EUROPEAN JOURNAL OF CANCER 43 (2007) 1687–1693

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the United Kingdom (UK)

S. Aballéa[a], A. Boler[b], A. Craig[c], H. Wasan[d,*]

[a]i3 Innovus, Uxbridge, Middlesex, United Kingdom
[b]Heron Evidence Development Ltd, Letchworth, Hertfordshire, United Kingdom
[c]Sanofi-aventis, Guildford, Surrey, United Kingdom
[d]Department of Cancer Medicine, Hammersmith Hospital, Imperial College of Science, Technology and Medicine, Du Cane Road, London W12 0HS, United Kingdom

ARTICLE INFO

Article history:
Received 27 November 2006
Received in revised form 23 April 2007
Accepted 2 May 2007
Available online 22 June 2007

Keywords:
Cost effectiveness
Oxaliplatin
Colon cancer
Chemotherapy
Adjuvant

ABSTRACT

The MOSAIC study was the first trial to show a statistically significant disease-free survival benefit for a treatment regimen for stage III colon cancer in the adjuvant setting. At 4 years, there was a 25% reduction in the risk of disease recurrence in these patients for the combination of oxaliplatin/5-FU/FA compared with 5-FU/FA alone ($p = 0.002$).

This analysis evaluates the long-term cost effectiveness of oxaliplatin given in combination with 5-FU/FA from the perspective of the NHS in the United Kingdom (UK). The cost per quality-adjusted life-year gained over a lifetime was calculated using patient level data from the MOSAIC trial. Trial data were available for a median of 4 years of follow-up, these data were then extrapolated to a lifetime horizon.

The estimated incremental lifetime cost per quality-adjusted life-year of oxaliplatin/5-FU/FA compared with 5-FU/FA alone in patients with stage III postoperative colon cancer is £4805. This compares favourably with other accepted interventions in oncology.

1. Introduction

In 2003, there were 21,600 new cases on colon cancer diagnosed in the United Kingdom (UK).[1–4] Approximately a quarter of all these cases are classified as stage III at initial presentation. After complete surgical resection, patients with the stage III colon cancer have a 50–60% chance of developing recurrent disease.[5]

Over the last 15 years 5-FU based adjuvant therapy has become the mainstay of treatment for patients with stage III colon cancer. Pooled data from seven randomised controlled trials in patients with stage II or III colon cancer suggest that 5-FU/FA regimens increase disease-free survival at 5 years from 55% to 67% and overall survival from 64% to 71% when compared to surgical resection alone.[6]

In September 2004, the European Medicines Evaluation Agency (EMEA) approved combination therapy of oxaliplatin with 5-FU/FA (5-fluorouracil/folinic acid) for the adjuvant treatment of stage III colon cancer. Approval was based on the results of the large, multicentre, international MOSAIC study, which reported a 25% reduction in the risk of disease recurrence in stage III patients for the combination of oxaliplatin and 5-FU/FA in the de Gramont regimen compared with de Gramont 5-FU/FA alone.[7,8] Since approval of this combination regime, a second study, NSABP C-07, validates the MOSAIC trial by reporting similar results with oxaliplatin given with a bolus regimen of 5-FU/FA.[9]

The increasing incidence of cancer, the increasing availability of new oncology treatments and technology appraisal programmes such as those initiated by the National

* *Corresponding author:* Tel.: +44 (0) 208 383 3057; fax: +44 (0) 208 383 3054.
E-mail address: wasan@cancer.org.uk (H. Wasan).
0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.05.001

Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC) and the All Wales Medicine Strategy Group (AWMSG) have resulted in a clear need for comprehensive economic evidence for new treatments within the UK.

In this paper, we present a cost effectiveness and cost utility analysis comparing oxaliplatin in combination with infusional 5-FU/FA to infusional 5-FU/FA alone in patients with stage III colon cancer from the perspective of the NHS in the UK. The evaluation uses 4-year follow-up patient level data from the MOSAIC trial, which has then been extrapolated to a lifetime horizon.

