Cost-effectiveness analysis of irinotecan plus fluorouracil/folinic acid compared with fluorouracil/folinic acid alone as first-line treatment for advanced colorectal cancer

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Objective. **An economic evaluation was conducted to test whether irinotecan in combination with fluorouracil and folinic acid was as cost-effective (within the Spanish Health Service) as fluorouracil and folinic acid alone in the first-line treatment of advanced colorectal cancer.**

Methods. **Efficacy data from the study by Douillard et al were used. Data on resource use for the two groups of patients were collected for 41 spanish patients and the assigned costs were from various Spanish sources. The incremental cost-effectiveness ratios of the alternatives were calculated by comparing costs in relation to survival.**

Results. **Douillard´s trial showed an improved median survival of 2.80 months (0.233 years) in patients in the irinotecan group compared to the control group. Cumulative drug costs and other resource consumption per patient (e.g. average number of cycles per treatment) were higher in the irinotecan group. Patients in the control group required greater additional chemotherapy following the trial period. The average cost per patient was €22,280 and €14,016 in the irinotecan and control groups, respectively. The incremental cost per life-year gained in the basic case was €35,416.**

Conclusion. **The results indicate that the combination of irinotecan with fluorouracil and folinic acid can be considered cost-effective as first-line treatment of advanced colorectal cancer in the spanish setting.**

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Análisis coste-efectividad del tratamiento en primera línea del cáncer colorrectal avanzado con irinotecan y fluorouracilo/ácido folínico en comparación con irinotecan y fluorouracilo/ácido folínico solo

Objetivo. **Se hizo una evaluación económica desde la perspectiva del Sistema Nacional de Salud, para evaluar la hipótesis de que la utilización de irinotecan en combinación con fluorouracilo y ácido folínico sea coste-efectiva en comparación con fluorouracilo y ácido folínico solamente, en el tratamiento en primera línea del cáncer colorrectal avanzado.**

Métodos. **Se utilizaron los datos de eficacia del estudio de Douillard et al. La información sobre la utilización de recursos de los dos grupos de pacientes se recogieron de 41 pacientes españoles, y los costes se obtuvieron de varias fuentes españolas. Se calculó la razón coste-efectividad incremental comparando los costes y la supervivencia de las alternativas.**

Resultados. **En el ensayo clínico de Douillard se produjo un aumento de la mediana de supervivencia en el grupo de irinotecan de 2,80 meses (0,233 años) en comparación con el grupo control. Los costes acumulados farmacológicos y el consumo de otros recursos por paciente (por ejemplo el número medio de ciclos por tratamiento) fueron mayores en el grupo de irinotecán. Los pacientes del grupo control necesitaron más tratamientos adicionales, una vez finalizado el ensayo. El coste medio**

por paciente fue de 22.280 euros (€) and 14.016 € en los grupos irinotecán y control, respectivamente. En el caso básico del estudio el coste incremental por año de vida ganado fue de 35.416 €.

***Conclusión.* Los resultados indican que la combinación de irinotecan con fluorouracilo y ácido folínico puede considerarse coste-efectiva en el tratamiento en primera línea del cáncer colorrectal avanzado en España.**

Palabras clave: cáncer colorrectal, análisis de costes, irinotecán, evaluación económica.

INTRODUCTION

Cancer is one of the most important public health problems in developed countries. Indeed, colorectal cancer is the second cause of cancer mortality only surpassed by lung cancer. It has been estimated that approximately 6% of the population will suffer colorectal cancer of which 40% will die as a result of the disease, depriving them of on average of seven years of life[1].

In Spain the estimated incidence value in 1990 was 23 per 100,000 inhabitants. An increase of the incidence of colorectal cancer in Spain over the last decades has been observed in all regions with widely varying regional results from 15 per 100,000 inhabitants in Granada to 26.5 per 100,000 inhabitants in Asturias in 1993[2].

In contrast to the incidence, the mortality due to colorectal cancer is descending in almost every country. In the international context, Spain has some of the lowest rates in Europe[3]. Specific high-risk groups include males and in those over 55, colorectal cancer occurs infrequently in those under 40 with a rapidly increasing incidence beginning at 50 years[4].

Until recently the patient with advanced colorectal cancer had few chemotherapy treatment options. The main anti-tumour agent for colorectal cancer for four decades has been fluorouracil[5] administered in combination with folinic acid in order to modulate its anti-tumour activity[6]. However the prognosis of patients with advanced colorectal cancer on this therapy remained poor. During the last few years, new medications have been developed with the aim of improving efficacy and reduce toxicity. Two recent studies indicate that irinotecan (actually available as first and second line therapy for advanced colorectal cancer) achieves a significant improvement in terms of both progression-free survival and overall survival[7-10].

