

Economic impact of sequencing treatments with oral therapies for chronic lymphocytic leukemia in Spain

Impacto económico de la secuenciación de tratamientos con terapias orales para la leucemia linfocítica crónica en Spain

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Abstract

Introduction: Chronic lymphocytic leukemia represents a burden for the Spanish National Health System (NHS). **Objective:** This study estimated the total cumulative costs per patient over 10 years of different treatment sequences with oral therapies for adults with chronic lymphocytic leukemia financed by the Spanish NHS. **Method:** We conducted a survival model, which included up to 3 lines of therapy. Patients were categorized into 4 alternative states: first-, second-, third-line therapies, and death. Each state distribution was determined based on data from clinical trials. The treatment sequences including oral chronic lymphocytic leukemia therapies most widely used in clinical practice in Spain, were included. Only direct costs were contemplated. The study analyzed 2 population scenarios: patients with and without deletion in 17p [del(17p)]. **Results:** In the del(17p) scenario, a mean total cost of all sequences was estimated at € 589,685.67 (€ 411,826.29 for the sequences starting with venetoclax + obinutuzumab and € 678,615.36 for the remaining sequences). For the scenario without del(17p), a mean cost of all sequences was estimated at € 556,115.80 (€ 269,148.58 for those starting with venetoclax + obinutuzumab and € 670,902.69 for the rest). **Conclusions:** Starting first-line therapy with venetoclax + obinutuzumab, regardless of del(17p), would mean estimated savings for the Spanish NHS between € 265,000 and € 405,000 per patient.

Keywords: Burden of disease. Spain. Chronic lymphocytic leukemia. Financial model. Oral drug administration. National Health System.

Resumen

Introducción: La leucemia linfocítica crónica supone una carga para el Sistema Nacional de Salud (SNS) español. **Objetivo:** Este estudio estimó los costes totales por paciente acumulados durante 10 años de diferentes secuencias de tratamiento con terapias orales financiadas en Spain para adultos con leucemia linfocítica crónica. **Método:** Se empleó un modelo de supervivencia que contemplaba hasta tres líneas de tratamiento. Los pacientes se distribuyeron en cuatro estados: terapia de primera línea, de segunda línea, de tercera línea y muerte. La distribución para cada estado se basó en los datos de eficacia de los ensayos clínicos. Se incluyeron las secuencias de tratamiento con terapias orales más comúnmente utilizadas en la práctica clínica española y solo se consideraron los costes directos. Se contemplaron dos escenarios poblacionales: pacientes con y sin delección 17p [del(17p)]. **Resultados:** En el escenario con del(17p) se estimó una media de

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costes totales de 589.685,67 €, siendo 411.826,29 € para las secuencias iniciadas con venetoclax + obinutuzumab y 678.615,36 € para el resto de las secuencias. Para el escenario sin del(17p) se estimó una media de costes de 556.115,80 €, siendo 269.148,58 € para las secuencias iniciadas con venetoclax + obinutuzumab y 670.902,69 € para el resto de las secuencias. **Conclusiones:** El inicio del tratamiento con venetoclax + obinutuzumab, independientemente de del(17p), supondría un ahorro para el SNS español de entre 265.000 € y 405.000 € por paciente.

Palabras clave: Carga de la enfermedad. España. Leucemia linfocítica crónica. Modelo económico. Administración de terapias orales. Sistema Nacional de Salud.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults in Western countries¹. According to the Institut National de la Santé et de la Recherche Médicale (INSERM), in 2022, the prevalence of CLL in Europe was estimated to be 48/100,000². In Spain, the estimated incidence rate ranges between 3.0 and 4.0/100,000^{3,4}.

CLL significantly impacts patient survival and health-related quality of life and poses a considerable economic burden on the Spanish National Health System (SNS)^{1,5}.

Until a decade ago, first-line therapy (1L) for CLL patients was based on chemoimmunotherapy. The introduction of oral therapies with new therapeutic targets, such as Bruton tyrosine kinase inhibitors (ibrutinib and acalabrutinib), phosphatidylinositol-3-kinase inhibitors (idelalisib), and anti-apoptotic protein BCL-2 inhibitors (venetoclax), has changed the approach to initiating treatment. These specific inhibitors disrupt important signaling pathways for CLL cell proliferation and have increasingly replaced chemoimmunotherapy due to their significantly improved tolerability and efficacy^{5,6}. The introduction of these drugs has transformed the therapeutic landscape, setting new therapeutic goals for this disease to achieve deep and durable responses with minimal toxicity⁷. Therefore, fixed-duration treatment regimens, such as those based on venetoclax, could be a way to minimize toxicity by keeping patients free from treatment and, therefore, free from drug-related adverse events (AEs)⁸. Overall, these advances have significantly improved CLL management, and new treatments have paved the way for establishing optimal combination and sequencing strategies⁶.

