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ORIGINAL ARTICLE

Cost-reduction analysis for oral versus intravenous fludarabine (Beneflur®) in Spain

Julio Delgado,[a] Laia Febrer,[b] Diana Nieves,[c] Carme Piñol,[b] and Max Brosa[c,*]

[a]*Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[b]*Bayer Shering Pharma, Barcelona, Spain*
[c]*Oblikue Consulting, Barcelona, Spain*

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Abstract
Introduction: Various international studies have shown that fludarabine is effective, safe, and efficient for treating B-cell chronic lymphocytic leukaemia (B-CLL). The purpose of the present study was to carry out a cost-minimization analysis for 2 alternative forms of fludarabine (oral and intravenous) used to treat B-CLL in Spain.
Methods: The presence of clinical evidence about the treatment equivalence of the 2 options being compared (oral fludarabine vs intravenous fludarabine) led us to carry out a cost-minimization analysis. A pharmacoeconomic model was constructed to compile data from the literature and experts' opinions in order to determine the use of health resources associated with the treatment; unit costs were obtained from Spanish databases. The analysis contemplated 2 perspectives: that of the national health service, which includes only direct health costs, and the social perspective, which also includes the indirect costs that result from loss of productivity.
Results: Although fludarabine in its oral form has a higher purchase price than generic intravenous fludarabine does, increased administration costs for the latter, which is used in hospitals, mean that oral fludarabine use produces total savings of #euro1908 and #euro1292 for single-drug therapy and combined therapy with cyclophosphamide, respectively. Including indirect costs increased the savings associated with the oral form of the drug.
Conclusions: In B-CLL patients, treatment with oral fludarabine has a lower cost than treatment with intravenous fludarabine, in both single-drug therapy and combined therapy. Various sensitivity analyses confirmed these results and showed that oral fludarabine should be the treatment of choice for B-CLL in Spain, unless contraindicated.

*Corresponding author.
E-mail address: max.brosa@oblikue.com (M. Brosa).

PALABRAS CLAVE
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Fludarabina intravenosa;
Leucemia linfocítica crónica de células B;
España

Análisis de minimización de costes de fludarabina (Beneflur®) oral vs. vía intravenosa en España

Resumen

Introducción: Fludarabina ha demostrado su eficacia, seguridad y eficiencia en el tratamiento de la leucemia linfocítica crónica de células B (LLC-B) en diversos estudios internacionales. El objetivo del presente estudio fue realizar un análisis de minimización de costes de 2 formas alternativas de fludarabina (oral e intravenosa) para el tratamiento de la LLC-B en España.

Métodos: La existencia de evidencias clínicas sobre la equivalencia terapéutica de las 2 opciones comparadas (fludarabina oral frente a fludarabina intravenosa) llevó a la realización de un análisis de minimización de costes. Se construyó un modelo farmacoeconómico que combinó datos de la bibliografía y la opinión de expertos para determinar el uso de recursos sanitarios asociados al tratamiento, y los costes unitarios se obtuvieron de bases de datos españolas. El análisis consideró 2 perspectivas: a) la del Sistema Nacional de Salud, que incluía sólo los costes directos sanitarios, y b) la perspectiva social, que además de éstos, incluía los costes indirectos derivados de la pérdida de productividad.

Resultados: Aunque la forma oral de fludarabina tiene un coste de adquisición mayor que la especialidad farmacéutica genérica de fludarabina intravenosa, los mayores costes de administración de esta última, de uso hospitalario, se tradujeron en unos ahorros totales asociados a fludarabina oral de 1.908 y 1.292 € en monoterapia y tratamiento combinado con ciclofosfamida, respectivamente. La inclusión de los costes indirectos aumentó los ahorros asociados a la forma oral.

Conclusiones: El tratamiento de los pacientes con LLC-B con fludarabina oral presenta unos costes menores respecto a fludarabina intravenosa, tanto en monoterapia, como en tratamiento combinado. Diversos análisis de sensibilidad confirmaron estos resultados, en los que se constata que la forma oral de fludarabina debería ser la opción de elección en el tratamiento de la LLC-B en España, salvo que se contraindique.

