Pergamon

European Journal of Cancer, Vol. 35, No. 13, pp. 1796–1804, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00186-0

Original Paper

Irinotecan in Second-line Treatment of Metastatic Colorectal Cancer: Improved Survival and Cost-effect Compared with Infusional 5-FU

T.J. Iveson,[1] T. Hickish,[2] C. Schmitt[3] and E. Van Cutsem[4]

[1]Royal South Hants Hospital, Southampton and Salisbury Hospital NHS, Brintons Terrace, Southampton, SO14 0YG; [2]Royal Bournemouth and Poole Hospitals, Bournemouth, U.K.; [3]ARCOS, Issy-les-Moulineau, France; and [4]University Hospital Gasthuisberg, Leuven, Belgium

In a recent multicentre, randomised, controlled, open-label study (Rougier and colleagues, *Lancet* 1998, 352, 1407–1412), irinotecan significantly increased survival without any deterioration in quality of life compared with best-estimated infusional 5-fluorouracil (5-FU) therapy in the setting of second-line treatment for metastatic colorectal cancer. The aim of the cost-effectiveness analysis reported here was to compare the economic implications, from a U.K. perspective, of replacing 5-FU therapy [either as a single agent (Lokich regimen, B2) or in combination with folinic acid (de Gramont regimen, B1, or AIO regimen, B3)] with irinotecan as second-line therapy for metastatic colorectal cancer. Resource utilisation data collected prospectively during the study, supplemented by both a questionnaire to investigators and local expert clinical opinion, were used as a basis for estimating cumulative drug dosage, chemotherapy administration and treatment of complications. Drug acquisition costs were derived from the British National Formulary (March 1998), and unit costs for clinical consultation and services were derived from relevant 1996/1997 cost databases. Although cumulative drug acquisition costs per patient were higher with irinotecan than with infusional 5-FU therapy, these were at least partially offset by lower cumulative costs per patient associated with administration of therapy and treatment of complications in the irinotecan arm than in the 5-FU arm. Based on the incremental costs per life year gained (LYG), irinotecan was considered to be cost-effective by commonly accepted criteria compared with either the B1 or B2 regimens. Irinotecan was cost-saving compared with the B3 regimen (that is significant survival gain and a reduction in costs). Thus, not only is there strong evidence for the use of irinotecan as standard second-line therapy in metastatic colorectal cancer, but the results of this prospective economic evaluation have shown that irinotecan also represents good value for money in this clinical setting. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: irinotecan, metastatic colorectal cancer, cost-effectiveness analysis, 5-fluorouracil, chemotherapy, survival benefit
Eur J Cancer, Vol. 35, No. 13, pp. 1796–1804, 1999

INTRODUCTION

WITH EVER-INCREASING constraints on healthcare expenditure, clinicians are increasingly being asked to consider both the clinical and economic implications of new treatments and whether they represent value for money compared with currently available therapeutic options. The emergence of irinotecan (Campto®, Rhône-Poulenc Rorer, Anthony, France) as second-line therapy for metastatic colorectal cancer has prompted the need for such an evaluation.

The aim of this paper was to compare the economic implications, from a U.K. perspective, of replacing infusional 5-fluorouracil (5-FU) therapy (either as a single agent or in

Correspondence to T.J. Iveson.
Received 18 Feb. 1999; accepted 17 Jun. 1999.

combination with folinic acid) with irinotecan as second-line therapy for metastatic colorectal cancer. Other than drug acquisition costs, the analysis also considered costs associated with treatment delivery and with disease complications. Indirect costs, although important, have not been included as the data have been analysed from the viewpoint of purchasers in the National Health Service (NHS). This analysis is based on clinical and resource utilisation data collected prospectively as part of the recently published multicentre, randomised, controlled study comparing irinotecan with infusional 5-FU therapy in patients with metastatic colorectal cancer which demonstrated increased survival and maintenance of quality of life [1].

Colorectal cancer

Colorectal cancer is the second most common cause of cancer death in the U.K. and Western developed nations, representing approximately 12% of all cancer deaths [2, 3]. Annually in the U.K., there are over 28 000 new cases of colorectal cancer and over 19 000 deaths due to metastatic disease [4].

At the commencement of this study, 5-FU-based chemotherapy as first-line treatment had been shown to be superior to best supportive care alone with respect to both increased survival and improved quality of life in patients with metastatic disease [5]. Patients with metastatic disease have therefore been offered chemotherapy with the aim of palliating symptoms, improving quality of life and prolonging survival. Yet despite the proven benefits of 5-FU-based chemotherapy, almost all patients with metastatic disease will eventually become resistant to 5-FU.

