Magdalena PIOTROWSKA
Monika DŁUGOSZ-DANECKA
Małgorzata JAKÓBCZYK
Anastazja STÓJ
Wojciech JURCZAK

Low incidence of ibrutinib discontinuation in real-life experience

Ibrutynib jest rzadko odstawiany z powodu działań niepożądanych – podsumowanie praktyki klinicznej

Department of Haematology, Jagiellonian University Medical College, Krakow, Poland
Head:
Prof. dr hab. n. med. Wojciech Jurczak

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Introduction: Despite advances in chronic lymphocytic leukemia (CLL) treatment strategies, the high-risk cases with certain cytogenetic and molecular aberrations respond poorly to immunochemotherapy. Targeted therapies have become the standard of care, especially in relapsed/refractory (R/R) cases. Bruton tyrosine kinase (BTK), an essential element of the B-cell receptor (BCR) signaling pathway, was extensively investigated as a potential therapeutic target in B-cell malignancies. Ibrutinib, the first-in-class BTK inhibitor registered for CLL therapy, is efficient and broadly used.

Objectives: We analyzed the real-life experience with the ibrutinib monotherapy in relapsed/refractory (R/R) high-risk CLL patients.

Material and Methods: Retrospective analysis included 30 high-risk patients with R/R CLL treated with ibrutinib monotherapy until disease progression or unacceptable toxicities precluded further therapy.

Results: After the median number of ibrutinib cycles equal to 37, overall response rate (ORR) was 86.7% with a complete remission (CR) rate of 34.6% , partial remission (PR) rate of 42.3% and partial remission with lymphocytosis (PRL) rate of 23.1%. Three patients (10%) had a stable disease (SD) and one (3.3%) progressive disease (PD) confirmed after the second cycle of ibrutinib. The median progression free survival (PFS) was not reached after a median follow-up of 48 months; the estimated PFS at 36 months was 78%. Five patients (16.7%) relapsed. Among the five patients that died, four of them from disease progression, one from second lung cancer. Grade ≥ 2 adverse events (AEs) occurred in 22 patients (73.3%), including grade-3 AEs in 10 patients (33.3%) and grade-4 AEs in 7 patients (23.3%). Dose interruptions or reductions due to AEs were noted in 11 patients (36.7%) with any episodes of ibrutinib discontinuation.

Wstęp: Pomimo postępu w leczeniu przewlekłej białaczki limfocytowej (CLL), chorzy wysokiego ryzyka, z potwierdzonymi aberracjami cytogenetycznymi i molekularnymi, słabo odpowiadają na immunochemioterapię. U tych chorych standardem postępowania, szczególnie w chorobie opornej/nawrotowej, są terapie celowane. Kinaza tyrozynowa Brutona (BTK), istotny element szlaku sygnałowego receptora limfocyta B (BCR), została szczegółowo przebadana jako potencjalny cel terapeutyczny w nowotworach z limfocytów B. Ibutynib, pierwszy w swojej klasie inhibitor BTK, zarejestrowany do leczenia przewlekłej białaczki limfocytowej, jest skuteczny i szeroko stosowany w tej grupie pacjentów.

Cel pracy: Celem pracy była analiza stosowania ibrutynibu w praktyce klinicznej u chorych z nawrotową/oporną postacią przewlekłej białaczki limfocytowej wysokiego ryzyka.

Materiał i Metodyka: Analizą retrospektywną objęto 30 pacjentów wysokiego ryzyka z nawrotową/oporną postacią przewlekłej białaczki limfocytowej, leczonych ibrutynibem w monoterapii do czasu progresji choroby lub wystąpienia toksyczności wykluczającej dalsze leczenie.

Wyniki: Przy medianie cykli leczenia 37, odsetek odpowiedzi na leczenie (ORR) wyniósł 86,7%, przy odsetku całkowitej remisji (CR) 34,6%, częściowej remisji (PR) 42,3% i częściowej remisji z limfocytozą (PRL) 23,1%. Trzech pacjentów (10%) uzyskało stabilizację choroby (SD); u jednego chorego (3,3%) potwierdzono po drugim cyklu progresję choroby (PD). Mediana czasu wolnego do progresji (PFS) nie została osiągnięta przy medianie obserwacji trwającej 48 miesięcy; szacowany PFS po 36 miesiącach wyniósł 78%. U 5 pacjentów (16,7%) wystąpiła progresja procesu. Pięciu chorych zmarło, czterech z powodu progresji przewlekłej białaczki limfocytowej, jeden z powodu raka płuc. Zdarzenia niepożądane stopnia ≥ 2 (AE) wystąpiły u 22 chorych (73,3%), w tym stopnia 3 u 10 (33,3%) i stopnia

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Correspondence to:
Magdalena Piotrowska
Department of Hematology,
Jagiellonian University Medical College
Kopernika 17, 31-501 Krakow, Poland
phone: +48 695 980 176
e-mail: piotrowm@op.pl

Conclusion: Our data confirms the efficacy and safety of ibrutinib monotherapy in R/R high-risk CLL patients with no incidence of discontinuation therapy due to AE.

