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Economical evaluation of drugs

Medical care consumption in a phase III trial comparing irinotecan with infusional 5-fluorouracil (5-FU) in patients with metastatic colorectal cancer after 5-FU failure

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We evaluated economic implications of treatment with irinotecan, following a RCT which demonstrated significantly increased survival at 1 year with irinotecan (45%) compared to infusional 5-fluorouracil (5-FU) (32%) in patients with metastatic colorectal cancer. Medical care consumption data were collected prospectively alongside the trial, with 256 patients followed for a median of 10 months. Follow-up was prolonged beyond treatment failure and medical care consumption was not protocol driven, enabling a realistic evaluation of economic implications. Medical care consumption associated with chemotherapy administration was lower with irinotecan as compared with infusional 5-FU. The cumulative number of days in hospital due to treatment toxicity and cancer complications, which is the key cost driver, was 14.4 (95% CI: 10.7–18.1) with irinotecan versus 17.5 (95% CI: 11.7–23.3) with infusional 5-FU. Thus, the survival benefit with second-line irinotecan compared to infusional 5-FU in patients with advanced colorectal cancer was achieved without increasing medical care consumption.

Key words: 5-Fluorouracil, colorectal cancer, irinotecan, medical care consumption, phase III.

Introduction

Irinotecan (CAMPTO®), a topoisomerase I inhibitor, is a novel cytotoxic agent which interferes with DNA replication and cell division, eventually leading to tumor cell death.

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A large phase III multicenter randomized trial compared irinotecan with infusional 5-fluorouracil (5-FU)-based regimens considered as the best estimated second-line treatment in metastatic colorectal cancer. Two-hundred and sixty-seven patients who had failed a first line 5-FU-based therapy were randomized to either the irinotecan arm (133 patients) or the 5-FU-based arm (134 patients). Overall survival in the irinotecan arm was significantly longer than in the infusional 5-FU arm (p=0.035). One year survival was 45% in the irinotecan arm compared to 32% in the infusional 5-FU arm. Progression-free survival also showed a significant difference in favor of irinotecan (p=0.030), with a median progression-free survival of 4.2 months with irinotecan and 2.9 months with infusional 5-FU. Analysis of quality of life showed no significant difference between irinotecan and 5-FU,[1–3] either at baseline or over time.

Because more and more economic constraints are placed on health care providers, there is a need to demonstrate that clinical benefits of new innovative treatments can be achieved at a reasonable cost. Furthermore, methodologically robust methods are required to assess accurately the overall impact of new treatments on medical care consumption and costs. Assessing overall impact implies going beyond drug acquisition and administration cost. The cost of management of toxicities and cancer complications must also be taken into account.

Most economic evaluations of cancer therapies to this date have used data collected retrospectively and made indirect comparisons between treatments. In this phase III trial economic data were collected prospectively, thereby allowing a direct comparison of economic implications between irinotecan and infu-

sional 5-FU regimens. The results may help to assess the magnitude of the costs associated with the increased clinical benefit of irinotecan.

Patients and methods

Patient population

Details can be found in the publication by Rougier *et al.*[3]

Treatments

Patients were randomized to irinotecan (arm A) or to infusional 5-FU (arm B). Patients randomized to irinotecan were to receive 350 mg/m^2 as a 90 min i.v. infusion once every 3 weeks (300 mg/m^2 in patients aged $\geqslant$70 years or WHO performance status 2). Patients randomized to the infusional 5-FU arm were to receive one of three regimens, chosen by each investigator according to the center's current practice (Table 1). Treatment was administered until disease progression, unacceptable toxicity or patient refusal occurred.

Out of 267 randomized patients, 256 received at least one cycle of treatment (127 in the irinotecan arm and 129 in the infusional 5-FU arm).

Data collection

Medical care consumption data were prospectively recorded with a median follow-up of 10 months and a maximum follow-up of 16 months. At each patient visit, any hospital admission since the last visit was recorded, together with the reason for admission, the type of hospital department and the length of stay. Outpatient consultations with GPs and nurses were also recorded.

Planned medical care consumption related to chemotherapy administration was excluded from prospective data collection since it is not an outcome of the trial but rather results from a choice that is dependent on the health care system in existence in each center. The data were therefore collected retrospectively. For each regimen, investigators were asked to indicate how they administer chemotherapy for patients similar to those enrolled in the study. Data collected included drug administration setting (inpatient/outpatient), length of stay in case of inpatient administration, central catheterization performed specifically for this line of chemotherapy and use of pumps. Questionnaires were sent to all of the 46 investigators participating in the trial.

