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Internet pharmaco-economic studies in metastatic colorectal cancer

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Abstract

An interactive Web site has been developed: http://smbh7.smbh.univ-paris13.fr, which uses a Markov model to calculate the management costs for metastatic colorectal cancer. This site allows drug usage costs, daily tariff costs per site, local ISA point values and the cost to the society of the chemotherapies prescribed to be recorded by cycle in a de-centralised manner. The overall cost of treatment may be calculated by one of these four units from the time when the first chemotherapy was administered until the patient has escaped from first or second line treatment. The median time to progression and the median survival time are key parameters used to calculate costs as they determine the number of patients who remain on treatment, course by course. Effectiveness results have been measured in terms of progression free survival or of global survival. Eight treatment strategies have been examined. It is possible to add new treatment regimens or new compounds into the existing pre-formatted tables. This software enables budgets to be planned depending on the regimen used and the number of patients treated. It also allows the different treatment options to be classified with respect to their incremental cost effectiveness ratio, which is defined by the additional cost of one treatment option compared to another divided by the corresponding increase in effectiveness.

Keywords: Metastatic colorectal cancer; Regimens; Cost; Budgetary forecast; Cost effectiveness ratio

1. Introduction

Pharmaco-economic studies must use unequivocal data collected under optimal conditions of quality and reliability in order to be accepted. In this field, the preferred instrument to collect economic information is the randomised trial. Conducting such trials on an international level and on several sites requires costly and time-consuming human and material resources. It is quite often not possible to overload case report forms by introducing too many economic variables. Collecting detailed economic data by administration regimen considerably increases the workload in the case report forms. The Internet offers new possibilities in this area. It may not only facilitate collection of cost data in each investigating centre but also facilitate combining these data together on a national or international level, within the context of a multi-centre trial.

2. Patients, materials and methods

2.1. Administration scheme

The standard quantities used in each of the eight protocols studied were defined with reference to three criteria: dose, duration of infusion and time between courses of treatment (Appendix).

1. LV5FU2 alone [1] consists of one administration every 2 weeks for 2 consecutive days of an infusion of 200 mg/m^2 of folic acid with a bolus of 400 mg/m^2 of 5FU over 10 min followed by a continuous 22-h infusion at a dose of 600 mg/m^2.
2. CPT11 in association with LV5FU2 [2] is administered every 2 weeks as treatment for 2 days at a dose of 180 mg/m^2. On day 1, the patient receives a dose of 180 mg/m^2 of CPT11 in a 90-min infusion. One h later folinic acid is administered for two min by infusion at a dose of 200 mg/m^2. A bolus of 5FU is then administered at a dose of 400 mg/m^2 for 10 min followed by a continuous 22-h infusion at a dose of 600 mg/m^2. The same protocol is repeated on day 2 except that no further infusion of CPT11 is given.
3. The FOLFOX4 protocol [3] contains the same doses of folinic acid and 5FU, i.e. a 200 mg/m^2 infusion of folinic acid over 2 days every 2 weeks, on days 1 and 2, followed by a bolus of 400 mg/m^2 of 5FU for 10 min, followed by a continuous 22 h infusion at a dose of 600 mg/m^2 on the first and second days. Irinotecan is replaced by Oxaliplatin, which is administered on the first day of treatment at a dose of 85 mg/m^2.
4. Another version of the CPT11 + LV5FU protocol [4] is currently undergoing experimental second line use under the protocol name FOLFIRI. This uses CPT11 at the same dose of 180 mg/m^2 associated with higher doses of 5FU administered both as a bolus (400 mg/m^2) immediately after the injection of 200 mg/m^2 folinic acid and as a continuous infusion at a dose of 2400–3000 mg/m^2 up to 48th h after starting treatment. The hospital admission may then be reduced to 1 day if administration of the chemotherapy in a hospital setting is combined with a continuous infusion on an outpatient basis, using portable pumps. This protocol is repeated every 2 weeks.
5. Simplifications of the administration regimens designed for CPT11 have also been adopted for Oxaliplatin in the FOLFOX6 protocol [5]. The use of a Y tube infusion system on day 1 enables folinic acid (dose 400 mg/m^2) to be injected simultaneously with a dose of 100 mg/m^2 of Oxaliplatin. The 5FU is then administered as a bolus at a dose of 400 mg/m^2 two min after the infusion has started. This is followed by a continuous infusion on an outpatient basis of 2400–3000 mg/m^2. This protocol is repeated every 15 days.
6. The association LV5FU2 + Oxaliplatin used in the FOLFOX2 protocol [6] is now obsolete. This was given over 2 days every 2 weeks as a 500 mg/m^2 infusion of folinic acid on days 1 and 2, followed by

a continuous infusion of 1500–2000 mg/m^2 of 5FU over 22 min on days 1 and 2. Oxaliplatin was only administered on the first day of treatment, at a dose of 100 mg/m^2.

7. CPT11 alone [7] is now only used as second line therapy in very specific situations. It is administered at a dose of 350 mg/m^2, as a short infusion (30 min) every 3 weeks.
8. CPT11 has been tested in association with Oxaliplatin [8] for third and fourth line use. It was administered every 3 weeks at a dose of 200 mg/m^2 of CPT11 and 85 mg/m^2 of Oxaliplatin. These two agents have not yet been clearly found to act synergistically.

The mean body surface area used in our calculations was 1.75 m^2. In view of the different lengths of the courses, all expenditure associated with administration of CPT11 or CPT11 and Oxaliplatin for 21 days has been calculated as a mean unit cost per day and multiplied by 14 days in order to be able to compare the cost of the four other protocols administered in 2 week courses.

