**Risk of Major Bleeding with Ibrutinib in Patients with Thrombocytopenia – A retrospective single center Canadian study**

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**Introduction:** Ibrutinib, an oral Burton Kinase inhibitor, is a highly effective treatment for patients with chronic lymphocytic leukemia (CLL). Previous studies reported an increased risk of bleeding due to impaired platelet function. Patients with CLL experience significant thrombocytopenia, which increases their risk for bleeding. This population was excluded from major trials and data is lacking to inform management in this setting.

**Methods:** This is a single center retrospective study of adult patients with CLL who received single agent ibrutinib in London, Ontario, Canada between January 2014 to December 2020. 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. Secondary objectives included evaluating the association of relevant variables with bleeding. Bleeding events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system. A major bleed was defined as CTCAE grade 3 or higher as well as bleeding in the central nervous system. To assess the effect of independent variables on the outcome of bleeding, univariate analysis using chi square and t-tests was performed. Multivariate analysis was then preformed with the variables that were significant (p<0.05) on univariate analysis, using logistic and cox regression models.

**Results:** A total of 170 patients were included in this study. In total there were 54 bleeding events documented in 42 patients (24.7%). Of those, 19 (35% ) were major bleeding events that occurred in 17 patients. The mean platelet (PLT) nadir, defined as lowest PLT count at any point during ibrutinib treatment, was 73.3 in patients with major bleeding compared to 115.6 in patients with minor and 91.19 in patients with no bleeding events.

On the univariate analysis, when we compared patients with major bleeding to patient with no bleeding, PLT nadir (OR xx p=0.09) , haemoglobin (hb) < 100 at the time of ibrutinib initiation (OR XX , p=0.027) and anticoagulation (ORxx, p=0.009) were the potential predictors of major bleeding. Comparing patients with major bleeding and patients with minor or no bleeding, PLT nadir (OR xx, p=0.045) , hb <100 (OR xx p=0.036) and anticoagulation (OR xx, p=0.06) were similarly the potential predictors for major bleeding. Grade 3 thrombocytopenia, defined as PLT nadir < 50 at any point during treatment with ibrutinib was not associated with increased risk of major bleeding (p=0.2).

To confirm the significance of these variables, multivariate analysis was performed. When we compared patients with major bleeding to patients with no bleeding, PLT nadir (p=0.008) and anticoagulation (p=0.001) were confirmed to be the potential predictors of major bleeding. When comparing patients with major bleeding and patient with minor or no bleeding, PLT nadir (OR xx p=0.005) and hb <100 (ORxx, p=0.005) were the potential predictors of major bleeding.

**Conclusions:** Although not common, Ibrutinib is associated with increased risk of major and minor bleeding and identifying patients that are at higher risk of bleeding is essential. This retrospective Canadian study was done with the primary objective to assess the association between PLT count and major bleeding in patients on ibrutinib for treatment of CLL. In this analysis patients with major bleeding tend to have lower PLT counts compared to patients with minor or no bleeding, with mean PLT nadir of 73.3. However grade 3 thrombocytopenia (PLT nadir<50) was not associated with increased risk of major bleeding. Other important predictors of increased risk of bleeding while on ibrutinib includes concurrent anticoagulation and anemia (Hb <100).

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| **Characteristic** | **(N = 170)** |
| Age at Diagnosis (mean) | 63.9 |
| Men (%) | 105 (61.8%) |
| Rai Stage at Diagnosis (%) |  |
| 0 | 57 |
| 1 | 49 |
| 2 | 22 |
| 3 | 5 |
| 4 | 17 |
| Unknown |  |
| High Risk Cytogenetics (%) |  |
| Present | 71 (41.8%) |
| Absent | 78 (45.9%) |
| Unknown | 21 (12.3%) |
| Anticoagulant | 32 |
| Antiplatelet | 32 |
| Patients with Documented Bleeding Events | 42 (24.7%) |
| Major Bleed | 17 |
| Minor Bleed | 25 |