Another important challenge with these new treatments is their economic impact¹. Therefore, to provide information on treatment sequencing from an economic perspective, this study aims to estimate the direct health care costs of different treatment sequences containing oral therapies for adult CLL patients in the Spanish health care setting.

Method

To estimate the total cumulative costs per patient over 10 years for different oral treatment sequences for adult CLL patients from the perspective of the Spanish SNS, a model previously developed in France was adapted to the Spanish health care context⁹. The model aims to estimate the total costs of different treatment sequences containing oral therapies funded by the Spanish SNS for CLL in two patient populations: with and without deletion on the short arm of chromosome 17 [del(17p)]. This differentiation is due to the different prognoses and risks associated with each population¹⁰.

For model adaptation, a targeted literature review was conducted to find the necessary variables. Subsequently, a group of experts (hematologists and hospital pharmacists) validated the scenarios, treatment sequences, and assumptions by consensus and completed the necessary information for the analysis.

Study design and population

The analysis includes adult patients diagnosed with previously untreated CLL who were treated with up to 3 lines of treatment, with, at least, first-line therapy in the sequence containing oral therapies. Patients were categorized based on the presence or absence of del(17p). Since CLL is a chronic disease, the model used a 10-year time horizon. Each year, patients were distributed into 4 alternative disease states: first line-therapy (1L), second-line therapy (2L), third-line therapy (3L), and death⁹. It was assumed that patients were treated until progression, or the maximum duration specified in the technical data sheet of each drug, without considering treatment discontinuation for reasons other than disease progression and no treatment gap between progression and the start of the next line.

The distribution of patients for each therapy line and death was based on progression-free survival (PFS) and overall survival (OS) data from published clinical trials on each of the considered therapeutic options. The annual PFS rates of 1L therapy were used to estimate

Table 1. Data and sources of efficacy used in the model (by alphabetical order)

	Without del (17p)	With del (17p)	Observations	Ref.
PFS in 1L*				
Acalabrutinib	78% at 48 months	76% at 48 months [†]	Exclusion criteria: del (17p)	11
Ibrutinib	59% at 84 months	59% at 84 months [†]		12
Venetoclax + obinutuzumab	74% at 48 months	44.1% at 48 months		13
PFS in 2L and subsequent [§]				
Acalabrutinib	Median 38.4 months [¶]	Median 32.9 months	Phase I study	14
Ibrutinib	Median 44.1 months [¶]	Median 40.6 months		15
Idelalisib + rituximab	Median 20.8 months	Median 18.7 months [†]		16
Venetoclax (exclusively 3L and subsequent)	71% at 15 months	Median 16 months		17
Venetoclax + rituximab	Median 55.1 months	Median 47.9 months		18
OS				
Acalabrutinib	76.5% at 40.9 months [¶]	76.5% at 40.9 months [¶]	Phase I study	14
Ibrutinib	Median 67.7 months [¶]	Median 67.7 months [¶]		15
Idelalisib + rituximab	Median 50.9 months [†]	Median 28.5 months [†]		16
Venetoclax	84% at 24 months [¶]	84% at 24 months [¶]		17
Venetoclax + rituximab	82.1% at 60 months [¶]	82.1% at 60 months [¶]		19

*Although the data used are the best available evidence, there is a limitation in the RESONATE-2¹² trial, which does not include patients with del (17p).
[†]del (17p) and/or TP53 mutation.
[‡]del (17p) as inclusion criterion.
[§]As a limitation, although it would have been better to use the time to next treatment as a parameter instead of PFS, since this is not always available, another available parameter was used.
[¶]Regardless of del (17p) status.
del (17p): deletion in the short arm of chromosome 17. 1L: first-line therapy; 2L: second-line therapy; 3L: third-line therapy; OS: overall survival; PFS: progression-free survival.

the proportion of patients remaining in 1L. Patients progressing from 1L were distributed to 2L-3L, according to the PFS and OS rates of 2L therapy that year, and death (after 2L or 3L). The model assumed that all patients received, at least, 2 lines of therapy before death.