These standard costs for the strategies studied that represent the resources consumed per fixed 14 day treatment cycle have been assessed as a function of the point of view in question, in terms of costs of use, daily tariff costs, DLG costs and costs to society.

2.2. Choice of value unit

The cost framework that must be considered in any economic evaluation must relate to the budgetary concerns of the party whose involvement is sought in a health care project [9]. There is no all encompassing study in this field; an evaluation performed for one type of contributor must only consider this party's point of view. Four value units have been chosen to transform the resources consumed into costs: the daily tariff, the SAI point value for the relevant diagnostic reference group, the drug usage costs and the costs to society. In the description of chemotherapy methods listed above, we may use any of the following as value units; quantity of drugs and materials purchased and the hospital admission day or admission period. These units are good indicators of the quantity of resources used. The choice used depends on to whom the evaluation will be addressed [10,11].

Table 1
Choice of orientation

Social security	Daily tariff cost (DTC)
Hospital Directorate	Diagnostic reference group (DRG)
Head Pharmacist	Drug usage cost (DUC)
Legal authorities	Costs to society (DRG+DUC)

If the purpose of the exercise for an institution is to present a convincing case to its normal associates in the social security system, the daily cost tariff should be used. In each department (region) one of the funds for the three main social security groups — the general group for salaried workers, the group for self-employed workers and the group for farm workers — acts as the single interface for its related hospitals. Each month, this fund pays 1/12 of the total allocated annual payment on behalf of all of the sub-groups. It then subsequently applies to the corresponding funds to be reimbursed for the sums of money paid in advance. The daily tariff cost (DTC) therefore allows the costs of the total annual funding to be divided between the social security groups pro rata for the number and length of admissions for the affected subjects taken care of in the institution. This cost value unit is therefore only of accounting significance. It should not be used in pharmaco-economic evaluations unless these are designed for the social security system. This throws very considerable doubt on the contents of pharmaco-economic assessments that are currently undertaken on an international level. Most of these cumulate the costs of procedures, which are evaluated from micro-economic studies and the admission costs, calculated by multiplying the day cost by the length of admission. Information collected in this way is of no value, firstly because it uses tariffs and not costs, and secondly because it results in double charging; tariffs evaluated from the total actual costs, which already include these procedures in most European countries (Table 1).

For the director, costs must be calculated as summary of activity index (SAI) points, by diagnostic reference groups, as the total theoretical grant made to the institution run by the directorate is calculated from a breakdown of the diseases treated in the hospital by DRG, weighted by the SAI point coefficients associated with each DRG. Any treatment that reduces the length of hospital admissions in the hospital frees beds for new admissions, resulting in additional DRG being admitted. The value of these DRG will be lower than the additional variable costs associated with admitting a new patient. This therefore gives the institution greater financial flexibility.

None of the two value units described above are of significance to the careful and well-advised purchaser, the Head Pharmacist. What is important to this person, is the savings that may be made in his department as a result of using one drug in preference to another. These calculations must therefore be made using standard drug usage costs (DUC), i.e. using costs with standard values, set in advance. These values will refer both to quantities of resource consumed and to unit costs. The standard quantities used in each of the protocols for colonic cancer, for example, are defined by means of three criteria: dose, duration of infusion and time be-

Table 2
Data used

Strategies	Source	Phase	Line	Number of patients	GS (weeks)	TTP (weeks)	PFS (weeks)
LV5 FU2	Douillard [2]	III	1st	177 evaluable	56	16	–
CPT11+LV5FU2	Douillard [2]			174 evaluable	75	28	–
LV5 FU2	De Gramont [3]	III	1st	208 evaluable	69	–	26
FOLFOX4	De Gramont [3]			209 evaluable	69	–	38
FOLFOX2	De Gramont [9]	II	2nd	60 eligible	64	–	26
FOLFOX6	Maindrault Goebel [5]	II	2nd	60 evaluable	46	–	23
CPT11 alone	AMM Dossier	II	2nd	363 eligible	39	18	–

tween cycles. These three parameters directly determine the drug acquisition costs, their preparation costs and the value of the consumables required for the drugs to be administered. Unit costs are listed in the departmental accounts section and are obtained from the drug acquisition costs, consumable acquisition costs and the standardised actual costs of pharmacy staff.

It is important, when negotiating with statutory authorities, to go beyond the tariff approach and to identify the additional costs or the savings that are actually made if a new treatment is introduced. In this case, we must calculate the true opportunity cost of an initiative, i.e. the value of what is avoided as a result of what is done. In this case, we exclude the seven sections relating to variable medical costs from the 17 constituents of cost analysed in the PMSI study, and we replace these with real costs that are directly attributable to using a specific protocol. If it is not possible to use this process, the drug usage costs may be added to the DRG value (in SAI points) to calculate the costs of a hospital admission to the society. This is undoubtedly a rather crude approach and implies the need for two systems, although it is acceptable if only a small number of values are counted twice.

2.3. Selection of the comparator

The LV5FU2 regimen published by De Gramont is more effective in terms of objective response and is better tolerated in haematological and mucosal terms. It has become the reference regimen in France for first line palliative treatment [1].

An alternative line of chemotherapy is given after a patient has escaped from treatment with LV5FU2. In the absence of knowing actual practice and in order to retain a treatment that is loyal to each of the new compounds that are currently being studied, we have assumed that 50% second line chemotherapies use CPT11 alone and 50% use FOLFOX6.

We decided to illustrate the potentials of the interactive software by comparing the performance of conventional LV5FU2 chemotherapy, followed in the event of failure, by CPT11 and FOLFOX6 in the ratio 50/50 to those of two new treatment regimens, the respective costs and benefits of which currently need to be evaluated: CPT11 + LV5FU2 followed by FOLFOX6 in the event of escape and FOLFOX4 followed by CPT11 alone in the event of escape.