The purpose of this study was to estimate the cost-effectiveness of irinotecan in combination with fluorouracil and folinic acid (5FU/FA) against 5FU/FA alone, in the first-line treatment of advanced colorectal cancer, from the perspective of the National Health System.

PATIENTS AND METHODS

Clinical, resource and cost data used in the analysis are described below. It should be noted that only direct costs were collected given that the perspective of the analysis was that of the National Health System. Costs and efficacy were estimated for two groups of patients: those patients receiving irinotecan with the addition of 5FU/FA and those receiving the same regimen of 5FU/FA. Data from the study by Douillard et al[9] were used in order to estimate the number of life-years gained (i.e. additional survival as a consequence of the use of irinotecan). In the Douillard study, each investigator chose one of two proposed regimens for 5FU/FA according to local clinical practice or preference: De Gramont (every 2-week period, irinotecan, 180 mg m 2 as a 90-minute intravenous [iv] infusion+folinic acid 200 mg m^2 iv over 2 h followed by 5FU 400 mg m 2 as an iv bolus then 5FU 600 mg m 2 as a continuous iv infusion over 22 h day-1 given during the first 2 days of every 2 week period) or Arbeitsgemeinschaft Internische Onkologie, cooperative german group for oncology (once weekly, irinotecan, 80 mg m^2 as a 90-min iv infusion+5FU 2300 mg m^2 per day iv over 24 h with folinic acid 500 mg m^2 iv total dose given during 24 hours per week for 6 weeks, with 2-week rests between cycles). Hence for each 6 week cycle this meant 3 chemotherapy sessions for the De Gramont group and 6 sessions for the weekly schedule.

Clinical data

Patient characteristics of the two treatment arms have been described previously[9]. Treatment with the combination of irinotecan+5FU/FA was significantly superior to 5FU/FA alone in terms of median overall survival (16.8 months compared with 14.0 months) in the intent-to-treat patient population. This translates to 2.8 months or 0.233 life-years gained for the irinotecan combination. Life-years gained was the major efficacy parameter in the analysis.

Resource utilisation

In order to obtain information about the utilisation of resources from the moment of randomisation for the two groups of patients, data of a sub-group of 41 spanish patients (22 treated with a combination of irinotecan and 5FU/FA therapy and 19 treated with 5FU/FA alone) included in the study by Douillard et al were used.

The main groups of resource utilisation that were considered are the following (taking into consideration the availability of such resource information). The amount of study alternatives: irinotecan, 5FU and FA; the type of setting for administering the study

drugs: outpatient clinic or hospitalised (two days of inpatient stay for hospital administration and two days of day hospital care for the outpatient option for each session in accordance with the De Gramont schedule); the medications used to treat tumour related pain; haematological and bio-chemical analyses; additional hospital admissions due to adverse events and/or other reasons; additional outpatient services including emergency visits, doctor visits and visits to other health care professionals which were included in the resource utilisation collection form and the use of additional chemotherapy drugs during the follow-up period after the termination of the study treatment.

Unit costs

Drug costs were based on the total dosage of each patient included in the spanish sub-group. The cost of irinotecan was based on the value published in the Catalogue of Pharmaceutical Specialties (year 2001)[11]. The hospitalisation and outpatient care costs were derived from a health care costs database that contains information from a range of sources including hospital annual reports, data presented at conferences and data obtained in local spanish studies[12]. Average costs from these sources are used since the spanish health care system is decentralised and no one source is considered to be representative of the whole of Spain. The range of costs and the number of sources used are presented in table 1. Although not all costs were originally from the same year, all costs were standardised to the year 2001 using the general consumer price index published by the National Institute of Statistics in Spain.