4 u 7 pacjentów (23,3%). Z powodu zdarzeń niepożądanych u 11 chorych (36,7%) obserwowano przerwy w leczeniu lub redukcję dawki ibrutynibu, bez zakończenia leczenia.

Wnioski: Nasze dane potwierdzają skuteczność i bezpieczeństwo stosowania ibrutynibu w monoterapii u wysokiego ryzyka chorych z nawrotową/oporną postacią przewlekłej białaczki limfocytowej, bez konieczności trwałego przerwania leczenia z powodu zdarzeń niepożądanych.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia subtype diagnosed in the Western world, with an incidence rate of 4.2/100,000 increasing to >30/100,000 per year in the elderly population above 80 years of age [1]. Despite impressive advances in CLL treatment strategies and the development of novel, more effective drugs, the disease remains incurable by conventional modalities in the majority of patients [2]. Chromosomal and molecular abnormalities including TP53 mutation (TP53), 17p deletion (del 17p) and 11q deletions (del 11q) have an impact on treatment decisions and identify the group of high-risk patients, poorly responding to immunochemotherapy [3]. Inhibiting Bruton tyrosine kinase (BTK) – an essential part of the B-cell receptor (BCR) signaling pathway – is widely used in B-cell malignancies [4,5]. Although immunochemotherapy still remains the standard of care for treatment-naïve (TN) CLL without del 17p/TP53 [1], with modifications in elderly, comorbid patients [6-8], ibrutinib, an oral, covalent BTK inhibitor is considered an effective therapeutic option, extending the duration of response. BTK inhibitors improved clinical outcomes and are registered for high-risk and relapsing/refractory CLL patients [9-11]. They became the biggest breakthrough in lymphoma therapy since the introduction of rituximab, an anti-CD20 monoclonal antibody. Although ibrutinib is generally well tolerated, a tendency for side effects such as bleeding, rashes, atrial fibrillation (AF), arthralgia and pneumonitis was observed, which could be partly due to inhibition of targets other than BTK [11-14].

Material and Methods

Patients

A total of 30 patients with relapsed/refractory (R/R) CLL were evaluated in this retrospective analysis. The diagnosis of CLL, as well as indications for starting the treatment, was based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines [15]. Patients were required to have adequate hepatic and renal function with absence of active infections. Patients with uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia, severe hematopoietic insufficiency, bleeding diathesis or coagulopathy, recent hemorrhagic events, concomitant treatment with warfarin or prior exposure to ibrutinib were excluded.

Treatment

Treatment consisted of ibrutinib, 420 milligrams (mg) continuously daily by month (one cycle = 28 days). Patients remained on treatment until disease progression or unacceptable toxicities precluded further therapy. Ibrutinib was held for any 3-4 grade toxicity according to to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [16]. Ibrutinib was held for any grade 3-4 toxicity until the adverse event (AE) returned to baseline or resolved completely. If the grade 3-4 AE reoccurred, the dose of ibrutinib was reduced. Granulocyte colony-stimulating factor (G-CSF) was not used for primary prophylaxis of neutropenia, but secondary prophylaxis was allowed according to local standards. Clinical and laboratory assessment were performed every cycle of treatment. Computed tomography (CT) assessment was performed every six months Electrocardiography (ECG) was done every 3 months or when the clinical symptoms of arrhythmia appear. Efficacy data (response rate and progression-free survival) and safety data were collected. Response to treatment with computed tomography (CT) was assessed according to IWCLL guidelines every 6 months or in case of clinical suspicion of progression [15].

Statistical analysis

Progression free survival (PFS), estimated by the Kaplan-Meier method, was defined as the time from treatment initiation to the last date on which the disease activity was assessed, including death for any reason. Follow-up time was too short to achieve meaningful overall survival (OS) results. A multi-parameter analysis of factors predicting response to the treatment including cytogenetics was also performed. Statistical analyses were performed using the software Statistica, version 10 (StatSoft, Krakow, Poland).

Results

Between November 2014 and December 2018, 30 R/R high-risk CLL patients were treated with ibrutinib in Department of Hematology, Jagiellonian University in Krakow. Patients characteristics and demographics are presented in table I.