2.4. Evaluation of efficacy data

The costs of follow-up that are not the same as the costs of a treatment course, are influenced by the extent of the benefit obtained from treatment. This is why we introduced the most recent and best validated efficacy data (Table 2) in order to calculate the predicted costs of first and second line management, based on a simplified Markov model.

Two types of data were taken from the trials:

1. The median survival or global survival (GS) is the number of weeks after which half of the patients had not died.
2. The median time to progression (or TTP) is the number of weeks after starting treatment when 50% of patients have relapsed or died as a result of the disease. When we consider all causes of death combined we refer to progression free survival (PFS).

The indirect comparison of the performances of CPT11 + LV5FU2 and FOLFOX4 measured in terms of the median time to progression (TTP) and global survival (GS) in the Douillard trial [2] and in the Gramont trial [3] is limited for four reasons:

1. The respective performances of the two chemotherapies were not measured in the same trial. At first sight the inclusion criteria are similar although there is no reason to assume that the response rates were confirmed with the same rigour in both trials.
2. The end points, median time to progression (TTP) and median survival time without progression (PFS, progression free survival) are not strictly superimposable.
3. The performances of the comparator LV5FU2 are markedly different in the two publications: 10 weeks longer in the Gramont trial compared to the Douillard trial: 26 weeks versus 16 weeks for the median time to progression (TTP) and 13 weeks more for the median global survival time (GS): 69 vs. 56 weeks. Data published were presented in months.

For the purposes of this analysis these have been transformed into weeks using a conversion factor of 4.33 (52 weeks/12 months).

4. There were no significant differences in terms of global survival between FOLFOX4 and LV5FU2 in the Gramont trial.

In order to attempt to resolve the situation we adopted the following assumptions (Table 3):

1. The findings taken from the Douillard trial on LV5FU2 were used as the reference points to estimate performance of this association in terms of global survival (SG) and median time to progression (TTP).
2. For FOLFOX4, we have added the corresponding differential found in the Gramont trial between the LV5FU2 arm and the FOLFOX4 arm to these baseline values, when this was statistically significant, i.e. 38–26 weeks is 12 for the median time to progression and 0 weeks for global survival.
3. For CPT11, the results published in the Douillard trial have been reproduced as they are.

2.5. Calculation of the cost of patient follow-up

Projected management costs for first and second line treatment were calculated over a given follow-up period by estimating the number of patients who remained on treatment each week. These numbers were obtained from the median survival period (GS) and from the median time to progression (TTP). The simplified Markov model uses the DEALE method [12] and the equations that come from this to calculate the probability of relapse or death:

$$P(t_0, t) = 1 - [1 - (e^{-\mu})^i]$$

$P(t_0, t)$ is the cumulative probability of the non-occurrence of an event (relapse or death) over time intervals i from t_0 to t, where t is the length of the follow-up period; μ is the relapse or death rate, which is constant for each interval i; $e^{-\mu}$ is the proportion of patients who have not died or relapsed at the end of interval i; $1 - e^{-\mu}$ is the probability of death or relapse during interval i; $1 - [1 - (e^{-\mu})]$ is the probability of survival or remission during interval i; $[1 - (e^{-\mu})^i]$ is the cumulative probability of survival or remission during all intervals i, from 0 to t.

When the clinical parameters are expressed as median survival time (GS) or time before escape from treatment, μ is given by the 1 – the natural logarithm of 0.5 divided by the number of calendar units j in which 50% of the patients have not experienced the event in question:

$$\mu = -\ln(0.5)/j$$

In, for example, the first line FOLFOX4 regimen followed by administration of CPT11 alone after the first line chemotherapy has failed, the median time to progression or death and global survival for the FOLFOX4 regimen from the hypothesis are 28 and 56 weeks respectively.

1. The probability of relapse or death during the interval ($i = 2$) is equal to 0.0483:
2. The probability of death during the interval ($i = 2$) is equal to 0.0245:
3. The probability of relapse alone during the interval ($i = 2$) is equal to 0.0483–0.0245, i.e. 0.0238 (Table 4).

In all 24% of patients treated first line with FOLFOX4 will relapse by the end of the second week. These patients will all be treated second line with another protocol, the TTP of which is 18 weeks. Patients who relapse on first line treatment at the end of week j will be treated second line by the second line protocol until the end of the follow-up period (i–j) as long as a further event (relapse or death) does not occur. The probability that patients who have relapsed on first line therapy at the end of the second week will follow second line treatment until the last week of follow-up ($i = 5$) is therefore 0.0238×0.824 (Table 4).

The numbers of relapsed patients who are treated by second line chemotherapy may be estimated during the number of weeks in question by adding together the weighted probabilities of continuing treatment throughout the follow-up period, i.e.

Table 3
Central assumptions in the model

Trials	Protocol	Median time to progression (TTP)	Median global survival (GS)
Douillard [2]	LV5FU2	16	56
	CPT11 + LV5FU2	28	75
De Gramont [3] differential TTP and GS adjusted from the Douillard LV5FU2 data	LV5FU2	16[a]	56[a]
	FOLFOX4	28[a]	56[a]

[a] The trial findings were adjusted based on assumptions 1, 2 and 3.

Table 4
Calculation of second line treatment numbers

End of week considered	Probability of relapse on first line treatment	Number of weeks	Probability of continuing on second line treatment
1	0	0	1
2	0.0238	1	0.925
3	0.0351	2	0.890
4	0.0459	3	0.857
5	0.0564	4	0.824

$$(0 \times 0.824) + (0.0238 \times 0.857) + (0.0351 \times 0.890) + (0.0459 \times 0.925) = 0.0943$$

The total cost is given by the sum of the costs of first line treatment and the costs of second line management of patients who relapse after first line therapy.