Introduction

Chronic lymphocytic leukaemia (CLL) is a malignant haematopoietic disorder that causes an anomalous proliferation of lymphocytes which are extremely differentiated but immunologically incompetent. These lymphocytes can spread throughout the lymphatic and haematopoietic system and cause lymphocytosis, an increase in the volume of lymph glands, hepatosplenomegaly, anaemia, and thrombocytopenia.[1]

CLL is one of the most common leukaemias in North America and Europe, accounting for approximately 30% of cases,[2] and the global incidence is lower than 1%–5.5% per 100 000 people.[3] B-lymphocytes CLL (B-CLL) accounts for approximately 97% of all cases of CLL while T-cell CLL only accounts for 3%[4] The average age at which CLL is diagnosed is 64-70[3] and survival at 5 years in patients over 65 is approximately 68%, although this depends on the disease stage.[3]

The treatment options for CLL depend on different aspects, such as the stage of the disease, the erythrocyte count, leukocytes and platelets, presence of symptoms (for example: fever or weight loss), response to the initial treatment, or whether there is a recurrence of the disease.[5] Chemotherapy is not normally necessary in the early stages of the disease (stage 0 to A according to the Rai or Binet classification, respectively) or if this remains stable.[5] Traditionally, the initial treatment for patients with CLL has been chlorambucil with or without steroids. However, the appearance of purine nucleoside analogues, such as fludarabine, have led to an improvement in the general response rate, in the rate of complete remission and in progression-free survival, although it is not been proven to significantly increase overall survival.[6] The use of fludarabine is authorised as first line treatment in patients with B-CLL with sufficient bone marrow reserves and with advanced disease, Rai stage III/IV (Bidet stage C), or in Rai stage I/II (Bidet stage A/B) with symptoms related to the disease or evidence of progression. Combined treatment of fludarabine and cyclophosphamide has shown greater response rates than with fludarabine alone in naïve patients with CLL.[7-9]

The intravenous formulation of fludarabine has been used in Spain for more than 10 years. However, the most recent oral form has shown equivalent efficacy and a safety profile similar to that of intravenous fludarabine.[10-12] In its recommendations, the National Institute of Clinical Excellence[13] prioritises the use of oral fludarabine due to its better cost-effectiveness ratio and only recommends the use of intravenous fludarabine in cases in which the oral form is contraindicated.

The objective of the present study was to perform a cost reduction analysis for oral fludarabine versus the intravenous form in the treatment of CLL in Spain.

Methods

Type of analysis

A cost reduction analysis was performed comparing the oral and intravenous forms of fludarabine in the treatment of CLL, within the scope of the Spanish National Health System. The comparison of oral and intravenous fludarabine was based on differences in healthcare costs, since previous studies showed that both forms had similar efficacy in the treatment of CLL.[10-12]

Pharmacoeconomic model

The analysis was performed by means of a simple pharmacoeconomic model, which was used to estimate the direct healthcare costs of both options from the data available and explicit assumptions. The model, which was constructed using Microsoft Excel 2003, combined data on the use of healthcare resources in the treatment of patients with CLL, who were administered oral or intravenous fludarabine, taken from the bibliography, and the opinion of clinical experts via a specific questionnaire, in which the data relating to direct healthcare costs were considered, including the pharmacological costs, costs relating to the administration of the treatment and those corresponding to the treatment of adverse events (Table 1). The comparison was performed for monotherapy with fludarabine and combined treatment with cyclophosphamide. In addition, a sensitivity analysis was performed taking into account, apart from the healthcare costs, the indirect costs resulting from the loss of productivity due to the patient and their companion having to take leave from work.

Table 1 shows the use of healthcare resources associated with the 2 options compared in the analysis, in which it was considered that the treatment regimen for CLL is 6 cycles and the dose for each cycle as follows: for monotherapy, 25 mg/m^2 a day with the intravenous form or 40 mg/m^2 a day with the oral form, both administered for 5 days; in combined treatment with cyclophosphamide the dose was 25 mg/m^2 a day of fludarabine with 25 0mg/m^2 a day of intravenous cyclophosphamide for 3 days, or 24 mg/m^2 a day of fludarabine with 150 mg/m^2 a day of oral cyclophosphamide for 5 days.

Table 2 shows the unit costs of the resources used in the model and their sources. In the case of intravenous fludarabine, the generic drug was used, since this is the least expensive. All of the costs are expressed in euros at the 2007 rate and no discount was applied, given the short timeframe of the analysis (6 months).

