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Clinical experience and safety of venetoclax in the treatment of patients with chronic lymphocytic leukemia – real-world data from a hemato-oncology center

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The treatment of patients with CLL has undergone significant changes in recent years. Standard chemoimmunotherapy is changing to targeted inhibition with modern drugs. The listed drugs have better efficacy and significantly improve the overall survival of patients according to registry clinical studies. In a retrospective analysis, we evaluated 43 patients with CLL who underwent venetoclax treatment at the Hematology Department, University Hospital and Polyclinic F. D. Roosevelt Banská Bystrica, Slovakia (FNsP FDR BB) in 2019-2024. The aim of this work was to evaluate retrospectively the efficacy and safety of venetoclax in the treatment of patients with CLL. The median age of patients at the time of initiation of venetoclax treatment was 58 years, range 41-79 years. The majority of patients, 27 (63%) were men and 16 (37%) were women. Patients were treated with venetoclax in the first and higher line, in combination with obinutuzumab, with rituximab, and in monotherapy. Of these, 16 (37%) patients were after previous treatment with ibrutinib. Treatment indications and response assessment were based on the 2018 international workshop on the Chronic Lymphocytic Leukemia (iwCLL) Criteria. Patients were evaluated after at least 2 months of treatment until disease progression. The effect of treatment was assessed by objective examination of the patient, possibly by imaging examination (USG, CT scan) and evaluation of blood parameters. Adverse effects were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In case of disease progression, treatment was interrupted. The results of our work confirmed the efficacy and safety of venetoclax in combination with obinutuzumab, and rituximab, even as monotherapy in patients with CLL. The efficacy of the above regimens in our group of patients is comparable to that in clinical studies, even in patients with high-risk genetic features, such as 17p deletion and unmutated IgVH status. Treatment with venetoclax was also effective and well tolerated in patients after previous treatment with ibrutinib. The limitations of our evaluation are the small patient population and the short median follow-up of patients. In line with the conclusions of clinical trials and retrospective analysis from real-life practice, we can say that venetoclax-based treatment regimens are highly effective in patients with CLL in the first and higher line of treatment, with acceptable and well-manageable toxicity. This treatment is also effective in patients after previous treatment with ibrutinib.

Key words: venetoclax; chronic lymphocytic leukemia; treatment efficacy; adverse effects

Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia in adults in the Western world, with an average age of approximately 70 years at the time of diagnosis. Its incidence is 4.2/100,000 population per year and rises to over 30/100,000 in people >80 years of age. Nevertheless, routine screening for CLL is not recommended at any age [1–3]. It typically occurs in older patients and has a highly variable clinical course. The number of patients has increased in recent years, and 20–30% of newly diagnosed patients are currently younger than 55 years. However, this is due not only to the increase in incidence but also to better detection. Knowledge about the pathogenesis of the disease has increased recently, and diagnostic and treatment options have changed radically over the past few years [4, 5].

It is still true that only patients with active, symptomatic disease or with advanced Binet or Rai stage require treatment. Treatment with standard chemoimmunotherapy is being replaced by the advent of targeted therapy with Bruton's

tyrosine kinase inhibitors and BCL2 inhibitors [6]. The first targeted anticancer drug acting on the apoptotic pathway used in clinical practice is venetoclax [7, 8]. We know that tumor formation can occur when a tumor cell can bypass apoptotic signaling and avoid apoptosis. One way its activity is by increasing the expression of antiapoptotic proteins of the BCL-2 family [9]. Venetoclax is a specific BCL-2 inhibitor, belonging to a group of anticancer drugs called BH3 mimetics, because they mimic the role of proapoptotic "BH3-only" proteins [10]. In 2016, venetoclax was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with chronic lymphocytic leukemia with a deletion of the short arm of chromosome 17, which contains the TP53 gene, which encodes the p53 tumor suppressor [11]. In 2018, venetoclax was then approved in combination with the anti-CD20 antibody rituximab for patients without this deletion. The predecessor of venetoclax was another substance, navitoclax, which had to be withdrawn from clinical testing because it caused severe thrombocytopenia in patients. It later turned out that the problem with navitoclax was its lack of specificity. Navitoclax was a polyselective inhibitor with an affinity for two antiapoptotic proteins BCL-2 and BCL-XL simultaneously. Venetoclax was therefore designed as a monoselective inhibitor with affinity only for BCL-2. This created a sufficiently wide therapeutic window for the treatment of tumors with typically increased expression of this protein. Healthy cells, in which antiapoptotic proteins are represented evenly, are less sensitive to the inhibitor [10].