Second-line therapy

The observation that responses will occur with infusional 5-FU in disease resistant to intravenous (i.v.) bolus 5-FU has led to the use of infusional 5-FU regimens as second-line therapy. However, response rates are usually low [6]. Furthermore, as no randomised studies comparing the various infusional 5-FU regimens are available, it is difficult to draw firm conclusions about the superiority of any regimen.

Irinotecan is currently the only licensed agent available as second-line therapy for metastatic colorectal cancer after failure of a 5-FU-based regimen. Irinotecan has a different mechanism of action to that of 5-FU, based on inhibition of DNA topoisomerase 1, and has demonstrated antitumour activity in a wide range of *in vitro* and *in vivo* experimental models of colorectal cancer [7]. In phase II trials [8–10] irinotecan has been shown to be active in 5-FU-resistant disease and a recent randomised phase III trial [11] has demonstrated that second-line treatment with irinotecan significantly prolonged survival compared with best supportive care alone (1-year survival rates: 36% versus 14%, respectively). Moreover, irinotecan significantly improved quality of life and delayed the onset of tumour-related symptoms. This was the first study to demonstrate a significant survival advantage and improved quality of life of chemotherapy over best supportive care in the second-line clinical setting.

The recent multicentre, randomised, controlled, open-label study by Rougier and colleagues [1] compared treatment with irinotecan or high-dose infusional 5-FU therapy in patients with advanced metastatic colorectal cancer. A total of 256 patients in 46 centres throughout Europe (Belgium, France, Germany, Italy, The Netherlands, Spain, and Switzerland), received at least one cycle of treatment; 127 patients were treated with irinotecan (treatment arm A) and 129 patients were treated with one of three infusional 5-FU therapy regimens (treatment arm B) (see Table 1).

Treatment regimens B1, and B3 are outlined in Table 1. Each centre was permitted to use two of the three infusional 5-FU regimens, depending on preferred clinical practice and the type of 5-FU regimen used as first-line therapy, and were then obliged to continue with these two regimens throughout the study. Selection of the 5-FU treatment regimen was made prior to randomisation. Treatment was given until disease progression, unacceptable toxicity or patient refusal.

Prospective economic data collection was supplemented by an investigator questionnaire about resource utilisation within each treatment arm. The aim of this paper was to relate these data to relevant costs in the U.K. and to evaluate the economic implications of the difference in survival between the two treatment arms.

PATIENTS AND METHODS

Clinical and resource utilisation data used for economic assessments in this paper are described below. These data provide the basis for calculating the direct costs associated with each treatment group and for carrying out an economic evaluation comparing the treatment groups with respect to their outcomes and associated costs. Since the primary clinical endpoint was survival, tumour response evaluation and other examinations were measured according to normal clinical practice, which meant that the medical care consumption was not protocol-driven.

Clinical data

The clinical data reported by Rougier and colleagues [1] and summarised in Tables 2 and 3 were used as source data for this paper.

Table 1. *Details of study treatments used in patients in the study of irinotecan versus infusional* 5*-FU therapy* [1]

Regimen	Treatment
A ($n = 127$)	Irinotecan, 350 mg/m^2 as a 90-minute infusion once every 3 weeks (cycle length: 3 weeks)
B1*† ($n = 35$)	Folinic acid 200 mg/m^2 intravenously (i.v.) over 2 h followed by 5-FU 400 mg/m^2 as an i.v. bolus then 5-FU 600 mg/m^2 as a continuous i.v. infusion over 22 h on the first 2 days of every 2-week period (cycle length: 2 weeks)
B2†‡ ($n = 39$)	5-FU 250–300 mg/m^2/day as a prolonged continuous i.v. infusion using a portable infusion pump, until evidence of progression or toxicity.
B3†§ ($n = 55$)	5-FU 2600–3000 mg/m^2 per day i.v. over 24 h with or without folinic acid 20–500 mg/m^2 i.v. per day every week for 6 weeks, with 2-week rests between cycles. (cycle length: 1 week)

*De Gramont regimen [12]. †Collectively, the B treatment arm is referred to as infusional 5-FU therapy. ‡Lokich [13]. §Arbeitsgemeinschaft Internistische Onkologie (AIO) regimen [14].

Table 2. Baseline characteristics of patients in the study of irinotecan versus best-estimated infusional 5-FU therapy [1]

Characteristic	Irinotecan ($n = 127$)	All 5-FU therapy ($n = 129$)
Age median (range), year	58 (30–75)	58 (25–75)
Male:female, %	57:43	65:35
WHO performance status, %		
0	57	54
1	35	43
2	8	3
Tumour-related symptoms, %	47	48
Pain, %	37	33
Organ involvement, %		
1 organ	48	47
2 organs	34	36
≥3 organs	18	18
Site of metastases, %		
Liver	79	76
Lung	35	41
Peritoneum	15	10
Tumour progression, %		
While on previous 5-FU	58	68
≤3 months of last 5-FU	38	23
>3 months after last 5-FU	5	9

The two treatment arms were balanced with respect to patient and tumour characteristics at baseline. In each treatment arm, approximately 50% of patients had tumour-related symptoms and 18% of patients had involvement of three or more organs (see Table 2). All patients had previously received 5-FU therapy, which had been palliative in the majority of patients (87% in the irinotecan treatment arm and 85% in the 5-FU treatment arm); 14% of patients had received only adjuvant therapy. All patients had progressed while on adequate 5-FU-based chemotherapy or within 3 months of administration of a 5-FU-based regimen.