3. Results

3.1. Standard cost per patient per 21 days cycle

3.1.1. Usage costs per patient

These are the charges (drugs, staffing, materials) that are directly related to the use of a chemotherapy protocol, and which may allocated without discussion or debate or calculation, to the pharmacy sector, i.e. acquisition costs, preparation costs and administration costs for the chemotherapy. This definition makes no assumptions about the extent of the fields considered (costs which are directly attributable to the protocol being studied or indirect costs applicable to pharmacy as a whole, and which cannot be sub-divided), nor about the rules relating to variation of expenditure (variable and fixed costs), nor to the temporal horizon used (immediate consequences of the treatment administered or late consequences due to immediate or cumulative toxicity associated with the treatment).

1. Drug acquisition costs may be calculated almost immediately from the recommended dose and body surface area of the patient. These two units are multiplied together and are then divided by the contents of each treatment unit in order to obtain the number of bottles required to administer the treatment. This number is multiplied by the unit price negotiated between the hospital and the pharmaceutical company to determine drug acquisition costs to the hospital. Administration of CPT11 alone to a patient with a body surface area of 1.75 m^2 requires 6×100 mg/5 ml bottles at a unit cost of 173 Euros (189 US $) and one 40 mg/5 ml bottle costing 70 Euros (76 US $). The total costs (including taxes) for a 21 days course is therefore 1109 Euros (1208 US $) (Rate of exchange: 1 Euro = 1.09 US $), i.e., 740 Euros (807 US $) for 2 weeks treatment. These calculations are performed using the same principle for the combination protocols LV5FU2 + Oxaliplatin, LV5FU2 + CPT11 and CPT11 + Oxaliplatin. The drug acquisition costs of combinations of LV5FU2 with either CPT11 or Oxaliplatin are invariably less expensive than CPT11, either alone or in combination with Oxaliplatin.
2. We know that the cost of treatment is not limited to the drug acquisition costs and that we need to include both the salaries of professional staff who prepare the chemotherapy and the cost of consumables and equipment needed to administer the chemotherapy (Table 5). The association LV5FU2 + CPT11 and FOLFIRI is also less expensive when these factors are included in the drug costs, i.e. 700 and 711 Euros (763 and 774 US $). The most expensive combination is that of LV5FU2 and Oxaliplatin; 849 Euros (925 US $) for FOLFOX2, which is the most expensive of all of the protocols studied, and 756 Euros (824 US $) for the simplified FOLFOX6 regimen. In contrast to these two protocols, the FOLFOX4 regimen costs less because the dose of folinic acid is considerably lower. The cost of the CPT11 + LOHP protocol is slightly higher than the cost of CPT11 alone 797 Euros versus 757 Euros (868 vs. 825 US $), LV5FU2 is less expensive because it costs 1/6th of the other six comparators: 122 Euros (132 US $) (Fig. 1).

3.1.2. Standard costs expressed as daily tariff costs

The costs of the eight chemotherapy regimens are proportional to the duration and nature of the hospital admissions they incur. Treatments based on LV5FU2 require a conventional 2-day hospital admission every 15 days. Treatments based on CPT11, either alone or in association with Oxaliplatin, are administered every 3 weeks and only require 1 day's admission to a day hospital. The simplified protocols, FOLFOX6 and FOLFIRI, also only require a single day hospital admission although this takes place every 15 days. Using the daily tariff costs of a provincial anti-cancer centre as the basis for the calculation, i.e. 695 Euros (757 US $) for the day hospital and 817 Euros (890 US $) for all

hospital admissions lasting more than 24 min, the following standard costs may be obtained: 1636 Euros (1783 US $) per 14-day cycle for treatments based on LV5FU2, 695 Euros (757 US $) for the simplified protocols, and 464 Euros (505 US $) for treatments based on CPT11 every 3 weeks.

3.1.3. Standard costs expressed as ISA points by diagnostic reference group (1996)

Each hospital admission must be classified into a diagnostic reference group, each of which is associated with an ISA point coefficient (ISA: French Combined Activity Index) the magnitude of which reflects the relative amounts of resources mobilised. Two groups are particularly important in oncology, one associated with outpatient chemotherapy and the other with chemotherapy involving a full hospital admission.

DRG 681, which represents the former type of management is valued at 204 ISA points. DRG 593, which corresponds to the latter carries 839 points. The national unit value of an ISA point in 1996 was 2.137 Euros (2.32 US $). The cost of chemotherapies involving conventional hospitalisation and based on LV5FU2 is therefore 1793 Euros (839 × 2.137 Euros) (1954 US $) per 14 day cycle (Table 6). The cost of chemotherapies administered in a day hospital using CPT11 alone or in combination with Oxaliplatin is 291 Euros (317 US $) per 14-day cycle, whereas FOLFOX6 and FOLFIRI protocols cost 436 Euros (475 US $).