Since the primary endpoint was survival, tumor response evaluation and other examinations were undertaken according to normal practice, which meant that medical care consumption was not protocol driven.

Statistical analysis

The population for the analysis was the treated population (256 patients: 127 in the irinotecan arm and 129 in the infusional 5-FU arm). Medical care consumption data from the 46 centers participating in the trial were aggregated and no adjustments were made.

Because of study cut-off, most patients are usually not followed until death, so that the data are right-censored. Two recently proposed methods were used: that of Lin *et al.*[4] and that of Zhao and Tsiatis.[5] Both methods are non-parametric, i.e. they are free from any assumption about the distribution of medical care consumption. Lin's methodology was preferred, because it enables estimation of confidence intervals (CI) for the means. However, the comparison of the Lin estimates with the Zhao and Tsiatis estimates is considered in the discussion.

Because patients were followed for economic data for a maximum of 16 months, the estimates that are provided are 16 month estimates. In other words, medical care consumption is estimated up to death or

Table 1. Details of the treatments used

Arm	No. of patients	Treatment
A	127	irinotecan 350 mg/m^2 i.v. as a 90 min i.v. infusion once every 3 weeks[3]
B1	35	leucovorin 200 mg/m^2 i.v. over 2 h followed by 5-FU 400 mg/m^2 i.v. bolus; then 5-FU 600 mg/m^2 continuous i.v. infusion over 22 h/day on the first 2 days of every 2 week period[11]
B2	39	5-FU 250–300 mg/m^2/day as a prolonged continuous i.v. infusion[12]
B3	55	5-FU 2.6–3.0 g/m^2/day over 24 h with or without leucovorin 20–500 mg/m^2/day i.v. weekly for 6 weeks with 2 week rests between cycles[13]

16 months from randomization. It is a restricted means approach. Non-parametric methods could not provide lifetime estimates. However, an attempt to evaluate lifetime means is presented in the discussion.

Tests are presented for the most important cost drivers. Two-sided *t*-tests for the equality of means under the assumption of unequal variances were used.

Results

Chemotherapy administration

The mean treatment duration with irinotecan (4.4 months) was significantly longer than with infusional 5-FU (3.6 months; $p < 0.01$). The number of treatment infusions received in both arms is shown in Table 2. The actual doses received were very close to those described in Table 1, with a relative dose intensity above 94% in all arms, except in arm B3 (81%).

Out of the 46 questionnaires to document medical care consumption directly associated with chemotherapy administration that were sent to the investigators, 40 questionnaires were completed and returned (87%). The number of centers with complete answers is displayed for each item in Table 3.

Table 3 presents the setting for the administration of chemotherapy, and the number of consultations, outpatient and inpatient hospital stays directly associated with chemotherapy administration. Medical care consumption in the 5-FU arm depends on the regimen chosen and on the centers' usual practice, but overall, administration of irinotecan required fewer inpatient and outpatient care consumption than any 5-FU regimen, with the exception of regimen B2 (prolonged continuous infusion).

Table 2. Chemotherapy drug consumption (no. of infusions)

	Irinotecan	Infusional 5-FU		
		B1	B2	B3
No. of patients	127	35	39	55
No. of infusions	761	238	3623	412
Mean no. of infusions per patient	6.0	6.8	92.9	12.9

Table 3. Medical care consumption related to chemotherapy administration

Arm		No. of centers/total no. of centers replied (%)		
		Chemotherapy administration modality	Central catheterization performed specifically for this line of treatment	Use of pumps
A	every 3 weeks:			
	1 day in day hospital	21/34 (62)	5/34 (15)	4/35 (11)
	1 consultation	6/34 (18)		
	other	7/34 (20)		
B1	every 2 weeks:			
	2–3 days in day hospital	9/16 (56)	4/12 (33)	7/12 (58)
	2–3 days full hospitalization	4/16 (25)		
	other	3/16 (7)		
B2	every 4 weeks:			
	2–4 days in day hospital	10/14 (71)	10/15 (67)	15/15 (100)
	1–4 consultations	3/14 (21)		
	other	1/14 (7)		
B3	every week for 6 weeks + 2 weeks rest:			
	1 consultation	4/12 (33)	9/13 (69)	13/16 (81)
	1–2 days in day hospital	4/12 (33)		
	1–2 days full hospitalization	4/12 (33)		

Percentages in parentheses.

