Pergamon

European Journal of Cancer, Vol. 32A, Suppl. 5, pp. S13–S17, 1996

Printed in Great Britain
0959–8049/96 $15.00+0.00

PII: S0959-8049(96)00334-6

Cost of Treating Advanced Colorectal Cancer: A Retrospective Comparison of Treatment Regimens†

P. Ross,[1] J. Heron[2] and D. Cunningham[1]

[1]The Cancer Research Campaign Section of Medicine and the GI Unit, Royal Marsden Hospital and Institute of Cancer Research, Downs Road, Sutton, Surrey; and [2]Diagnosis Healthcare Consulting, 19 King Edward Street, Macclesfield, Cheshire, U.K.

Introduction of new agents on to hospital drug formularies requires the demonstration of efficacy, safety and cost advantages. An audit of the total monthly costs of 'Tomudex'™* (raltitrexed; administered every 3 weeks), a drug recently introduced for the treatment of advanced colorectal cancer, and three 5-fluorouracil-based regimens [5-day daily bolus (Mayo); continuous ambulatory pump; 48-h continuous infusion (De Gramont)] was undertaken. Patient-specific costs associated with fluids, concomitant medication and consumables were largely negligible, but chemotherapy was the main cost driver in the raltitrexed and De Gramont groups. Fixed inpatient costs were highest for the patients receiving the De Gramont regimen which required more inpatient stays each month. Total costs (patient-specific plus fixed costs) were lowest in patients on the Mayo regimen (mean £954.03; median £659.68), followed by patients in the ambulatory pump (mean £1207.61; median £749.19), raltitrexed [mean £1256.93; median £1087.14 (mean £1117.85; median £959.34 when costs of protocol-driven visits were excluded)], and De Gramont groups (mean £2028.52; median £1775.66). The pattern of costs varied considerably between regimens, such that high drug costs, for example those associated with raltitrexed therapy, were partially offset by reductions in hospital visits and stays.

Key words: advanced colorectal cancer, 5-fluorouracil, health-economics, raltitrexed
Eur J Cancer, Vol. 32A, Suppl. 5, pp. S13–S17, 1996

INTRODUCTION

COLORECTAL CARCINOMA, one of the three most frequent cancers in men and women, is responsible for 10–11% of all cancer deaths [1]. Although the majority of patients present with surgically resectable disease, earlier dissemination has often occurred, such that almost 50% of patients presenting with colorectal cancer die with metastatic disease [2]. Even with surgical advancement, a corresponding increase in cure rate has not been achieved [3], and treatment for patients with locally advanced or metastatic disease remains largely palliative and aimed at maintaining or improving quality of life.

The standard chemotherapeutic agent for advanced colorectal cancer, 5-fluorouracil (5-FU), has been therapeutically modulated in various regimens and combinations in an attempt to enhance effectiveness. As a bolus infusion, 5-FU monotherapy produced variable response rates (up to 20%) [3], but, by continuously administering low-dose 5-FU via an ambulatory pump, higher responses (30% versus 7% for bolus administration) have been achieved [4]. Even higher response rates, exceptionally to 48% [5], have been obtained by combining folinic acid (leucovorin) with 5-FU, although the addition has not improved overall survival compared with 5-FU alone, according to a recent meta-analysis [6]. The most suitable dose of folinic acid remains a controversial area, but the most common treatment regimen for advanced colorectal cancer, 5-FU plus low-dose folinic acid (20 mg/m^2), administered by rapid intravenous injection on 5 consecutive days each month (Mayo regimen), produces an acceptable balance between response rates, survival, toxicity and drug costs [7, 8]. In a recent study comparing best supportive care either with or without the addition of primary chemotherapy (etoposide, leucovorin, 5-FU every 3 weeks or leucovorin plus 5-FU every 2 weeks), patients receiving primary chemotherapy had significantly improved or prolonged high quality of life and longer overall and quality-adjusted survival [9].

Raltitrexed, a folate-based thymidlyate synthetase inhibitor, is a new palliative treatment for advanced colorectal cancer, administered by one short 15-min infusion every 3 weeks. In a trial of 439 patients with advanced disease, comparable objective response rates of 20% in raltitrexed patients and 13% in patients receiving the Mayo regimen were recorded after a mean follow-up of 5.3 months. Furthermore, toxic effects, which are frequent with 5-FU/folinic acid bolus regimens (WHO grade 3/4 leucopenia and mucositis), were significantly lower ($P < 0.001$) in patients receiving raltitrexed [10].