Sensitivity analysis

Two types of sensitivity analysis were performed to assess the influence of uncertainty of the parameters in the study results and confirm their soundness: a scenario analysis and a probabilistic sensitivity analysis (PSA). The scenario analysis was performed by constructing 2 extreme scenarios, in which, on the one hand, the most favourable costs were used and, on the other, the most unfavourable were used for treatment with oral and intravenous fludarabine within the existing variability for the healthcare costs in Spain, both for monotherapy and combined treatment. The PSA was based on a non-parametric Monte Carlo simulation, following the international recommendations on uncertainty analysis in economic assessment studies within the healthcare sector.[19-20]

Table 1. Use of healthcare resources used in the model

	Use of resources (per cycle)	IV	Oral	Source
Drugs				
Fludarabine (monotherapy)	mg/day	42.5 (5 days)	68 (5 days)	9
Fludarabine + cyclophosphamide	mg/day	42.5 fludarabine + 425 cyclophosphamide (3 days)	40.8 fludarabine + 255 cyclophosphamide (5 days)	9
Administration				
Hospital EC	Visits	1	1	Panel of experts
Outpatient hospital (attached)	Sessions	3-5	0	9
Adverse events				
Diarrhoea	Visit + treatment symptomatic + hospitalisation (stage III-IV)	11.3%patients (stage I-II)	34.6%patients (stage I-II)	10, 12
		0% patients (stage III-IV)	3.8% patients (stage III-IV)	
Productivity lost due to leave from work				
Patient/companion (per day of treatment)	Days	1	0	14

EC indicates external consultations; IV, intravenous.

Table 2. Unit costs of resources used in the mode

	Minimum unit cost		Maximum unit cost		Source
	IV	Oral	IV	Oral	
Direct costs					
Pharmacological costs					
Fludarabine (cost/mg)	€1.998	€2.534	€1.998	€2.534	15
Cyclophosphamide (cost/mg)	€0.0034	€0.0027	€0.0052	€0.0027	15
Administration costs					
Hospital EC	€55.20		€55.20 €		16
Outpatient session	€122.21	—	€192.81	—	16
Costs of adverse events					
Diarrhoea (stage I-II)	€0		€64.2		17
Diarrhoea (stage III-IV)	€607.7		€1.335.41		17
Indirect costs					
Productivity lost due to leave from work - patient/companion (€/day/person)	€63.4		€10.6		18

EC indicates external consultations; IV, intravenous.

Thus, the simulation of a cohort of 1000 patients was performed in which a log-normal distribution was assigned to the different cost variables. The analysis was conducted under the assumption that not all patients behave like the *typical* patient and the aim of the PSA was to explicitly show the variability that could exist between the different individuals analysed. In the present study, for example, the cost of treating an episode of diarrhoea is not a constant parameter; the incorporation of this uncertainty is the object of the PSA.

Results

The results of the cost analysis of oral and intravenous forms of fludarabine are shown for monotherapy (Table 3) and combined treatment (Table 4), separating the different direct costs from the indirect costs. The analysis shows that in general, the additional cost of purchasing the oral form of fludarabine is completely recompensed by the lower administration cost, which in the intravenous form is penalised by the use of outpatient hospital sessions for administration. The therapeutic cost saving of oral fludarabine is €1908 and €1292, respectively, in the case of monotherapy and combined treatment. It was also observed that, due to the fact that the administration regimen is 5 days per cycle in the case of intravenous monotherapy in comparison with 3 in combined treatment, the pharmacological costs are greater for monotherapy.

The indirect costs for leave from work are also affected by the treatment regimen and are greater in treatment

Table 3. Healthcare costs in the treatment of patients with chronic lymphocytic leukaemia with fludarabine in monotherapy

	Average		Minimum		Maximum	
	IV	Oral	IV	Oral	IV	Oral
Direct costs						
Pharmacological costs						
Fludarabine (monotherapy)	€ 2547.9	€5320.4	€2547.9	€5320.4	€2547.9	€5320.4
Costes administración						
Administration costss	€331.2	€331.2	€331.2	€331.2	€331.2	€331.2
Hospital EC	€4725.3	€0.0	€3666.3	€0.0	€5784.3	€0.0
Costs of adverse events						
Diarrhoea	€3.6	€48.0	€0.0	€23.1	€7.3	€73.0
Indirect costs						
Productivity lost due to leave from work						
Patient and companion	€2535.0	€0.0	€1901.3	€0.0	€3168.8	€0.0

EC indicates external consultations; IV, intravenous.

Table 4. Healthcare costs in the treatment of patients with chronic lymphocytic leukaemia with fludarabine in combined treatment

	Average		Minimum		Maximum	
	IV	Oral	IV	Oral	IV	Oral
Direct costss						
Pharmacological costs						
Fludarabine + cyclophosphamide	€1561.7	€3060.9	€1561.7	€3060.9	€1561.7	€3060.9
Administration costs						
Hospital EC	€331.2	€331.2	€331.2	€331.2	€331.2	€331.2
Outpatient hospital	€2835.2	€0.0	€2199.8	€0.0	€3470.6	€0.0
Costs of adverse events						
Diarrhoea	€3.6	€48.0	€0.0	€23.1	€7.3	€73.0
Indirect costs						
Productivity lost due to leave from work						
Patient and companion	€1521.0	€0.0	€1140.8	€0.0	€1901.3 €	€0.0

EC indicates external consultations; IV, intravenous.

