Clinical and economic benefits of irinotecan in combination with 5-fluorouracil and folic acid as first line treatment of metastatic colorectal cancer

D Cunningham*,1, S Falk2 and D Jackson3
1 Department of Medicine, Royal Marsden NHS Trust, Davis Road, Sutton, Surrey SM2 5PT, UK; 2Bristol Oncology Centre, Bristol, UK; 3Aventis Pharma, West Malling, UK

The combination of irinotecan plus 5-fluorouracil and folic acid has clinical and survival benefits over 5-fluorouracil and folic acid alone in the setting of first line treatment of metastatic colorectal cancer. The aim of this cost-effectiveness analysis was to compare the economic implications, from a UK health commissioner perspective, of the two treatment arms (de Gramont regimen) in this setting. Resource utilisation data collected prospectively during the study were used as a basis for estimating cumulative drug dosage, chemotherapy administration, and treatment of complications during first line therapy. Resource utilisation associated with further chemotherapy in patients who had progressed during the study was derived from a retrospective case note review. Drug acquisition costs were derived from the British National Formulary (September, 2001) and unit costs for clinical consultation and services were taken from the latest relevant cost database. Cumulative costs per patient associated with further chemotherapy were lower in the irinotecan plus 5-fluorouracil and folic acid treatment arm. Based on incremental costs per life-year gained of £14,794, the combination of irinotecan plus 5-fluorouracil and folic acid can be considered cost-effective by commonly accepted criteria compared with 5-fluorouracil and folic acid alone. Thus, clinical and economic data demonstrate that irinotecan, either in combination with irinotecan plus 5-fluorouracil and folic acid in the first line setting or as monotherapy in the second line setting, has a major role in the management of metastatic colorectal cancer.

Keywords: irinotecan; metastatic colorectal cancer; cost effectiveness analysis; 5-fluorouracil; chemotherapy; first line therapy

With changes in population demographics, healthcare expenditure is subject to continual review and financial constraint. 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 options. Irinotecan (Campto®, Aventis Pharma) is now widely accepted in the USA and Europe as an acceptable second line therapy for metastatic colorectal cancer based on clinical and economic considerations (Rougier et al, 1998; Iveson et al, 1999). Recent data (Douillard et al, 2000) have shown that irinotecan, in combination with 5-fluorouracil and folic acid (5-FU/FA) provides a survival advantage over 5-FU/FA alone, and this indication for first line treatment in metastatic colorectal cancer is reflected in the product licence. The implication of these clinical data have prompted the need for further pharmacoeconomic evaluation in this clinical setting. Colorectal cancer is the second most common cause of cancer death in the UK and Western developed nations, representing about 12% of all cancer deaths (Schmoll, 1994; Van Triest et al, 1995). Annually in the UK, there are over 27,000 new cases of colorectal cancer and over 18,000 deaths due to metastatic disease (Cancer Research Campaign, 1995). In the absence of treatment, median survival from first diagnosis of metastatic colorectal cancer is short (typically 6—9 months) and quality of life is increasingly compromised by both physical and psychological symptoms associated with progression of disease (Seymour et al, 1997).

In the UK, palliative chemotherapy is offered to an increasing number of patients with metastatic colorectal disease. At present 5-FU, usually modulated by FA, is regarded as standard first line therapy for metastatic colorectal cancer, with median survival time of about 10—12 months (The Advanced Colorectal Cancer Meta-analysis Project, 1992). Although there is no consensus of a ‘gold standard’ schedule for these drugs, the de Gramont regimen (de Gramont et al, 1997) is most commonly used in the UK (Seymour et al, 1997). Additionally, in the absence of clear evidence of the best therapeutic option in this setting, other factors such as convenience, cost and quality of life influence clinical practice (Seymour et al, 1997).