Introduction of any new therapeutic agent on to a hospital

Correspondence to D. Cunningham.
* 'Tomudex' is a trademark, the property of Zeneca Limited.
† Some of the data contained in this manuscript were not presented at the ECCO 8 meeting.

Table 1. List of patient-specific and fixed (hospital) costs included in the analysis

Patient-specific costs	Fixed costs
Chemotherapy	Inpatient stays
Concomitant medication	Outpatient visits
Fluids	Operations
Tests	Helpline (ambulatory regimen)
Consumables	

drug formulary now requires not only the demonstration of efficacy and safety, but increasingly cost advantages. A cost analysis study into the treatment of gastrointestinal carcinoma, based on survival and quality of life data, concluded that it is cost-effective to treat advanced colorectal cancer with chemotherapy [9], but a cost comparison of the treatment options was not considered. Standard treatment of colorectal cancer with bolus 5-FU/low-dose folinic acid is easy to manage clinically and relatively inexpensive with respect to drug costs [11], but necessitates inconvenient and costly daily clinic visits during treatment periods. Ambulatory administration of 5-FU is also effective and less toxic, but requires an indwelling catheter and accessible patient counselling [12]. The drug cost of any new agent, such as raltitrexed, may be relatively expensive, but may incur lower non-drug related costs. Therefore, this retrospective study, from a prospective database of an academic gastrointestinal oncology unit, was undertaken to audit the actual costs to the hospital associated with raltitrexed and three 5-FU-based treatment regimens, irrespective of efficacy implications.

PATIENTS AND METHODS

Study population

Between January 1995 and May 1995, the records of selected patients with advanced colorectal cancer, who had received one of four defined chemotherapeutic regimens, were audited at the Royal Marsden Hospital. Patient data were included, irrespective of age, sex and duration of disease, providing that the treatment was first line. Incomplete records or non-defined chemotherapy were excluded. Patients in the raltitrexed arm were all participants in a phase II/III trial programme.

Treatment

The four chemotherapeutic regimens were: 5-FU (425 mg/m^2) plus low-dose folinic acid (20 mg/m^2), by bolus injection, every day for 5 days and repeated at 28-day intervals (bolus or Mayo regimen); 5-FU (400 mg/m^2) by bolus i.v. injection plus high-dose folinic acid (200 mg/m^2) by 2-h infusion followed by 22-h infusion of 5-FU (400 mg/m^2), for 2 days at 14-day intervals, either as an in- or outpatient (De Gramont regimen); 5-FU (300 mg/m^2 per day) administered continuously via an ambulatory pump (pump regimen); raltitrexed (3 mg/m^2), by 15-min infusion at 21-day intervals. The scheduled treatment periods were 18 weeks for raltitrexed (6 cycles) and 24 weeks for the other three regimens or until the patient died or stopped treatment for any reason.

Definition of costs

Total costs were divided into patient-specific and fixed costs (Table 1). Patient-specific costs were: chemotherapy (dependent upon the drug dosage, number of doses per cycle, length of cycle and the between-cycle interval), concomitant medication and intravenous fluids; diagnosis and laboratory monitoring and consumables (including infusion pumps). Fixed costs in this study were limited to those associated with inpatient stays, outpatient visits, operations and the provision of a telephone helpline service for patients with infusion pumps.

Since the study was performed from the hospital's viewpoint, direct costs which were not accounted for in the present analysis included general practitioner visits and patients' travelling expenses. Indirect costs such as loss of earnings of patients and carers, and intangible costs and benefits, such as quality of life, were also not considered in this study. In addition, the system of accounting for pharmacy charges has not been fully developed and therefore was not included.

Quantification of costs

Costs were calculated for every patient on an individual basis, using an Excel Spreadsheet, and although the resources used (for example, the number of visits or drugs consumed) varied between the different treatment regimens, the unit resource costs remained constant. The cost of raltitrexed (£116/vial) was supplied by the manufacturer and other drug costs were obtained from the British National Formulary (September 1994) [13]. Where partial vials of raltitrexed were used to reconstitute doses, it was assumed that unused portions were discarded. The costs of fluids and blood products were obtained from the National Blood Transfusion Service (UK). Average costs of laboratory tests, diagnostic procedures and surgical procedures, including the insertion of indwelling catheters, were provided by the hospital. In- and outpatient hosptial costs were obtained from the Office of Health Economics (1995) [14]. Costs totalling less than £0.01 were excluded from the cost calculations.