Treatment with irinotecan significantly prolonged survival compared with that observed with infusional 5-FU therapy (median survival: 10.8 versus 8.5 months respectively, $P = 0.035$) (Table 3). The median survival gain with irinotecan was 2.3 months (0.19 years). Moreover, irinotecan significantly delayed progression of disease compared with 5-FU: 1-year survival rates were 44.8% versus 32.4%, respectively. Progression-free survival was significantly longer in the irinotecan arm (4.2 (range 0.9–14.2) versus 2.9 (range 0.8–12.8) months, respectively, $P = 0.03$) [1].

A higher proportion of patients in the irinotecan arm than in the 5-FU arm experienced at least one grade 3 or 4 adverse event (69% versus 54%, respectively, $P = 0.013$) (Table 3). However, the fact that a similar proportion of patients in each treatment arm experienced at least one serious adverse event requiring hospitalisation (41% in the irinotecan arm versus 39% in the 5-FU arm) or were withdrawn due to non-fatal toxicity (10% versus 6%, respectively) is indicative of a similar severity of toxicity with irinotecan or 5-FU [1]. Furthermore, analysis of quality of life data did not indicate any significant difference between the two treatment arms [1].

Resource utilisation data. In estimating the economic impact of irinotecan use within the U.K. setting, it is insufficient to examine only the drug acquisition costs, as hospitalisation for administration of treatment, nursing time and equipment use must also be considered. In addition, costs associated with complications of treatment and of the disease need to be examined. These can be broadly categorised as hospitalisation costs (other than for routine administration of chemotherapy), consultation costs and costs for clinical and laboratory services. At each assessment in the study, any hospital admission since the last visit was recorded, together with the reason for admission, type of ward and the length of stay. General practitioner (GP) consultations and nurse visits, as well as inpatient and outpatient consultations with clinical and oncology personnel, were also recorded. These data were recorded prospectively as an integral part of the Case Report Form (CRF) and presented as average figures for either the irinotecan arm or the combined 5-FU regimens.

Drug acquisition costs. The mean number of treatment cycles (for B1 and B3) and mean number of weeks of treatment (for B2) given over the study period were determined from data collected in the study on the total number of injections or days of treatment. The median cumulative

Table 3. Clinical results of the study comparing irinotecan with best-estimated infusional 5-FU therapy [1]

	Irinotecan	All 5-FU therapy	*P* value
Overall survival			
1-year survival rates (%)	44.8% (95% CI)	32.4% (95% CI)	0.035
Median survival (months)	10.8 (9.5–12.8)	8.5 (7.7–10.5)	
Survival gain* with irinotecan	0.19		
Incidence of adverse events (%)			
At least one grade 3 or 4 event†	69	54	0.013
Diarrhoea	22	11	NS
Vomiting	14	5	NS
Nausea	11	4	NS
Leucopenia/neutropenia	14	2	NS
Pain	17	13	NS
Asthenia	13	12	NS
Cutaneous, including hand and foot syndrome	1	8	NS
Non-neutropenic infection	1	4	NS
Hospitalised for serious event	41	39	NS

*Calculated as the difference in median survival per year; = (10.8−8.5)/12. †In accordance with the National Cancer Institute (NCI) Common Toxicity Criteria. CI, confidence interval.

treatment duration was 4.2 months (mean: 4.7 months) for irinotecan. A mean of 6.0 treatment cycles of irinotecan were given over this period; 6.8 treatment cycles were given in the B1 treatment group, 13.3 weeks of treatment were given in the B2 treatment group (continuous infusion), and 12.9 cycles of treatment were given in the B3 treatment group (see Table 1). The dose per cycle (or weeks of treatment for group B2) was calculated based on the mean number of treatment cycles (or weeks of treatment) given per patient over the study period. The cumulative dose per patient (mg) was calculated from the trial data [1] using a mean body surface area of 1.8 m^2 collected in the trial.

Cumulative costs per patient for each treatment are based on acquisition costs given in the British National Formulary [15] and allow for wastage. Where there was more than one option for the same product, the lowest cost alternative has been used for specific vial sizes. Drug costs were calculated by estimating the number of vials needed to provide the required dose for each cycle or week of treatment and then multiplying by the mean number of cycles or weeks of treatment required per patient.

