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Research Article

Platelet Function and Bleeding Tendency in Patients under Ibrutinib Therapy

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Abstract

Background: Ibrutinib is a first-generation covalent Bruton's kinase (BTK) inhibitor approved for the treatment of mantle-cell lymphoma (MCL), CLL, and Waldenstrom macroglobulinemia (WM). BTK is expressed on platelets and is believed to play a central role in platelet activation through GPIb and GPIV pathway. However, the clinical significance of BTK inhibition is unclear in terms of bleeding.

Objectives: To identify possible alterations in hemostasis caused by ibrutinib in patients who start taking the drug. Baseline hemostasis will be analyzed and studies will be repeat after a period of treatment with the drug. To monitor the development of haemorrhagic adverse effects in patients who start taking ibrutinib.

Patients/Methods: We enrolled 11 patients, with a median age of 63 years old (range, 53-88). Haemostasis studies and complete blood count were performed on days 0, 10, and 30 after initiation of ibrutinib intake. Five patients had the diagnosis of CLL, 5 patients had MCL and 1 patient had WM.

Results and Conclusion: During a period of follow-up of 6 months, 3 out of 11 (27%) developed grade 1 bleeding adverse events (Common Toxicity Criteria (CTC)). More than half of the patients had altered hemostasis before starting treatment with ibrutinib, which could be justified by the biology of the disease itself, as has been suggested in other studies in patients with CLL. We believe that col/epi may be a test of greater utility and simplicity than aggregation with ristocetin to assess platelet function in patients receiving ibrutinib.

Keywords: Platelet function and bleeding tendency; Ibrutinib therapy; Chronic lymphocytic leukemia

Introduction

Recently, Kazianka, et al. [1] have published a paper in which bleeding tendency in chronic lymphocytic leukemia (CLL) patients treated with ibrutinib has been analized. The major goal of the study was to establish an association between bleeding and platelet function during ibrutinib treatment. They assessed ristocetin-induced platelet aggregation (RIPA) in 64 patients with CLL under ibrutinib, registering bleeding episodes during a median follow-up period of 10.9 months. Median RIPA measured at time of bleeding was significantly impaired compared with time points when no bleeding was observed, regardless of platelet count. Consecutive samples before and after start of ibrutinib were available in 11 patients. A decline in platelet aggregation from 17 to 9 U was observed when therapy was initiated (P=0.019). When ibrutinib was discontinued or suspended, the median values increased from 12 to 54 U (P: 0.004).

Ibrutinib is a first-generation covalent Bruton's kinase (BTK) inhibitor approved for the treatment of mantle-cell lymphoma (MCL), CLL, and Waldenstrom macroglobulinemia (WM). BTK is expressed on platelets and is believed to play a central role in platelet activation through GPIb and GPIV pathway [2,3]. However, the clinical significance of BTK inhibition is unclear in terms of bleeding. Bleeding has been reported as a side effect, with 8% of patients presenting severe hemorrhage [4]. Nevertheless, it is known that patients with congenitally deficient BTK (X-linked agammaglobulinemia) do not exhibit increased bleeding [5].

Objectives

To identify possible alterations in hemostasis caused by ibrutinib in patients who start taking the drug. Baseline hemostasis will be analyzed and studies will be repeat after a period of treatment with the drug.

To monitor the development of haemorrhagic adverse effects in patients who start taking ibrutinib.

Patients/Methods

We conducted a prospective study including patients diagnosed with MCL, CLL, or WM treated in second-line or higher therapy consisting of ibrutinib as single-agent therapy. We recorded bleeding-related adverse events. Haemostasis studies and complete blood count were performed on days 0, 10, and 30 after initiation of ibrutinib intake. Fresh blood specimens were drawn into heparin containing tubes and analyzed by impedance aggregometry in Multiplate Analyzer (Siemens). RIPA, Araquidonic Acid (AA), ADP and TRAP as agonists were tested.

Citation: Laso RV, Mascuñano RC, García-Raso A, Domínguez JMA, Bonilla TC, Saenz MP, et al. Platelet Function and Bleeding Tendency in Patients under Ibrutinib Therapy. Ann Hematol Oncol. 2017; 4(11): 1179.