Costs for patients with ambulatory pumps were for the telephone helpline and pump equipment. The helpline service is manned by two full-time nurses but is shared by all departments within the Royal Marsden Hospital. The cost of this service per patient (£50) was calculated from the total salary costs (£50 000 per year) divided by the number of benefiting patients (1000). An infusion pump is expensive initially but the cost is 'amortised' or spread over its expected useful life. It is estimated that a pump costing £1700 will be used by three different patients each year for 5 years (cost per patient: £112). An administration kit costing £10 per 28-day cycle will also be used by these patients, but pump servicing costs, which are not borne by this department, were not included in these calculations.

Statistical methods

Chemotherapy is usually given in treatment cycles which vary in length. Since it is not valid to compare the costs of cycles of different lengths, the calculations were made on a 'per month' basis. The number of visits (days/month) and some cost data were non-normal in distribution. Although the median value was a more appropriate summary statistic than the mean for the number of visits, as it was not affected by outlying values which effectively skew the data distribution. It is not uncommon for cost data to be non-normally distributed. Therefore, mean treatment costs were calculated for each treatment group, as the mean accounts for the small number of patients (outliers) who generate the greatest costs. Confidence intervals for the total costs were calculated using the method of Gardner and Altman [15].

Table 2. Demographic characteristics

	Mayo	De Gramont	Pump	Raltitrexed	Overall
Patient number	23	31	31	31	116
Age (years)					
Mean (sd)	63.9 (8.9)	60.3 (7.8)	60.8 (9.2)	63.3 (11.0)	61.9 (9.4)
Median (Range)	65.0 (47–78)	62.0 (45–71)	62.0 (39–72)	64.0 (30–81)	63.0 (30–81)
Sex					
Male	19 (83%)	17 (55%)	12 (39%)	20 (65%)	68 (59%)
Female	4 (17%)	14 (45%)	19 (61%)	11 (35%)	48 (41%)

RESULTS

Patients

The records of 124 patients were initially entered on to an Excel Spreadsheet, comprising 31 in each treatment group. However, 8 patients in the Mayo group were subsequently excluded either because the treatment was second line (5), they received an additional chemotherapeutic agent (1) or drug information was missing (2).

The demographic summary of the study population is presented in Table 2. Patients were aged between 30 and 81 years in all treatment groups, with an overall mean age of 61.9 years. There were more males than females (59% versus 41%) in the whole study population, but in the ambulatory pump group there were more females (61%) than males (39%). All patients had a diagnosis of advanced colorectal cancer.

Visits

The median number of hospital visits required for each regimen is presented in Table 3. The Mayo regimen, which requires visits on 5 consecutive days each month, recorded the highest number of monthly outpatient visits (median 4.5). The median number of inpatient visits for this regimen was zero. Raltitrexed recorded a monthly median of 3.2 outpatient visits, although many of these were required by the clinical trial protocol for regulatory monitoring, not for patient management. From the recommended dosing schedule (one administration every 3 weeks), a lower monthly adjusted median (1.3) may be expected. A monthly median of 0.4 inpatient visits was recorded in the raltitrexed group. The De Gramont regimen, including patients receiving treatment as out- or inpatients, recorded the fewest outpatient visits (0.9), but as expected from the treatment method (infusion over 48 h every 2 weeks), the inpatient median (4.2) was far higher than the other three regimens. Patients receiving continuous 5-FU recorded low numbers of both in- and outpatient visits.

Costs

The mean monthly treatment costs are presented in Table 4. For each of the treatment groups, the patient-specific costs associated with fluids, concomitant medication and consumables were largely negligible, but tests were a large cost component. Chemotherapy was the main cost driver in the raltitrexed and De Gramont groups (£456.52 and £393.38, respectively), resulting in comparable total patient-specific costs. These were greater than for the ambulatory and Mayo groups.

Outpatient costs were highest in the Mayo group (£329.96),

Table 3. Median number of visits per month

Patient type	Mayo	De Gramont	Pump	Raltitrexed	Adjusted raltitrexed
Outpatient	4.5	0.9	1.1	3.2	1.3
Inpatient	0.0	4.2	0.6	0.4	0.4
Total	5.2	5.3	1.7	3.6	2.0

which requires visits on 5 consecutive days each month. The raltitrexed group also recorded high costs, because of the high number of protocol-driven visits. In routine clinical practice a lower number (1.3 versus 3.2) may be anticipated and is shown in the 'Adjusted raltitrexed' column in Table 4. Mean inpatient costs, which were low in the Mayo, raltitrexed and ambulatory groups, were far higher with the De Gramont regimen, because 18 out of 31 patients spent two 48-h periods as inpatients each month.

