Farmacia Hospitalaria 47 (2023) T69–T74

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Original

[Translated article] Adherence and quality of life in patients with chronic lymphocytic leukemia treated with oral antineoplastic drugs

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ARTICLE INFO

Article history:
Received 4 June 2022
Accepted 7 August 2022
Available online 23 January 2023

Keywords:
Chronic lymphocytic leukemia
Antineoplastic agents
Treatment adherence
Quality of life

ABSTRACT

Objective: To evaluate adherence and quality of life to oral antineoplastic treatment in patients with chronic lymphocytic leukemia. To compare adherence and quality of life according to treatment subgroups and treatment-line subgroups.

Methods: We conducted a descriptive prospective study from June to November 2021 in a tertiary care hospital. Patients with chronic lymphocytic leukaemia, seen at the Oncology Pharmacy and treated with oral antineoplastic drugs for at least 6 months prior to inclusion in the study were included. Adherence was assessed using Morisky's 8 item Medication Adherence Scale and leftover pills counts, considering adherents if their adherence rate was ≥90%. Quality of life was assessed with Euro-Qol EQ-5D-3L questionnaire, Functional Assessment of Chronic Illness Therapy – Fatigue scale and QLQ-C30 questionnaire from European Organization for Research and Treatment of Cancer. Two interviews were scheduled: at the time of inclusion and at 3 months. The clinical history was reviewed and demographic and clinical variables were collected. The data statistical analysis was carried out with SPSS® 25.0 software.

Results: Twenty three patients were included, all of them showed an adherence rate higher than 90%; 20 patients were considered high adherent, and 3 patients médium adherent to treatment according to Morisky's 8 item Medication Adherence Scale. The results of the EQ-5D-3L questionnaire showed that the patients were all of them autonomous in their personal care and daily activities, 69.6% did not have any mobility problems and 78.3% did not have anxiety/depression; 56.5% had some type of pain. Eighteen patients had no fatigue, and 5 had mild/moderate fatigue according to Functional Assessment of Chronic Illness Therapy – Fatigue scale. The results of the EORTC QLQ-C30 questionnaire showed that patients had a high /healthy functional level, a good quality of life and a low level of symptoms. Analysis by treatment subgroups and by treatment-line subgroups did not show statistically significant differences in adherence or quality of life.

Conclusions: Patients diagnosed with chronic lymphocytic leukemia and treated with oral antineoplastic therapies showed a high adherence rate and referred a good quality of life.

Adherencia y calidad de vida en los pacientes con leucemia linfocítica crónica tratados con antineoplásicos orales

Palabras clave:
Leucemia linfocítica crónica
Antineoplásicos orales

RESUMEN

Objetivos: Evaluar la adherencia y la calidad de vida de los pacientes con leucemia linfocítica crónica tratados con antineoplásicos orales. Comparar la adherencia y la calidad de vida según el fármaco recibido y según la línea de tratamiento.

DOI of original article: https://doi.org/10.1016/j.farma.2022.11.006.
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https://doi.org/10.1016/j.farma.2022.12.010

Adherencia terapéutica
Calidad de vida

Método: Estudio descriptivo prospectivo realizado de Junio a Noviembre de 2021 en un hospital terciario. Se incluyeron pacientes con leucemia linfocítica crónica, atendidos en la consulta de Farmacia Oncológica y tratados con antineoplásicos orales desde al menos 6 meses antes de la inclusión en el estudio. Se estimó la adherencia mediante el cuestionario *Morisky's 8 item Medication Adherence Scale* y el recuento de medicación sobrante, considerándose adherentes si su tasa de adherencia era ≥90%. Para evaluar la calidad de vida, se utilizó el cuestionario EQ-5D-3L del grupo EuroQol, la escala *Functional Assessment of Chronic Illness Therapy – Fatigue* y el QLQ-C30 de la European Organization for Research and Treatment of Cancer. Se programaron dos entrevistas: en el momento de la inclusión y a los 3 meses. Se revisó la historia clínica, recogiéndose variables demográficas y clínicas. El análisis estadístico se realizó con el programa SPSS® 25.0.