Drug acquisition costs for the B1 and B3 treatment regimens included the cost of folinic acid as well as the cost of 5-FU. The actual doses of 5-FU and irinotecan given to each patient were recorded on the CRFs. However, folinic acid dosage was not recorded on the CRFs. For the B1 treatment group, the folinic acid dosage stipulated by the protocol (that is 200 mg/m^2) was used for estimating dosage. For the B3 treatment group, supplementary data obtained from questionnaires sent to the investigators after the study indicated that the most frequently used dose was 500 mg/m^2, and this dose was therefore used in calculations.

Treatment administration costs. Expert clinical opinion was sought on issues relating to the need for hospitalisation for administration of each type of chemotherapy and the means by which this was administered (by insertion of a tunnelled central line catheter and/or the use of pumps). As the B3 regimen is commonly used in Germany, estimates for the number of days of hospitalisation and day hospital attendance were based on data provided by 40 investigators in the supplementary questionnaire relating to resource use [16]. It was considered that all infusional 5-FU regimens would require insertion of a tunnelled central line catheter by a doctor, as well as the use of disposable pumps for each cycle or week of treatment. The cost of inserting the tunnelled central line was estimated to be £250, taking into account that the procedure would involve one-half day hospital stay as well as a chest X-ray. The weekly cost of disposable pumps was estimated at £62 and included the cost of the pharmacist's time.

Based on current U.K. practice, it was assumed that administration of irinotecan would require 1-day hospital attendance per cycle, the B1 regimen (de Gramont) would require 2-day hospital attendances per cycle and the B2 regimen (Lokich) would require 1-day hospital attendance per week of treatment. With respect to the B3 regimen, data collected in the supplementary questionnaire indicated that approximately 50% of patients would receive the treatment as an inpatient and 50% would receive the treatment as 1-day hospital attendance. Therefore, the B3 regimen was divided into B3a and B3b treatment groups, respectively, and costed accordingly.

Hospitalisations were costed on the basis of 1996/1997 extra-contractual referral tariffs (that is tariffs negotiated between a hospital and a local authority other than that responsible for the hospital) collected from 12 NHS Trusts in the U.K. (Qost database). General medicine and surgery ward tariffs were divided by the official average length of stay published by the Department of Health [17] in order to obtain a '*per diem*' cost. The tariffs covered all types of inpatient resources consumed.

Costs associated with complications of treatment and disease. All unplanned hospitalisations were recorded prospectively on the CRF. Hospital admissions due to complications include those associated with adverse events resulting from administration of chemotherapy and those resulting from disease complications. As costs vary between departments, data relating to the proportion of inpatient days spent in different departments were also collected. Data for hospitalisation due to planned chemotherapy administration were excluded. However, if hospitalisation for chemotherapy administration was prolonged because of adverse events, the hospital stay was retained in the calculation.

Outpatient visits were also categorised by the type of consultation. Other resource items recorded on the CRFs included the number and type of medical services provided and/or procedures performed including nurse visits, radiotherapy, X-rays, laboratory tests and blood transfusions.

Unit costs for hospitalisation, specialist consultations and laboratory and diagnostic tests were derived from the Qost database (1996/1997) as previously described. The consultation tariff included the costs of procedures performed during the attendance. As laboratory and diagnostic tests were usually performed at the hospital, outpatient Trust tariffs were used in the costing of these services. Health professional, nurse and GP consultations were costed on the basis of the Personal Social Services Research Unit (PSSRU) handbook [18]. As nurse and health professional costs were given in hours, it was assumed that each consultation would be of 0.5 h duration.

Cumulative costs per patient were calculated using estimates of the cumulative number of hospitalisations, consultations, and clinical and laboratory services required per treatment arm derived from the trial data [16]. Estimates were not differentiated between the three 5-FU regimens as it was assumed that there were no differences between the treatment groups with respect to the frequency of complications of treatment and of disease. These estimates were incorporated in the calculation of overall costs for each 5-FU regimen.

Overall costs. The overall cumulative costs per patient of each treatment was the sum of drug acquisition costs, chemotherapy administration costs and the cost of complications of treatment and disease. The incremental costs and outcome with irinotecan over each 5-FU regimen were compared. A cost-effectiveness (C/E) ratio per life year gained (LYG) was calculated for each infusional 5-FU regimen as the difference in overall costs between irinotecan and the 5-FU regimen divided by the difference in median survival between irinotecan and 5-FU (that is 2.3 months, or 0.19 years, see Table 3).

RESULTS

Costs associated with chemotherapy

Cumulative drug acquisition and administration costs per patient are summarised for each treatment regimen in Tables 4 and 5.