Irinotecan is a novel chemotherapeutic agent that acts to inactivate DNA topoisomerase 1 and inhibit cell division (Shimada et al, 1994). There is no evidence of any cross-resistance with 5-FU (Creemers et al, 1994). In the second line setting for metastatic colorectal cancer, irinotecan has been shown to significantly improve survival compared with best supportive care alone (Cunningham et al, 1998) or 5-FU with or without FA (Rougier et al, 1998). In the first line setting for metastatic disease, Phase II studies in chemotherapy-naïve patients have shown promising activity, with response rates ranging from 19—32% when adminis-
Cost-effectiveness of irinotecan plus 5-FU/folinic acid

D Cunningham et al

TREATMENT ARM B: 5-FU/FA alone (n=186)

EITHER

(n=43) de Gramont regimen every 2 weeks (see above)*

1 cycle=6 infusions (7 weeks)

OR

(n=25) Weekly AIO regimen (see above)*

1 cycle=6 infusions (7 weeks)

*de Gramont et al (1997).  3Weh et al (1994). As described in the trial paper (Douillard et al, 2000).

Table 1 Details of treatment regimens used in the study of combination irinotecan+5-fluorouracil/folinic acid (FU/FAC) therapy versus 5-FU/FA therapy alone

MATERIALS AND METHODS

Clinical and resource utilisation data used for economic assessments in this study are described below. These data provide the basis for calculating the direct costs associated with each treatment arm and for carrying out an economic evaluation comparing the treatment arms with respect to their outcomes and associated costs. Only data relating to patients who received the de Gramont regimen were included in the costs analysis (the AIO regimen is not used in the UK) (Seymour et al, 1997), although overall survival was based on all patient data (see Douillard et al, 2000). The control arm (5-FU/FA) was valid from a UK perspective as this regimen is most commonly used in the UK (Seymour et al, 1997). All resource utilisation data were collected thoroughly by prospective completion of Case Report Forms in the main trial (Douillard et al, 2000) and retrospective collation of data in the follow-up study. Both the clinical endpoints and conclusions drawn from the subset for resource utilisation are valid due to the methods used for collection of data.

Clinical data

Patient characteristics of the two treatment arms of the study have been previously summarised and reported (see Douillard et al, 2000). Treatment with the combination of irinotecan+5-FU/FA was significantly superior to 5-FU/FA alone with respect to response rate (41% vs 23%, P<0.001) in the evaluable patient population, and was significantly superior to 5-FU/FA alone with respect to median time to disease progression (6.7 months vs 4.4 months, P<0.001) and median overall survival (16.8 months vs 14.0 months, P<0.028) in the intent-to-treat patient population. The median survival gain of the combination of irinotecan and 5-FU/FA over 5-FU/FA alone (2.8 months or 0.23 life-years saved) was achieved despite the fact that, of patients who received 5-FU/FA alone, 58.3% received further chemotherapy and 31% were subsequently treated with a regimen containing irinotecan. Life-years saved was a major efficacy parameter used in the most-effectiveness analysis.

Resource utilisation data

In estimating the economic impact of irinotecan in combination with 5-FU/FA as first line treatment for metastatic colorectal cancer within the UK, it is insufficient to examine only the drug acquisition costs. Hospitalisation (inpatient and outpatient settings) for administration of treatment, nursing time and equipment use must also be considered. In addition, costs associated with the toxicity of treatment, most commonly diarrhoea and neutropenia, and complications of the disease need to be examined. These later costs can be broadly categorised as hospitalisation costs (other than for routine administration of chemotherapy), consultation costs and costs for clinical and diagnostic 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 length of stay as a single agent (Pitol et al, 1994; Conti et al, 1996; Rougier et al, 1997). These preliminary data were confirmed by a multicentre, randomised, controlled, open-label study (Douillard et al, 2000) (see below), and resulted in the combination or irinotecan with 5-FU/FA being licensed as a first line therapy for metastatic colorectal cancer.

Douillard et al (2000) compared treatment with the combination of irinotecan+5-FU/FA with 5-FU/FA alone in patients with metastatic colorectal cancer; 385 patients received at least one cycle of treatment; 199 patients received the combination of irinotecan+5-FU/FA (treatment arm A) and 186 patients received 5-FU/FA alone (treatment arm B) (see Table 1 for treatment regimens) until the occurrence of disease progression, unacceptable toxicity or withdrawal of consent. In a separate follow-up study in French and UK centres, 62 patients who progressed during the study were followed for up to 3 years until death or trial cut-off date (median range): 14.7 (11.5–21.1) months).