Resultados: Se incluyeron 23 pacientes: todos fueron adherentes según el recuento de medicación; y 20 presentaron adherencia alta, y 3 media, según *Morisky's 8 item Medication Adherence Scale*. Los resultados del cuestionario EQ-5D-3L mostraron que los pacientes eran autónomos para su cuidado personal y sus actividades cotidianas, el 69,6% no tenían problemas de movilidad, el 78,3% no tenía ansiedad/depresión y el 56,5% presentaba algún tipo de dolor. Dieciocho pacientes no tenían fatiga, y 5 presentaron fatiga leve/moderada según los resultados de la escala *Functional Assessment of Chronic Illness Therapy – Fatigue*. Los pacientes tenían un nivel funcional alto/saludable, una calidad de vida buena y un bajo nivel de sintomatología según los resultados del cuestionario QLQ-C30. El análisis por subgrupos de tratamiento y línea de tratamiento, no mostró diferencias estadísticamente significativas en la adherencia y en la calidad de vida.

Conclusiones: Los pacientes con leucemia linfocítica crónica en tratamiento con antineoplásico oral presentan una elevada tasa de adherencia al mismo y refieren tener una buena calidad de vida.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the Western World, with an incidence of 5.7 cases per 100,000 inhabitants every year[1]. Median age at diagnosis is 72 years[1]. Since the disease affects mainly elderly individuals, it is often accompanied by at least one severe comorbidity[2].

The condition can manifest itself in several ways, some patients experiencing an indolent and stable course and others demonstrating a more aggressive form, with cytogenetic alterations that sometimes result in poorer prognosis[3,4]. 80–85% of patients remain asymptomatic, and only patients with an active form of the disease (15—20%) requiring treatmen.[5].

New treatment options for CLL have been introduced in recent years, which have resulted in changes to the clinical guidelines. Such therapies, which have been classified into first-line and post-relapse treatments, include oral antineoplastics, Bruton's tyrosine kinase inhibitors (ibrutinib and acalabrutinib), phosphatidylnositol kinase 3 inhibitors (idelalisib) and inhibitors of the anti-apoptotic protein B-cell lymphoma (venetoclax).

Adherence to these drugs may not always be optimal as their use typically involves daily administration at the patients' home, longer treatment times and the risk of adverse events. This is a particularly serious concern as poor adherence may negatively impact the patients' response and survival and lead to an increase in healthcare costs as more consultations and hospital admissions are usually necessary. For those reasons, the World Health Organization has identified poor adherence as a public health problem[6].

On the other hand, the symptoms associated with the disease, the adverse events resulting from existing treatments, and the knowledge that CLL is an incurable condition, may take a significant toll on the patients' quality of life. Quality-of-life measurements could provide an in-depth understanding of the impact that the disease and its treatment have on the patients' perception of their wellbeing.

Some published studies have evaluated adherence to oral antineoplastics in patients with other hematologic neoplasms such as chronic myeloid leukemia (CML)[7,8] and multiple mieloma[9,10]. Other authors have looked into the quality of life of patients with CLL receiving either no treatment or conventional treatment[11,12]. However, few studies have evaluated adherence to the new oral antineoplastic drugs and the quality of life of patients who take them[13].

The purpose of this study was to determine the adherence to oral antineoplastic treatment and the quality of life of patients with CLL. The secondary goals included a comparison of adherence and quality of life according to the drug received and the line of treatment applied.

Methods

This was a descriptive retrospective study carried out between June and November 2021 in a third-level hospital. Subjects comprised all the patients with CLL in at the oncology unit of the hospital's pharmacy department treated with oral antineoplastics (ibrutinib, acalabrutinib, idelalisib or venetoclax) since at least 6 months prior to inclusion. Patients treated with clinical research samples in the context of a clinical trial were excluded. The study was approved by the regional Ethics Committee for Research with Medicinal Products.

Adherence was measured using both the standardized 8-item Morisky Medication Adherence Scale (MMAS-8)[14] and the leftover pill counting method[15]. In the latter case, the adherence rate was calculated using the following formula:

$$\frac{(number\ of\ units\ dispensed - number\ of\ units\ leftover)}{(prescribed\ number\ of\ units\ per\ day\ x\ number\ of\ days\ between\ the\ two\ appointments)} \times 100$$

Patients whose adherence was ≥90% were considered adherent. The 90% threshold was selected based on the published literature, more specifically, on the study by Marin *et al*[8].

Quality of life was measured on the basis of three questionnaires: the QLQ-C30 questionnaire, developed by the European Organization for Research and Treatment of Cancer (EORTC)[16,17]; the EQ-5D-3L questionnaire, created by the EuroQol Group[18]; and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale[19].