The median age at the diagnosis was 56 years (range 36-74), at the start of treatment with ibrutinib was 65 years (range 40-83) with a male/female ratio of 2.3. Before starting the ibrutinib therapy the assessment of genomic aberrations: deletion of the short arm of chromosome 17 (del 17p), deletion of the long arm of chromosome 11 (del 11q), deletion of the long arm of chromosome 13 (del 13q), trisomy of chromosome 12 (tri 12) by fluorescence in situ hybridization (FISH), molecular asses-

Table I
Patient and disease characteristics.
Charakterystyka pacjentów i choroby.

Patient Demographics	
Male n, (%) Median age at the diagnosis Median age years (range) ≥ 70 years, n (%) Median ECOG PS, n (%)	21 (70) 56 (36-74) 65 (40-83) 10 (33.3) 1 (0-2)
Disease characteristics at the start of treatment with ibrutinib	
Rai stage I, n (%) Rai stage II, n (%) Rai stage III, n (%) Rai stage IV, n (%)	7 (23.3) 10 (33.3) 7 (23.3) 6 (20)
Median number of previous lines of therapy, n (range)	3 (1-6)
Cytogenetics (n=30)	
1. 17p deletion, n (%) 2. 11q deletion, n (%) 3. Trisomia 12, n (%) 4. 13q deletion, n (%)	18 (10.1) 8 (15.9) 4 (17.4) 12 (26.1)
Mutation status (n=10)	
TP53 mutated, n (%)	4 (25)
IGVH status (n=11)	
Unmutated, n (%)	10 (90.9)

Abbreviations: ECOG PS – Eastern Cooperative Oncology Group Performance Status, IGVH - immunoglobulin heavy-chain variable-region gene.

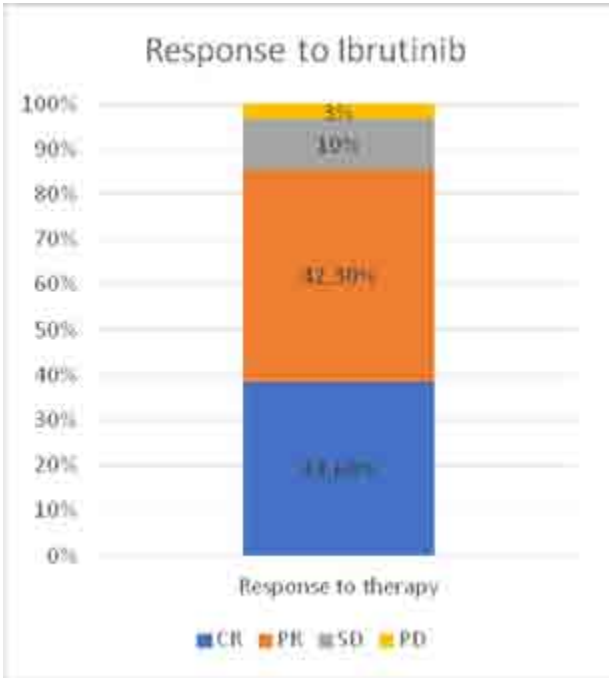

Figure 1
Response rates to ibrutinib therapy.
Odsetek odpowiedzi na leczenie ibrutynibem.