The aim of this study was to compare the economic implications, from a UK health commissioner perspective, of differences in clinical benefit (response and time to progression) and survival between the combination of irinotecan+5-FU/FA and 5-FU/FA alone as first line therapy for metastatic colorectal cancer. The analysis is based on clinical and resource utilisation data collected prospectively as part of the study (Douillard et al, 2000), as well as data relating to further chemotherapy in patients with disease progression during the study which were collected via a retrospective case note review. Costs associated with drug acquisition, treatment delivery, disease complications, and the use of second line chemotherapy were included. Indirect costs, although important, have not been included, as the data have been analysed from the viewpoint of commissioners in the National Health Service (NHS).

Clinical data

1678

Clinical
Cost-effectiveness of irinotecan plus 5-FU/folinic acid
D Cunningham et al

1.8 m² collected in the trial. The median treatment duration was
by the mean number of infusions per patient of each treatment.
to provide the required dose for each infusion and then multiplying
the lowest cost alternative was used for specific vial sizes.
British National Formulary (BNF; September 2001) with allowance
provided in terms of increased survival.
2). It is useful to note at this point that the higher treatment dura-
the study period was lower with 5-FU/FA than with the combina-
ter 7.83 m² gm l⁻¹ (Douillard et al, 2000). Correspondingly, the
calculated cumulative number of infusions per patient given over
the study period was lower with 5-FU/FA than with the combina-
treatment (9.66 vs 12.08 infusions, respectively) (Tables 1 and
It is useful to note at this point that the higher treatment duration
with irinotecan+5-FU/FA combination arm is reflective of the
safety of the regimen. Thus whilst more cycles may appear to
constitute higher costs, these need to be offset against the gains
provied in terms of increased survival.
Cumulative drug costs per patient were based on costs given in the
British National Formulary (BNF; September 2001) with allowance
for wastage. Where there was more than one option for the same
product, the lowest cost alternative was used for specific vial sizes.
Drug costs were calculated by estimating the number of vials needed
to provide the required dose for each infusion and then multiplying
by the mean number of infusions per patient of each treatment.

### Treatment administration costs during the study

As administration of the study treatment was defined in the proto-
col, data relating to treatment delivery were not collected on the
CRF. Both treatment arms required insertion of a tunneled central
line catheter by a doctor as well as the use of an infusional device.
Prospective data collection provided an estimate of the proportion
of inpatient hospitalisations and day hospital attendances required
per infusion in each treatment arm (see Table 3).

Hospitalisations were costed on the basis of 1997/98 extra-
contractual referral tariffs (i.e., tariffs negotiated between a hospital
and a local authority other than that responsible for the hospital)
collected from 12 NHS Trusts in the UK (Qost database). General
medicine and surgery ward tariffs were divided by the official aver-
age length of stay published by the Department of Health (1993/
94) (Department of Health Government Statistical Service, 1993)
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 during the study

All unplanned hospitalisations were recorded prospectively on the
Case Report Form. Hospital admissions due to complications
included those associated with adverse events resulting from
administration of chemotherapy and those resulting from disease
complications. Data for hospitalisation due to planned chemother-
apy administration were excluded. However, if hospitalisation for
chemotherapy administration was prolonged because of toxicity,
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 related to the number of nurse visits
and radiotherapy (Table 4).

Unit costs for hospitalisation, specialist consultations and diag-
nostic costs were derived from the Qost database (1997/98) as
previously described. The consultation tariff included the costs of
procedures performed during the attendance. As diagnostic tests
were usually performed at hospital, outpatient Trust tariffs were
used in the costing of these services. Health professional, nurse
and GP consultations were costed on the basis of Personal Social
Services Research Unit (PSSRU) handbook (Netten and Dennett,
1998). As nurse and health professionals costs were given in hours,
it was assumed that each consultation would be of 0.5 h duration.

Overall cumulative costs per patient associated with complica-
tions in each treatment arm were calculated using estimates of
the cumulative number of hospitalisations, consultations, and clin-
ical and diagnostic services required per treatment arm derived
from the trial data.