2. Patients and methods

2.1. Study design

Clinical results from the MOSAIC trial with a 3-year follow-up have been reported previously.[7] The MOSAIC study was an international, multicentre, randomised prospective trial of 2246 participants, 60% who had stage III colon cancer and the remainder with stage II. The primary end-point of the MOSAIC trial was the proportion of patients who, 3 years after randomisation, were alive and free of colon cancer disease. Disease-free survival (DFS) was defined as the time from randomisation to relapse or death, whichever occurred first; this outcome is accepted as a valid clinical end-point.[10] A secondary end-point was overall survival (OS): that is, the proportion of patients who were alive at a particular point in time but not necessarily free of colon cancer.

Our analysis required assumptions relating to the probabilities of survival and disease recurrence following diagnosis of stage III cancer. We assumed that the first 4 years' survival of such patients matches the experience of the participants of the MOSAIC trial in the first 4 years following randomisation; that survival in the 5th year could be extrapolated from the first four using Weibull distributions; and that survival in subsequent years matched the general mortality of the UK as observed in standard life tables.[11] This final assumption requires that there are no recurrences of colon cancer beyond 5 years from diagnosis. The lifetime analyses were curtailed after 50 years. Survival from the 4th to 5th year was extrapolated, as the trial data were not mature.

For our base case we used a lifetime analysis, reflecting the long-term outcomes associated with adjuvant chemotherapy in patients with stage III colon cancer. The quality-adjusted life-year (QALY) was the primary outcome for this analysis. Disease-free years (DFY) and life years gained (LY) were also calculated in the analysis. We used the recommended UK treasury rate of 3.5% per annum to discount flows of costs and health effects to present values.

Utilities were not collected in the MOSAIC trial and were sourced from the literature for this study.[12] Resource utilisation data were derived from the MOSAIC trial and were supplemented with data from the literature, and validated by UK clinical experts. Unit costs were sourced from the literature. The perspective considered was direct costs to the NHS. Direct costs included the cost of chemotherapy, outpatient visits, laboratory tests, adverse events and surgery.

2.2. Study population

The inclusion criteria for patients in the MOSAIC trial have been published previously.[3] In summary, patients were aged between 18 and 75 years and had undergone complete surgical resection of histologically proven stage II (T3 or T4, N0, M0) or stage III (any T, N1 or N2, M0) colon cancer as defined by the presence of the inferior pole of the tumour above the peritoneal reflection (at least 15 cm from the anal margin).

For our base-case analysis only patients with stage III colon cancer have been considered, reflecting current treatment practice in the UK.

2.3. Treatment regimens

Treatment commenced no later than 7 weeks post-surgery. Patients were randomised to the following treatment groups (Fig. 1):

- *5-FU/FA group*: 2-h infusion of 200 mg/m^2 FA followed by a 400 mg/m^2 bolus of 5-FU day 1 followed by a 22-h protracted infusion of 600 mg/m^2 5-FU days 1–2, every 14 days for 12 cycles.
- *Oxaliplatin/5-FU/FA group*: 2-h infusion of 85 mg/m^2 oxaliplatin simultaneously with 200 mg/m^2 FA followed by a 400 mg/m^2 bolus of 5-FU day 1 followed by a 22-h protracted infusion of 600 mg/m^2 5-FU days 1–2, every 14 days for 12 cycles.

2.4. Effectiveness assessment

We chose the QALY as our primary measurement of effectiveness as this incorporates the health related quality of life (HRQoL) of the patient as well as overall survival. In addition, this universal outcome permits comparison with other economic evaluations. Utility is valued on an index where 1 represents perfect health and 0 represents death.

2.4.1. Utility

There are limited quality of life data available for the different health states in colon cancer and none specific to the adjuvant setting at the time of analysis. We based our utility estimates on a study by Ramsey and colleagues[12] who administered the health utility index 3 (HUI-3) questionnaire to 173 survivors of colorectal cancer. Although the authors of this study did not specifically provide values for patients with and without relapse, they showed that the average HUI scores were 0.85 for survivors versus 0.65 for patients in their last year of life. The latter value was used as a proxy for the utility in patients with relapse and so we assumed that relapses were associated with a disutility of 0.2.