Table 5. Analysis of cost minimisation with fludarabine in monotherapy or combined treatment.

	IV	Oral	Difference
Fludarabine			
Conservative scenario	€6545.4	€5724.5	—€820.9
Medium scenario	€7608.0	€5699.6	—€1908.4
Favourable scenario	€8670.6	€5674.6	—€2996.0
Fludarabine + ciclofosfamide			
Conservative scenario	€4092.7	€3465.0	—€627.7
Medium scenario	€4731.7	€3440.1	—€1291.7
Favourable scenario	€5370.8	€3415.1	—€1955.6

IV indicates intravenous.

with fludarabine in monotherapy and only have an impact on intravenous administration.

The sensitivity analysis for the scenarios in Table 5 show that oral fludarabine generates an economic saving of between €821 and €2996 in the case of monotherapy and between €628 and €1956 in combined treatment. Thus, the different scenarios studied showed that fludarabine is the most favourable pharmacological option in economic terms for the treatment of patients with CLL.

The results of the PSA (Figures 1 and 2) represent the variability in the economic saving associated with oral fludarabine in comparison with intravenous fludarabine, both in monotherapy and combined treatment. Thus, on generating the simulation of 1000 patients, it could be observed that the administration of oral fludarabine could produce a saving in comparison with intravenous fludarabine in all cases.

Discussion

There is currently limited information available on the pharmacoeconomic analysis of fludarabine in the treatment of patients with CLL. This study shows that the healthcare cost of administering oral fludarabine is lower than the intravenous form in the treatment of CLL in Spain. These data coincide with an analysis performed by NICE,[14] with results provided by Schering, in which the cost of purchasing the drug, administration, prophylaxis, follow-up and adverse effects during 4.1 cycles was #pound6032 and #pound3714 for intravenous and oral fludarabine respectively (in this study the cost was €7608 and €5700, respectively). However, data provided by Roche[14] showed an even higher cost for intravenous fludarabine (#pound11 808), due to the fact that this study used higher costs for the adverse effects and the duration of treatment was 6 cycles rather than

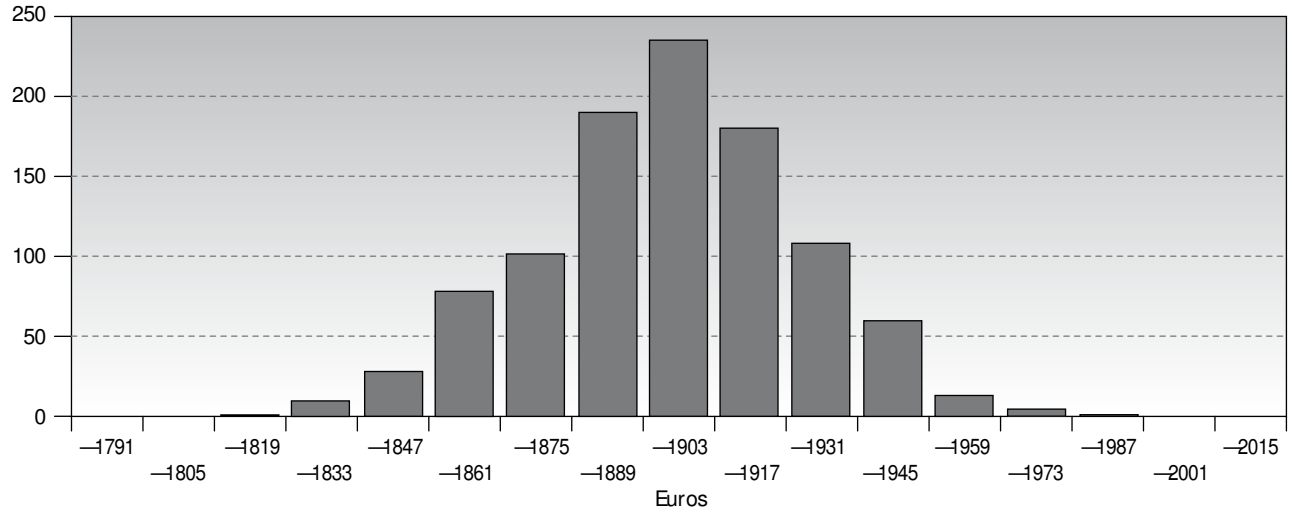

Figure 1 Multivariate sensitivity analysis. Economic saving of oral fludarabine compared with intravenous fludarabine in combined treatment. Simulation of 1000 patients.