3.1.4. Standard costs to the community

Diagnostic reference groups 681 and 593 reflect the cost of 'non-intensive' maintenance chemotherapy. The variable medical costs that they refer to, and particularly consumable costs, are a very poor reflection of the cost of new treatments. In order to evaluate the consequences of the appearance of these new treatments on

Table 5
Standard usage costs for cytotoxic agents per 14-day cycle (Euros)

	FOLFOX2	CPT11+LOHP	CPT11 alone	FOLFOX6	LV5FU2 + CPT11	FOLFIRI	FOLFOX4	LV5FU2
Drug acquisition cost	772	771	740	681	634	623	542	45
Preparation of treatment								
Consumables	14	4	3	14	14	14	14	14
Staff	15	3	4	13	15	15	15	15
Sub-total 2	29	7	7	27	29	29	29	29
Administration of treatment								
Consumables	39	13	11	39	39	39	39	39
Sub-total 3	39	13	11	39	39	39	39	39
Equipment								
Portable pump	9	6	0	9	9	9	9	9
Pump adapter	0	0	0	0	0	0	0	0
Sub-total 4	9	6	0	9	9	9	9	9
Drug usage cost	849	797	758	756	711	700	619	122

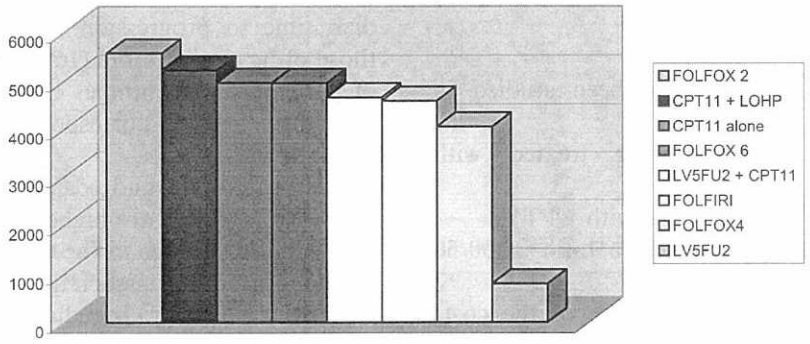


Fig. 1. Classification of standard usage costs for the eight strategies studied.

Table 6
Standard costs of cytotoxic agents per 14-day cycle to society (Euros)

	FOLFOX2	LV5FU2+CPT11	FOLFOX4	LV5FU2	FOLFOX6	FOLFIRI	CPT11+LOHP	CPT11 alone
Usage cost	849	711	619	122	756	700	796	757
DRG cost	1793	1793	1793	1793	436	436	291	291
Cost to society	2642	2504	2412	1915	1192	1136	1087	1052

Table 7
One-year usage costs for first line treatment of 100 patients (Euros)

	LV5FU2 then CPT11alone or FOLFOX6	FOLFOX4 then CPT11 alone	CPT11+LV5FU2 then FOLFOX6
Drug acquisition	47 359	802 366	939 114
Treatment preparation	30 518	42 824	42 824
Treatment administration	50 382	70 687	70 687
Drug usage cost	128 260	915 877	1 052 625

Table 8
One-year costs to society of first line treatment of 100 patients (Euros)

	LV5FU2 then CPT11 alone or FOLFOX6	FOLFOX4 then CPT11 alone	CPT11+LV5FU2 then FOLFOX6
Daily tariff costs	1 726 290	2 421 588	2 421 588
DRG costs	1 892 580	2 654 855	2 654 855
Cost to society	2 020 870	3 570 748	3 707 496

society itself we have to add the additional cost of the new treatments compared to the old ones to the existing DRG values. We have therefore assumed that the sum of the DRG value and the drug usage cost of these new substances produces a good approximation of the cost to society. These were 2504 Euros (2729 US $) for the association LV5FU2 + CPT11 versus 1136 Euros (1238 US $) for the same association in the FOLFIRI protocol and 2642 Euros (2879 US $) for the association FOLFOX2, 2412 Euros (2629 US $) for FOLFOX4, and 1192 Euros (1299 US $) for FOLFOX6, compared to 1915 Euros (2087 US $) for LV5FU2 alone, 1052 Euros (1146 US $) for CPT11 alone and 1087 Euros (1184 US $) when CPT11 is used in association with Oxaliplatin (Table 6).

3.2. Annual predicted budget per 100 patients on three therapeutic regimens

Three therapeutic regimens have been studied in more detail:

1. CPT11 + LV5FU2, relapse being treated with FOLFOX6,
2. FOLFOX4, relapse being treated with CPT11,
3. LV5FU2, relapse being treated in a ratio of 50/50 with FOLFOX6 or CPT11 alone

In order to produce a better estimate of the costs incurred by these three approaches, either from the point of view of the pharmacist or from the point of view of society, taking account of the opportunity cost of the strategies, we have calculated the cost of first and second line therapy and total costs to treat 100 patients for 1 year.

3.2.1. Annual first line treatment cost of 100 patients

The drug usage cost (Table 7) for the regimen LV5FU2 are considerably lower than those of its comparators 128 260 vs. 900 877 vs. 1 652 625 Euros (139 803 vs. 981 955 vs. 1 801 361 US $). The same results can be observed concerning the cost to society (Table 8) 2 020 870 vs. 3 570 748 vs. 3 707 496 Euros (2 202 748 vs. 3 892 115 vs. 4 041 170 US $).

There are two reasons for this: firstly the standard acquisition cost of LV5FU2 is 1/5–1/6 of that of CPT11 + LV5FU2 or FOLFOX4 and secondly the median time to progression for LV5FU2 is lower than those of its comparators (16 vs. 28 weeks). The number of patients who continues first line treatment is therefore lower and the corresponding costs are reduced to the same extent.

The drug usage and society costs of CPT11 associated with LV5FU2 are higher than those of FOLFOX4 due to the difference in the drug acquisition of the two agents. The former association offers a survival advantage over the latter. It reduces the likelihood of stopping treatment because of death. Because the time to progression is the same across the two treatments, it

increases the probability of stopping chimiotherapy due to a relapse. The probability of remaining on first line treatment remain unchanged but the number of patients who are going to receive a second line of chimiotherapy increases.