Venetoclax is approved in Slovakia for patients with CLL in monotherapy and in combination with rituximab and obinutuzumab. Since June 2024, it can also be used in patients with CLL in first-line treatment in combination with ibrutinib.

The aim of this work was to retrospectively evaluate the efficacy and safety of venetoclax in the treatment of patients with CLL at the Hematology Department of the F.D. Roosevelt University Hospital in Banská Bystrica (FNsP FDR BB). Until now, mostly only the results of clinical studies have been published. The patient population in these studies is mostly selected. Hereby we would like to present real-world data based on the unselected population of patients who are indicated for the treatment with kinase and signaling pathways inhibitors.

Table 1. Patient characteristics.

Baseline characteristics	All N=43
Age/median, range	59 (41–79)
Men	27 (63%)
Women	16 (37%)
CIRS score, mean (± SD)	6 (±1.6)
<6	30/43 (70%)
>6	13/43 (30%)
Creatinine, median, range	84 (48–231)
eGFR (ml/min/1.73m^2) median, range	1.2 (0.4–1.78)
Absolute lymphocyte count at baseline, median, range	41.6 (0.68–411)
Prior ibrutinib treatment, n (%)	16/43 (37%)
RAI stage, n (%)	
I	1 (2%)
II	12 (28%)
III	6 (14%)
IV	24 (56%)
Binet stage, n (%)	
A	2 (5%)
B	16 (37%)
C	25 (58%)
CL–IPI, n (%)	
low risk (0–1)	5(12%)
medium risk (2–3)	9 (22%)
high risk (4–6)	17 (41%)
very high risk (7–10)	10 (24%)
Performance status, n (%)	
1	36 (84%)
2	7 (16%)
Deletion 17p, n (%)	
present	13 (32%)
not present	28 (68%)
IGHV status, n (%)	
mutated	20 (46%)
unmutated	20 (46%)
unknown	3 (7%)

Patients and methods

Patient population. In a retrospective analysis, we evaluated 43 patients with CLL who underwent venetoclax treatment at the Hematology Department of the FNsP FDR BB in 2019–2024. The basic characteristics of the patients are summarized in Table 1. The median age of the patients at the time of initiation of venetoclax treatment was 58 years, range 41–79 years.

Most patients were in very good clinical condition-performance status (PS) according to ECOG (Eastern Cooperative Oncology Group), grade 1 was determined in 38 (84%) patients. Patients were assessed with a CIRS score (Cumulative Illness Rating Scale) with a mean of 6, of which 30 (70%) patients had fewer comorbidities with a CIRS score below 6, and 13 (30%) patients were treated for multiple diseases with a CIRS score above 6. We also assessed renal parameters of patients undergoing venetoclax treatment, the median creatinine in patients was 84 μmol/l, in the range of 48–231 μmol/l. An important indicator of the risk of lysis syndrome in patients is the baseline absolute lymphocyte count, in our group of patients the median of this value was 41.6×10^6/l, in the range of $1.68–411\times10^6$/l. In our cohort of 43 patients, 15 (35%) patients received venetoclax in the first-line treatment, 8 (19%) patients in the second-line treatment, and 20 (46%) patients in the third to sixth-line treatment. More than a third of patients (16) (37%) had undergone previous treat-

ment with ibrutinib (Bruton kinase inhibitor). Most patients had Rai stage IV (24) and Binet stage C (25) patients (58%). According to the International Prognostic Index CLL-IPI, 5 (12%) patients were low risk, 9 (22%) patients were intermediate risk, 17 (41%) patients were high risk, and 10 (24%) patients were very high risk. According to high-risk genetic markers, 17p deletion was present in 13 (32%) patients and unmutated IgVH was present in 20 (46%) patients. Due to unavailability, TP53 mutations were not examined.

Treatment indications and response assessment were based on the 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Criteria [12].

Patients were treated with venetoclax in combination with obinutuzumab, rituximab (monoclonal anti-CD20 antibodies), and as monotherapy. The decision on which regimen to use in the treatment of the patient was based on the patient's line of treatment. The venetoclax-obinutuzumab (VO) regimen was used in patients in the first-line treatment, venetoclax-rituximab (VR) in the second-line treatment, and venetoclax monotherapy (V) in the second- to sixth-line treatment. The drugs were prepared and administered according to the recommendations in the SPC of the drug.