Two telephone interviews were scheduled: the first one at the time of inclusion and the second one at three months from inclusion. The first interview was dedicated to administering the questionnaires, obtaining demographic data and asking patients about leftover medication. At the second interview, questions were asked again about leftover medication and the adherence rate was calculated.

The patient's electronic medical records were reviewed and the following data was recorded: sociodemographic variables (sex, age), clinical variables (including comorbidities, according to the Cumulative Illness Rating Scale (CIRS-G)[20], cognitive status (according to Pfeiffer's

test[21], current and previous treatment, time from initiation of current treatment, adverse events [according to the Common Terminology Criteria for Adverse Events[22] (CTCAE) v5.0 scale] and concomitant medication.

Statistical analysis

A descriptive analysis was carried out of the variables collected during the study. Quantitative variables are expressed as absolute values and percentages. Quantitative variables are presented as mean ± standard deviation (variables with parametric distribution) and median and interquartile range (variables with nonparametric distribution). The Kolmogorov–Smirnov test was used to evaluate the distribution of data.

The comparison of variables between the groups was carried out by means of Student's t test for parametric variables and using Mann–Whitney's U test for nonparametric variables. To analyze correlations between two qualitative variables, use was made of Pearson's correlation coefficient (r) for parametric data and Spearman's correlation coefficient (rho) for nonparametric data. Statistical significance was set at a p value <0.05.

The statistical analysis was carried out using version 25.0 of the SPSS software package (IBM) for PCs.

Results

Twenty-eight patients were identified as candidates for participation in the study. Two patients died before giving informed consent and three had their treatment modified. The final sample comprised 23 patients: 15 males and 8 females, with a mean age of 69.7 (± 8.02) years. Mean score on the CIRS-G scale was 6.13 (± 4.14), with 18 patients showing no cognitive impairment and 5 showing moderate–mild impairment on Pfeiffer's test. The median number of concomitant treatments was 5 (range: 1–12) and the median number of previous treatments for CLL was 1 (range: 0–5). Eighteen patients were on treatment with ibrutinib (8 of them were taking the drug as first-line treatment) and 5 were taking venetoclax (none as first-line treatment). No patients were on acalabrutinib or idelalisib. Mean time on those oral antineoplastics up to inclusion in the study was 1.57 (± 0.98) years.

Fourteen patients did not demonstrate any adverse reaction to the treatment during the performance of the study. The other patients did present adverse events (AEs), all of them grade 1 or 2. AEs included hypertension (3 patients), hematuria (2 patients), myelotoxicity (1 patient), constipation (1 patient), and epistaxis and musculoskeletal disorders (1 patient).

Twenty patients (86.9%) demonstrated high adherence and three (13.1%) moderate adherence according to the MMAS-8 test. Table 1 shows non-adherence as measured by the answers of patients to the different questions in the questionnaire. The questions eliciting higher levels of non-adherence were questions 1 (Do you sometimes forget to take your medication?), 4 (Do you sometimes forget to take your medicines when you go on a trip or when you leave home?), and 8 Do you often find it difficult to remember that you must take all your medicines?).

Mean adherence according to the leftover pill counting method was 98.07% (± 2.21). All patients considered themselves to be adherent to treatment (overall adherence was >90%). A detailed analysis of adherence percentages shows that 20 patients presented with an adherence rate > 95% and 3 patients were seen to have an adherence rate between 90 and 95%. These 3 patients were the same ones who demonstrated moderate adherence on the MMAS-8 test.

The results of the EQ-5D-3L questionnaire (Table 2) showed that all patients were autonomous for self-care and 91.3% (21 patients) were autonomous for their activities of daily living (ADLs), 69.6% (16 patients) experienced no mobility problems, 78.3% (18 patients) did not report anxiety or depression, and 56.5% (13 patients) presented with some degree of pain. No patient claimed to have "many problems" on any of the dimensions evaluated.

Table 1
Adherence to treatment according to the MMAS-8 test.