### Cost associated with further chemotherapy

Data relating to resource utilisation associated with progression
and further chemotherapy were derived from a retrospective case

---

**Table 2** Cumulative drug acquisition costs per patient* during study

|                | Irinotecan+5-FU/FA | 5-FU/FA |
|----------------|--------------------|---------|
|                | S-FU | FA | S-FU | FA |
| Cumulative dose (mg)* | 3914 | 21 744 | 4349 | 17 388 | 3478 |
| No. of infusions| 12.08 | 12.08 | 12.08 | 9.66 | 9.66 |
| Dose/infusion (mg) | 324 | 1800 | 360 | 1800 | 360 |
| Infusion cost/drug (£) | 419.00 | 13.97 | 126.07 | 13.97 | 126.07 |
| Total cost/infusion (£)* | 419.00 | 140.04 | 13.97 | 140.04 |
| Total drug cost (£)* | 6753.20 | 1352.79 |

*Only those patients who initially received de Gramont regimen (either alone or in combination with irino-
tecan). Calculated using a mean body surface area of 1.8 m², as determined from the trial (Douillard et al,
2000). Refer to Table 1, treatment regimens. Costs are derived from the BNF (March, 1999), based on the
use of 5 ml vials (£1.30 each) and 2 ml vials (£53 each) for irinotecan, 20 ml vials (£3.97 each) and 10 ml
vials (£2.06 each) for 5-FU, and 35 ml vials containing 10 mg ml⁻¹ (£90.98 each) and 10 ml vials containing
3 mg ml⁻¹ (£35.09 each) for folinic acid (FA), with allowance for wastage.
Note review for 62 patients in centres in France and the UK who had progressed during the study. Costs associated with further therapy following disease progression were categorised as either drug costs (i.e., drug acquisition costs and costs associated with treatment delivery) or disease progression costs (i.e., costs associated with further hospitalisation and radiotherapy).

Information was collected on all treatment regimens used for further chemotherapy in each treatment arm. Wherever possible, calculation of the number of infusions administered for each treatment regimen was based on published sources (see Table 5). Assumed cumulative costs per patient for each treatment regimen were based on acquisition costs given in the British National Formulary (BNF, March 1999), with allowance for wastage, and included costs associated with treatment delivery. The actual cumulative drug costs per patient associated with further chemotherapy were then calculated by multiplying the proportion of patients who had received further therapy during follow-up (i.e., 39.4% in the irinotecan+5-FU/FA combination treatment arm and 58.3% in the 5-FU/FA treatment arm) (Douillard et al., 2000).

Retrospective data collection was used to estimate the total cumulative hospitalisation and radiotherapy costs per patient associated with disease progression. The actual cumulative costs per patient associated with disease progression were then calculated by multiplying the proportion of patients in each treatment arm who had progressed during the study.

### Overall costs

In the setting of first line therapy, the overall cumulative costs for each treatment arm represented the total sum of costs associated with first line therapy and costs associated with disease progression (i.e., costs associated with further hospitalisation and radiotherapy).

Information was collected on all treatment regimens used for further chemotherapy in each treatment arm. Wherever possible, calculation of the number of infusions administered for each treatment regimen was based on published sources (see Table 5). Assumed cumulative costs per patient for each treatment regimen were based on acquisition costs given in the British National Formulary (BNF, March 1999), with allowance for wastage, and included costs associated with treatment delivery. The actual cumulative drug costs per patient associated with further chemotherapy were then calculated by multiplying the total assumed cumulative drug costs per patient of further therapy by the proportion of patients in each treatment arm who had received further therapy during follow-up (i.e., 39.4% in the irinotecan+5-FU/FA combination treatment arm and 58.3% in the 5-FU/FA treatment arm) (Douillard et al., 2000).

Retrospective data collection was used to estimate the total cumulative hospitalisation and radiotherapy costs per patient associated with disease progression. The actual cumulative costs per patient associated with disease progression were then calculated by multiplying the proportion of patients in each treatment arm who had progressed during the study.