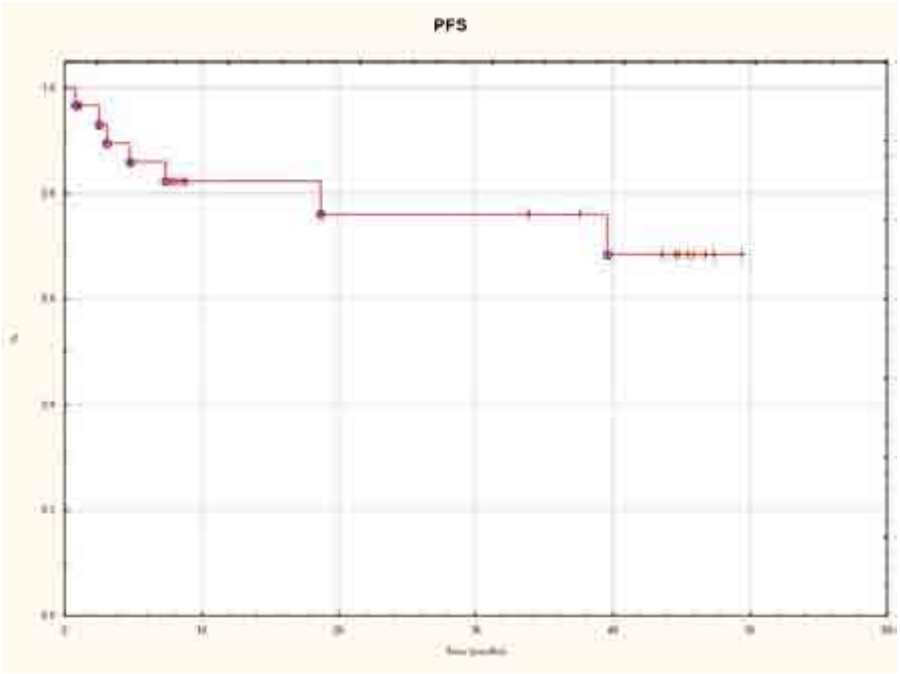

Figure 2.
Progression-free-survival in the analyzed group.
Przeżycie wolne do progresji w analizowanej grupie.

sment of TP53 mutation and the analysis of immunoglobulin heavy-chain variable--region gene (IGHV) mutation were performed in 30, 10 and 11 patients, respectively [17,18]. Unfavorable risk factors such as 17p deletion, 11q deletion, TP53 mutation and unmutated IGHV genes were found in 10%, 16%, 25% and 91% (among the subjects with the tests performed) of patients, respectively.

The median number of previous lines of treatment was 3 (range 1-6); the most commonly used regimens were RFC (rituximab, fludarabine, cyclophosphamide) and RB (rituximab, bendamustine). The median number of ibrutinib cycles was 37 (range 2-50).

Overall response rate (ORR) was 86.7% with a complete remission (CR) rate of 34.6%, partial remission (PR) rate of 42.3% and partial remission with lymphocytosis (PRL) rate of 23.1%. Three patients (10%) had a stable disease (SD), and one (3.3%) progressive disease (PD) confirmed after the second cycle of ibrutinib (Fig. 1).

The median PFS was not reached after a median follow-up of 48 months; the estimated PFS at 36 months was 78% (Fig. 2).

The estimated OS at 36 months was 79%. Five patients (16.7%) relapsed, 1 of them having achieved CR, 2 PRL , 1 with SD and 1 with PD. Among the five patients that died, four of them due to disease progression, one from second lung cancer. There were no episodes of Richter transformation.

Treatment was well tolerated and toxicities were consistent with those previously described in patients receiving long-term therapy with ibrutinib. In the analyzed group, grade ≥ 2 AEs occurred in 22 patients (73.3%), including grade-3 AEs in 10 patients (33.3%) and grade-4 AEs in 7 patients (23.3%). The most frequent grade 3-4 AEs were neutropenia (7 patients, 23.3%), infections (3 patients, 10%), pneumonia (2 patients, 6.7%), thrombocytopenia (2 patients, 6.7%) and anemia (2 patients, 6.7%). There were no episodes of febrile neutropenia. Only one episode of FA was noted. Three patients (10%) required hospitalization related to AEs (infection, pneumonia, anemia). Dose interruptions and reductions due to AEs were noted in 11 patients (36.7%) with any episodes of ibrutinib discontinuation in the analyzed group.

Discussion

The treatment strategies in R/R CLL settings have undergone significant changes during the past few years, due to the development of new, targeted agents, including BTK inhibitors. Ibrutinib – the first-in-class, irreversible BTK inhibitor – was approved by the Food and Drug Administration (FDA) for the treatment of CLL/small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma(MZL) and mantle cell lymphoma (MCL) and European Medicine Agency (EMA) for the treatment of CLL, MCL and WM [11-12,19-20]. In addition to BTK inhibition, ibrutinib targets several other kinases including: interleukin-2-inducible T-cell kinase (ITK), epidermal growth factor receptor (EGFR) and tyrosine kinase expressed in hepatocellular carcinoma (TEC), which may contribute to some of its reported toxicities [21]. The initial registration of ibrutinib in CLL was based on the results of two clinical trials presenting the clinical benefit of the drug in R/R cases: PCYC-1102 and the extension study PCYC-1103 [11,22]. The phase 1b/2 PCYC-1102 study enrolled 85 patients with R/R CLL or SLL (33% with del 17p) dividing into two groups receiving ibrutinib orally once daily in two different doses: 51 patients – 420 mg and 34 patients – 840 mg. ORR and complete response rate (CRR) to ibrutinib monotherapy was 71% and 3.3%, with similar responses in high--risk cases with del 17p or an unmutated IGHV. The ORR was the same in both groups: in the group treated with the dose of 420 mg (71%, 2 complete responses, 34 partial responses) and with 840 mg (71%, 24 partial responses) and an additional 20% and 15% of patients in the respec-