As the risk of relapse is small after 5 years, HRQoL for disease-free survivors is considered to be the same as for the general population. A weighted utility average of EQ-5D tariffs from the 1996 Health Survey for England[13] was calculated for each year of follow-up using the estimated distribution by age and gender for patients alive and free of disease at the beginning of the year.

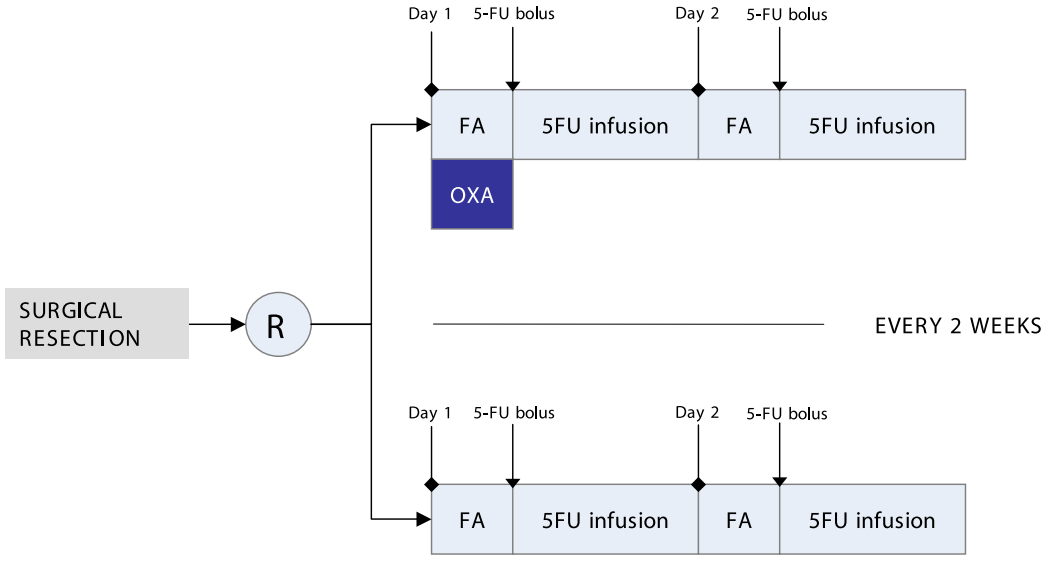

Fig. 1 – Randomisation of treatment in the MOSAIC study.

As chemotherapy-related toxicities have a negative impact on HRQoL, we included a series of utility decrements associated with these. Due to the lack of utility data in colon cancer relating to these toxicities, we used values from the literature for chemotherapy to treat other cancers as a proxy.[14–16]

2.5. *Economic assessment*

Where possible we inferred resource use from the case report forms from the MOSAIC trial. Where we could not infer resource use from the MOSAIC trial data, we made estimates based on external sources (literature and expert opinion).

The following categories of resource use were included in the analysis:

- study chemotherapy;
- 'replacement chemotherapy', for patients who discontinued the study chemotherapy regimen due to toxicities;
- treatment associated with non-serious toxicities;
- serious adverse events;
- treatment for disease monitoring during chemotherapy and afterwards;
- treatment for relapses.

Costs were for the year 2003. National reference costs were used for physician consultations, imaging procedures, post-treatment procedures and surgical interventions for relapses.[17] The costs of various laboratory tests came from a personal communication from Dr. Linda Wilson (Freeman Laboratories, Newcastle). Drug costs were obtained from the BNF.[18]

2.6. *Statistical methods*

Statistical analysis was performed in SAS 8.2. At the time of our analysis, data from the MOSAIC trial were available for a median follow-up of 44.2 months. There were sufficient data to calculate DFS empirically for up to 4 years, using the Kaplan–Meier method. A Weibull model was used to extrapolate DFS from 4 to 5 years, and UK life tables for extrapolating DFS beyond 5 years.