Total (n = 23) (%)	
1. Do you sometimes forget to take your medication?	13.04
2. Sometimes people do not take their medicine due to reasons other than forgetfulness. Think about the last two weeks. Did you fail to take your medicine any day?	0
3. Have you ever taken fewer tablets than you were supposed to or have you stopped taking them without telling your doctor because you they made you feel worse?	0
4. Do you sometimes forget to take your medicines when you go on a trip or when you leave home?	4.35
5. Did you take your medicines yesterday?	0
6. Do you sometimes skip your medication when you feel your symptoms are under control?	0
7. Taking your medicines every day is really inconvenient for some people. Do you feel it is a nuisance to follow your treatment plan?	0
8. Do you often find it difficult to remember that you must take all your medicines?	
a) Never/rarely	86.95
b) Every now and then	4.35
c) Sometimes	8.7
d) Often	0
e) Always	0
Score on the MMAS-8 questionnaire:	
High adherence: 0 points	
Moderate adherence: 1–2 points	
Low adherence: 3–8 points	

The results of the EORTC QLQ-C30 questionnaire (Table 3) showed high scores on all functional scales, which means that the patients' functional level was high/healthy. Patients obtained top median scores (100 points) on three of the functional scales. Specifically, they could carry out their ADLs with no impediments (median: 100 points; range: 100–100); they could lead a normal social/family life without interference from their treatment (median: 100 points; range: 100–100), and their degree of anxiety, concern and irritability, and the intensity of their symptoms as assessed on this scale were very low (median: 100 points; range: 83–100). According to the EORTC QLQ-C30 scale, the score for overall health status/quality of life was 66.5 points (range: 58–83) out of 100, which denotes good health and a satisfactory quality of life. As regards symptoms-related items, patients had a low level of symptoms (fatigue: 11.11 (0–22.22), pain 16.66 (0–49.99) and nausea/vomiting 16.66 (0–33). Symptoms such as dyspnea (0; 0–0), insomnia (0; 0–6.38), anorexia (0; 0–0) and diarrhea (0; 0–0) were not reported.

The mean score on the FACIT-T scale was 46 (± 4.77), which indicates an absence of fatigue (Table 4).

The treatment subgroup analysis (ibrutinib *vs* venetoclax) did not demonstrate statistically significant adherence-related differences between the results of the MMAS-8 questionnaire (ibrutinib: 15 highly adherent patients and 3 moderately adherent ones; venetoclax: 5 highly adherent patients; p = 0.083) and those obtained following application of the leftover pill counting method (97.96 ± 1.46 *vs*

Table 2
Results of the EQ-5D-3L questionnaire.

Total (n = 23) (%)			
	No problems	Some/moderate problems	Severe problems
Mobility	69.6	39.4	0
Self-care	100	0	0
Usual activities	91.3	8.7	0
Pain/discomfort	43.5	56.5	0
Anxiety/depression	78.3	21.7	0

Table 3
Results of the EORTC QLQ-C30 questionnaire.

		Análisis por subgrupos (p < 0,05; Prueba de U Mann–Whitney)					
	Median (interquartile range)	Ibrutinib Median (interquartile range)	Venetoclax Median (interquartile range)	p value	1st line Median (interquartile range)	Other lines Median (interquartile range)	p
Functional scales							
Physical function	93.2 (79.8–100)	100 (91.66–100)	73.33 (69.99–86.66)	0.19	100 (88.33–100)	93.33 (73.33–100)	0.265
Activities of daily living	100 (100–100)	100 (100–100)	100 (83.33–100)	0.638	100 (100–100)	100 (100–100)	0.825
Emotional role	100 (83–100)	100 (83.33–100)	83.33 (66,66–100)	0.257	100 (88.33–100)	100 (66.66–100)	0.728
Cognitive function	83 (66.5–100)	83.33 (66.66–100)	83.33 (74.99–100)	0.801	88.33 (70.83–100)	83,33 (66.66–100)	0.875
Social function	100 (100–100)	100 (100–100)	100 (83.33–100)	0.538	100 (100–100)	100 (100–100)	0.632
Overall health score/quality of life	66.5 (58–83)	66.64 (56.23–83.33)	74.98 (58.31–79.15)	0.914	70.81 (60.39–83.33)	66.64 (49.98–83.33)	1
Symptomatic scale							
Fatigue	11.11 (0–22.22)	11.11 (0–24.99)	11.11 (0–44.44)	0.857	0 (0–11.11)	11.11 (11.11–44.44)	0.47
Pain	16.66 (0–49.99)	0 (0–20.83)	16,66 (8.33–33.33)	0.325	11,11 (0–29.19)	0 (0–33.33)	0.636
Nausea/vomiting	16.66 (0–33)	0 (0–0)	0 (0–0)	0.857	0 (0–0)	0 (0–0)	0.636
Single-item questions							
Dyspnea	0 (0–0)	0-(0–0)	0-(0–0)	0.325	0 (0–0)	0 (0–0)	0.825
Insomnia	0 (0–6.38)	0 (0–10.58)	0 (0–10.58)	0.745	0 (0–33.33)	0 (0–33.33)	0.548
Anorexia	0 (0–0)	0 (0–0)	0-(0–0)	1	0 (24.99)	0 (0–0)	0.636
Constipation	0 (0–0)	0 (0–0)	0-(0–0)	0.587	0 (0–0)	0 (0–0)	1
Diarrhea	0 (0–0)	0 (0–0)	0-(0–0)	0.587	0 (0–0)	0 (0–0)	0.975
Economic impact	0 (0–0)	0 (0–0)	0-(0–0)	1	0 (0–0)	0 (0–0)	1