3.2.2. One year second line treatment cost of 100 patients

As more patients escape from first line treatment on LV5FU2 than with the other two treatment options, the costs of second line treatment (Tables 9 and 10) are higher after failure of treatment with LV5FU2 than they are in a similar situation with one of the other two comparators.

The second line user costs of the association of CPT11-LV5FU2 and FOLFOX4 are 185 695 Euros (202 407 US $) and 123 512 Euros (134 628 US $) per 100 patients treated per year respectively and the costs of the same associations to society are 292 794 Euros (319 145 US $) and 158 305 Euros (172 552 US $) respectively. The proportion of patients who stop first line treatment as a result of dying with CPT11 + LV5 FU2 is lower than FOLFOX4; therefore the proportion of patients undergoing second line treatment is greater.

3.2.3. Total cost of treatment:

Despite the fact that the user cost (Table 11) and cost society (Table 12) are higher in second line for LV5 FU2 than those of the comparators, its overall costs is considerably lower due to the saving realised in the first line of treatment. (the society cost of the regimen LV5FU2 is 0.56 times that of its comparators).

As the first and second line costs of the regimen CPT11 + LV5FU2 are higher than those of the regimen FOLFOX4 the total costs are also higher (Tables 11 and 12): in terms of cost of use per 100 patients for 1 year these are 1 238 321 Euros (1 349 769 US $) versus 1 030 275 Euros (1 122 999 US $) and in terms of cost to society 4 000 000 Euros (4 360 000 US $) vs. 3 729 053 Euros (4 064 667 US $).

Table 9
Usage costs of second line treatment of 100 patients for 1 year (Euros)

	LV5FU2 then CPT11 alone or FOLFOX6	FOLFOX4 then CPT11 alone	CPT11+LV5FU2 then FOLFOX6
Drug acquisition	243 405	120 901	167 344
Treatment preparation	6 031	962	6 534
Treatment administration	10 809	1 649	11 817
Treatment usage cost	260 245	123 512	185 695

Table 10
One-year costs to society of second line treatment of 100 patients (Euros)

	LV5FU2 then CPT11 alone or FOLFOX6	FOLFOX4 then CPT11 alone	CPT11+LV5FU2 then FOLFOX6
Daily tariff costs	203 557	70 092	170 901
DRG costs	127 542	72 351	107 084
Costs to society	388 534	158 305	292 794

Table 11
Total usage costs of 100 patients treated for 1 year (Euros)

	LV5FU2 then CPT11 alone or FOLFOX6	FOLFOX4 then CPT11 alone	CPT11+LV5FU2 then FOLFOX6
Drug acquisition	290 763	914 122	1 106 458
Treatment preparation	36 565	43 802	49 359
Treatment administration	61 206	72 351	82 504
Treatment usage cost	388 534	1 030 275	1 238 321

Table 12
Total costs to society of 100 patients treated for 1 year (Euros)

	LV5FU2 then CPT11 alone or FOLFOX6	FOLFOX4 then CPT11 alone	CPT11+LV5FU2 then FOLFOX6
Daily tariff costs	1 929 863	2 491 695	2 592 504
DRG costs	2 020 137	2 698 779	2 761 939
Costs to society	2 408 702	3 729 053	4 000 290

Table 13
Differential total costs (Euros) and effectiveness (weeks)

Protocol	CPT11+LV5FU2 regimen–FOLFOX4 regimen	FOLFOX4 regimen–LV5FU2 regimen	CPT11+LV5FU2 regimen–LV5FU2 regimen
Usage cost	2081	6419	8496
Daily tariff cost	1008	5618	6626
DRG cost	632	6786	7418
Cost to society	2712	13 206	15 918
Effectiveness progression free survival	0	8.50	8.50
Effectiveness global survival	2.89	0	0.44

Table 14
Differential cost-effectiveness ratios in terms of progression free survival (Euros)

Protocol	FOLFOX4 regimen–LV5FU2 regimen			CPT11+LV5FU2 regimen–FOLFOX4 regimen			CPT11+LV5FU2 regimen–LV5FU2 regimen		
$\Delta C/\Delta E$	Euros/week	Euros/year	$/year	Euros/week	Euros/year	$/year	Euros/week	Euros/year	$/year
Usage cost	756	39 267	42 801	CPT11+LV5FU2 dominated			CPT11+LV5FU2 dominated		
Cost to society	1554	80 794	88 065						

Table 15
Differential cost-effectiveness ratios in terms of global survival (Euros)

Protocols	FOLFOX4 regimen–LV5FU2 regimen			CPT11+LV5FU2 regimen–FOLFOX4 regimen			CPT11+LV5FU2 regimen–LV5FU2 regimen		
$\Delta C/\Delta E$	Euros/week	Euros/year	$/year	Euros/week	Euros/year	$/year	Euros/week	Euros/year	$/year
Usage cost	FOLFOX4 dominated			719	37 398	40 763	2940	152 904	166 665
Cost to society				938	48 762	53 150	5507	286 351	312 122

3.3. Differential cost-effectiveness ratios for three treatment regimens

Differential costs and effectiveness obtained for a patient followed up for 1 year and the corresponding differential cost-effectiveness ratios [13] are shown in Tables 13 and 14.

In terms of costs to society the regimen CPT11 + LV5FU2 is more expensive than the regimen FOLFOX4, 2712 Euros (2956 US $) and FOLFOX4 is itself more expensive than the reference regimen LV5 FU2, 13 206 Euros (14 394 US $). The difference between the first two regimen is however 1/5 of the difference between the FOLFOX4 regimen and the control arm. Over the two lines of treatments, the societal cost of CPT11 + LV5 FU2 with respect to the LV5 FU2 is equal to 15 918 Euros (17 358 US $) per patient, per year.