A parametric survival model was used after 4 years because the data in the MOSAIC trial were sparse after this point. There was no a priori justification for any particular distribution so various models were tested, including Weibull, exponential, loglogistic, lognormal and generalised gamma. Probabilities of DFS from the Weibull model were shown to fit Kaplan–Meier values beyond 4 years. This model is also relatively simple and has the reasonable property of monotonically changing underlying hazard with time, and so was adopted for our purposes.[19]

3. Results

The clinical results showed a 25% reduction in the risk of disease recurrence in stage III patients for the combination of oxaliplatin with 5-FU/FA compared with 5-FU/FA alone at 4 years ($p = 0.002$). Neutropenia, diarrhoea and vomiting were the most frequent grade 3 or 4 adverse events in the oxaliplatin/5-FU/FA arm.[7]

3.1. *Disease-free survival and overall survival*

DFS and OS modelled over a lifetime horizon are shown in Fig. 2. Over the course of the initial 4-year follow-up there were 194 occurrences of relapse or death in patients treated with a combination of oxaliplatin and 5-FU/FA compared with 245 of these events in patients treated with 5-FU/FA. The analysis of DFS with the Kaplan–Meier approach predicted that 69.1% of oxaliplatin treated patients would be disease-free at 4 years compared with 60.7% in the 5-FU/FA arm (log rank test: $p = 0.002$). When DFS was extrapolated to 5 years, a gain of 0.084 DFY (0.074 with discounting) in oxaliplatin treated patients is predicted between the 4th and 5th year of follow-up. Beyond 5 years, the lifetime analysis estimated that the average gain was 1.78 DFYs per patient (1.05 DFY with discounting).

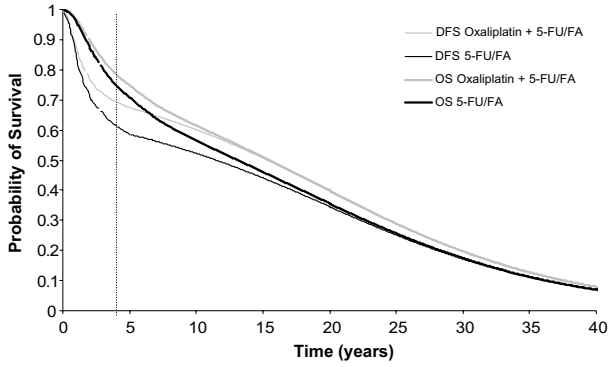

Fig. 2 – DFS and overall survival curves over 40 years[e].

There were no significant differences between treatment arms in terms of overall survival at the 4-year trial follow-up. Patients in the MOSAIC study are to be followed up for a minimum of 6 years for the final overall survival analysis, as 40% of patients with disease recurrence were still alive at 4 years.[8] Our analysis predicts a survival gain of 1.29 years (0.71 years with discounting) associated with treatment with the combined oxaliplatin and 5-FU/FA regimen between 4 years and 50 years.

3.2. *Effectiveness*

Table 1 reports numbers of DFYs, life years (LYs) and QALYs gained per patient during the 4-year trial follow-up. We calculated a total gain of 0.06 QALYs over the 4 years for patients receiving oxaliplatin and 5-FU/FA compared with 5-FU/FA alone.

Patients treated with oxaliplatin plus 5-FU/FA when compared with 5-FU/FA alone were predicted to experience 1.25 additional years of DFS, 0.77 LY and 0.68 QALYs beyond 4 years of follow-up (Table 2).