Table 4. Cumulative drug acquisition costs per patient

	Irinotecan	B1 (5-FU) ($n=35$)		B3 (5-FU) ($n=55$)	
		5-FU	Folinic acid	5-FU	Folinic acid
(a) Irinotecan and B1 and B3 5-FU infusional regimens					
No. of cycles of treatment*	6.00	6.80		12.90	
Cumulative dose per patient					
mg/m^2	1988	13 490	2720	32 488	3677
mg†	3578	24 282	4896	58 478	6619
Dose per cycle (mg)	596	3571	720	4533	900
Infusion cost per drug (£)‡	£780.00	£31.76	£193.36	£38.46	£221.86
Total cost per cycle (£)	£780.00	£225.12		£260.32	
Total drug cost (£)	£4680	£1531		£3358	

	B2 (5-FU) ($n=39$)	
	5-FU	Folinic acid
(b) B2 5-FU infusional regimen		
No. of weeks treatment*	13.3	
Cumulative dose per patient		
mg/m^2	22 276	0
mg†	40 097	0
Dose per cycle (mg)	3015	0
Infusion cost per drug (£)§	£25.26	£0.00
Total cost per cycle (£)	£25.26	
Total drug cost (£)	£336	

*Refer to Table 1, treatment regimens. †Calculated using a mean body surface area of 1.8 m^2, as determined from the trial [1]. ‡Costs are derived from the British National Formulary [15], based on the use of 5 ml vials (£130 each) for irinotecan, 100 ml (£19.23 each), 20 ml (£3.97 each) and 10 ml (£2.06 each) vials for 5-FU, and 35 ml vials containing 10 mg/ml (£90.98 each) and 5 ml vials containing folinic acid, with allowance for wastage. §Costs are derived from the BNF (March 1998) [15], based on the use of 100 ml (£19.23 each), 20 ml (£3.97 each) and 10 ml (£2.06 each) vials for 5-FU, with allowance for wastage.

As anticipated, cumulative drug acquisition costs per patient were higher in the irinotecan arm than in any of the 5-FU treatment groups (B1 £1531, B2 £336 and B3 £3358 versus £4680 for irinotecan) (Table 4). The acquisition cost of the B2 treatment group was considerably lower than that of the other two infusional 5-FU treatment groups due to the lack of folinic acid in the B2 regimen.

However, the higher acquisition costs for irinotecan were at least partially offset by the lower administration costs for this treatment (Table 5). It was estimated that administration of irinotecan required only 1-day attendance per cycle (total of 6 days attendance per study period) representing a cumulative administration cost per patient of £323. By comparison, resource utilisation per patient was substantially higher with each of the three 5-FU regimens: £1405 for the B1 regimen, £1792 for the B2 regimen and £1745 and £2768 for the B3 regimen, depending on place of administration (Table 5).

Costs associated with treatment and disease complications

Cumulative costs per patient associated with treatment and disease complications are summarised in Table 6. Data have been summarised for each treatment arm rather than each individual treatment regimen as it has been assumed that estimates of the number of hospitalisations, consultations and laboratory and diagnostic tests derived from the clinical trial data were similar with each 5-FU regimen [16].

The cumulative cost per patient associated with complications of treatment and of disease was lower in the irinotecan arm than in the 5-FU arm (difference in favour of irinotecan, £605) (Table 6). Hospitalisation was the most important factor influencing cost considerations for complications of treatment and disease. Overall, patients in the irinotecan arm spent an average of 3.1 days (95% confidence interval (CI), −3.7 to 10.0 days per patient) less in hospital due to complications than those receiving infusional 5-FU therapy (Table 6), explaining the observed reduction in cumulative costs per patient.

There were no meaningful differences between the two treatment arms with respect to cumulative costs per patient associated with clinical consultations and services. Additionally, there was no evidence of any major substitution between inpatient and outpatient medical care consumption (Table 6).

Total costs

The study used mean cumulative doses received by each treatment group divided by the mean number of cycles to estimate the costs of treatment. When cumulative costs per patient associated with drug acquisition, administration of chemotherapy, and complications were considered together, it is apparent that the overall cumulative costs per patient with irinotecan were somewhat higher than those associated with either the B1 or B2 regimens (difference in favour of 5-FU, £1463 and £2270, respectively), although irinotecan resulted in savings when compared with either of the B3 regimens (Table 7).