### RESULTS

Costs during the study

Cumulative costs during the study are summarised by treatment arm in Tables 2, 3 and 4. As anticipated, cumulative drug acquisi-
tion costs during the study were substantially higher in the irinotecan+5-FU/FA combination treatment arm than the 5-FU/FA treatment arm (£6753 vs £1353, respectively) (Table 2). Cumulative costs associated with treatment delivery (Table 3) and with drug toxicity and disease complications (Table 4) were generally similar in each treatment arm.

Costs during follow-up

However, the higher cumulative costs per patient associated with first line treatment with irinotecan+5-FU/FA were offset by substantially lower cumulative costs per patient during the trial and follow-up period, probably attributable to reduced disease progression in the combination treatment arm (39.4% vs 58.3% of patients, respectively) (Douillard et al, 2000). Both cumulative drug costs per patient (£2007 in the irinotecan+5-FU/FA arm vs £3601 in the 5-FU/FA arm) (Table 5), and cumulative disease progression costs per patient during follow-up (£1484 vs £2460, respectively) (Table 6) were up to 45% lower in the combination treatment arm.

Total costs

When cumulative costs per patient associated with first line (during study) and further (during follow-up) chemotherapy were considered together, it is apparent that the overall cumulative costs per patient in the irinotecan+5-FU/FA combination treatment arm were higher than those associated with 5-FU/FA alone (difference in costs, £3452) (Table 7).

However, treatment with the combination of irinotecan+5-FU/FA in the first line setting also resulted in a significant gain in median survival over 5-FU/FA alone (0.23 life-years (Douillard et al, 2000)). Cost-effectiveness analysis of incremental costs and survival relative to 5-FU, demonstrated that treatment with the combination of irinotecan+5-FU/FA in the first line setting resulted in incremental costs per LYG of £14 794. Sensitivity analyses based on UK data alone showed that there was little change in incremental costs per LYG when rates were varied to reflect UK practice (£16 015).

DISCUSSION

Combination treatment with irinotecan+5-FU/FA is now licensed as a first line therapy for metastatic colorectal cancer. Compared with 5-FU alone, the combination of irinotecan+5-FU/FA offers a significant survival advantage without detriment to quality of life (Douillard et al, 2000).

However, the introduction of new treatments to hospital formularies requires demonstration of cost as well as clinical

---

Table 5  Cumulative overall drug costs per patient* associated with further chemotherapy** during follow-up

| Follow-up chemotherapy | Irinotecan+5-FU/FA | 5-FU/FA |
|------------------------|-------------------|--------|
|                        | Per cent of patients | Total costs (£) | Per cent of patients | Total costs (£) |
| Irinotecan              | 1.61               | 23.81   |
| 5-FU/FA (Mayo regimen)  | 1.61               | –       |
| 5-FU/FA (de Gramont regimen)* | 4.84       | 3.18    |
| 5-FU/FA (Lokich regimen)* | 9.68       | 6.35    |
| Irinotecan+5-FU/FA (de Gramont regimen)* | 19.36     | 12.70   |
| Oxaliplatinb           | 1.61               | –       |
| Oxaliplatinb+irinotecanb | –             | 7.94    |
| Oxaliplatinb+5-FU/FA (de Gramont regimen) | 41.93     | 26.98   |
| Mitomycin Cc           | 4.84               | 1.59    |
| Mitomycin C+S-FU/FAd   | 6.45               | 9.52    |
| Raltrexed              | 1.61               | –       |
| Chronotherapye         | 3.23               | 7.93    |
| Assumed total cumulative costsf | 100.00   | 5093.50 |
| Per cent patients receiving second line therapy* | 39.4      | 2006.76 |

*Only those patients who initially received de Gramont regimen (either alone or in combination with irinotecan) during study. **Most of these data relate to second-line therapy, although it is recognised that a small proportion of third-line therapy may be included. Treatment regimens as described in: aIveson et al (1999). bLevi et al (1993). cHartmann et al (1998). dRoss et al (1997). eLevi et al (1997). fCosts are derived from the BNF (March, 1999). gFrom trial data (Douillard et al, 2000).