3.3. *Costs*

3.3.1. *Cost of treatment during initial 4-year follow-up*

Direct costs associated with adjuvant treatment of colon cancer were calculated for the first 4 years of follow-up. The major cost component was the study chemotherapy. It accounted for approximately 69% of the total cost in the oxaliplatin/5-FU/FA group and 57% in the 5-FU/FA group, excluding costs after relapse. The addition of oxaliplatin to 5-FU/FA increased the cost of chemotherapy by £3923. The next main component was the cost of relapses, which was lower by £1026 in the oxaliplatin/5-FU/FA group than in the 5-FU/FA group. Total costs within 4 years of resection were greater by £3407 in the oxaliplatin and 5-FU/FA group, than in the 5-FU/FA group.

[e] The vertical line at 4 years represents the frontier between parts of the curves obtained with the Kaplan–Meier method (within trial analysis) and parts based on extrapolation methods).

Table 1 – Effectiveness outcomes for the 4-year follow-up of the trial, discounted by 3.5%

	Oxaliplatin + 5-FU/FA	5-FU/FA	Difference
DFYs	3.101	2.903	0.198
LYs	3.439	3.384	0.055
QALYs before relapse	2.635	2.467	0.168
QALYs after relapse	0.220	0.313	−0.093
QALYs lost due to adverse events	−0.019	−0.003	−0.016
Total QALYs	2.837	2.777	0.060

Table 2 – Effectiveness outcomes predicted beyond 4 years, discounted by 3.5%

	Oxaliplatin + 5-FU/FA	5-FU/FA	Difference
DFYs	11.153	9.906	1.247
LYs	11.739	10.971	0.768
QALYs	9.257	8.577	0.680

3.3.2. *Treatment costs beyond 4 years*

The estimated average monthly cost of follow-up (follow-up consultations, imaging procedures, laboratory tests and carcinoembryonic antigen tests) was the same in both treatment groups in years 3 and 4 at £32 and £35, respectively. We predicted that the average monthly cost of follow-up during year 5 would decrease and estimated a monthly cost of £23, and for subsequent years, the cost of monitoring cancer survivors was estimated to be £6 per month.

For patients who relapsed beyond the 48-month trial analysis, we estimated the unit cost of treating a relapse to be £10,725, regardless of treatment group. This estimate was based on a weighted average of the costs of local recurrence, liver or lung metastases or other disseminated disease. For these patients we estimated the cost of follow-up subsequent to relapse to be £1962 over a lifetime, based on previous follow-up costs and survival after relapse estimated from the Weibull model. Adding this to the cost of treating a relapse, we obtained a total unit cost per relapse of £12,687.

Table 3 – Costs beyond 4 years, discounted at 3.5% per annum

	Oxaliplatin/ 5-FU/FA (£)	5-FU/FA (£)	Incremental costs (£)
Cost of relapses occurring in year 5 (treatment + follow-up)	204	300	−96
Cost of follow-up for patients relapsing during years 1–4	408	547	−139
Cost of follow-up for patients with no relapse	740	644	95
Total	1352	1491	−140

Costs accrued beyond 4 years are reported in Table 3. Based on DFS curves extrapolated from 4 to 5 years, fewer relapses occurred in the oxaliplatin plus 5-FU/FA group than in the 5-FU/FA group during year five. Therefore, costs of relapses were lower in the oxaliplatin plus 5-FU/FA group. The incremental cost predicted beyond 4 years (–£140) is small compared to the incremental cost in the first 4 years of treatment (£3407).

Table 4 – ICERs and associated confidence intervals for each analysis for the stage III subgroup

Analysis time-horizon	Outcome	ICER (£)	95% LCL	95% UCL
50 years	DFY	2620	Dominant	8108
	LY	4254	Dominant	Dominated
	QALY	4805	Dominant	45,658
4 years	DFY	17,206	–	–
	LY	61,942	–	–
	QALY	56,780	–	–

Upper and lower confidence intervals were derived from the bootstrap analysis. LCL, lower confidence level; UCL, upper confidence level; Dominant, Oxaliplatin plus 5-FU/FA is more effective and less costly than 5-FU/FA alone; Dominated, 5-FU/FA alone is more effective and less costly than oxaliplatin plus 5-FU/FA.