However, treatment with irinotecan also resulted in a significant gain in median survival over 5-FU (see Table 3). Cost-effectiveness analysis of the incremental costs and survival demonstrated that treatment with irinotecan can be considered cost-effective. Compared with both B1 and B2

Table 5. Cumulative drug administration costs per patient

		Irinotecan		(B1) 5-FU		B2 (5-FU)		B3a (5-FU)		B3b (5-FU)	
	Unit cost	Quantity	Cumulative cost	Quantity	Cumulative cost	Quantity	Cumulative cost	Quantity	Cumulative cost	Quantity	Cumulative cost
Hospitalisation costs*		(visits or days)		(visits or days)		(visits or days)		(visits or days)		(visits or days)	
In-patient stay per cycle†	£195.19	0		0	£0.00	0	£0.00	1	£195.19	0	£0.00
Day hospital attendance per cycle†	£53.91	1	£53.91	2	£107.82	1	£53.91	0	£0.00	1	£53.91
		(cycles)		(cycles)		(weeks)		(cycles)		(cycles)	
Cumulative subtotal‡		6.00	£323.46	6.80	£733.18	13.3	£717.00	12.9	£2517.95	12.9	£695.44
Catheter & pump costs											
Insertion of tunnelled central line catheter§	£250.00	0	£0.00	1	£250.00	1	£250.00	1	£250.00	1	£250.00
Disposable pump‖	£62.00	0	£0.00	6.8	£421.60	13.3	£824.60	0	–	12.9	£799.80
Cumulative subtotal			£0.00		£671.60		£1074.60		£250.00		£1049.80
Cumulative administration costs			£323		£1405		£1792		£2768		£1745

*Based on Qost costs. †Or weeks of treatment for B2 infusional regimen, see Table 1. ‡Calculated by multiplying by the number of cycles or weeks of treatment. §Includes the costs of doctor time, 0.5 day hospital stay and chest X-ray. ‖Includes the costs of all disposables and pharmacist time.

Table 6. Cumulative costs per patient associated with complications of disease and treatment

		Irinotecan		All 5-FU therapy	
	Unit cost (£)	Cumulative quantity*	Total costs (£)	Cumulative quantity*	Total costs (£)
Hospitalisation†	195.19	14.4 days	2810.74	17.5 days	3415.83
Consultation category‡		(visits)		(visits)	
Oncologist	128.33	2.57	329.81	2.65	340.07
Radiologist§	61.69	0.07	4.32	0.24	14.81
Gynaecologist	40.14	0.04	1.61	0	0.00
Surgeon	54.35	0.05	2.72	0.06	3.26
Dermatologist	50.76	0.01	0.51	0.02	1.02
Urologist	82.71	0.04	3.31	0.05	4.14
General physician	66.97	0.02	1.34	0.18	12.05
Emergency unit	44.00	0.04	1.76	0.04	1.76
Other specialists	61.69	0.19	11.72	0.26	16.04
General practitioner	9.00	2.58	23.22	1.46	13.14
Service costs‖		(visit or test)		(visit or test)	
Nurse visits¶	12.00	3.22	38.64	1.91	22.92
Laboratory tests**	16.78	0.63	10.57	0.02	0.34
Radiotherapy††	122.67	0.05	6.13	0.06	7.36
X-rays	38.28	0.06	2.30	0	0.00
Blood transfusions	100.00	0.01	1.00	0.02	2.00
Total			3250.00		3855.00

*Estimated from clinical trial data [1]. †Unit cost for hospitalisation obtained from Qost. ‡Unit costs for consultation categories obtained from PSSRU (general practitioner) and Qost (other consultation categories). §Assumed that unit cost is as per other specialist, as defined by Qost. ‖Unit costs obtained from Qost. ¶Assumed District nurse visit. **Assumed panel of tests including full blood count and biochemical screen. ††Assumed outpatient attendance.

regimens, the incremental costs per LYG with irinotecan were relatively modest (£7700 per LYG for B1 and £11 947 per LYG for B2), while irinotecan dominated (survival gain and reduced costs) the B3 regimen (Table 7).

Drug acquisition costs were also calculated based upon individual patient data (£4758.66 for irinotecan, £1495.06 for B1, £336.27 for B2 and £3364.63 for B3). Cost-effectiveness ratios calculated in this manner were comparable with results gained from using mean cumulative doses received (£8298 per LYG for B1, £12 360 per LYG for B2 and cost saving for B3). In all cases irinotecan could be considered cost-effective using the criteria stated above.

DISCUSSION

Clinical data [1] have clearly demonstrated a significant survival benefit without deterioration in quality of life with irinotecan compared with infusional 5-FU therapy in the setting of second-line treatment of metastatic colorectal cancer. However, economic data relating to the treatment of colorectal cancer are limited. Retrospective economic analyses [19] have demonstrated that reductions in the number of hospital visits and the duration of hospital stay may counteract the higher drug acquisition costs of a new treatment. But, to date no prospective economic evaluation has been performed. Thus, prospective data collection of resource uti-

Table 7. Comparison of overall cumulative costs per patient and cost-effectiveness per life year gained (LYG) with irinotecan and 5-FU infusional therapy

