



# Toxicity and Outcomes of Ibrutinib in Chronic Lymphatic Leukemia-Real-World Results from the Study of 215 Patients in Argentina

Horacio Fernández Grecco<sup>1</sup>, Pablo Valdemoros<sup>1</sup>, Maria Jose Mela Osorio<sup>2</sup>, Miguel Pavlovsky<sup>2</sup>, Carolina Pavlovsky<sup>2</sup>, Astrid Pavlovsky<sup>2</sup>, Juan Dupont<sup>3</sup>, Dardo Riveros<sup>3</sup>, Juan Altuve<sup>3</sup>, Gonzalo Ferini<sup>4</sup>, Victoria Otero<sup>4</sup>, Fernando Warley<sup>4</sup>, Fernando Bezares<sup>5</sup>, Alicia Enrico<sup>6</sup>, Laura Kornblihtt<sup>7</sup>, Silvana Cugliari<sup>8</sup>, Augusto Miroli<sup>9</sup>, Manuel Bonder<sup>10</sup>, Alicia Bistman<sup>11</sup>, Julio Pose<sup>12</sup>, Marta Zerga<sup>13</sup>, Maria Cabrejo<sup>1</sup>, Jorge Jerez<sup>1</sup>, Maria Cardenas<sup>14</sup>, Patricio Pereyra<sup>15</sup>, Juan Maradei<sup>16</sup>, Ana Portalez<sup>17</sup>, Fernanda Tosin<sup>18</sup>, Virginia Gilli<sup>19</sup>, Rodrigo Vallejo<sup>20</sup>, Noelia Masachessi<sup>21</sup>, Eriberto Roveri<sup>22</sup>, Susana Mari<sup>23</sup>, Magali Colucci<sup>24</sup>, Basilio Pertiné<sup>25</sup>, Noemi Pintos<sup>1</sup>

<sup>1</sup>Department of Hematology, Sanatorio Julio Mendez, Buenos Aires, Argentina

<sup>2</sup>Department of Hematology, Fundaleu, Buenos Aires, Argentina

<sup>3</sup>Department of Hematology, Centro de Educacion Medica e Investigacion Clinica, Buenos Aires, Argentina

<sup>4</sup>Department of Hematology, Hospital Italiano, Buenos Aires, Argentina

<sup>5</sup>Department of Hematology, Hospital Alvarez, Buenos Aires, Argentina

<sup>6</sup>Department of Hematology, Hospital Italiano La Plata, Buenos Aires, Argentina

<sup>7</sup>Department of Hematology, Hospital de Clinicas Jose de San Martin Universidad de Buenos Aires, Buenos Aires, Argentina

<sup>8</sup>Department of Hematology, Instituto Roffo Universidad de Buenos Aires, Argentina

<sup>9</sup>Department of Hematology, Hospital Churrua, Buenos Aires, Argentina

<sup>10</sup>Department of Hematology, Sanatorio Trinidad Mitre, Buenos Aires, Argentina

<sup>11</sup>Department of Hematology, Hospital Ramos Mejia, Buenos Aires, Argentina

<sup>12</sup>Department of Hematology, Sanatorio Otamendi, Buenos Aires, Argentina

<sup>13</sup>Department of Hematology, Hospital Aleman, Buenos Aires, Argentina

<sup>14</sup>Department of Hematology, Hospital Italiano San Justo, Buenos Aires, Argentina

<sup>15</sup>Department of Hematology, Hospital Posadas, Buenos Aires, Argentina

<sup>16</sup>Department of Hematology, Hospital Emilio Ferreyra, Bahia Blanca, Argentina

<sup>17</sup>Department of Hematology, Hospital Centeno, La Pampa, Argentina

<sup>18</sup>Department of Hematology, Hospital El Cruce, Buenos Aires, Argentina

<sup>19</sup>Department of Hematology, Hospital Entre Rios, Entre Rios, Argentina

<sup>20</sup>Department of Hematology, Hospital Bernardo Houssay, Buenos Aires, Argentina

<sup>21</sup>Department of Hematology, Centro Oncologico San Luis, San Luis, Argentina

<sup>22</sup>Department of Hematology, Sanatorio Norte Rosario, Santa Fe, Argentina