3.4. *Incremental cost-effectiveness ratio*

Adjuvant chemotherapy with oxaliplatin plus 5-FU/FA is more effective than the 5-FU/FA regimen, but is also more costly. It costs £4805 per QALY gained over 50 years. Table 4 reports the incremental cost-effectiveness ratios (ICERs) for the primary and secondary outcomes of interest for both the lifetime (50 years) analysis and the initial 4-year trial follow-up.

3.5. *Sensitivity analysis*

We carried out a series of sensitivity analyses to explore the effect of conceivable changes in some of our assumptions and data inputs.[19] We ran 11 different sensitivity analyses and scenarios. Finally, we used the bootstrap method to assess the impact of uncertainty surrounding efficacy data from the MOSAIC study. The bootstrap method is a simulation-based technique involving repeated sampling of patient level data.[11]

3.5.1. *Sensitivity analyses and scenarios*

The results from 11 deterministic analyses are reported in Table 5. Ten of these produced substantially similar results,

Table 5 – Sensitivity and scenario analyses undertaken

Code	Description	ICER cost per QALY (£)	Notes
Base case	Oxaliplatin/5-FU/FA versus 5-FU/FA	4805	Stage III patients, lifetime
(a)	Oxaliplatin/5-FU/FA versus 5-FU/FA		Benefits and costs limited to short term
	4-year follow-up	56,780	
	5-year follow-up	35,369	
(b)	NSABP C-07 treatment scenario Oxaliplatin + Mayo Clinic Regimen (bolus) versus Mayo Clinic Regimen; lifetime model	6244	Cost of 5-FU/FA replaced by bolus regimen used in X-ACT study
(c)	Oxaliplatin + capecitabine versus capecitabine; lifetime model	6214	Cost of 5-FU/FA replaced by capecitabine
(d)	Disutility associated with toxicity	+0.20: 4869 –0.20: 4728	Alter utility values associated with adverse events by +20% and –20%
(e)	Discount rates	0%: 2810 6%: 6510	Discount rates for benefits and costs were altered to 0% or 6%
(f)	Disease monitoring costs	4801	Include all ultrasounds in the analysis (in the base-case analysis, ultrasounds performed within 9 months of the last included ultrasound were excluded)
(g)	Long-term follow-up	4776	Assume one colonoscopy (cost £165) every 4 years from year 6 onwards (base-case follow-up costs £72 per year)
(h)	Disutility associated with relapse	0.0: 5528 0.4: 4189	Utility associated with relapse was altered by –0.0 or –0.4 (base-case assumption was –0.20)
(i)	Disutility associated with hospitalisation	0%: 4798 100%: 4805	Alter utility values associated with hospitalisation to 0% decrement and 100% decrement (base-case assumption 50% decrement)
(j)	Higher cost of treating relapse Assuming that patients are treated as recommended by recent NICE Guidance (No. 33)	4106	Assume that all relapsing patients receive combinational chemotherapy in the advanced setting
(k)	Stage II and stage III patients	7210	Add stage II patients from MOSAIC to base-case analysis

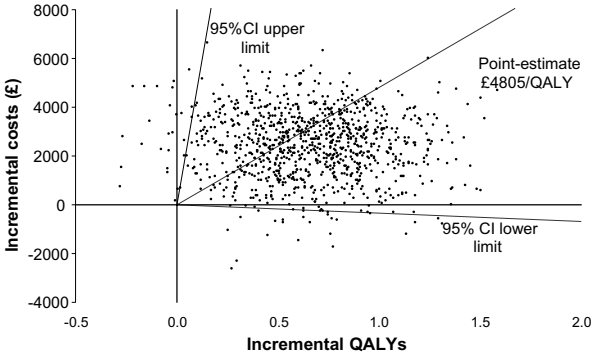

Fig. 3 – Results of bootstrap analysis on the cost-effectiveness plane, for the analysis over 50-year time-horizon.