	Overall cost (£)				
Cost category	Irinotecan	(B1) 5-FU	(B2) 5-FU	(B3a) 5-FU	(B3b) 5-FU
Chemotherapy					
Drug costs	4680	1531	336	3358	3358
Administration	323	1405	1792	2768	1745
Complications	3250	3855	3855	3855	3855
Total	8253	6791	5983	9981	8958
Difference in costs		1462	2270	− 1728	− 705
Difference in survival		0.19	0.19	0.19	0.19
Cost-effectiveness ratio* per LYG		7695	11 947	Dominated†	Dominated†

*Cost-effectiveness ratio (C/E) per LYG was defined as:

$$C/E = \frac{\text{total cost}_I - \text{total cost}_{5\text{-FU}}}{\text{survival}_I - \text{survival}_{5\text{-FU}}}$$

where I = irinotecan and 5-FU = 5-fluorouracil infusional therapy. †Dominated, indicates that irinotecan is more cost-effective than 5-FU and is associated with a significant survival gain.

lisation during the study by Rougier and colleagues [1] has provided an ideal opportunity for evaluating the cost-effectiveness of irinotecan compared with infusional 5-FU therapy in the second-line setting of colorectal cancer.

The results of this cost-effectiveness analysis have shown that the increased survival and improved tumour control seen with irinotecan were achieved with only relatively small increases in costs compared with the 5-FU infusional regimens (Table 7). Compared with what is currently used in the U.K. for first-line treatment of colorectal cancer (either the de Gramont or Lokich 5-FU regimens), the incremental costs per LYG with irinotecan were modest (£7695 per LYG for the de Gramont regimen and £11 947 per LYG for the Lokich regimen). The use of mean cumulative doses to calculate drug acquisition costs has been questioned, however, comparable results were obtained using individual patient data which supports the use of mean cumulative costs in this analysis.

The parameters used in this cost-effectiveness analysis were the mean total cost and the median survival. This may be the subject of some contention, as there are other estimates of survival, such as mean or lifetime estimates, and other estimates of costs, such as lifetime estimates. However, the choice of parameters used in this analysis was based on consistency with the clinical trial results and using the least possible assumptions for costs. Therefore, median survival and mean costs were considered to be appropriate within this context. Mean survival is usually not reported in oncology studies as survival distribution is skewed by patients with a very long survival. Lifetime estimates of survival and costs require assumptions as both use non-parametric methods to extrapolate beyond data observed in the trial. Despite these limitations, cost-effectiveness ratios were calculated using lifetime estimates in a sensitivity analysis. Results using lifetime estimates did not change the conclusions of the analysis reported here (incremental costs per LYG: £10 104 versus the de Gramont regimen and £14 942 versus the Lokich regimen).

Hospitalisation was the most important factor influencing cost considerations. When divided into treatment and follow-up phases, more hospital days were accrued for complications during treatment in the irinotecan arm compared with the 5-FU arm (5.9 versus 3.1 days per patient, respectively) [16]. However, after treatment cessation the number of hospital admissions was higher in the 5-FU arm than in the irinotecan arm (14.4 versus 8.5 days per patient, respectively), attributable to the significant survival gain of irinotecan over 5-FU.

There is no generally accepted limit for cost-effectiveness; in fact, trying to establish such a limit may be contentious [20]. However, choices are inevitable. Following review of available economic evaluations and previously suggested guidelines, Laupacis and colleagues [21] have advocated the adoption of a new technology or treatment if more effective than current practice and costing less than Canadian $100 000 (that is less than £40 000) per quality adjusted life year gained (QALY). Within this limit, the costs involved with the introduction of a new procedure or therapeutic agent are considered reasonable. The authors have quoted the example of hospital haemodialysis being one of many routinely adopted therapies within this range of incremental costs relative to outcome.

To give a U.K. cost perspective, the incremental costs of irinotecan over 5-FU in second-line treatment of colorectal cancer should be compared with the reported incremental costs of other cancer treatments in the U.K. The Economics and Operational Research Division of the Department of Health has previously reviewed the available cost-effectiveness studies [22]. Although not defining a limit at which the incremental costs and clinical benefits of a treatment favour its introduction into routine clinical practice, it has quoted a number of studies which warrant comparison with our study. The incremental cost per LYG following high-dose chemotherapy with autologous bone marrow transplantation in women with metastatic breast cancer has been quoted at £18 800 (1989/1990 costs). The incremental cost per LYG of chemotherapy for advanced non-small cell lung cancer was £10 372, and for induction chemotherapy (cisplatin and vinblastine) plus high-dose radiation therapy for non-small cell lung cancer without distant metastases, the incremental cost per LYG was £7960. For hospital haemodialysis, the cost per LYG was £33 000 [22]. It is important that these costs are adjusted periodically to account for changes in the costs of medical services and treatments. Thus, current available data [22] indicate that incremental costs per LYG of £15 000 for a cancer treatment could be considered reasonable and hence cost-effective compared with currently accepted best practice. Based on these considerations, treatment with irinotecan is associated with a modest increase in cost compared with 5-FU, which together with the significant survival gain demonstrated for irinotecan [1], justifies its use as a cost-effective second-line treatment for metastatic colorectal cancer.