<sup>23</sup>Department of Hematology, Hospital Blas Dubary, Buenos Aires, Argentina

<sup>24</sup>Department of Hematology, Instituto Conciencia, Neuquen, Argentina

<sup>25</sup>Department of Hematology, Instituto Medico de Alta Complejidad, Salta, Argentina

## Email address:

[horaciogreccof@hotmail.com](mailto:horaciogreccof@hotmail.com) (Horacio Fernández Grecco), [pablo.valdemoros@gmail.com](mailto:pablo.valdemoros@gmail.com) (Pablo Valdemoros),

[mjmela@fundaleu.org.ar](mailto:mjmela@fundaleu.org.ar) (Maria Jose Mela Osorio), [mpavlovsky@fundaleu.org.ar](mailto:mpavlovsky@fundaleu.org.ar) (Miguel Pavlovsky),

[cpavlovsky@fundaleu.org.ar](mailto:cpavlovsky@fundaleu.org.ar) (Carolina Pavlovsky), [astridp@intramed.net](mailto:astridp@intramed.net) (Astrid Pavlovsky), [jcdupont643@gmail.com](mailto:jcdupont643@gmail.com) (Juan Dupont),

[dardoriveros@hotmail.com](mailto:dardoriveros@hotmail.com) (Dardo Riveros), [jialtuve@hotmail.com](mailto:jialtuve@hotmail.com) (Juan Altuve), [gonzalo.ferini@hospitalitaliano.org.ar](mailto:gonzalo.ferini@hospitalitaliano.org.ar) (Gonzalo Ferini),

[victoria.otero@hospitalitaliano.org.ar](mailto:victoria.otero@hospitalitaliano.org.ar) (Victoria Otero), [fernando.warley@hospitalitaliano.org.ar](mailto:fernando.warley@hospitalitaliano.org.ar) (Fernando Warley),

[raybezares@gmail.com](mailto:raybezares@gmail.com) (Fernando Bezares), [aliciaenricomattos@gmail.com](mailto:aliciaenricomattos@gmail.com) (Alicia Enrico), [lauko09@gmail.com](mailto:lauko09@gmail.com) (Laura Kornblihtt)

dracugliari@gmail.com (Silvana Cugliari), augustomiroli@hotmail.com (Augusto Miroli), drmanuelbonder@hotmail.com (Manuel Bonder), abistmans@hotmail.com (Alicia Bistman), juliopose@hotmail.com (Julio Pose), melizerga@hotmail.com (Marta Zerga), mariacabrejo@hotmail.com (Maria Cabrejo), jorgejerez\_81@hotmail.com (Jorge Jerez), maria.cardenas@hospitalitaliano.org.ar (Maria Cardenas), patriciohernanpereyra@gmail.com (Patricio Pereyra), noemasa@yahoo.com.ar (Noelia Masachessi), eribertoveri@gmail.com (Eriberto Roveri), sulilian24@hotmail.com (Susana Mari), maga\_col@hotmail.com (Magali Colucci), bptertine@gmail.com (Basilio Pertiné), noemipintos@yahoo.com.ar (Noemi Pintos)

\*Corresponding author

## To cite this article:

Horacio Fernández Grecco, Pablo Valdemoros, Maria Jose Mela Osorio, Miguel Pavlovsky, Carolina Pavlovsky, Astrid Pavlovsky, Juan Dupont, Dardo Riveros, Juan Altuve, Gonzalo Ferini, Victoria Otero, Fernando Warley, Fernando Bezares, Alicia Enrico, Laura Kornblihtt, Silvana Cugliari, Augusto Miroli, Manuel Bonder, Alicia Bistman, Julio Pose, Marta Zerga, Maria Cabrejo, Jorge Jerez, Maria Cardenas, Patricio Pereyra, Juan Maradei, Ana Portalez, Fernanda Tosin, Virginia Gilli, Rodrigo Vallejo, Noelia Masachessi, Eriberto Roveri, Susana Mari, Magali Colucci, Basilio Pertiné, Noemi Pintos. Toxicity and Outcomes of Ibrutinib in Chronic Lymphatic Leukemia - Real-world Results from the Study of 215 Patients in Argentina. *International Journal of Clinical and Experimental Medical Sciences*. Vol. 9, No. 3, 2023, pp. 42-48. doi: 10.11648/j.ijcems.20230903.11