Efficacy

The model used exponential distributions to extrapolate PFS and OS curves, assuming that patients progressed or died at a constant rate. The model also assumed that treatment efficacy was independent of the previous treatment received.

For efficacy data, information available from clinical trials was selected based on the following criteria:

- Information available from phase III clinical trials for each treatment and population (with/without del(17p)).
- Information from studies with the longest follow-up time.
- If median PFS or OS was available, this information was used; otherwise, the proportion of surviving patients at the longest follow-up was used according to the PFS and/or OS curves.
- If information was not available for populations with and without del(17p), the available information was selected regardless of the deletion status.
- In the absence of information from a phase III study, information from a phase II study was selected.

The efficacy data and sources used in the model are presented in table 1 and were validated and prioritized by clinical reference experts.

Treatment sequences

For the 2 model scenarios, with and without del(17p), treatment patterns were defined considering monotherapy or combination therapies funded by the SNS, and their use in clinical practice in patients with and without del(17p) was validated by reference experts (Table 2).

Costs

This evaluation was conducted from the perspective of the Spanish SNS, considering only direct health care costs (updated to 2023 euros): pharmacological, administration, transportation, tests performed, routine visits, and AE management.

To estimate the pharmacological cost, the dose and frequency of each treatment for the first year and subsequent years were collected from the technical data sheet of each drug, all validated by reference experts. Finally, the cost of each treatment sequence resulted from summing the costs of the drugs that composed it, according to their duration.

Table 2. Treatment sequences containing oral therapies for chronic lymphocytic leukemia considered in the model (by alphabetical order)

1L	2L	3L
Patients with del (17p) Acalabrutinib Ibrutinib Venetoclax + obinutuzumab Venetoclax + rituximab Acalabrutinib Venetoclax Idelalisib + rituximab	Acalabrutinib Venetoclax + obinutuzumab Venetoclax + rituximab Venetoclax + rituximab Ibrutinib Idelalisib + rituximab Idelalisib + rituximab	Ibrutinib Venetoclax + obinutuzumab Venetoclax + rituximab Venetoclax + rituximab Venetoclax + rituximab Idelalisib + rituximab Venetoclax
Patients without del (17p) Acalabrutinib Ibrutinib Venetoclax + obinutuzumab Venetoclax + rituximab Ibrutinib Acalabrutinib Venetoclax	Acalabrutinib Ibrutinib Venetoclax + rituximab Venetoclax + rituximab Ibrutinib Venetoclax Idelalisib + rituximab	Ibrutinib Venetoclax + obinutuzumab Venetoclax + rituximab Ibrutinib Idelalisib + rituximab Idelalisib + rituximab Venetoclax + rituximab

del (17p): deletion on the short arm of chromosome 17; 1L: first-line therapy; 2L: second-line therapy; 3L: third line therapy.

The administration cost was considered only for sequences including IV drugs (obinutuzumab and rituximab), with administration frequency determined according to the dosing regimen specified in the technical data sheet.

The model also assumed a single transportation cost²⁰ at the start of therapy for AE management. However, experts agreed that not all patients with AEs would require medical transport, estimating that this would only occur in 5% of patients with AEs, considering the same proportion regardless of therapy and therapy-line.

The monitoring cost included routine tests and follow-up visits. Experts estimated that the mean annual use of health care resources was the same for all treatments, except for venetoclax, for which additional specific resources were agreed upon. Follow-up costs were applied to all living patients each year of the analysis. According to the monitoring validated by the experts, a total annual cost per patient was estimated regardless of the treatment sequence²⁰.

Additionally, a single cost of palliative care associated with the death state was estimated regardless of the previous treatment²⁰.

In all patients, for combinations with venetoclax, a single cost of tumor lysis syndrome prevention during the up-titration period was assumed, including the cost of hospitalization in the hematology department, biochemical tests, prophylactic drugs (allopurinol and rasburicase), and patient transport²⁰, calculated using unit costs for low, moderate, and high-risk patients, as well

as the proportion of patients at each risk level^{18,21}. Experts also estimated the inclusion of three blood counts, three general biochemistry tests, and one immunophenotype test at the start of treatment with venetoclax regimens, regardless of the risk group.

The cost estimates of AEs associated with each treatment sequence was limited to those of grade 3/4 reported in clinical trials and occurring in $\geq 5\%$ of patients. The frequency of each AE for each treatment was obtained from the literature. AE-related costs were applied as a 1-time cost at the start of therapy (i.e., year 1 for 1L therapies and years 2 to 10 for 2L and 3L therapies), and AE rates based on relapsed or refractory CLL patients were used for 2L and 3L therapies.