Venetoclax was used in all regimens at a dose of 400 mg, orally, daily in 28-day cycles after a 5-week titration, the so-called ramp-up phase, when the dose was gradually increased from 20 mg through 50 mg, 100 mg, and 200 mg to a final dose of 400 mg.

In combination with rituximab, venetoclax was administered from the first day of the 1st cycle and then, after the completion of venetoclax titration, rituximab was added from the 8th day of the 2nd cycle, which was administered intravenously at an initial dose of 375 mg/m^2, in subsequent cycles at a dose of 500 mg/m^2 in total in 6 cycles. Venetoclax in the VR regimen was continued until the 24th month of treatment, inclusive.

In the obinutuzumab regimen, venetoclax was administered starting on day 22 of cycle 1, with obinutuzumab administered intravenously as a 1,000 mg loading dose administered on days 1, 8, and 15 of the first treatment cycle. To reduce the incidence of infusion-related reactions in patients, the first dose of obinutuzumab was administered over 2 days (day 1 [100 mg] and day 2 [900 mg]). In each subsequent treatment cycle (cycles 2 to 6), patients were administered obinutuzumab at a dose of 1,000 mg on day 1 only, through cycle 6, for a total of 8 administrations. Venetoclax was administered for a total of 12 months. In monotherapy, patients received venetoclax until disease progression or acceptable tolerance to treatment.

Premedication was routinely administered prior to treatment to minimize the incidence of treatment-related reactions. Before rituximab, standard premedication was administered with paracetamol 1,000 mg orally, hydrocortisone 100 mg i.v. and bisulepin 1 mg i.v.

In premedication before obinutuzumab, dexamethasone 24 mg i.v. in 100 ml infusion of 0.9% sodium chloride solution, bisulepin 1 mg i.v. and paracetamol 1,000 mg orally was administered.

Patients were evaluated after at least 2 months of treatment until disease progression. The effect of treatment was assessed by objective examination of the patient, or by imaging examination (USG, CT examination) and evaluation of blood parameters. Adverse effects were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In case of disease progression, treatment was discontinued.

Statistical analysis. Quantitative variables (e.g., age, laboratory values) were processed using descriptive statistics – using the number of measurements, mean, standard deviation, or median. Qualitative variables (e.g., gender, disease stage, response to treatment) were processed using absolute and relative frequency. Data on overall patient survival, progression-free survival, and treatment retention were processed using the Kaplan-Meier curve. Due to the low number of patients, it was not possible to statistically compare the individual groups. The only testing performed was the use of the Fisher exact test when comparing the treatment response in patients pretreated vs. not pretreated with ibrutinib. The difference in treatment response between the groups of patients pretreated vs. not pretreated with ibrutinib in the qualitative variable was tested using the Fisher exact test of independence. The level of significance was chosen as α=0.05.

Results

The final analyzed dataset included 43 patients with CLL treated with venetoclax in combination with obinutuzumab (15 patients, 35%), in combination with rituximab (6 patients, 14%), and as monotherapy (22 patients, 51%) (Figure 1). Patients received venetoclax in the first to sixth lines of treatment, of which all patients treated with the VO regimen were in the first line of treatment and the VR regimen in the second line of treatment. Patients treated with venetoclax monotherapy were in the second to sixth lines of treatment (Figure 2).

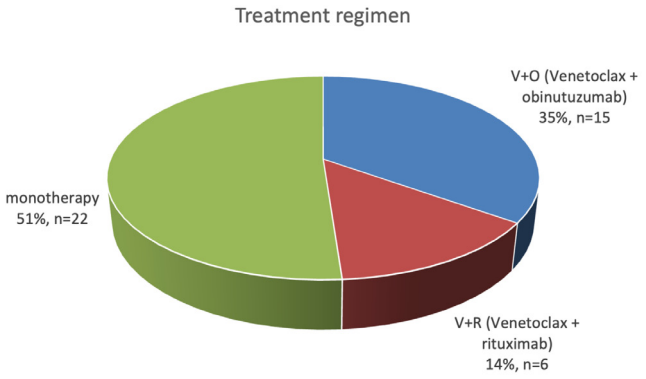

Figure 1. Treatment regimen used.