**Received:** December 30, 2022; **Accepted:** February 16, 2023; **Published:** May 17, 2023

**Abstract:** Different pivotal works allowed the approval of ibrutinib as a CLL treatment, both in the first line and in relapsed/refractory patients, the adverse effects differ from conventional chemotherapy, the discontinuation rate was 10%, but in different real-life studies, showed a higher number of complications and medication suspension rates of 40 to 50%. To know the reality of the use of ibrutinib in CLL in our environment, we designed this work with the objectives of evaluating the safety profile of the drug with the description of the adverse effects, their incidence, and their severity. The clinical efficacy will also be studied with the determination of the response achieved, calculation of overall survival (OS) and progression-free survival. Also as an additional objective, the discontinuation rate and its causes will be obtained. A total of 215 patients in 26 centers throughout the country were retrospectively analyzed. 189 patients (88%) had a global response, and the majority 58% achieved a partial response. The 5-year overall survival was 60%, with no difference between patients with different numbers of previous lines. The progression-free survival of the entire group was 5.06 years. 44.7% of the population, presented at least 1 adverse effect. The most frequent ones were: bleeding, thrombocytopenia, pneumonia and diarrhea. Others presented: anemia, neutropenia, infections, AF, HTA, arthralgia, rash, opportunistic infections. Most adverse events were mild to moderate in grade and generally occurred within the first 6 months. The main cause of treatment suspension was the appearance of adverse effects, 37 patients had to suspend it, 27 due to adverse effects (72.97%). In our work, we found that ibrutinib, as a single agent, has outstanding activity in CLL, with a significant percentage of overall responses, even in patients with several lines of prior treatment. Most of the adverse effects were of a mild to moderate degree. The cardiovascular effects of TKI, HBP, and AF, are in percentages similar to those reported in other studies. If we analyze the percentage of treatment discontinuation, which is 17%, mostly due to adverse effects, this finding is similar to pivotal studies. In conclusion, our real-life study confirms the important activity of ibrutinib in patients with CLL, in the first line and relapses, highlighting the low percentage of treatment discontinuation in our environment. We believe our work reflects the real life and daily care of patients with CLL, under treatment with ibrutinib in our environment.

**Keywords:** Ibrutinib, Toxicities, Real Word

## 1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, with a mean age at diagnosis of 71 years. This disease is characterized by a clonal expansion of morphologically mature and immunologically incompetent B lymphocytes, CD5 + and CD23 +. They accumulate in the blood, bone marrow, spleen, and lymph nodes. [1, 2-7].

The patients who required treatment received different chemioimmunotherapy schemes, which are difficult to carry out in elderly patients and patients with poor prognostic

factors, such as 17p or alterations in the TP53 gene, present worse clinical evolution and shorter survival. [1].

In recent years, new drugs have emerged with advances in understanding the disease's biology.

The discovery of the role of Bruton tyrosine kinase (BTK) in the survival of B lymphocytes allowed the emergence and development of BTK inhibitor drugs such as ibrutinib. [7].

Ibrutinib binds covalently to BTK through cysteine at position 481, it is an irreversible inhibitor, with a potent inhibitory effect for more than 24 hours and a half-life of 2 to 3 hours.

In vivo and in vitro studies have shown that ibrutinib

inhibits the survival, proliferation, and migration of CLL cells.

It is the first BTK inhibitor to be approved for the treatment of CLL and other lymphoproliferative diseases such as mantle lymphoma. [3-4].

This approval was the result of various clinical studies: the RESONATE study showed that ibrutinib significantly prolonged progression-free survival and overall survival at 12 months (90 vs 81%), compared with ofatumumab in relapsed/refractory patients with LLC.

It maintained its positive results even in high-risk or unfavorable subgroups such as patients with 17 p.

In RESONATE II, ibrutinib was compared with chlorambucil in patients with CLL, without previous treatment, showing favorable results in terms of progression-free survival was 90% at 18 months in the ibrutinib group and 52% in the group of chlorambucil. [3].