Results

Table 3 shows the costs for each treatment sequence included in the model, and figure 1 illustrates the cost per patient for each sequence in each scenario.

The model shows that the cost per CLL patient is higher in the first year, regardless of the treatment sequence and the presence or absence of del(17p), with pharmacological costs being the largest component of the total cost in all cases (Fig. 1).

In the del(17p) population scenario, the estimated mean total cost of the sequences was €589,685.67, with €411,826.29 for sequences starting with venetoclax + obinutuzumab and €678,615.36 for the rest. Similarly, in the population without del(17p) scenario,

Table 3. Costs associated with each treatment for chronic lymphocytic leukemia considered in the model

Treatment	Pharmacological cost			Follow-up cost	Transportation cost		Specific costs for venetoclax [§]	AE-related costs
	Annual (1 st year)	Annual (following years)	Treatment duration		Annual (1 st year)	Single, for the management of AE [†]		
1L Acalabrutinib Ibrutinib Venetoclax + obinutuzumab	€73,884,72 €73,884,72 €95,438,46	€73,884,72 €73,884,72 €0,00	Until progression Until progression Fixed duration therapy for only 1 year	€1893,28	€0,00 €0,00 €4037,58	€0,62 €1,55 €2,69	€2199,08	€856,35 €2178,15 €4816,72
2L Acalabrutinib Ibrutinib Venetoclax + rituximab	€73,884,72 €73,884,72 €76,780,28	€73,884,72 €73,884,72 €74,360,04	Until progression Until progression Fixed duration therapy for 2 years, including a 5-week up-titration period within the first year for venetoclax, and rituximab administered only during the first 6 cycles	€1893,28	€0,00 €0,00 €2691,72	€1,07 €1,19 €2,62	€2199,08	€1441,79 [‡] €1632,50 €4638,18
3L Acalabrutinib Idelalisib + rituximab Venetoclax Venetoclax + rituximab	€73,884,72 €58,969,43 €64,948,86 €76,780,28	€73,884,72 €47,138,00 €74,360,04 €74,360,04	Until progression Until progression, with rituximab administered only within the first 6 cycles Until progression, with a 5-week up-titration period within the first year Fixed duration therapy for 2 years, including a 5-week up-titration period within the first year for venetoclax, and rituximab administered only during the first 6 cycles	€1893,28	€0,00 €2691,72 €0,00 €2691,72	€1,07 €1,50 €2,52 €2,62	€2199,08 €2199,08	€1441,79 [‡] €1965,89 [‡] €2933,16 [‡] €4638,18 [‡]

*Annual cost of resources used, regardless of therapy.

[†]Assumes only 1 annual cost for sequences including IV drugs, calculated by multiplying the annual administration frequency by the sum of individual costs (patient transport, hospital visit for drug administration, and hospital pharmacy visit).

[‡]Grade 3/4 AEs occurring in ≥ 5% of patients in, at least, 1 treatment group in clinical trials, with 5% of patients requiring transportation due to the occurrence of AEs.

[§]Costs applicable to venetoclax-based regimens and independent of patient type.

^{||}Assumes the same frequencies as 2L for each treatment regimen.

For drugs with variable doses based on patient weight or body surface area, 70.0 kg and 1.7 m² (means for Spanish CLL patients) were assumed²². Prices considered were the laboratory sale price without VAT, published in the Official Pharmacists' Database²³, with deductions in full compliance with Royal Decree-Law 8/2010, modified by Royal Decree-Law 9/2011, updated as of September 2022²⁴.

AE: adverse event; 1L: first-line therapy; 2L: second-line therapy; 3L: third-line therapy.

**Figure 1.** Total and annual cost of chronic lymphocytic leukemia per patient by treatment sequence.

Acala: acalabrutinib; del(17p): deletion on the short arm of chromosome 17; Ibru: ibrutinib; Ide + R: idelalisib + rituximab; 1L: first-line therapy; 2L: second-line therapy; 3L: third-line therapy; V + O: venetoclax + obinutuzumab; V + R: venetoclax + rituximab.

the estimated mean total cost of the sequences was €556,115.80, with €269,148.58 for sequences starting with venetoclax + obinutuzumab and €670,902.69 for the rest.