98.1 ± 2.41; p = 0.908). As far as quality of life was concerned, no significant differences were observed between the EORTC questionnaire (Table 3) and the FACIT-F scale (45.78 ± 5.31 *vs* 46.8 ± 2.05; p = 0.518). When the same data was analyzed according to lines of treatment (first line *vs.* other lines) no significant differences were observed between the results of the MMAS-8 questionnaire (1st line: 8 highly adherent patients; other lines: 12 highly adherent patients and 3 moderately adherent patients; p = 0.082) and those obtained when applying the leftover medication method (97.52 ± 2.42 *vs* 99.09 ± 1.33; p = 0.106). Differences were also absent with respect to quality of life, according to the EORTC QLQ-C30 questionnaire (Table 3), and fatigue (45 ± 5.3 *vs* 47.88 ± 2.99; p = 0.178).

Discussion

The present study evaluated adherence and quality of life in patients diagnosed with CLL treated with the new oral antineoplastic agents for at least 6 months. The results obtained showed that patients treated with ibrutinib or venetoclax demonstrated high adherence rates, according to the MMAS-8 questionnaire and the leftover pill counting method. According to the EQ-5D-3L and EORTC QLQ-C30 questionnaires all of them had a good quality of life. Application of the FACIT-F questionnaire revealed an absence of fatigue.

Incorporation of oral antineoplastics to the treatment of CLL has resulted in an improvement in terms of efficacy as these agents are capable of controlling the disease even in patients with adverse genetic and/or molecular factors. The severity associated with neoplastic disease may make one presume optimal adherence. However, there tends to be wide variability, with adherence rates in hemato-oncologic patients ranging between 14% and 100%[23].

In the context of CLL, Garner *et al.*[13] analyzed the impact of adherence on the real-world health outcomes of CLL patients treated with ibrutinib for at least 6 months. They calculated the adherence rate on the basis of dispensing records and set the adherence threshold at 95%. However, the mean adherence rate of their patients stood at 91.7%. The authors concluded that, even if their data was based on a limited patient sample, their lower-than-expected adherence rate warranted the establishment of oral chemotherapy management programs that provided information on adverse event management, reviewed drug–drug interactions and encouraged collaboration with other specialists in order to overcome the barriers to adherence. The authors also recognized that pharmacists were ideally placed to spearhead such programs. The good tolerance to treatment exhibited by the patients and the fact that they received pharmaceutical care at every appointment with the pharmacy department may have contributed to the good adherence outcomes eventually obtained in the study.

Table 4
Fatigue evaluation according to the FACIT-F scale.

Level of fatigue (score)	Total (n = 23) (%)
No fatigue (45–52 points)	78.26
Mild fatigue (31–44 points)	17.39
Moderate fatigue (21–30 points)	4.35
Severe fatigue (0–20 points)	0

On the other hand, quality of life data is becoming increasingly important in connection with hemato-oncologic patients as it allows an assessment not only of the impact of disease but also of the impact of any intervention on the patients' ADLs, making it therefore possible to analyze potential differences between treatments,

Youron *et al*[24] was the first study to evaluate quality of life in patients with CLL treated with the new oral antineoplastics (ibrutinib). These authors evaluated quality of life in patients with CLL by means of the EORTC QLQ-C30 and QLQ-CLL17 questionnaires[25], and compared their results with those of a control group made up of healthy individuals. All the subjects had to fill out the questionnaire once during the course of the study, except for those on chemotherapy, who filled it out at the beginning and at the end of treatment. The study concluded that patients treated with ibrutinib scored higher on social functioning and demonstrated less fatigue and appetite loss than those on chemotherapy. Moreover, those patients obtained lower scores on the items related to “future health and functioning concerns” than patients treated with chemotherapy on the QLQ-CLL17 questionnaire.