When overall survival was compared, it was 98% with ibrutinib versus 85% in the chlorambucil group.

The aforementioned studies, and others, showed the important activity of ibrutinib in this pathology and led to the approval of this drug for use both in the first line and in relapsed/refractory patients.

Although it does not present the typical adverse effects of chemotherapy, it has a characteristic profile of adverse effects, among which the most frequent are: diarrhea, gastrointestinal disturbances, infections, especially of the upper respiratory tract, pneumonia, opportunistic infections, rash, arthralgia, and less frequent but significant from the clinical point of view, hypertension, AF and bleeding. [5-12, 14].

On the other hand, it requires continuous administration until progression or intolerance, so data on adverse effects and safety are important.

It is common to find a discrepancy in the results of clinical studies compared to studies carried out in the so-called real world or real life, especially in the area of oncohematology. In the case of ibrutinib, in general, these latter studies showed a greater number of adverse effects and a higher rate of abandonment or discontinuation of the medication. [1-3].

For example, real-life jobs reported a higher incidence of opportunistic infections, and a discontinuation rate close to 40-50%. [13, 15-16]

Clinical studies generally enroll younger patients, with fewer comorbidities and with better general conditions than in usual clinical practice.

For this reason, knowledge of the real world is increasingly important, especially with new molecules and especially those that require continuous use until progression.

To know the reality in our environment regarding the use of ibrutinib, we designed this study.

## 2. Goals

Primary: Evaluate the safety profile of the drug with the description of the adverse effects, their incidence, and their severity.

The clinical efficacy will also be studied with the determination of the response achieved, the calculation of overall survival (OS) and progression-free survival.

Also as an additional objective, the discontinuation rate and its causes will be obtained.

## 3. Materials and Methods

Retrospective, descriptive, multicenter study of patients with CLL who received ibrutinib as monotherapy, in the first line or in subsequent lines between March 1st, 2016, and March 1st, 2021. The treating physicians had to complete the requested information in an Excel spreadsheet.

The severity of the adverse effects was reported according to the CTCAE in its version 5.0 of November 2017.

The response degrees were established according to the iw LLC guidelines.

CLL patients older than 18 years were included.

Patients who received ibrutinib in combination with another CLL medication, for example, anti-CD20 antibodies, were excluded.

Overall survival was defined as the time from the start of ibrutinib treatment until death from any cause. Data from patients who were alive were censored on the last contact date.

Survival function estimates were made using the Kaplan-Meier method, and the comparison between strata of said functions was based on the log-rank test. Hazard ratios were estimated using stratified Cox proportional hazards models. In a complementary way, the restricted mean survival times were calculated.

In the description of quantitative variables, mean and standard deviation were used for cases of normal distributions, or median and interquartile range for the others.

All tests were performed at 5% significance, and interval estimates at 95% confidence.

All analyzes were performed using Stata software, version 16.0.

## 4. Results

A total of 215 patients were evaluated, 108 were treated in 14 centers in the Autonomous City of Buenos Aires (CABA), 33 patients were treated in 5 centers in the Province of Buenos Aires (PBA) and the rest were reported by 7 centers in the interior of the country.

The clinical and demographic characteristics of the patients are shown in table 1.

**Table 1.** Clinical and demographic characteristics of the patients.

Mean age	70 years (37- 94)
Sex n° y%.	Woman: 80 (37,2%), Men: 135 (62,8%)
Staging Binet, n°	A: 39 B: 58 C: 40
Staging Rai, n°	0-II: 145 III-V: 67

ECOG%	0: 60%
	I: 26%
	II: 10%
	III a V: 4%
CIRS n.º	0: 19
	I- II: 35
	III-IV: 28
	mas de V: 42
Previous line of treatment n.º y%.	Without treatment: 83 (38,6%)
	1 ó 2 previous lines: 108 (50,23%)
	3 previous lines: 18 (8,37%)
	4 o more lines: 6 (2,79%)
Cytogenetic n.º y%	Normal: 89 (60,96%)
	Not done: 41 (28,08%)
	Complex karyotype: 12 (8,22%)
	Others alterations: 4 (2,74%)
Del 17 (p) n.º y%	del 17 (p) absent: 152 (73,08%)
	del 17 (p) present: 56 (26,92%)

The median follow-up was 67.6 months

The IGVH mutational status was performed only in 118 patients, 54.9% of the total population. Of these 118 patients, 66 patients, 30.84%, were non-mutated, and 51 patients were mutated, 43.22%.