TABLE 1. **Costs used in the analysis (euros 2001)**

Resource item	Cost (euros)
Drugs (presentation)	
Irinotecan (1 vial x 100 mg)	218.92
5FU (10 vials x 250 mg)	9.20
FA (1 vial x 350 mg)	76.24
Hospitalisation (day)	Mean cost (range) (number of sources)[12]
Surgery	300.3 (138.6-459.2) (23)
Internal Medicine	252.0 (135.8-343.8) (28)
Oncology	307.8 (203.7-331.0) (4)
Traumatology	305.2 (136.9-424.1) (27)
ICU	1023.2 (694.9-1604.7) (29)
Day Hospital	141.7 (78.3-192.3) (22)
Emergency visits	98.1 (29.5-202.7) (57)
Visits	
Additional consultations	51.5 (29.8-73.3) (2)
Oncology	38.7 (27.3-59.3) (3)
Additional chemotherapy drugs (presentation)	
Oxaliplatin (1 vial x 20 ml)	481.12
Tomudex (1 vial x 2 mg)	190.42
UFT (60 sachets x 100 mg)	56.38
Tests	
Hematology	14.1 (14.1-14.1) (1)
Bio-chemical	64.1 (52.3-73.3) (9)

Survival

The measure of efficacy used in this economic study was the number of life-years gained. This term is a reference to the additional years of life obtained as a consequence of the addition of irinotecan to 5FU/FA treatment. The number of life-years gained based on the gain in median survival was derived directly from randomisation up to the end of the clinical trial as published by Douillard et al[9].

Cost-effectiveness analysis

In this economic analysis the incremental cost-effectiveness is defined as:

$(C_{I+5FU/FA} - C_{5FU/FA})/ (S_{I+5FU/FA} - S_{5FU/FA})$

where:

$C_{I+5FU/FA}$: total costs since randomisation of the irinotecan group;

$C_{5FU/FA}$: total costs since randomisation of the control group;

$S_{I+5FU/FA}$: average survival since randomisation of the irinotecan group;

$S_{5FU/FA}$: average survival since randomisation of the control group.

Economic model

An economic model was developed based on the underlying equation detailed above. The model was developed in order to compare the two treatment options in terms of their costs and survival and to undertake scenario analysis whereby the values of key parameters could be varied. This type of approach also permits the incorporation of new data that may become available at a future date (e.g. the results of a new clinical trial or more complete resource utilisation data).

Discount rate

Due to the limited time period considered in the analysis (just over one year) it was not considered necessary to discount neither the costs nor the survival.

Baseline case and sensitivity analysis

In the baseline case costs were assigned to the resources derived from the spanish sub-group analysis for the two treatment options that were then compared with the efficacy data derived from Douillard et al[9]. In the sensitivity analysis various scenarios were

considered by varying the values of key variables such as the cost of hospitalisation and additional survival obtained with irinotecan.

RESULTS

Patients characteristics

In table 2 basic data on the spanish sub-group at the point of randomisation are summarised. Information was available for a total of 41 spanish patients who participated in the Douillard study (22 from the irinotecan group and 19 from the control group).

Resource utilisation

Concerning the average number of cycles of study medication administered during the trial phase per patient one observes a greater number for the irinotecan group (5.2 versus 4.1 cycles). Clearly, a higher average number of cycles per patient will lead to a proportional increase in costs for this group. Less than 28% of patients in the irinotecan group received a minimum of three cycles of treatment compared with over 42% in the control group (table 3).

The average total amount of irinotecan administered per patient was 4,518 mg. In the case of 5FU and FA the amounts were approximately proportional to the average number of cycles according to study medication administered (table 3).

All patients in the spanish sub-group were treated according to the De Gramont regimen with the associated assumption that the total dosage would be administered during 48 hours of treatment: two days of hospital stay or three hours per day in an out-patient clinic for each session. In general, there were three sessions per treatment cycle, once again this information was extracted from the CRFs.

Apart from data on the main study medications, detailed information on the utilisation and dosage of those medications used to treat tumour related pain were collected.

With respect to the undertaking of diagnostic tests during all cycles the average numbers are presented in table 3. Again it is apparent that the average number of haematological and biochemical tests per patient is higher in the case of irinotecan in accordance with a higher number of cycles of administration per patient.

In addition to the utilisation of resources associated directly with the study medications, it was possible to identify and quantify certain resources related to the development of adverse events and additional follow-up medications. There were a total of 59 additional days of hospitalisation (an average of 2.7 per patient) for the irinotecan group and 33 (average 1.7) for the control group. In addition, approximately half of all patients required emergency visits (irinotecan: 50% and control: 53%). The number of external consultations ranged from 11 for the irinotecan group and 13 for the control group.