The regimen LV5FU2 is the least effective in terms of progression free survival, as its TTP is 16 weeks. The regimens FOLFOX4 and CPT11 + LV5FU2 provide a gain of 8.5 weeks without progression for a patient over 1 year. The regimen LV5FU2 is as effective in terms of global survival than the regimen FOLFOX4 but it is less effective than the regimen CPT11 + LV5FU2 (−2.9 weeks of life).

If cost effectiveness ratio of the three treatment regimens are compared in terms of progression free survival, the regimen

1. FOLFOX4 is more expensive and more effective than the regimen LV5FU2 (Table 14). Use of the former enables the patient to gain 8.5 weeks of progression free life, and from the point of view of the pharmacist costs an additional 756 Euros (824 US $), i.e. 42 801 US $ per year of progression free survival. From the point of view of society the week without progression costs 1554 Euros (16 953 US $), i.e. 88 065 US$ per year without progression.
2. CPT11 + LV5FU2 is more expensive and equally as effective as the FOLFOX4 regimen and is dominated, regardless of the type of cost examined.

In terms of global survival and regardless of the point of view considered (Table 15), the regimen CPT11 + LV5FU2 is more expensive and more effective than the FOLFOX4 and LV5FU2 regimens, al-

though FOLFOX4 is more expensive and equally effective compared to the LV5FU2. Only the regimens LV5FU2 and CPT11 + LV5FU2 are efficient.

If these two regimens are compared from the point of view of the pharmacist, administration of regimen CPT11 + LV5FU2 enables the patient to gain 2.89 years of life compared to the regimen LV5FU2 and is associated with an additional cost of 2940 Euros (3204 US $) per week of life gained, i.e. 152 904 Euros or 166 665 US $ per year of life gained. When considered in terms of the cost to society, the week of life gained in this case costs 5507 Euros, i.e. 286 351 Euros or 312 122 US $ per year of life gained.

3.4. Sensitivity analysis

In order to measure the impact of the effectiveness data on the ranking of the treatment regimens with respect to each other, we performed a sensitivity analysis using these baseline data and varying each type of data point (global survival and time to progression) separately.

Hypothesis 1 (*Comparison of two treatment regimens in terms of usage cost*).

3.4.1. End point: progression free survival

In terms of drug usage costs, the FOLFOX4 regimen is always less expensive than the CPT11 + LV5FU2 regimen (Table 16). When the TTP of FOLFOX4 is less than 28 weeks it becomes less effective than CPT11 + LV5FU2, making both of these treatments efficient. Above this threshold value the regimen FOLFOX4 then becomes the only efficient strategy in terms of progression free survival and drug usage cost. Varying global survival has no impact on these results.

3.4.2. End point: global survival

As the global survival associated with FOLFOX4 is less than that of CPT11 + LV5FU2, FOLFOX4 is less effective in terms of global survival. With a TTP of 28 weeks FOLFOX4 is less expensive than CPT11 + LV5FU2 and both of these treatments are efficient with differential cost-effectiveness ratios of 719 Euros (783 US $) and 37 398 Euros (40 763 US $) per week and per year respectively for the CPT11 + LV5FU2 regimen.

The ranking of these regimens against each other does not change if the TPP of the treatments is varied: FOLFOX4 has a higher TTP and a higher usage cost although it is still less expensive than CPT11 + LV5FU2. With a TTP of 36 weeks, CPT11 + LV5FU2 costs more than FOLFOX4 by 453 Euros (493 US $) per week of life gained, or 23 569 Euros (25 690 US $) per year of life gained (Table 17).

Hypothesis 2 (*Comparison of the two treatment regimens in terms of cost to society*).

3.4.3. End point: progression free survival

Both of these two protocols were equally effective with a TTP of 28 weeks. The regimen CPT11 + LV5FU2 is more expensive than the regimen FOLFOX4 and is therefore highly dominated (Table 18).

If the median time to progression for the FOLFOX4 regimen is increased it becomes more effective but also more expensive. When the TTP for FOLFOX4 is more than 33 weeks (i.e. a differential TTP of 5 weeks), its comparator becomes both less expensive and less effective. At a differential of 10 weeks TTP between the two regimens, the cost of a week of life gained without relapse for CPT11 + LV5FU2 is 393 Euros (428 US $) and a year of life gained without relapse costs 20 465 Euros (22 306 US $) (Table 18).

If the global survival is varied for FOLFOX4 the treatments remain as effective in terms of progression free survival; the higher the global survival of FOLFOX4 the more it costs; CPT11 + LV5FU2 remains dominated.

3.4.4. End point: global survival

FOLFOX4 is associated with a lower global survival than CPT11 + LV5FU2 (56 weeks vs. 75 weeks) and is therefore less effective than its comparator in terms of global survival.

If the median time to progression is increased (Table 19) the effectiveness in terms of global survival does not alter and only the cost increases. When the differential TTP between the two regimens exceeds 5 weeks, FOLFOX4 becomes more expensive than CPT11 + LV5FU2 and therefore dominated.

If the global survival associated with FOLFOX4 is changed up to 75 weeks FOLFOX4 then becomes more effective in terms of global survival and dominates CPT11 + LV5FU2.

4. Discussion

Ranking treatment regimens by their acquisition costs per year of life gained offers hospital pharmacists the means to evaluate the returns on their investment as represented by the amount of expenditure that falls on their budgets. There is a considerable amount to do in this field as, to our knowledge, there are no other instruments that allow technologies to be ranked as a function of their usage cost.