The infusion site and the infusion device are also documented in Table 3. The percentage of patients with central catheterization refers to the patients for which a central catheterization was performed specifically for second-line chemotherapy and it excludes patients who had a central line at inclusion, which were evenly distributed between groups. Administration of irinotecan involved less central catheterization and little use of pumps.

Thus, while 5-FU ± folinic acid has a low acquisition cost, it should entail administration costs that are likely to be higher than those of irinotecan.

Hospital care consumption due to toxicity and disease complications

The mean cumulative number of days spent in hospital (restricted mean) is shown in Table 4. This includes any hospitalization, whether due to adverse events or not, but excludes hospital admissions due to planned chemotherapy administration. If, however, hospitalization for chemotherapy administration was prolonged because of adverse events, the hospital stay was retained in the calculation.

The overall cumulative number of days is divided into those accrued during chemotherapy treatment and those accrued after treatment cessation. It can be expected that hospital stays during treatment are mostly attributable to toxic adverse events, while hospital stays after treatment cessation are mostly attributable to cancer complications.

In order to illustrate how the cumulative number of days in hospital is estimated, Figure 1 presents the probability of surviving (as estimated by the Kaplan-Meier method, upper curves) and the probability of being in hospital at each point in time (as estimated by the Lin *et al.* method, lower curves). Survival is thus partitioned into time spent in hospital and time spent outside of the hospital. The mean cumulative number of days in hospital is calculated as the area under the

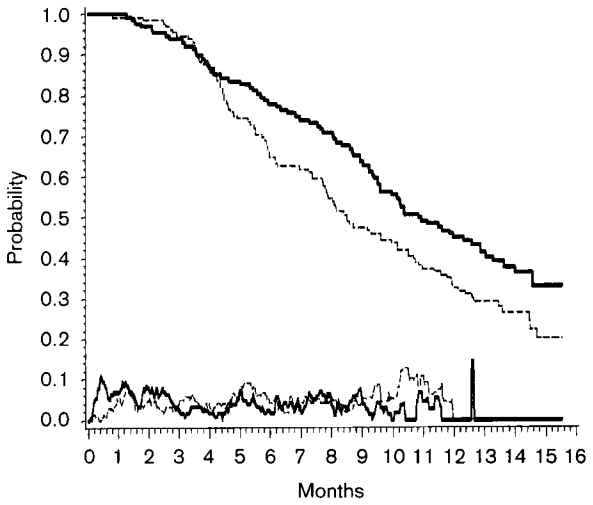

Figure 1. Probability of surviving (upper curves), and probability of being in hospital due to toxicity and disease complications (lower curves). Solid line, irinotecan; dotted line, infusional 5-FU.

Table 4. Medical care consumption due to toxicity and disease complications

	Irinotecan	Infusional 5-FU
No. of patients	127	129
No. of days in hospital, cumularive mean per patient	14.4	17.5
[95% CI]	[10.7; 18.1]	[11.7; 23.3]
No. of days in hospital during and after treatment		
during chemotherapy treatment	5.9	3.1
after chemotherapy treatment cessation	8.5	14.4
No. of days in hospital according to department type (*percent of total time in hospital according to department type*)		
internal medicine	7.4 (51.5)	10.3 (58.9)
oncology	3.1 (21.7)	1.8 (10.1)
surgery	2.8 (19.3)	2.8 (16.2)
ICU	0.1 (0.4)	0.1 (0.4)
other/unknown	1.0 (7.0)	2.5 (14.2)
No. of patients with at least one serious adverse event (*percent of patients with at least one serious adverse event*)		
during chemotherapy treatment	41 (32)	23 (18)
after chemotherapy treatment cessation	24 (19)	38 (30)
total	52 (41)	53 (41)

Percentages in parentheses.

curve of patients in hospital. Figure 2 shows how these hospital days accumulate over time.

The cumulative number of days per patient is lower in the irinotecan arm than in the infusional 5-FU arm, but the difference (−3.1 days) is not significant (p=0.37, approximate t-statistic for testing equality of means under the assumption of unequal variance). The 95% CI for the difference is [−10.0; 3.7].