Patients included in this study obtained higher scores than those in Youron *et al.* on all functional scales, except cognitive function. It should be mentioned that the median age in the samples was different, with patients in Youron *et al.* being younger (median: 59 years; range: 44–70) than those in the present study (mean age: 69.7 years ± 8.02). Age could explain the differences observed in cognitive status but cannot justify the higher functional scores obtained in our sample. As far as symptoms are concerned, patients in this study obtained better results, scoring 0 points on some of the symptoms. The only item where our patients obtained lower scores than Youron *et al.* was overall health

status. This may be due to the fact that those authors excluded patients with severe comorbidities whereas our study admitted all the patients who met the inclusion criteria.

The strengths of this study are related to the fact that, as recommended by the literature, a combination of two different methods was used to measure adherence[15]. This made it possible to obtain reliable complementary information and minimize the limitations of each one of the methods. Moreover, although an adherence rate ≥ 80% is considered acceptable for chronic cases (Dashputre *et al.*)[26], even for cancer patients, a threshold adherence rate ≥ 90% was selected for this study on the basis of the findings in Marin *et al.*[8], a seminal hemato-oncologic study that establishes a relationship between adherence and therapeutic outcome in patients diagnosed with CML with complete cytogenetic response treated with imatinib. The quality-of-life questionnaires used in the study (EORTC QLQ-C30, EQ-5D-3L and the FACIT-F scale) were selected based on the published literature and because they were commonly used in CLL clinical trials[27]. Finally, it must be highlighted that this study, which provides the first data available on the subject based on a Spanish sample, was carried out in conjunction with the hospital's Hematology Department as a stepping stone to carrying out a larger-scale multicenter study that may provide a better understanding not only of the patients' adherence rate and quality of life, but also of the factors capable of driving them. The study was also meant to pave the day to an analysis with greater statistical power.

One possible limitation of this study is that the leftover pill counting method for measuring adherence was applied on the telephone instead of face-to-face in the pharmacy department. The reason why pill counting was done remotely was that most patients were on the hospital's telepharmacy program, which comprised remote pharmaceutical care (telephone interviews), administered by an oncological pharmacist prior to dispatching medicines to the patient's home. All questionnaires and medication counts were done remotely through a telephone interview, following the same protocol for every patient.

Another limitation of this study was that the quality-of-life questionnaire was only administered once, which made it impossible to understand the effect of the progression of the disease or the improvement of the symptoms on the patients' wellbeing, or to gage the effect of the treatment on the patients' quality of life over a long period of time. It should be said that the CLL-specific QLQ-CLL17 questionnaire[25] (complementary to the QLQ-C30 questionnaire) was not included in our study because the questionnaire was being validated by the EORTC group at the time the study was conducted.

The reduced size of the sample and the high number of adherent patients may explain why no statistically significant differences were observed when the data was analyzed per treatment subgroup and per line of treatment. At the same time, those factors prevented a determination of the factors that could predict low adherence to treatment or impact the patients' quality of life.

In a nutshell, it can be concluded that patients with CLL treated with oral antineoplastics demonstrated a high rate of adherence and claimed to have a good quality of life, with high scores on functional scales, a low intensity of symptoms and no fatigue. The factors contributing to these good results include the patients' high tolerance to the treatment and the effective pharmaceutical care provided at the different consultations.

Contribution to the literature

This is the first study in Spain to contribute real world data on the adherence and quality of life of patients with chronic lymphocytic leukemia treated with the new oral antineoplastics. The results obtained in this pilot study will pave the way for the design of a larger-scale multicenter study on the subject that provides an understanding not only of adherence rates and quality of life but also of the factors that could be used as predictors of poor adherence and/or poor quality of life.

Funding

No funding.

Ethical considerations

This research project was authorized by the Ethics Committee for Research with Medical Products of Cantabria (internal code 2021/169 (decision 9/2021 of 14 May 2021).

Conflict of interest

María Ángeles Gil Lemus is a member of an advisory board sponsored by Takeda. Lucrecia.Yáñez San Segundo serves on advisory panels and participates in training activities, conferences and expert panels sponsored by Janssen, Astrazeneca, Beigene, Lilly, Abbvie, Gilead and Roche. Carlos Antonio Amado Diago does advisory work for Fresenius and participates in training activities and conferences sponsored by Faes Farma.

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