By assessing the risk of tumor lysis syndrome (TLS), 5 patients (12%) were at high risk and 38 patients (88%) were at intermediate risk.

Tumor mass reduction, so-called debulking was administered to 4 patients (9%), and the remaining 39 patients (91%) underwent venetoclax treatment directly according to the protocol. The rituximab-bendamustine regimen, or leukeran in combination with prednisone, was used as debulking. The decision to use debulking was up to the treating physician (usually based on the lymph node size and/or level of leukocytosis); it was not used in most patients. Infusion-related infusion reactions were recorded in 2 patients (5%) with clinical manifestations of fever and chills. These reactions were of moderate severity, the patients did not require hospitalization, and they completed the treatment completely on an outpatient basis. We did not observe TLS in patients.

The efficacy of the treatment was assessed based on the best response to treatment, after at least 2 months of treatment. The assessment of the treatment was in accordance with the iwCLL criteria, regardless of the duration of response, since we evaluated the patients after only two months of treatment. The overall response rate (ORR) in our cohort reached 100%, of which 40% of patients achieved a total of 40% complete remissions (CR) and 60% partial remissions (PR). The ORR was assessed in all patients, no patients were excluded. The high ORR reflected the correct indication of patients in relatively good clinical condition. In the first-line treatment, patients treated with VO achieved 40% CR and 60% PR, in the second-line treatment with the VR regimen 50% of patients achieved a CR and 50% of patients achieved a PR, and in venetoclax monotherapy, 36% of patients achieved a CR and 64% PR (Figure 3). Patients previously treated with ibrutinib also responded to venetoclax treatment. Similarly, patients with a 17p deletion responded to venetoclax treatment with a CR or PR. We separately evaluated patients after previous treatment with ibrutinib, a total of 16 patients, of which one patient received second-line combination therapy with VR, achieving a complete remission. The remaining 15

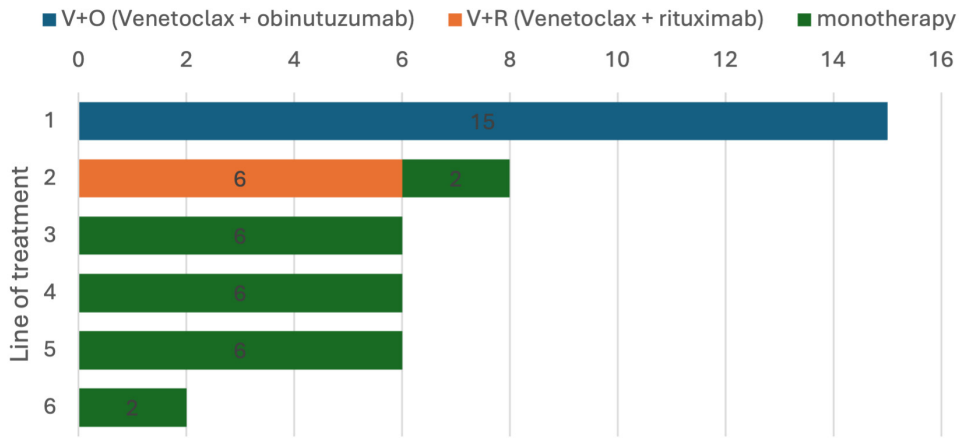

Figure 2. Treatment regimen vs. line of treatment.

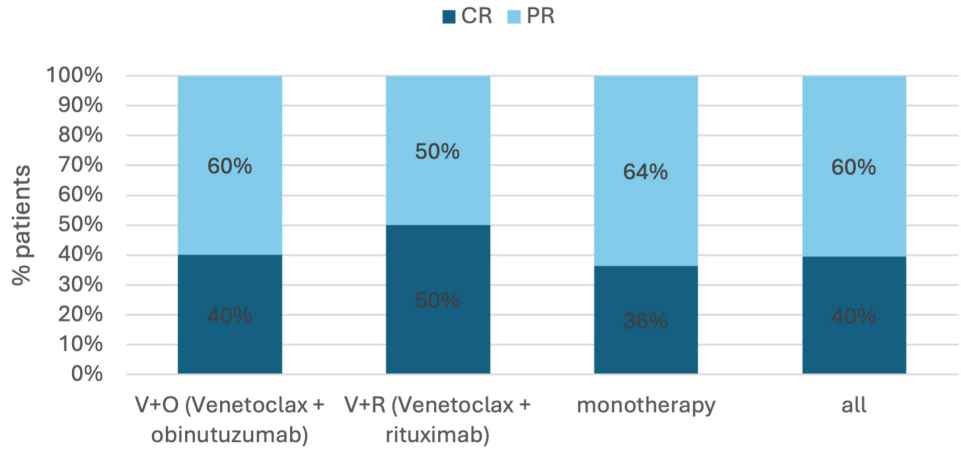

Figure3. Assessment of treatment response.