More hospital days are accrued during treatment in the irinotecan arm compared to the infusional 5-FU arm, while fewer days are accrued after treatment cessation. In both arms, the number of days accrued in the treatment phase is much lower than the number of days accrued after treatment was concluded. This result is supported by the incidence of serious adverse events observed during this trial. During treatment, the incidence of adverse events is higher in the irinotecan arm compared with the infusional 5-FU arm, but it is lower after treatment cessation, at a time when all patients are in a phase of tumor progression.

Overall, patients in the irinotecan arm spent 1.3 days in hospital per month (4.5% of their time) as compared to 1.9 days in hospital per month (6.2% of their time) for patients in the 5-FU arm. During treatment, the average number of days in hospital per month was 1.2 in the irinotecan arm (4.2% of their time) versus 0.8 in the 5-FU arm (2.7% of their time). After treatment was concluded, patients in the irinotecan arm spent 1.4 days per month in hospital (4.6% of their time) versus 2.6 days per month for patients in the 5-FU arm (8.6% of their time).

These findings might be explained by the fact that, during treatment, some specific adverse events like diarrhea and febrile neutropenia are manifest, while after treatment cessation, the clinical benefits derived from irinotecan could mean better tumor control and fewer needs for hospitalization.

Because the cost of inpatient days may vary according to the type of hospital department, the proportion of days spent in each department was also analyzed (Table 4). The proportion of days spent in costly departments (surgery and ICU) is very similar in both arms, which implies that the overall cumulative number of days is a very good proxy for hospital costs.

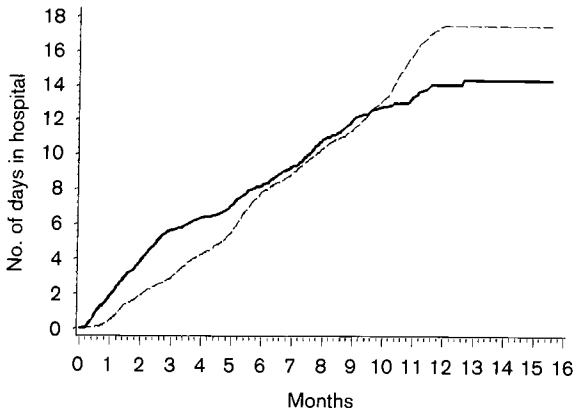

Figure 2. Number of days in hospital due to toxicity and disease complications, as they accumulate over time from treatment start (mean per patient). Solid line, irinotecan; dotted line, infusional 5-FU.

Outpatient care consumption due to toxicity and disease complications

While outpatient consultations and visits are much less costly per unit than days in hospital, it is important to describe outpatient care consumption which might bear on a different budget than inpatient care consumption. Table 5 shows the mean number of outpatient consultations and visits per patient.

The mean number of consultations is higher in the irinotecan arm compared to the infusional 5-FU arm, with the major difference being an extra 1.1 visits on average to the general practitioner. The number of nurse visits is also higher with a 1.3 visits difference.

Discussion

This phase III trial demonstrates that irinotecan increased survival and improved tumor control compared with infusional 5-FU, and that these benefits

Table 5. Outpatient care consumption (cumulative mean per patient)

	Irinotecan	Infusional 5-FU
Consultations		
GP	2.58	1.46
oncologist	2.57	2.65
radiologist	0.07	0.24
gynecologist	0.04	0.00
surgeon	0.05	0.06
dermatologist	0.01	0.02
urologist	0.04	0.05
internist	0.02	0.18
emergency unit	0.04	0.04
other specialists	0.19	0.26
Medical services		
nurse visits	3.22	1.91
laboratory tests	0.63	0.02
radiotherapy	0.05	0.06
X-rays	0.06	0.00
blood transfusions	0.01	0.02

were achieved without increased medical care consumption.

When drug administration costs are taken into account, it shows that infusional 5-FU administration entails significant hospital care consumption. Further, by including all inpatient and outpatient care consumption, it shows that medical care consumption apart from chemotherapy administration was comparable in both arms.

The estimates of medical care consumption in this study (excluding chemotherapy administration) are especially robust because of its design: economic data were collected prospectively, in a randomized trial, with no protocol-driven resource use and with an observation period extending beyond treatment failure, the point from which most of the costs are accrued.

As far as chemotherapy administration is concerned, most centers reported administering irinotecan on an outpatient basis (27 of 34 or 79%), but some centers (seven of 34 or 21%) reported administering irinotecan in a inpatient setting (1–3 days full hospitalization). This may be explained by the fact that irinotecan is a new drug and that investigators are especially cautious because they do not have sufficient practice with this drug. It can be expected that irinotecan will be administered more and more in an outpatient setting, as investigators gain experience with this new drug. The use of pumps is significantly less in the irinotecan arm and the small amount is due to four investigators using pumps to achieve exactly 90 min duration for the infusion.