Results and Conclusion

The normal ranges of the tests were 65-116 U for RIPA, 79-141 U for AA, 55-117 U for ADP, and 92-152 U for TRAP. Fresh blood specimens were drawn into citrate-containing tubes and analyzed by PFA assay (Siemens). Additional clotting tests were performed: APTT, PT, Von Willebrand factor antigen (VWF) and ristocetin cofactor (FVW:RCo).

In the period of study, we enrolled 11 patients, 7 were males and 4 females, with a median age of 63 years old (range, 53-88). Five patients had the diagnosis of CLL, 5 patients had MCL and 1 patient had WM. During a period of follow-up of 6 months, 3 out of 11 (27%) developed grade 1 bleeding adverse events (Common Toxicity Criteria (CTC)). Of these, 1 patient was under anticoagulant treatment with intermediate dose of enoxaparin, and another patient had basal low levels of VWF and FVW:RCo, suggesting a possible acquired Von Willebrand syndrome.

Mean RIPA values before starting ibrutinib were 51 U (range 6-93 U). Six out of eleven (54%) patients had low RIPA values before starting the treatment. After 10 days under ibrutinib, the values were similar (median 51 U, range 6-90 U). At day 30 of treatment the values improved (median 57 U, range 6-116 U).

There were 3 patients with mild bleeding complications. One of them was under anticoagulation treatment and showed normal RIPA values at 0, 10 and 30 days, without any worsering at time of bleeding. Another patient had low RIPA values at day 0 (14 U), this value improved at day 10 (32 U) and at day 30 (60 U). The other patient presented very low RIPA value at day 0 (6 U) and remained as low at 10 and 30 day (6 U). Every bleeding occurred between day 0 and 10 when second assessment was carried out.

The median of shutter speed collagen/epinephrine (col/epi) was 175 sec (range, 94-270) at baseline. After ibrutinib exposure, median of col/epi at 10 days was 231 sec (range, 108-287) (paired t-student test, p=0.037); and at 30 days was 142 sec (range, 79-300), (p=n.s., for both comparisons). We highlight that 6 out of 11 (54.5%) patients had a prolonged col/epi obturation time at baseline, including 2 out of the 3 patients with bleeding complications. Additionally, 4 of 11 patients (36.4%) had a prolonged shutter speed collagen/ADP at baseline, with a median of 105 sec (range, 63-190). After Ibrutinib exposure, median shutter speed Collagen/ADP at 10 days was 107 sec (range, 66-192), (p=n.s.); and at 30 days was 78 sec (range, 75-149), (p=n.s., for both comparisons).

The major clinical finding of the study of Kazianka, et al was that low RIPA values are strongly associated with bleeding tendency, and that these values could be used to monitor the risk of bleeding in this patient [1]. Our study contrasts with these results. More than half of our patients had reduced baseline RIPA values. After 10 days of treatment, when most hemorrhagic events occur, these values varied only slightly, and improved after 30 days of treatment. However, we did observe that the col/epi is clearly prolonged after 10 days of treatment. The prolongation occurred quite homogeneously in all patients. In 2 out of the 3 patients who presented hemorrhagic complications, prolongation of the col/epi obturation time occurred markedly. Interestingly, there was an overall improvement in values after 30 days of treatment, probably due to the benefit of ibrutinib on the biology of the disease.

Of our study, we would like to remark that more than half of the patients had altered hemostasis before starting treatment with ibrutinib, which could be justified by the biology of the disease itself, as has been suggested in other studies in patients with CLL [6]. This finding could explain, at least partially, the bleeding complications described in patients under ibrutinib treatment. We believe that col/epi may be a test of greater utility and simplicity than aggregation with ristocetin to assess platelet function in patients receiving ibrutinib under certain clinical situations.

Author's Contribution

RC, RV and AGR conceived and designed the research and critically reviewed the manuscript for important intellectual content. RV, AGR and JA analyzed and performed statistical analysis. RV, JA and AGR drafted the manuscript. RV, EA, RC, MP, JA and TC acquired and interpreted the data. PL and RC handled funding and critically reviewed the manuscript for important intellectual content.

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