patients were treated in second-line and higher-line settings with venetoclax monotherapy, with a CR rate of 20% and a PR rate of 80%.

The median follow-up for patients with the VO regimen was 9 (2–18) months, with the VR regimen 32 (11–45) months, and with venetoclax monotherapy 33 (2–56) months.

The progression-free survival (PFS) for patients treated with VO is 100% at the time of response assessment. The VR subgroup of patients had a median PFS of 31 months (95% CI, 21.3–46.3), and the median PFS was not reached in the venetoclax monotherapy group (Figure 4). In this group of patients, we evaluated the mean PFS, which was 40.2 months (95% CI, 30.0–50.4).

Overall survival (OS) at 24 and 36 months was 75% and 50%, respectively, in patients with VR and 76% and 68%, respectively, on venetoclax monotherapy. In patients treated with the first-line VO regimen, the OS was 100% (Figure 5).

Hematologic adverse events (all CTCAE grades) were reported in 68% of patients treated with the VO regimen, 83% of patients treated with VR, and 68% of patients treated with venetoclax monotherapy. The most common grade 3 or 4 hematologic adverse event was neutropenia. Grade 3 or 4 neutropenia developed in 26% of cases with VO, 33% of patients with VR, and 37% of patients with venetoclax. Grade 3 or 4 anemia was observed in 7% of patients with VO, 17% of patients with VR, and no patients treated with venetoclax monotherapy experienced grade 3 or 4 anemia. Grade 3 or 4 thrombocytopenia was not observed in any patient treated with venetoclax.

Grade 3 or 4 non-hematological adverse events were not observed, the most common in our patients were infectious complications, fully manageable on an outpatient basis, without the need for parenteral antibiotics. Treatment was discontinued in 8 patients (19%), of which 2 due to treatment toxicity (5%), 4 patients experienced disease progression (9%), and 2 patients died (5%).

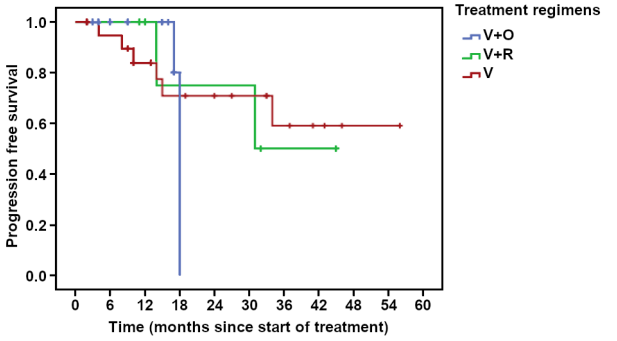

Figure 4. Progression-free survival.

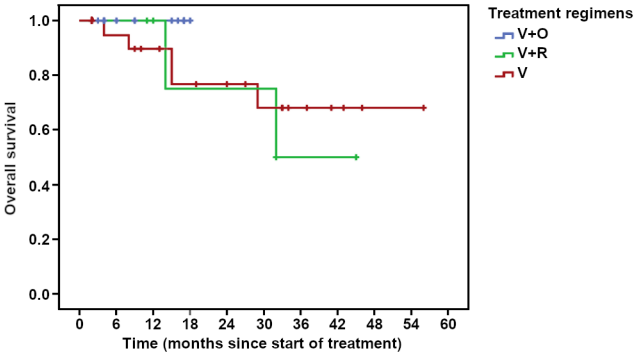

Figure 5. Overall survival of patients according to individual regimens. Differences in follow-up duration may influence observed OS rates.

Discussion

The results of our work confirmed the efficacy and safety of venetoclax in combination with obinutuzumab, rituximab, as well as in monotherapy in patients with CLL.