Treatments may also be ranked in terms of their cost to society. If the three treatment regimens are compared from this point of view, their differential cost effectiveness ratios (88 065 US$ for FOLFOX4 vs. LV5FU2 when the end point used is progression free survival and 312 000 US$ for CPT11 + LV5FU2 vs. LV5FU2

Table 20
League tables

Intervention	Cost-effectiveness ratio US $\$_{1993}$/year of life gained
β blockers for survivors of myocardial infarction	850
Mammography every 3 years for women between 50 and 65 years old	2700
Intensive care units for premature infants between 500 and 1000 g	18 000
Renal dialysis for chronic renal failure in 45–54-year-old patients	47 000
Pneumonia vaccination for children between 2 and 4 years old	170 000
Hormone replacement therapy for asymptomatic post-menopausal women between 55 and 70 years old	250 000

when the end point used is global survival), are above the thresholds that are considered by economists to be acceptable [14–17]. By comparing these ratios with the clear advantages associated with using other technologies [15] (Table 20), they appear to be even higher. The acceptable cost of survival for 1 year was first considered by Epstein in 1992 to be 30 000 US$ [14]. This reasonable cost limit for technology may be updated for 1999 to 50 000 US $.

If the regimens are ranked, however, as a function of their treatment costs from the point of view of society we also have to take account of the complications and re-admissions to hospital that are associated with these treatments. The differential costs that emerge for severe adverse events related either to the treatment or to the disease in fact represent savings that may be deducted from the drug acquisition costs for new compounds. It is also necessary in doing this that the three types of costs are consistent in both their definitions and their contents. It would be incorrect for example to calculate the cost of a treatment as the drug usage cost and to deduct savings made in toxic reactions or complications of the disease, which are avoided, valued using the daily tariff cost or near complete diagnostic reference group.

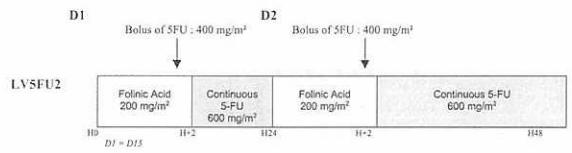
5. Conclusion

The use of the Internet to run these studies offers many advantages. Conventionally, data collection requires many visits to investigating centres and successive control procedures. Performing these studies on the Net optimises the movement and sharing of information between the different people taking part. In addition, the use of formatted registration interfaces facilitates information collection by rapid access to registration fields and allows the investigator himself to perform an initial check of the data. It is a preferred instrument for collecting quantities consumed and unit prices in the setting of an international study. We have in parallel, introduced budget planning instruments into the software that enable the hospital pharmacist to calculate the financial impact of treatments that his clinicians request. We consider that it is important in this area not to reduce the role of hospital pharmacists to one of merely collecting data and that they should be offered a tool that can help them run their department. In the same spirit we have tried to make available on line methods for calculating cost-effectiveness ratios, although results of these attempts still have to be improved so that in the future, the costs of toxic reactions and complications may also be included.

Appendix A. Chemotherapy administration regiments in metastatic colorectal cancer

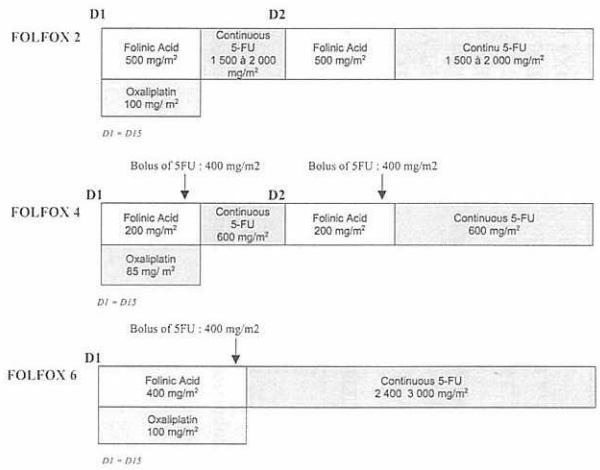
A.1. Description of the LV5FU2 administration regimens

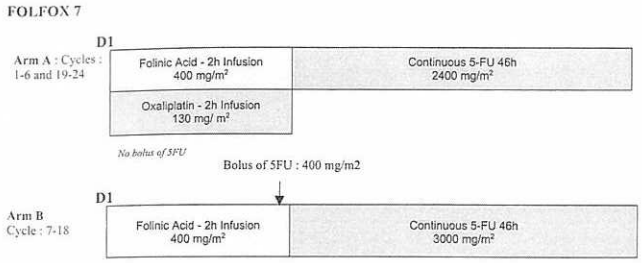
1. Description of the LV5FU2 administration regimens :



A.2. Présentation des schémas d'administration Oxaliplatine

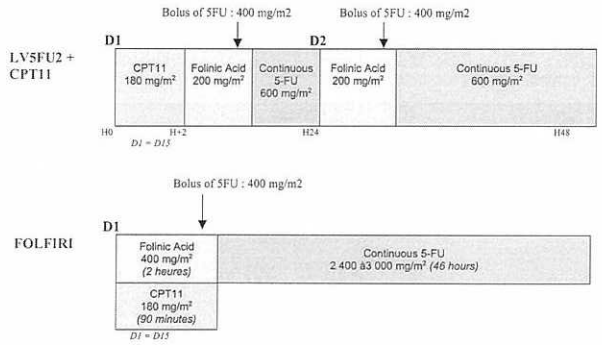
2. Présentation des schémas d'administration Oxaliplatine :





A.3. Description of the CPT11 administration regimens

3. Description of the CPT11 administration regimens:



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Biography

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