The most important additional component from the perspective of direct costs was that of the additional chemotherapy drugs used during the period of follow-up after the completion of cycles of study medication. As the original study did not record resource utilisation after the clinical trial it was necessary to make certain assumptions concerning the number of cycles, dosage and form of administration based on consultations with spanish oncologists since no addi-

TABLE 2. **Spanish patient characteristics at the moment of randomisation**

Characteristic	Irinotecan group (CPT-11 + 5FU/FA) (n=22)	Control group (5FU/FA) (n=19)
Male/Female (%)	15(68.2)/7(31.8)	8(42.1)/11(57.9)
Age (years)		
Average (range)	56(27-72)	57.3(39-72)
Median (range)	61(27-72)	57(39-72)
Height (cm) (range)	164(145-178)	161(147-176)
Loss of weight (%) (range)	3.9(0-23)	2.9(0-15)
Professional status		
Full-time	0(0.0)	1(5.3)
Part-time	2(9.1)	0(0.0)
Housewife	3(13.6)	6(31.6)
Retired	9(40.9)	4(21.1)
Unemployed	1(4.6)	0(0.0)
Sick leave	7(31.8)	8(42.1)
Total	22(100.0)	19(100.0)

TABLE 3. **Distribution of the number of cycles in the Spanish sub-group, chemotherapy administration, study drug utilisation (mg) and average number of diagnostic tests during all cycles**

	Irinotecan group (CPT-11+ 5FU/FA) (n=22)	Control group (5FU/FA) (n=19)
Number of cycles (all patients)		
1-3	6(27,3)*	8(42.1)
4-6	9(4.09)	8(42.1)
7-9	7(31.8)	3(15.8)
Total	22(100.0)	19(100.0)
Chemotherapy administration		
Hospital inpatient (days)	9.6	9.3
Day hospital (days)	20.1	14.4
Average drug utilisation (mg) per patient		
Irinotecan	4,518	-
5FU	50,069.5	40,301.6
FA	10,106.7	8,021.2
Type of diagnostic test (average number per patient)		
Haematological	29.6	22.8
Bio-chemical	15.4	12.1

* Number (%) of patients.

tional retrospective analysis was undertaken. Apart from irinotecan (equal distribution between in-patient and out-patient administration) it was assumed that the other chemotherapy treatments (5FU/FA, tomudex, UFT+FA, oxaliplatin) would not require an inpatient stay for administration.

Unit costs

Costs used in the analysis are summarised in table 1. Drug costs were derived from the Catalogue of Pharmaceutical Specialties[11] while costs for the health care resources were derived from a Spanish health care database containing information on hospital annual reports, local publications and data presented at national congresses and conferences[12].

Cost analysis

Total costs for the two treatment options are summarised in table 4. One observes that the cost of irinotecan represents approximately 40% of the total costs in the irinotecan group while in the control group the most significant cost component is that attributable to the additional follow-up chemotherapy treatment.

Survival

According to Douillard[9,13] there was a difference of 2.8 months (16.8 months against 14.0 months, $p < 0.028$) (0.233 life-years) in median survival gained as a consequence of the addition of irinotecan.

Cost-effectiveness analysis

By combining data from table 4 and survival results it was possible to calculate incremental cost-effectiveness ratios (table 5).
In the baseline case the incremental cost per life-year gained of irinotecan plus 5FU/FA against 5FU/FA (difference in cost/difference in efficacy of the two treatments) was 35,416 euros (€).

Sensitivity analysis

Table 6 summarises results of the sensitivity analysis assuming changes in the cost of irinotecan, the exclusion of the post-trial chemotherapy treatments, a ±25% change in the cost of hospital stay and changes in the number of life-years gained. The cost-effectiveness ratio is sensitive to some of these changes varying from 23,611 € to 49,023 € (based on the efficacy data from Douillard).
The sensitivity analysis indicates that the results are sensitive to the cost of irinotecan and the inclusion/exclusion of the post-trial chemotherapy treatments. In the case of the latter scenario, exclusion of the post-trial chemotherapy treatments leads to an increase in the incremental cost-effectiveness ratio of 38%.

TABLE 4. **Costs of the two options (euros, 2001)**

Resource item	Irinotecan group (CPT-11 + 5FU/FA)	Control group (5FU/FA)
Study drugs		
Irinotecan	9,891	
5FU	184	148
FA	2,201	1,747
Administration		
Hospitalisation	2,955	2,863
Day hospital	2,848	2,040
Concomitant medications (pain)	7	71
Tests	1,405	1,907
Additional admissions	986	817
Emergency visits	49	52
Additional visits	24	33
Additional chemotherapy including administration (following trial period)	3,141	6,316
Average total cost per patient	22,280*	14,016*

*Not including costs of concomitant medications or tests which would be included in global cost of hospitalisation.