The rest of the studies that are usually carried out by FISH, such as 13q, 11q, trisomy 12 or alterations in p53, were carried out in a minority of patients, so they could not be analyzed for the study.

Response to treatment with ibrutinib:

The mean continuous exposure to the medication was 14.7 months.

189 patients (88%) had a global response, the majority 58% achieved a partial response and only 30% of the total study population achieved a complete response. The rest of the patients had stable disease or progressed. Figure 1.

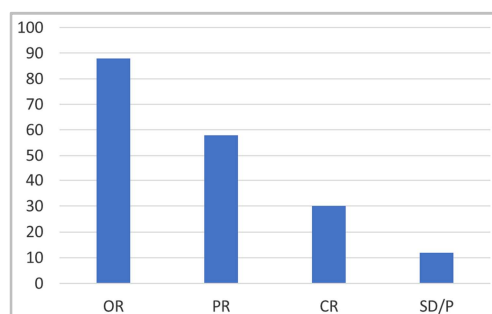


Figure 1. Depth of response.

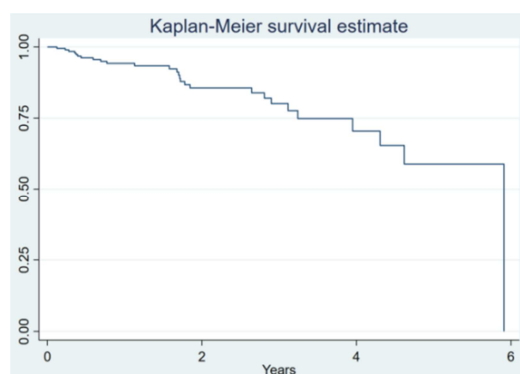


Figure 2. Overall survival.

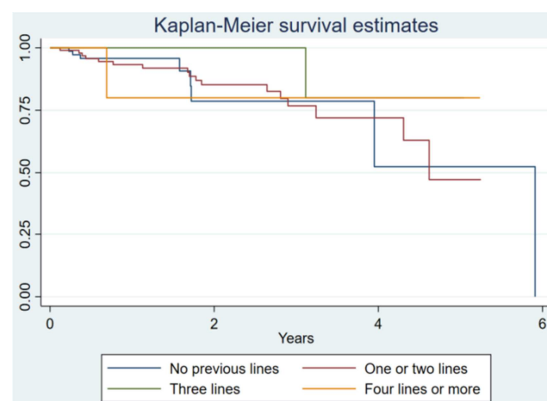


Figure 3. Survival/treatment lines.

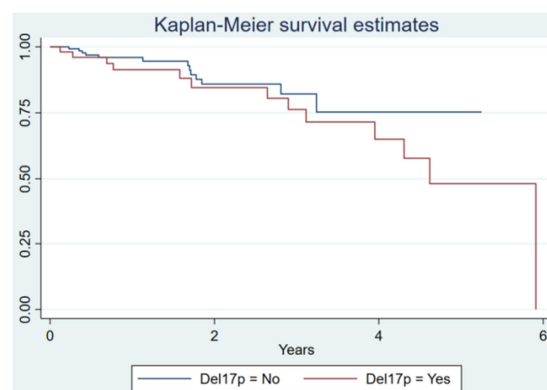


Figure 4. Survival with del 17p.

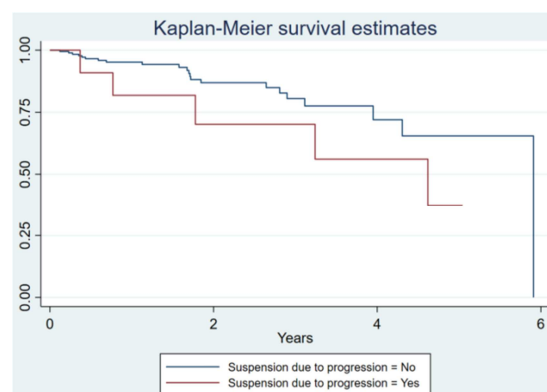


Figure 5. Progression-free survival.