Table 6  Cumulative overall costs per patients* associated with disease progression during follow-up

| Assumed costs | Unit cost (£) | Cumulative quantity | Total costs (£) | Cumulative quantity | Total costs (£) |
|---------------|--------------|---------------------|-----------------|---------------------|-----------------|
| Hospital admissionsb | 195.19 | 19.23 | 3753.50 | 21.47 | 4190.73 |
| Radiotherapyc | 122.67 | 0.1129 | 13.85 | 0.2382 | 29.22 |
| Total assumed costs | 3767.35 | 4219.95 |
| Per cent patients receiving second line therapyd | 39.4 | 1484.34 | 58.30 | 2460.23 |

*Only those patients who initially received de Gramont regimen (either alone or in combination with irinotecan) during study. bEstimated from follow-up clinical trial data. cUnit costs obtained from NIsost. dAssumed outpatient attendance. eFrom trial data (Douillard et al, 2000).
Cost-effectiveness of irinotecan plus 5-FU/folinic acid
D Cunningham et al

Table 7  Comparison of overall cumulative costs per 100 patients and cost-effectiveness per life year gained (LYG) with irinotecan+5-FU/FA compared with 5-FU/FA alone (de Gramont regimen)*

|                          | Irinotecan+ 5-FU/FA (£) | 5-FU/FA (£) |
|--------------------------|-------------------------|-------------|
| During study†             |                         |             |
| Drug acquisition costs   | 6753.20                 | 1352.79     |
| Drug administration costs| 1825.00                 | 1537.00     |
| Complication costs       | 1480.15                 | 1146.90     |
| During follow-up‡         |                         |             |
| Further chemotherapy costs| 2006.76                 | 3600.73     |
| Disease progression costs | 1494.34                 | 2462.23     |
| Total costs during study and follow-up | 13550 | 10098    |
| Difference in costs      | 3452                    |             |
| Difference in survival   | 0.23                    |             |
| Cost-effectiveness ratio/LYG§ | 14794                 |             |

*Only those patients who initially received de Gramont regimen (either alone or in combination with irinotecan) during study. †Refer to Tables 3, 4 and 5 for derivation. ‡Derived from clinical trial data (Douillard et al, 2000). §Refer to Tables 6 and 7. Derived from clinical trial follow-up data. §From clinical trial data. Abbreviated actual figure is 0.23333333 (Douillard et al, 2000). ³Cost-effectiveness ratio per life years gained (LYG) was defined as:

\[
\text{Cost-effectiveness ratio/LYG} = \frac{\text{total cost} - \text{total cost}_{\text{FU}}}{\text{survival} - \text{survival}_{\text{FU}}}
\]

where 1=irinotecan+5-fluorouracil/folinic acid therapy and 5-FU=5-fluorouracil/folinic acid therapy.

REFERENCES

British National Formulary (March 1999) Number 35. Cancer Research Campaign (1995) Factsheets 3.2 – 3.3 (UK Cancer Statistics) London: CRC
Conti JA, Kemeny NE, Saltz LB et al (1996) Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J Clin Oncol 14(3): 709 – 715
Creemers GJ, Lund B, Verweij J (1994) Topoisomerase I inhibitors: topotecan and irinotecan. Cancer Treat Rev 20: 73 – 96
Cunningham D, Pyrhonen S, James RD et al (1994) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352: 1413 – 1418
Department of Health, Government Statistical Service Hospital episode statistics. Volume I. Finished consultant episodes by diagnosis, operation and speciality, England: 1993 – 1994
Department of Health, Economic and Operational Research Division, Department of Health, 1994
Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355: 1041 – 1047
de Gramont A, Bosset J-F, Milan C et al (1997) 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 15: 808 – 815
Iveson TJ, Hickish T, Schmitt C, Van Cutsem E (1999) Irinotecan in second line treatment of metastatic colorectal cancer: improved survival and cost-effectiveness compared with infusional 5-FU. Eur J Cancer 35(13): 1796 – 1804
Levi F, Zidani R, Misset JL (1997) Randomised multicentre trial of chemotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. International Organization for Cancer Chronotherapy. Lancet 350(9079): 681 – 686

ACKNOWLEDGEMENTS

This study was supported by an unconditional educational grant from Aventis Pharma.

advantages. The new treatment must be shown to be cost-effective relative to current best practice, specifically with respect to value parameters such as survival gain. Defining arbitrary financial limits based on such value parameters is difficult, particularly as there is a general paucity of guidelines on which to base judgements. Yet choices are inevitable and necessary.