From the perspective of the Spanish SNS, treatment sequences starting with venetoclax + obinutuzumab generated the lowest total costs among commonly used sequences in Spain, regardless of del(17p) status. Therefore, it is estimated that the budgetary impact of sequences starting with venetoclax + obinutuzumab represents savings due to substantial reductions in treatment costs related to their finite duration. Considering the total sequence costs, mean savings would be €266,800 and €401,800 in sequences with and without del(17p), respectively (Fig. 1).

Discussion

In recent decades, CLL management has undergone significant clinical improvements due to the authorization of drugs that have allowed for the establishment of new combinations and treatment strategies^{1,6,7}. Various publications report data from registries or retrospective cohort studies that support the results of randomized studies with different sequencing strategies in clinical practice⁶. This study analyzes the economic impact, including treatment sequences containing oral therapies commonly used in clinical practice in Spain. The analysis suggests that those starting with venetoclax + obinutuzumab, in addition to providing clinically relevant efficacy and safety results in patients with and without del(17p), would allow the SNS to optimize health care resource utilization due to the savings they represent. In this sense, and pending direct comparison studies, current 1L data in the del(17p) scenario could suggest slightly lower PFS for finite treatment, although it would allow for retreatment^{11,25}.

The management of CLL should be personalized based, among other aspects, on the patient's clinical characteristics²⁶. This study assumes that all patients are treated with, at least, 2L before death, including 3L therapy sequences in the analysis. In clinical practice, the use of 3L in CLL is limited, with clinical trials being an option in these cases. Since the model does not consider this option, and although few patients will be candidates for 3L, the general principle assumed and validated by reference clinical experts was to use a previously unused therapeutic class, except for venetoclax in patients in whom relapse/refractoriness occurs long-term. Additionally, in patients without

del(17p), treatment with chlorambucil + obinutuzumab is an option used exclusively in the elderly population, so it cannot be vs the other therapeutic options included in the model and was excluded from the analysis.

The analysis shows that, for all treatments, the largest cost component is pharmacological, although its weight decreases in sequences starting with venetoclax + obinutuzumab, one of the widely recommended 1L drug combinations due to its high efficacy and fixed treatment duration²¹.

This study has some limitations, the first of which derives from the fact that the model represents a simplification of reality and, although based on the best possible evidence, will never be an exact representation of real clinical practice. Another limitation is the assumption of 3L therapy in all sequences included in the model, which does not always match clinical practice. This simplification of reality implies that the estimated costs in our analysis would be the maximum since most patients would not receive the complete therapeutic sequences presented in the model. Likewise, not considering treatment discontinuation for reasons other than disease progression and no treatment gap between progression and the start of the next line also implies maximum costs in the analysis results. An additional limitation is that the analysis was performed with reported drug prices, so the results could vary to the extent that there are differences between reported and funded prices. The impact of this difference could affect the magnitude of the difference between the evaluated sequences, but it is less likely to affect the direction of the favorable results obtained for strategies with venetoclax + obinutuzumab in 1L and, therefore, the study conclusion. Regarding efficacy, since the PFS and OS included in the model are derived from clinical trials, with the limitations this entails, it is possible that this represents an overestimation vs clinical practice. Finally, while the results could vary according to patient age, the model was not designed to estimate this cost sub-analysis, which could be incorporated into future studies.

The present analysis provides an estimate of the financial impact of treatment sequencing containing oral therapies in CLL for the Spanish SNS. Treatment sequences with venetoclax + obinutuzumab in 1L generated the lowest total costs among commonly used sequences in Spain, regardless of del(17p) status, representing cost savings for the SNS of approximately €266,800 and €401,800 in sequences with and without del(17p), respectively. This study can help define future

therapeutic strategies that, while ensuring the safety and efficacy profile, also contribute to the sustainability of the SNS.

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Conflicts of interest

T. Baumann has received fees for participation in training activities, lectures, and expert panels from AbbVie, AstraZeneca, Beigene, Gilead, Incyte, Janssen, Lilly, MSD, Novartis, and Roche. R. Lluch García has received fees for participation in training activities, lectures, and expert panels from AbbVie and Janssen. V. Martínez-Callejo has received fees for participation in expert panels from AbbVie. C. Ulibarrena has received fees for participation in conferences, presentations, expert panels, manuscript writing, or educational events from AbbVie and AstraZeneca. C. Barrull is an employee of IQVIA Spain. M. Gómez de Salazar and E. Villa are employees of AbbVie and may own AbbVie stock. M. Micaela Viña Romero has no conflicts of interest to declare. None of the authors received remuneration for drafting this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this

manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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