DISCUSSION

In this study the cost-effectiveness of irinotecan plus 5FU/FA as first-line treatment of advanced colorectal cancer was undertaken. Clinical data were obtained from a multinational clinical trial, resource utilisation from a sub-group analysis of spanish patients included in the clinical trial and costs from a spanish cost database. The results of the baseline case indicate that the cost per life-year gained with irinotecan is 35,416 €.
The results are most sensitive to the quantity of additional survival (expressed in terms of life-years gai-

TABLE 5. **Incremental cost-effectiveness ratio (ICER) (baseline analysis)**

Treatment group	Cost (€)	Effectiveness (LYG)	ΔC	ΔE	Average CE	ICER
Irinotecan group (CPT-11 + 5FU/FA)	22,280	1.400			95,486	
Control group (5FU/FA)	14,016	1.167			60,070	
Difference			8,264	0.233		35,416

LYG: lyfe-year gained. ICER: incremental cost (euros) per LYG.

Table 6. **Results of sensitivity analysis**

Variable	% change	Incremental cost-effectiveness analysis (cost (euros) per life-year gained)
Cost of irinotecan	-25%	26,869
	+25%	43,963
Exclusion of chemotherapy and administration after clinical trial		49,023
Cost of hospitalisation	-25%	35,032
	+25%	35,801
Life-years gained	+25%	28,333
	+50%	23,611
Efficacy from Saltz et al[10]		45,075

ned) that accrues as a consequence of the use of irinotecan in combination with 5FU/FA. Given the relatively short-term nature of the time horizon considered, longer periods of follow-up may indicate additional survival benefits for irinotecan patients (i.e. additional differences under the respective survival curves) and hence reduce the cost-effectiveness ratio (due to a higher rate of increase in survival compared with the increase in the difference in costs) although this is in no way certain given the shape of the survival curve as illustrated in the Douillard study.

It should be emphasised that the patients in the irinotecan group received on average an additional cycle of treatment (5.18 versus 4.11) increasing automatically the use of drugs, administrative resources, tests, etc. and hence the total cost. In other words, a possible increase in response to treatment or longer survival may lead to an increase in the utilisation of resources.

The analysis of concomitant medication use for tumour pain management indicates the limited contribution of this component to total costs whilst the lack of information on the use of other medication prevented their inclusion. However, as other researchers have indicated[14], the great majority of the costs of adverse events are attributable to the costs of personnel and hospital admissions that have been included in this analysis.

The use of follow-up treatment after the end of the clinical trial has been included although with certain limitations: principally, the lack of detailed information on treatment duration and dosage. Consultation with clinical experts has enabled this information to be estimated based on their clinical practice, but a conservative approach has been taken leading to the possibility that the benefits for irinotecan have been undervalued.

The baseline results indicate that they are comparable with the results with other european studies. In France[15] a cost per life-year gained of 32,574,9 € was estimated higher than the results obtained by a group of british investigators[13] of 22,931 € per life-year gained. It should be noted that these studies are not directly comparable with the present study given that in both cases additional resource surveys were undertaken in order to supplement the data obtained from the case report forms. In the study by Schmitt et al[15] the use of healthcare resources after the failure of irinotecan was considered. They collected additional data retrospectively in order to estimate the number of additional sessions of chemotherapy and other costs related to the disease. There were fewer hospital admissions in the case of irinotecan that compensated for part of the additional cost of the drug.

In a similar manner, information from the british study13 was collected as part of a research programme in various centres in Great Britain. This information complemented the data available from the clinical trial.

Clearly, this is a subgroup analysis based on a multinational clinical trial. Costs have been derived from various spanish sources and therefore we believe are representative of Spain rather than a particular regional health care system. It should be noted that costs within regions are often considerably variable. In addition, there is a high degree of networking between spanish Oncology centres reducing major differences in patient management from one region to another. However, given the relatively small spanish patient population considered the results should be interpreted with caution.

Colorectal cancer is one of the most frequent forms of cancer with one of the highest associated number of deaths in the general population. However, the introduction of irinotecan as first-line treatment has been shown to be clinically beneficial in the advanced stage of the disease. From an economic point of view this study provides preliminary data previously not available in Spain. There are no official spanish guidelines on the maximum value that a society may be willing to pay for an additional year of life although a point of reference could be $50,000 (approximately 50,000€) that is the amount accepted in some countries. Another perspective is to consider the cost-effectiveness ratios of drugs currently financed by the National Health System. In this context it would appear that the use of irinotecan would be considered to be more cost-effective than some of the cardiology drugs prescribed and reimbursed in Spain[16,17].

In conclusion, the combination of irinotecan with 5FU/FA can be considered to be cost-effective in the first line treatment of advanced colorectal cancer in the spanish setting.

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