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|  | **Univariate Analysis** | | **Multivariate Analysis** | |
|  | Major vs. None | Major vs. Minor + None | Major vs. None | Major vs. Minor + None |
| *Platelets (<50) (Y/N)* | 0.220 | 0.202 | - | - |
| *Platelet Nadir while on Ibrutinib* | 0.09 | 0.045 | 0.008 | 0.005 |
| *Anemia (hb < 100) (Y/N)* | 0.027 | 0.036 | 0.155 | 0.005 |
| *Anticoagulation (Y/N)* | 0.009 | 0.067 | 0.001 | 0.334 |
| *Anti-platelet (Y/N)* | 0.522 | 0.601 | - | - |
| *PMHx bleeding risk (Y/N)* | 0.215 | 0.204 | - | - |

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|  | **Univariate Analysis** | | | | **Multivariate Analysis** | | | |
|  | Major vs. Minor | Major vs. Minor + None | Major + Minor vs. None | Major vs. None | Major vs. Minor | Major vs. Minor + None | Major + Minor vs. None | Major vs. None |
| **Categorical Variables** |  | | | |  | | | |
| *Gender (Male vs. Female)* | 0.921 | 0.430 | 0.137 | 0.343 | - | - | - | - |
| *Platelets (<50) (Y/N)* | 0.268 | 0.202 | 0.564 | 0.220 | - | - | - | - |
| *Anemia (hb < 100) (Y/N)* | 0.228 | 0.036 | 0.05 | 0.027 | 0.326 | 0.005 | 0.001 | 0.155 |
| *Anemia (hb < 110) (Y/N)* | 0.299 | 0.066 | 0.064 | 0.052 | - | - | - | - |
| *HR Molecular/Cytogenetics (Y/N)* | 0.624 | 0.665 | 0.111 | 0.525 | - | - | - | - |
| *Anticoagulation (Y/N)* | 0.573 | 0.067 | 0.000 | 0.009 | 0.759 | 0.334 | 0.000 | 0.001 |
| *Anti-platelet (Y/N)* | 0.972 | 0.601 | 0.341 | 0.522 | - | - | - | - |
| *PMHx bleeding risk (Y/N)* | 0.325 | 0.204 | 0.493 | 0.215 | - | - | - | - |
| **Continuous Variables** |  | | | |  | | | |
| *Age* | 0.962 | 0.942 | 0.947 | 0.94 | - | - | - | - |
| *Platelet Nadir while on Ibrutinib* | 0.019 | 0.045 | 0.55 | 0.09 | 0.261 | 0.005 | 0.279 | 0.008 |
| *Platelet at the time of bleed* | 0.0037 | - | - | - | 0.320 | - | - | - |
| *hb at the time of bleed* | 0.001 | - | - | - | 0.773 | - | - | - |
| *Prior lines of therapy* | 0.397 | 0.224 | 0.148 | 0.403 | - | - | - | - |

Notes:

For the univariate analysis, the p-values for the categorical variables were determined through a chi-square test on the respective contingency tables, while the p-values of the categorical tests were determined by Welsch’s t-test.

For the multivariate analysis, two different regression models were fit. The regression models were only fit with variables that were significant in the univariate analysis to improve the model fit, and limit multicollinearity concerns. The first model was fit with: anticoagulation, platelet nadir, and anemia (hb <100). The p-values in the table above, for the multivariate analysis of anticoagulation, platelet nadir, and anemia (hb <100) reflect this first model. The second model was fit with platelet at the time of bleed, hemoglobin at the time of bleed, and anticoagulation. The p-values values in the table above, for the multivariate analysis of platelet and hemoglobin at time of bleed, reflect this second model.

Note that in general, the major vs. minor bleeding comparison for the multivariate analysis was not significant, and this is primarily due to the much smaller samples sizes (since most of our sample size had no bleeding events). So I would trust the univariate analysis more for this case. Also note, that while model 2 did not produce significant coefficients, the predictive performance of the model on a novel dataset was pretty good, therefore suggesting that some trends were captured correctly.