**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 (BTK) 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. Univariate and multivariate analysis using logistic regression model was used to assess the effect of independent variables on the outcome of bleeding.

**Results:** A total of 170 patients were included in this study. 54 bleeding events were documented in 42 patients (24.7%). 19 (35%) of the bleeding events were major that occurred in 17 patients. The mean platelet (PLT) nadir was 73.3 in patients with major bleeding events compared to 115.6 in patients with minor and 91.19 in patients with no bleeding events. On multivariate analysis PLT nadir was significantly lower in patients with major bleeding compared to patients with no bleeding (HRxx, p=0.008) and demonstrated a trend towards significance on univariate analysis (HR xx, p=0.08). However, there was no significant association between grade 3 thrombocytopenia (PLT<50) and increased risk of major or overall bleeding (HRXX,p=0.22 and HRXX, P=0.56, respectively). Rates of major bleeding in patients with platelet PLT nadir <50 was 15% compared to 8% in patients with PLT nadir > 50, this difference was not statistically significant (p= 0.4). PLT count at time of bleeding was lower in the patients with major bleeding events versus those with minor events (108.9 vs 172.26, HRxx p=0.0037). Factors that were associated with increased risk of overall and major bleeding as evident by both the univariate and multivariate analysis includes being on anticoagulation (HR 2.08, p<0.001) and having a haemoglobin < 100 (HR 1.21, pvalue 0.001).

**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 important. In this analysis patients with major bleeding tend to have lower PLT count compared to those with minor or no bleeding, however PLT nadir < 50 (grade 3 thrombocytopenia) was not significantly associated with increased risk of bleeding. Having a lower PLT count at the time of bleeding was a significant indicator of having a major bleeding event. Other important risk factors 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. 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.