologists who treat CLL in LHSC for list of the patients who are on ibrutinib to capture those patients that fill their prescription in any other pharmacy within the City of London.

*Patients Selection criteria:*

1.Inclusion criteria: all patients 18 years or older with CLL requiring treatment with single agent ibrutinib based on IwCLL 2019 criteria.

2.Exclusion criteria: Patients will be excluded if they have known bleeding disorder.

*Definitions:*

1.Significant thrombocytopenia – is defined as platelet count 50 or less at any point during the time patient is on treatment with ibrutinib.

2.Bleeding severity- is defined based on ISTH -SCC bleeding Assessment tool

- Major bleeding is defined as bleeding events with ISTH score 3 or 4

- Non-Major bleeding is defined as bleeding events with ISTH score 1 or 2

Abbreviations:

CLL: Chronic lymphocytic leukemia

ISTH-SCC: International society of thrombosis and hemostasis- scientific and standardization committee

IwCLL: international workshop on chronic lymphocytic leukemia