tive groups had a partial response with persistent lymphocytosis. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies, and the del 17p. Ibrutinib treatment promoted durable responses, irrespective of the dose. The estimated PFS at 30 months was 69%. However, in patients with del 17p, the median PFS was only 28 months [11,22]. Disease progression developed in 11 patients (13%) during follow-up, and in 7 of those patients the transformation to Richter's syndrome was observed; the median time from the initial diagnosis of CLL to transformation was 98 months (range 24 to 143). Among the 11 patients with PD, 10 patients had unfavorable cytogenetic mutations (del 17p or del 11q) [11,22]. In the next phase-2 trial (NCT01520519), ibrutinib was investigated in combination with rituximab to increase its efficacy in high-risk R/R CLL patients [23,34]. The response rates were better, with ORR/CRR at 95% and 23% respectively [23-24] Twenty-one out of 40 participating patients discontinued treatment: including 10 due to disease progression and 11 for other causes. The median PFS was 45 months in the whole group and 32.2 months in patients with del 17p. Median OS has not been reached but 14 (35%) patients died from disease progression, infections or other causes [23,24]. Those preliminary results were validated in the phase-3 study (RESONATE), where ibrutinib was compared with ofatumumab in 391 patients with R/R CLL. The results confirmed ibrutinib efficacy with both response rates and survival times (PFS and OS) better than in ofatumumab-treated patients [25-27]. The randomized phase-3 study (RESONATE-2) in 265 elderly, previously untreated CLL patients compared ibrutinib to chlorambucil (13). Response rates (ORR 86 vs 35%), PFS and OS (98 vs 85% at the median follow-up time of 18.4 months, $p<0.001$) were significantly better for ibrutinib. In additional phase-2 study (NCT01500733), ibrutinib's role TN patients with del 17p/TP53 was confirmed [28]. The results from our single center real-life experience demonstrate the similarly high percentages of response rates (ORR 86.7%), confirming the efficacy of the drug in daily practice in CLL patients with the poorest prognosis.

The incidence of AF in meta-analysis of four trials with a median follow-up of 26 months was 3.3/100 persons per year and even higher after longer exposure to the drug (9% in a study with a median therapy time of 46 months) [29-31]. In the elderly TN CLL population treated in the RESONATE-2 trial, ibrutinib was well tolerated: only 9% of patients were discontinued, compared to 23% treated by chlorambucil. The main reason for ibrutinib discontinuation included AF (2/8 patients) and hemorrhagic complications, grade 3 or higher (3/6 patients). According to long-term follow-up of RESONATE, RESONATE 2 and HELIOS studies the number of patients discontinuing ibrutinib therapy was ranged from 25% to 51% [13,26-27,32]. The higher proportions of discontinuation rates due to AEs, ranging from 12% to 32% were noted in other ibrutinib studies [33,35]. Ibrutinib was approved by the FDA and EMA in 2014 for R/R and high--risk TN patients with del 17 [36]. In our analysis, we demonstrated high efficacy of ibrutinib in monotherapy in R/R settings, with acceptable toxicity that did not lead to discontinuation of the drug. It should be added that in Polish reality, the lack of other effective, alternative treatment options, especially in high-risk R/R patients, requires introducing supportive treatment such as prophylactic antibiotics or antiviral drugs and G-CSF to control AEs and to maintain the only available salvage treatment. The results presented in our analysis prove that the appropriate management of supportive treatment in adverse events may result in a long-term benefits of ibrutinib treatment without discontinuing the drug.

Ibrutinib changed the therapeutic approach to CLL patients, despite emerging, acquired resistance, which mechanisms are under active investigation [33,37]. Most current strategies are aimed at inducing longer remissions with fewer side effect – this is a key concept that has contributed to the development of second generation, more selective BTK inhibitors.

The analysis has limitations, due to its retrospective character and the limited availability of the data on IGHV mutational status.

In conclusion, the data from this retrospective analysis confirms the high efficacy and safety of ibrutinib monotherapy in R/R high-risk CLL patients in routine clinical practice. Longer follow-up, together with MRD analysis, will provide additional information on the real-life effectiveness and safety.

Autorship statement

MP, MDD, WJ – performed the study and analyzed the data,

MP, MDD, WJ – designed the study,

MP, MDD, WJ, MJ, AS – had a substantial contribution to the conception and design of the work,

MDD, WJ – drafted the manuscript,

MDD, WJ– critically revised the manuscript for important intellectual content,

MP, MDD, WJ, MJ, AS – had a substantial contribution to the acquisition, analysis and interpretation of data for the work,

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written. All authors declare no conflict of interest.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The authors confirm that the tables and figures are original and have not previously been published.

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