The 5-year overall survival was 60%, with no difference between patients with different numbers of previous lines. Figure 2 and Figure 3. Survival was also evaluated about the presence of the 17 p deletion, and although the patients with this deletion had worse survival, the difference is not statistically significant ( $p: 0.27$ ). Figure 4.

The progression-free survival of the entire group was 5.06 years. Figure 5.

Toxicity:

44.7% of the population, 96 patients presented at least 1 adverse effect. Adverse effects can be divided into hematological and non-hematological, the most frequent hematological were: bleeding and thrombocytopenia, and within the non-hematological pneumonia and diarrhea. The following

table shows the frequency of the different side effects:

**Table 2.** Frequency of adverse effects.

HEMATOLOGICAL (n°, patients, %)	NON HEMATOLOGIC
Bleeding: 20 (9,3%)	Pneumonia: 24 (11,2%)
Thrombocytopenia: 19 (8,8%)	Diarrhea: 22 (10,2%)
Anemia: 16 (7,4%)	Infection: 21 (9,8%)
Neutropenia: 12 (5,6%)	AF: 21 (9,8%)

Other adverse effects reported were: hypertension (7.4%); arthralgia (6%); rash (5.1%) and opportunistic infections (3.3%).

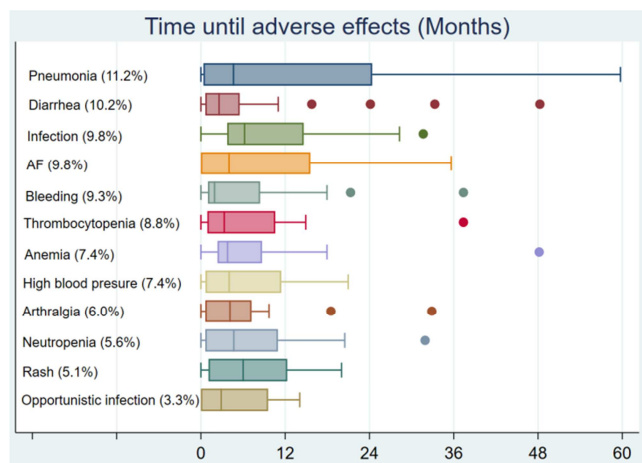
Of the 7 patients with opportunistic infections, 4 of them had had 1 or more lines of medical treatment.

The severity of adverse events was defined according to CTCAE version 5.0 of November 2017. Mild to moderate adverse events were considered to be those of grades 1-2, of said classification.

Most adverse events were mild to moderate in grade and generally occurred within the first 6 months, but some cases may occur up to 2 years and longer. Table 3. Figure 6.

**Table 3.** Severity of adverse events.

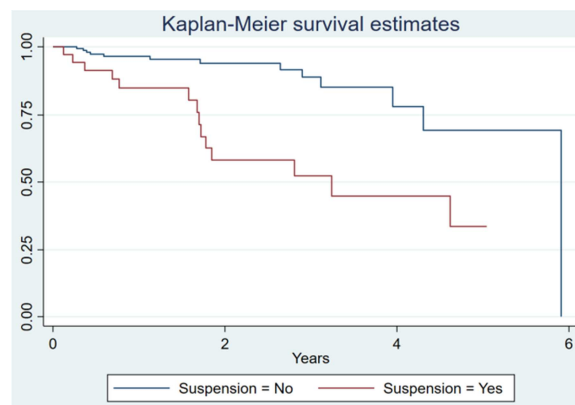
Adverse effects	Mild	Moderate	Severe
Pneumonia	4	19	1
Diarrhea	13	9	0
Infeccion	10	9	1
AF	7	10	0
Bleeding	12	6	1
Thrombocytopenia	8	8	0
Anemia	7	8	0
High blood pressure	9	7	0
Arthralgia	8	4	0
Neutropenia	2	9	1
Rash	6	1	3
Opportunistic infection	4	2	1