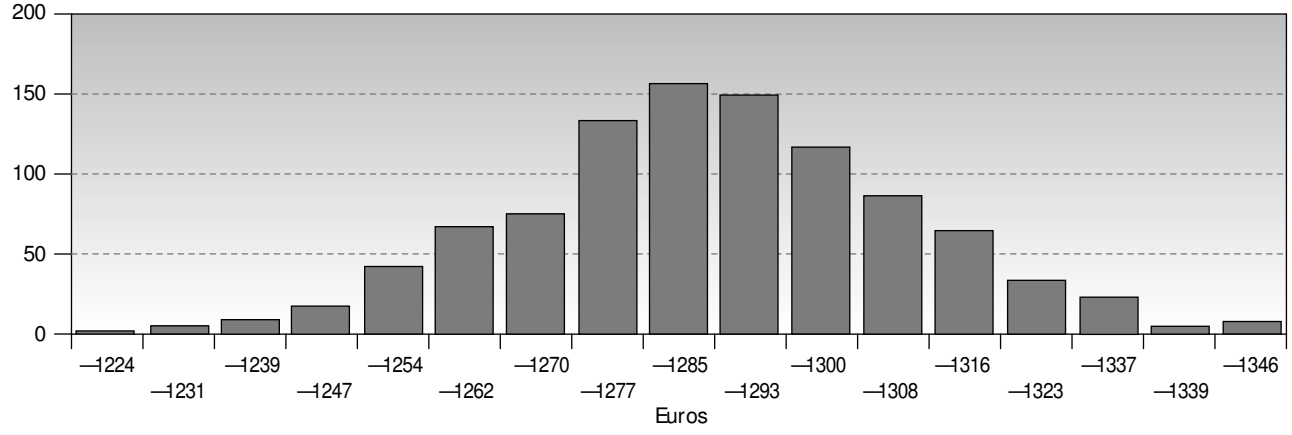

Figure 2 Análisis de sensibilidad multivariante. Ahorro económico de fludarabina por vía oral frente a vía intravenosa en tratamiento combinado. Simulación de 1.000 pacientes.

4.1. In a study in patients with non-Hodgkin's lymphoma, who followed the same treatment regimen as patients with CLL (6 cycles), the cost of purchasing and administering intravenous fludarabine was between €7269 and €8493.[21] These results are similar to those obtained in the present study, although the costs of adverse effects were not taken into account. The present study only considered diarrhoea as a relevant adverse effect since this is the only episode with a different incidence depending on the oral and intravenous form.[12] However, other studies considered other adverse effects with a significant economic load, such as neutropenia or infections,[22] which had a significant influence on the total costs for the treatment depending on the severity.[23]

This study presents 2 main limitations. Firstly, the therapeutic equivalence of the 2 options compared is based on data from international clinical trials, the results of which may not be the same in clinical practice in our environment. Thus, the greater comfort provided by the oral administration of fludarabine could provide additional benefits for patients that were not considered in this study. Secondly, due to the lack of better evidence, several parameters in the model referring to the use of healthcare resources were based on the opinion of experts. However, the influence of these parameters in the results was studied in detail in the sensitivity analysis, which showed that the results were sound.

The greater efficiency of the oral form of fludarabine was recently endorsed by NICE, whose cost effectiveness analysis showed that the oral treatment was #pount1200 per quality adjusted life year (QALY) gained, compared with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone),[14] representing a cost-effectiveness ratio well below the threshold of efficiency (#pound20 000-#pound30 000) commonly used in the United Kingdom,[24] while the intravenous form presented a cost per QALY gained of #pound69 500.

This cost reduction analysis has shown that oral fludarabine is associated with economic saving in the treatment of B-CLL, in comparison with intravenous fludarabine; this is mainly due to the fact that the administration costs of intravenous fludarabine are greater, since it requires more time in hospital and that of the healthcare staff. These results, along with the evidence available on the therapeutic

equivalence of both forms, mean that fludarabine should be the option of choice in the treatment of B-CLL in Spain, unless contraindicated.

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Conflict of interest

Julio Delgado participated as a clinical expert in the study. Laia Febrer and Carme Piñol work for Bayer HealthCare, which is the company sponsoring the study, Diana Nieves and Max Brosa have received a grant from Bayer to perform the research.

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