Our data suggest that venetoclax is effective in patients with high-risk genetic features, though larger studies are needed to confirm comparability to clinical trials. The limitations of our evaluation are the small patient population and the short median follow-up of patients. Despite the above, we can say that venetoclax treatment regimens are highly effective in patients with CLL in both first and higher lines of treatment, with acceptable and well-manageable toxicity. The median age of our patients was 58 years, ranging from 41 to 79 years. In the CLL13 [13] and CLL14 [14] studies, the median age ranged from 62 to 72 years, in the MURANO study [15] the median age was 64 years, in the retrospective analysis of the Polish CLL Working Group [16] and in the multicenter analysis of the UK CLL Working Group [17] the median age was 67 years. The lower median age in our patient group compared to clinical studies and retrospective analyses is probably due to the indication of treatment to younger patients already in the first-line (VO) setting. This possibility is new in the entire Europe, so there are not many published real-world data outside clinical studies. The efficacy of treatment was assessed based on the best response to treatment, after at least 2 months of treatment. The assessment of treatment was in accordance with the iwCLL criteria, regardless of the duration of response, as we assessed patients after only 2 months of treatment. Our assessment confirmed the rapid onset of the effect of venetoclax in patients with CLL. We have seen a high overall response rate of 100% with VO, VR, and monotherapy compared to the CLL13 [13] studies in fit patients (ORR 96% for VO) and the CLL14 [14] study in unfit patients (ORR 85% for VO). The effect of standard chemoimmunotherapy like FCR (fludarabine, cyclophosphamide, rituximab), which has been the gold standard for first-line treatment of CLL patients for many years, was lower in fit patients in the CLL13 study with an ORR of 88.8%. The superiority of VO over FCR-BR in fit patients was confirmed in the international, open-label randomized, phase III Cristallo study [18] with the primary endpoint of uMRD

presented at the 66th American Society of Hematology Annual Meeting & Exposition. More patients treated with venetoclax plus obinutuzumab achieved uMRD at month 15 than patients treated with FCR-BR (81.3% vs. 54.7%, respectively; 95% CI, 12.3–40.9; p = 0.0004). The study evaluated patients without del (17p) or TP53 mutations. In patients with R/R CLL treated with VR in the MURANO study [15] the ORR was 92.3%, in the Polish CLL Working Group [16] analysis the ORR was 95.3%. The overall response rate of patients evaluated by the UK CLL Working Group [17] was 88% for venetoclax monotherapy. The complete remission rate in our cohort was 40% for VO, 50% for VR, and 36% for venetoclax monotherapy. In the CLL13 study, the CR rate was 56.8% for fit patients treated with VO, and only 31% with FCR. Comparable results were also achieved in the CLL14 study (CR 50% for VO in unfit patients). In the MURANO study, undetectable minimal residual disease (MRD) was assessed as the deepest response for the VR regimen, with MRD negativity achieved in 70.3% of patients. In a retrospective analysis by the Polish CLL Working Group, CR was achieved in 69.2% of patients.

At the time of evaluation of our work, we observed lower CR values, which can be explained by the fact that treatment was not yet completed in patients in the first and second line. Patients are currently continuing the aforementioned treatment and subsequent result improvement can be awaited.

In our cohort, patients previously treated with ibrutinib also responded to venetoclax treatment, and patients with a 17p deletion also responded to venetoclax treatment with CR or PR. Given the small patient population, it was not meaningful to evaluate the statistical difference.

We separately evaluated patients after previous treatment with ibrutinib, a total of 16 patients were evaluated, of which one patient received combination VR treatment, achieving complete remission. The remaining fifteen patients were treated with venetoclax monotherapy, achieving a CR of 20% and a PR of 80%. Better results were achieved by colleagues in a multicenter analysis of the UK CLL Working Group [17], where the CR was 38% for venetoclax monotherapy in patients after prior treatment with Bruton's kinase inhibitors. The differences mentioned are probably due to our small patient population.