In conclusion, not only is there strong evidence for the use of irinotecan as standard second-line therapy for metastatic colorectal cancer [1], but the results of this prospective economic evaluation have shown that irinotecan also represents good value for money in this clinical setting. Moreover, if ongoing research indicates a role for irinotecan for first-line therapy of colorectal cancer, the cost-effectiveness of irinotecan in this setting would be expected to be even greater.

1. Rougier P, Van Cutsem E, Bajetta E, *et al*. Phase III trial of irinotecan versus infusional fluorouracil in patients with metastatic colorectal cancer after fluorouracil failure. *Lancet* 1998, **352**, 1407–1412.
2. Schmoll H-J. Colorectal carcinoma: current problems and future perspectives. *Ann Oncol* 1994, **5**(Suppl. 3), S115.
3. Van Triest B, van Groeningen CJ, Pinedo HM. Current chemotherapeutic possibilities in the treatment of colorectal cancer. *Eur J Cancer* 1995, **31A**, 1193–1197.
4. Cancer Research Campaign. Factsheet 18.1 1993.
5. Scheithauer W, Rosen M, Kernek GV, *et al*. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancr. *Br Med J* 1993, **306**, 752–755.
6. Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer—a tale of two drugs: implications for biochemical modulation. *J Clin Oncol* 1997, **15**, 368–381.
7. Shimada Y, Rothenberg M, Hilsenbeck SG, *et al*. Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumour colony-forming units. *Anti-Cancer Drugs* 1994, **5**, 202–206.
8. Van Cutsem E, Rougier Ph, Droz JP, *et al.* Clinical benefit of irinotecan (CPT-11) in metastatic colorectal cancer (CRC) resistant to 5-FU. *Proc Am Soc Clin Oncol* 1997, **16**, 268a (abstract).
9. Rougier P, Bugat R, Douillard JY, *et al.* Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naïve patients and patients pretreated with fluorouracil-based chemotherapy. *J Clin Oncol* 1997, **15**, 251–260.

10. Van Cutsem E, Cunningham D, ten Bokkel Huinink WW, *et al.* Clinical activity and benefit of irinotecan (CPT-11) in patients with colorectal cancer truly resistant to 5-fluorouracil (5-FU). *Eur J Cancer* 1999, **35**, 54–59.
11. Cunningham D, Pyrhönen S, James RD, *et al.* Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998, **352**, 1413–1418.
12. De Gramont A, Bosset J-F, Milan C, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French Intergroup Study. *J Clin Oncol* 1997, **15**, 808–815.
13. Lokich JJ, Ahigren JD, Gullo JJ, *et al.* A prospective randomised comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma. *J Clin Oncol* 1989, **7**, 425–432.
14. Weh MJ, Wäke HJ, Dieriamm J, *et al.* Weekly therapy with folinic acid (FA) and high-dose fluorouracil (5-FU) 24 hour infusion in pretreated patients with metastatic colorectal carcinoma. *Ann Oncol* 1994, **5**, 233–237.
15. British National Formulary. Number 35, March 1998.
16. Schmitt C, Blijham G, Jolain B. Prospective econcomic evaluation of a phase III trial comparing irinotecan with infusional 5-FU in patients with advanced colorectal cancer (abstract). Presented at the 20th meeting of the Society for Medical Decision Making, Cambridge, Massachusetts, U.S.A., 25–28 October, 1998.
17. Department of Health, Government Statistical Service. Hospital episode statistics. Volume 1. Finished consultant episodes by diagnosis, operation and specialty, England: 1992–93.
18. Netten A, Dennett J. *Unit Costs of Health and Social Care.* PSSRU, University of Kent, 1996.
19. Ross P, Heron J, Cunningham D. Cost of treating advanced colorectal cancer: a retrospective comparison of treatment regimens. *Eur J Cancer* 1996, **32A**(Suppl. 5), S13.
20. Freeberg KA, Paltiel DA. Cost effectiveness of prophylaxis for opportunistic infections in AIDS. An overview and methodological discussion. *Pharmacoeconomics* 1996, **14**, 165–174.
21. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization Tentative guidelines for using clinical and economic evaluations? *Can Med Assoc J* 1992, **146**, 473–481.
22. Department of Health, Economic and Operational Research Division, Department of Health, 1994.

Acknowledgement—This study was supported by an unconditional educational grant from Rhône-Poulenc Rorer.