In the UK, there are no guidelines for using clinical and economic evaluations, and no defined limit at which the incremental costs and clinical benefits of a treatment favour its introduction into routine clinical practice. However, tentative limits can be surmised from a recent Department of Health review of available cost-effectiveness studies (Department of Health, 1994). These data (Department of Health, 1994) suggest that incremental costs per LYG of £15 000 – £20 000 for a cancer treatment can be considered reasonable, and hence the treatment may be viewed as cost-effective compared with currently accepted best practice. Based on these considerations, treatment with irinotecan+5-FU/FA was associated with only a modest increase in cost compared with 5-FU/FA alone (as supported by sensitivity analyses involving only UK data), which together with the significant survival gain demonstrated for the combination treatment (Douillard et al, 2000), justifies its use as a first line therapy for metastatic colorectal cancer.

In conclusion, the results of the cost effectiveness analysis presented in this study, together with clinical evidence (Douillard et al, 2000), strongly support the use of irinotecan+5-FU/FA in the setting of first line therapy of metastatic colorectal cancer. Moreover, clinical (Rougier et al, 1998) and economic (Iveson et al, 1999) studies have confirmed the superiority of irinotecan in the setting of second line therapy. Thus, irinotecan, either alone or in combination with 5-FU/FA, represents an important therapeutic advance in the management of metastatic colorectal cancer.

Lévi F, Perpoint B, Garufi C, Focan C, Chollet P, Depres-Brummer P, Zidani R, Brienza S, Ithzaki M, Iacobelli S (1993) Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5-day continuous venous infusion at circadian rhythm modulated rate. Eur J Cancer 29A(9): 1280 – 1284
Netten A, Dennett J (1998) Unit costs of health and social care. University of Kent: Personal Social Services Research Unit (PSSRU)
Pitot HC, Wender D, O’Connell MJ et al (1994) A phase II trial of CPT-11 (irinotecan) in patients with metastatic colorectal carcinoma. A North Central Cancer Treatment Group (NCCTG) study. Proc Am Soc Clin Oncol 13: (Abstract 573):197
Ross P, Norman A, Cunningham D, Webb A, Iveson T, Padhani A, Prendive J, Watson M, Massey A, Popescu R, Oates J (1997) A prospective randomised trial of protracted venous infusion 5-fluorouracil with or without mitomycin C in advanced colorectal cancer. Ann Oncol 8(10): 995 – 1001
Rougier P, Bugat R, Douillard JY et al (1997) Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 15: 251 – 260
Rougier P, Van Cutsem E, Bajetta E et al (1998) Randomised trial of fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352: 1407 – 1412
Schmoll H-J (1994) Colorectal carcinoma: Current problems and future perspectives. Ann Oncol 5(Suppl 3): S115 – S121
Seymour MT, Stenning SP, Cassidy J (1997) Attitudes and practice in the management of metastatic colorectal cancer in Britain. Clin Oncol 9: 248 – 251
Shimada Y, Rothenberg M, Hilsenbeck SG et al (1994) Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumor colony-forming units. Anti-Cancer Drugs 5: 202 – 206
The Advanced Colorectal Cancer Meta-analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10: 896 – 903
Van Triest B, van Groeningen CJ, Pinedo HM (1995) Current chemotherapeutic possibilities in the treatment of colorectal cancer. Eur J Cancer 31A: 1193 – 1197
Weh HJ, Wilke HJ, Dierlamm J et al (1994) Weekly therapy with folinic acid (FA) and high-dose 5-fluorouracil (5-FU) 24-hour infusion in pretreated patients with metastatic colorectal carcinoma. Ann Oncol 5: 233 – 237