**Figure 6.** Time until adverse effects.

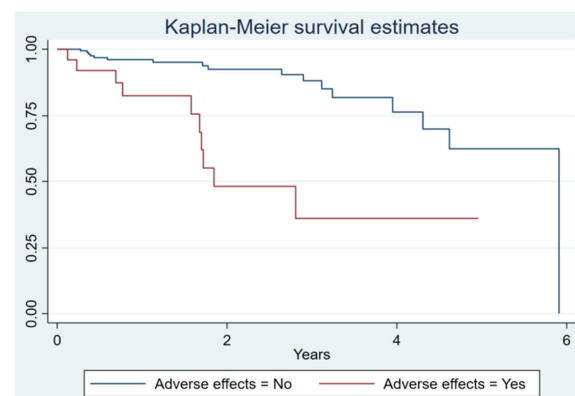
The main reason for discontinuing treatment was the appearance of adverse effects, 37 patients had to discontinue, 27 due to adverse effects (72.97%) and 10 patients due to progression, 5 of them with Richter syndrome.

As expected, the suspension affected the evolution, and the global survival was significantly lower, 3.14 years, in the group that suspended the treatment. Figure 7.



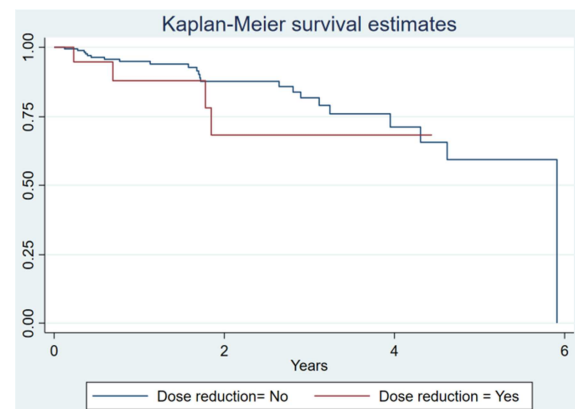
**Figure 7.** Survival with suspension of treatment.

If we analyze because of discontinuation, survival in patients who discontinued due to progression is much lower. 4.92 years vs. 2.79. Figure 8.



**Figure 8.** Cause of suspension.

19 patients reduced the dose, with no change in survival. Figure 9.



**Figure 9.** Survival according to dose reduction.

During the study period, 13 patients died, 13.08% of the included patients.

## 5. Discussion

In our work, we found that ibrutinib, as a single agent, has outstanding activity in CLL, with a significant percentage of

overall responses, even in patients with several lines of prior treatment.

The overall response of 88% is similar to the pivotal studies.

The global survival rate in our work is 5,06 years, observing that patients with deletion 17p had less chance of survival but didn't reach a statistically significant difference, showing the important activity of Ibrutinib in these type of patients.

Initial studies with Ibrutinib suggested that the progression of the disease was the main cause of discontinuation of treatment. On the contrary our work demonstrated that the appearance of adverse effects or intolerance was the main cause of suspension of treatment with Ibrutinib. In our work the percentage of treatment discontinuation, which is 17%, this finding is similar to pivotal studies (where it is 10%), but it is different from other real-life studies, in different countries, where the suspension rate reaches between 40 and 50%. [1-2]

This difference could be because most of the events are mild to moderate and could be managed with symptomatic medication and, on the other hand, to the fact that access to other therapeutic alternatives is difficult for the different health subsystems in our country.

It should be noted that close to 45% of the patients presented at least 1 adverse effect.

Analyzed in general, most of the adverse effects appear within the first 6 to 12 months of treatment, and some of them, such as pneumonia and infections, can appear up to 2 years after treatment but tend to decrease over time.

In our work, we divided adverse events into hematological and non-hematological.

Among the hematological, the most frequent were bleeding (9.3%) and thrombocytopenia (8.8%), the non-hematological, the 2 most found were pneumonia (11.2%) and diarrhea (10.2%).

Most of the adverse effects were of a mild to a moderate degree and only 8 patients had severe events.

Regarding the cardiovascular effects of TKI, HBP and AF, they were not the most frequent among non-hematological events and are in percentages similar to those reported in other studies.

Another interesting fact to highlight, which requires future prospective studies, is that the patients who reduced the dose of ibrutinib did not see their overall survival affected.