The mean total costs were lowest in the Mayo group, followed by ambulatory and raltitrexed groups. However, by using adjusted data for the anticipated number of raltitrexed dosing visits (1.3) needed during routine clinical practice, the total raltitrexed costs (mean £1117.85, median £959.34) were calculated to be comparable with the ambulatory and Mayo groups. The total monthly cost associated with the De Gramont regimen, whether administered on an inpatient or outpatient basis [mean £2353.01 and £1579.22, respectively and £2028.52 overall (median £1775.66 overall)], was much higher than the other regimens and comprised both high patient-specific and fixed costs. The mean total costs and associated 95% confidence intervals per month are illustrated in Figure 1 for each of the treatment groups.

CONCLUSION

The prognosis of colorectal cancer, one of the three most common cancers, depends ultimately upon the extent of disease spread at diagnosis. Despite recent advances in surgical techniques, many patients present with locally advanced or metastatic disease and for these individuals treatment is largely palliative. Raltitrexed is a new chemotherapeutic agent with response rates comparable to those of a 5-FU-based Mayo regimen [10]. Since Drugs and Therapeutics Committees often require efficacy, safety and economic benefits to be demonstrated before including a new agent on a drug formulary, the present study was undertaken to compare the relative costs of raltitrexed and three commonly used 5-FU-based regimens. This study of

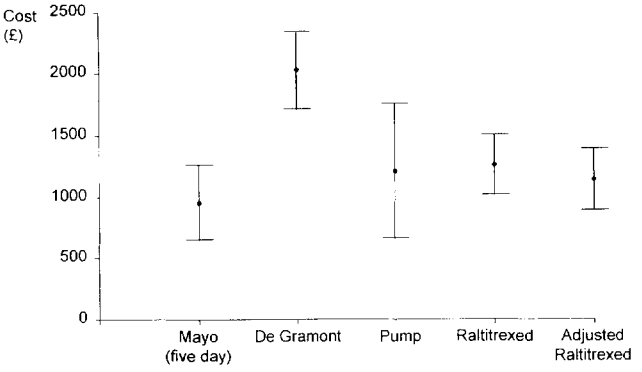

Figure 1. The total treatment costs (mean and 95% confidence intervals) per month (£) for each of the treatment groups.

Table 4. Mean treatment costs per month (£)

Cost type	Mayo	De Gramont	Pump	Raltitrexed	Adjusted raltitrexed
Chemotherapy*	74.16	393.38	93.22	456.52	456.52
Other drugs	50.66	71.27	17.30	32.77	32.77
Tests	188.04	195.03	301.95	226.41	226.41
Consumables	0.00	25.92	45.69	0.00	0.00
Fluids	7.46	22.97	9.16	20.62	20.62
Sub-total	320.31	708.58	467.32	736.32	736.32
Operations	10.85	108.90	138.45	0.00	0.00
Outpatient†	329.96	177.41	117.57	276.59	137.51
Inpatient	292.91	1027.14	471.57	244.02	244.02
Helpline	0.00	6.50	12.71	0.00	0.00
Sub-total	633.72	1319.94	740.29	520.61	381.53
Total (mean)	954.03	2028.52	1207.61	1256.93	1117.85
Approximate 95% CI for mean	649.11–1258.95	1715.10–2341.94	660.48–1754.73	1016.80–1497.06	876.20–1359.50
Total (median) (95% CI)	659.68 (524.89–1071.94)	1775.66 (1494.60–2384.90)	749.19 (592.73–1015.46)	1087.14 (986.95–1231.87)	959.34 (845.48–1055.20)

* Chemotherapy costs include the cost of folinic acid.
† Outpatient costs include the costs of clinic injections.
CI, confidence interval

mainly clinical trial participants, did not consider efficacy implications, but was merely an audit of the costs which were actually incurred, and which could be identified from the hospital records. No attempt was made to quantify the cost of services patients received outside the hospital in the study, nor were costs calculated after patients had completed their chemotherapy regimen because of disease progression, withdrawal due to adverse events or completion of the treatment protocol.