For infusional 5-FU regimens, the results are quite convergent with those of a previous study.[6] Future developments in chemotherapy for advanced colorectal cancer may change this picture somehow. A new de Gramont schedule (arm B1) requiring only 2 days in day hospital per month and several oral agents are under development (oral irinotecan, UFT, capecitabin).

Regarding statistical methods, comparisons were made between the Lin estimates and the Zhao and Tsiatis estimates, and an excellent convergence was found between the results obtained using the two methods. For the cumulative number of days in hospital, which is a major cost driver, the estimate in the irinotecan arm using the Lin method was 14.4 days, while the estimate using the Zhao and Tsiatis method was 14.3 days. In the infusional 5-FU arm, the corresponding estimates were 17.5 and 16.9 days.

Non-parametric methods were chosen for this analysis, in order to minimize the number of assumptions to be made. Unfortunately, non-parametric methods cannot deliver lifetime estimates when the observational window is limited, to 16 months in this study. A simple method to extrapolate outside this observational window is to estimate survival past 16 months, using a Weibull parametric model, and to multiply the number of days of survival thus obtained by an estimate of average medical care consumption per patient per unit of time. Applying this method, the following estimates were obtained for the cumulative number of days in hospital: 16.0 days for the irinotecan arm and 18.1 days for the infusional 5-FU arm. This again demonstrates that medical care consumption with irinotecan and with infusional 5-FU are comparable.

There was one outlier in the infusional 5-FU arm. Leaving this outlier out yields an estimated 16.0 days in this arm, compared with 17.5 when the outlier is included. The 95% CI for the difference between the irinotecan arm and the 5-FU arm becomes [−7.9; 4.6]. The comparability of medical care consumption between the two arms is thus confirmed.

CI for the cumulative number of days in hospital are large and economically significant differences might not be detected with such a sample. However, we chose to report these results because the design of this study is especially robust (prospectively collected data, direct comparison, no protocol-driven medical care consumption). Enhancing statistical power could be achieved by either increasing the number of patients to be included or by extending the follow-up for economic data.

The small number of patients is also responsible for the erratic variations of the curves in Figures 1 and 2. In particular, from month 12 onwards, the number of patients alive and not censored was less than 10 in the irinotecan arm and less than six in the infusional 5-FU arm.

As reported above, medical care consumption data from the 46 centers participating in the trial were aggregated and no adjustments were made. A total of 11 countries were involved, with 71% of patients (181 of 256) recruited in four countries: Italy, Belgium, Germany and Spain. Aggregating clinical data from different countries is usually not an issue. Aggregating economic data, however, may be more problematic, because of differences in health care insurance systems, which may in turn produce differences in patterns of medical care consumption.

Analysis could have been limited to country subgroups, but because of lack of power, these analyses would not have been conclusive. Instead, we investigated possible differences in practice patterns between countries by studying the proportion of patients hospitalized and the length of stay for diarrhea, the most frequent adverse event in this trial.

We found good convergence between countries, with an apparent greater variability between centers in the same country than between different countries. This is in line with previous findings.[7] Thus aggregating medical care consumption data across different countries may be no more problematic than aggregation across different centers in one single country. In this phase III trial, randomization was stratified by center so that individual practice does not systematically bias one treatment arm.

Country-specific adjustments using treatment protocols specific to each country can also be performed.[8,9] These adjustments, however, would have to be based on expert advice, which is less robust than collecting data in a prospective study.

Examination of the use of outpatient care consumption reveals that the mean number of outpatient visits is similar in both arms for oncologists and other consultants, but it is higher for GPs in the irinotecan arm. This might reflect guidelines for the management of side effects which encourage people to visit a GP as soon as the problem occurs.

This study was not designed to enable evaluation of other resource items such as investigations and concomitant drug therapy. From previous studies, however, it appears that the major cost drivers are hospital stays and administration of chemotherapy.[10]

Conclusion

The increased survival with irinotecan as second-line chemotherapy was achieved with no significant increase in medical care consumption. Formal cost-effectiveness of irinotecan as compared to infusional 5-FU remains to be established. This study should serve as a basis for evaluating cost-effectiveness in different settings using local cost and clinical practice data.

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