Regarding opportunistic infections, they occurred in a low percentage of patients, and more than half of the cases had at least 1 line of prior treatment.

## 6. Conclusion

Our real-life study confirms the important activity of ibrutinib in patients with CLL, in the first line and relapses, with a tolerable safety profile, highlighting the low percentage of treatment discontinuation in our environment.

Although our study has some limitations, such as its retrospective nature, we believe it reflects the real life and daily care of patients with CLL, under treatment with ibrutinib in our environment, given the participation of numerous health centers from different parts of our country.

## References

- [1] Winquist M, Askild A, Andersson P, Karlsson K, Karlsson C, Lauri B, et al. Real-world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: data from 95 consecutive patients treated in a compassionate use program. A study from the Swedish Chronic Lymphocytic Leukemia Group. *Haematologica* 2016 101 (12); 1573- 1580.
- [2] Mato A, Nabhan C, Thompson M, Lamanna N, Brander D, Hill B, et al. Toxicities and outcomes of 616 ibrutinib- treated patients in the United States: a real-world analysis. *Haematologica* 2018 103 (5) 874-879.
- [3] Barr P, Robak T, Owen C, Tedeschi A, Bairey O, Bartlett N, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. *Haematologica* 2018 103 (9) 1502-1510.
- [4] O'Brien S, Furman R, Coutre S, Flinn I, Burger J, Blum K, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood* 2018 131 (17) 1910- 1919.
- [5] Lipsky A, Farooqui M, Tian X, Martyr S, Cullinane A, Nghiem K, et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. *Haematologica* 2015 100 (12) 1571- 1578.
- [6] Coutre S, Byrd J, Hillmen P, Barrientos J, Barr P, Devereux S, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. *Blood advances* 2019 3 (12) 1799- 1807.
- [7] Woyach J, Ruppert A, Heerema N, Zhao W, Booth A, Ding W, et al. Ibrutinib Regimens versus Chemoinmunotherapy in Older Patients Untreated CLL. *N ENGL J MED* 2018 1- 12.
- [8] Chen L, Bose P, Cruz N, Jiang Y, Wu Q, Thompson P, et al. A pilot study of lower doses of ibrutinib in patients with chronic lymphocytic leukemia. *Blood* 2018 132 (21) 2249-2259.
- [9] Lad D, Malhotra P, Khadwal A, Prakash G, Jain A, Varma S, et al. Reduced Dose Ibrutinib Due to Financial Toxicity in CLL. *Indian J Hematol Blood Transfus* 2019 35 (2) 260-264.
- [10] Hilal T, Banacloche J, Leis J. Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: Linking mechanisms with infections. *Blood Reviews* 2018 32 387-399.
- [11] Rogers K, Mousa L, Zhao Q, Bhat S, Byrd J, Boghdady Z, et al. Incidence of opportunistic infections during ibrutinib treatment for B-cell malignancies. *Leukemia* 2019 LETTER.
- [12] Williams A, Baran A, Meacham P, Feldman M, Valencia H, Newsom-Stewart C, et al. Analysis of the risk of infection in patients with chronic lymphocytic leukemia in the era of novel therapies. *Leukemia & Lymphoma* 2017.
- [13] Jain P, Keating M, Wierda W, Sivina M, Thompson P, Ferrajoli A, et al. Long-term Follow-up of Treatment with Ibrutinib and Rituximab in Patients with High-Risk Chronic Lymphocytic Leukemia. *Clin Cancer Res* 2017 23 (9) 2154-2158.
- [14] Weerdt I, Koopmans S, Kater A, van Gelder M. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. *Haematologica* 2017 102 (10) 1629-1639.

- [15] Falchi L, Baron J, Orlikowski C, Ferrajoli A. BCR Signaling Inhibitors: an Overview of Toxicities Associated with Ibrutinib and Idelalisib in Patients with Chronic Lymphocytic Leukemia. *Mediterr J Hematol Infect Dis* 2016 8 1-12.
- [16] Tobinai K, Ogura M, Ishizawa K, Suzuki T, Munakata W, Uchida T, et al. Safety and tolerability of ibrutinib monotherapy in Japanese patients with relapsed/refractory B cell malignancies. *Int J Hematol* 2016 103 86-94.