The major cost components of the four regimens were different; the De Gramont regimen, with high inpatient and chemotherapy costs, was the most expensive method, costing more than twice as much as the Mayo regimen, which had low patient-specific costs. Raltitrexed had much higher drug costs than the Mayo regimen, but these were partially offset by the reduced number of outpatient visits required during routine clinical administration. It should be noted, however, that some major cost drivers, which would increase Mayo and De Gramont costs (nursing time to set up infusions, pharmacy charges) were not considered in the analysis, due to the absence of data. In addition some of the costs included within the continuous 5-FU infusion regimen (cost of pumps, cost of helpline) are likely to be low compared to other cancer centres, as the Royal Marsden has a large number of patients over which to amortise these costs. Two other factors that relate to the continuous 5-FU regimen, but were not included in the analysis, were the cost of servicing the pumps and the cost of sending out drugs to patients. Furthermore, it should be recognised that there may be differences between European countries in respect of patient-specific and fixed costs. Thus, the results of such an analysis could vary across Europe.

There is insufficient information available to judge whether raltitrexed has any effect on survival. However, patient convenience and quality of life are very important in the palliative treatment of these terminally ill patients. Patients administered raltitrexed would need to make one visit for a short 15-min infusion every 3 weeks (monthly median 1.3) compared with five visits every month with Mayo, or a 2-day in-patient stay every 2 weeks with the De Gramont regimen. In addition, patients receiving continuous 5-FU have to wear an infusion pump at all times. It may be anticipated that the reduction in in- and outpatient visits, as achieved by raltitrexed or the ambulatory pump regimens, may allow an increased throughput of patients through busy oncology units, without a need for expanding existing facilities in terms of bed numbers or staff complement.

This preliminary economic analysis, which did not include some direct and indirect costs, has indicated that the total cost of raltitrexed is comparable to that of continuously administered 5-FU and Mayo regimens, and lower than the De Gramont regimen. The low frequency of raltitrexed administration may reduce the number of visits to a level comparable with that for continuous infusion, without the need for support services or wearing a continuous pump. A further prospective study, taking into account the direct costs omitted from this study, routine clinical practice (rather than trials), clinical differences between treatment regimens and patient preferences would provide a more comprehensive comparison of the regimens.

1. Boring CC, Squires TS, Tong T, *et al.* Cancer statistics, 1994. *CA Cancer J Clin* 1994, **44**, 7–26.
2. Willet CG, Tepper JE, Cohen AM, *et al.* Failure patterns following curative resection of colonic carcinoma. *Ann Surg* 1984, **200**, 685–690.
3. Levitan N. Chemotherapy in colorectal carcinoma. *Surg Clin North Am* 1993, **73**, 183–198.
4. Lokich JJ, Ahlgren JD, Gullo JJ, *et al.* A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. *J Clin Oncol* 1989, 7, 425–432.
5. Petrelli N, Herrera L, Rustum Y, *et al.* A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987, 5, 1559–1565.

6. Kemeny NE, Conti JA, Bertino JR. Chemotherapy for colorectal cancer. *N Engl J Med* 1994, **331**, 680–681.
7. Poon MA, O'Connell MJ, Moertel CG, *et al.* Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989, **7**, 1407–1418.
8. Buroker TR, O'Connell MJ, Wieand HS, *et al.* Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *J Clin Oncol* 1994, **12** (1), 14–20.
9. Glimelius B, Hoffman K, Graf W, *et al.* Cost-effectiveness of palliative chemotherapy in advanced gastrointestinal cancer. *Ann Oncol* 1995, **6**, 267–74.
10. Cunningham D, Zalcberg JR, Rath U, *et al.* 'Tomudex' (ZD1694), a new and effective therapy for advanced colorectal cancer has a significantly lower incidence of severe mucositis and leucopenia than standard therapy: results of an open, randomised multicentre trial of 'Tomudex' versus 5-fluorouracil (5-FU) and leucovorin (LV). *Eur J Cancer* 1995, **31A**, (12), 1945–1954.
11. Herrmann R. Systemic treatment of colorectal cancer. *Eur J Cancer* 1993, **29A**, 583–86.
12. MacDonald JS. Continuous low-dose infusion of fluorouracil: is the benefit worth the cost? *J Clin Oncol* 1989, **7**, 412–414.
13. *British National Formulary*. September edition. London, British Medical Association and Pharmaceutical Press, 1994.
14. Office of Health Economics. *Compendium of Health Statistics*, 9th edition, 1995.
15. Gardner MJ, Altman DG. Statistics with Confidence—Confidence Intervals and Statistical Guidelines. The Universities Press, Belfast, *British Medical Journal*, 1989, 72–73.

Acknowledgements—Zeneca Pharma UK provided the research grant to undertake this study and S-cubed Data Operations, Sheffield performed the statistical analysis.