When comparing patients previously treated with ibrutinib and those not treated with it, no statistically significant difference was found in the overall response rate to venetoclax treatment (p = 0.121), although the assessment of PFS would be more meaningful to compare the effectiveness of treatment in individual patient groups. The median follow-up of patients with the VO regimen was 9 (2–18) months, with the VR regimen 32 (11–45) months, and with venetoclax monotherapy 33 (2–56) months. The different median follow-up is directly related to the treatment options for patients with CLL in Slovakia. PFS and OS could not be compared in our entire patient population with data from clinical trials and real-world practice, as we followed patients with VO and VR for a short time, and patients had not completed treatment yet. In patients on venetoclax monotherapy, at a median follow-up of 33 (2–56) months, the median PFS has not been reached. OS at 24 and 36 months was 76% and 68%, respectively, for patients on venetoclax monotherapy. Comparable PFS and OS results were obtained in the UK CLL working group [17], where at a median follow-up of 15.6 months, 1-year PFS was 65% in patients on venetoclax monotherapy and 1-year OS was 75.1%. The presented PFS and OS results in patients on venetoclax monotherapy reflect effective treatment in patients with CLL, including high-risk patients, taking into account the current limitations of the dataset.

Overall, adverse events of any grade in our patients occurred in 68% of patients with VO, 83% with VR, and 68% of patients with venetoclax monotherapy. The most common grade 3 or 4 hematologic adverse event was neutropenia. Grade 3 or 4 neutropenia developed in 26% of patients with VO, 33% with VR, and 37% of patients on venetoclax monotherapy. Grade 3 or 4 anemia was observed in 7% of patients with VO, 17% with VR, and no patients treated with venetoclax monotherapy experienced grade 3 or 4 anemia. Grade 3 or 4 thrombocytopenia was not observed in any patient in our cohort. We observed a lower incidence of grade 3 or 4 adverse events than in clinical trials and real-world analyses. The differences are probably due to the small number of patients in our cohort.

In the CLL13 study [13], the most common hematological adverse event was grade 3 or 4 neutropenia in 45.2% of fit patients treated with VO, and in 53% of patients treated with FCR, at 4-year follow-up. Comparable results were also seen in the CLL14 [14] study (unfit patients), where grade 3 or 4 neutropenia was present in 51.9% of patients. In the MURANO study [15] evaluating patients with R/R CLL treated with VR, neutropenia was the most frequently reported, in a total of 60.8% of patients of any grade, of which 57.7% of patients had grade ≥3 neutropenia. In a retrospective analysis by the Polish CLL Working Group [16], neutropenia of any grade was reported in 74.4% of patients and in 57.3% of patients grade ≥3. Non-hematological adverse events of grade 3 or 4 were not reported in our cohort. The most common infectious complications in our patients were those that were manageable on an outpatient basis, without the need for parenteral antibiotics and hospitalization.

In the CLL13 study (fit patients), grade 3 infections were recorded in 13.2% of patients with VO, and in 18.5% of patients with FCR. Grade 4 infections were not documented in any patient. On the contrary, a slightly higher incidence of grade 3 or 4 infections was documented in the CLL14 study, 17.1%. In the MURANO study, the incidence of infectious complications was also 17.5% of patients.

We cannot clearly explain the lower incidence of infections in our patients; the most likely explanation may be the younger age and the proximity of patients to the hospital, so any medical intervention could start shortly after the first

signs of infection as well as a limited number of patients and the lower median age of our patients. It is possible that immunoglobulin substitution in patients with severe hypogammaglobulinemia with IgG values < 4.0 g/l and signs of infection also played a role. The absence of TLS in our patients was likely due to thorough supportive care measures and close follow-up of patients in outpatient care.

While our results align with clinical trial data, differences in patient selection, supportive care, and real-world treatment adherence should be considered when making direct comparisons.

In accordance with the conclusions of clinical studies and retrospective analyses from real-world practice, venetoclax regimens in combination with an anti-CD20 antibody or as monotherapy can be considered effective regimens with good effect in patients with CLL in the first and higher line of treatment. Our data suggest that venetoclax is effective in patients with high-risk genetic features, though larger studies are needed to confirm comparability to clinical trials. We will continue to follow the patients in our cohort, and in patients with venetoclax in the first line of treatment, we plan to evaluate MRD by flow cytometric analysis of peripheral blood. We expect results comparable to clinical studies. Treatment-related toxicity was comparable and manageable on an outpatient basis. Patient tolerance and adherence to treatment were very good, and complications of treatment were managed without the need for hospitalization.

This progress in the treatment of CLL patients means a better quality of life, as they are not exposed to the toxicity of chemotherapy, which, unlike targeted inhibition by modern drugs, affects all dividing cells and can therefore also have a mutagenic effect.

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