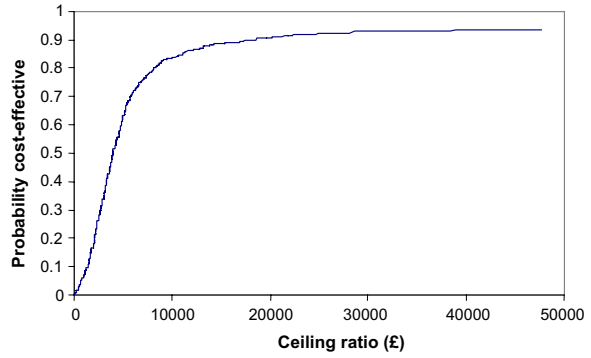

Fig. 4 – Cost-effectiveness acceptability curve for cost per QALY, based on the lifetime analysis.

resulting in a cost per QALY of up to £7210. The remaining sensitivity analysis considering the 4-year trial follow-up or 5 years as alternative time-horizons resulted in a cost per QALY £56,780 or £35,369, respectively.

3.5.2. *Bootstrap analysis*

The results from the bootstrap analysis showed that the variability of the results, especially health benefits, was large (Fig. 3). Over the 50-year time-horizon, treatment with oxaliplatin plus 5-FU/FA was both more effective and less costly than 5-FU/FA alone in more than 2.5% of replications.

The cost-effectiveness acceptability curve (Fig. 4) shows that the probability of oxaliplatin plus 5-FU/FA being cost-effective compared to 5-FU/FA in stage III patients is 94.7% for a cost-effectiveness threshold of £20,000 per QALY gained and 96.7% for a threshold of £30,000 per QALY gained.

4. Discussion

The estimated incremental lifetime cost per QALY of oxaliplatin plus 5-FU/FA compared with 5-FU/FA alone in patients with stage III postoperative colon cancer is £4805. This figure is supported by two other economic evaluations that have been conducted using the MOSAIC dataset and utilising a similar methodology. A US study reported a cost per QALY gained of US$22,800 after discounting costs and outcomes at 3% per annum,[19] while a German study reported a cost per QALY gained of €10,200 after discounting at 5% for costs and outcomes.[20] In this same disease setting, the estimated cost per life year gained for capecitabine compared to 5-FU/FA was £3899 (after discounting at 3.5% for costs and outcomes).[21] In addition to these evaluations, the calculated cost per QALY of £4805 compares favourably with other treatment accepted by NICE in the UK.[22]

It should be noted that there are limitations with any economic analysis conducted using clinical trial data. The MOSAIC trial was not designed for the purpose of an economic analysis. Nevertheless, a large part of the resource utilisation could be inferred from the clinical data reported in the Case Report Forms. Estimating such resource utilisation can lead to an overestimate of resource use due to protocol-driven patient management; however, this was addressed through consultation with UK clinicians to ensure that our assumptions reflected current NHS practice.

Another possible limitation of this particular study might be the actual use of intravenous bolus 5-FU/FA within the UK rather than the infusional regimen used within the MOSAIC study. The recent publication of the NSABP C-07 study has however shown similar efficacy results regardless of the route of administration of 5-FU/FA. Using the data from this new study, a cost per QALY of £6244 was estimated for oxaliplatin in combination with a bolus 5-FU/FA regimen, suggesting that this regimen is also cost-effective in the UK.

Finally, the availability of relevant utility values for the calculation of QALYs was limited. We believe that the current economic evaluation used the best available values and the results of the sensitivity analysis suggest that the impact of this parameter on long-term results is modest. Nevertheless, this is an area where future research would be beneficial.

In conclusion, the analysis presented here demonstrates that adding oxaliplatin to 5-FU/FA in the adjuvant setting in stage III colon cancer patients represents a cost effective use of NHS resources. Ongoing trials of oxaliplatin are investigating its use in combination with the oral form of 5-FU/FA (capecitabine) in the adjuvant setting. Safety data published so far have shown that this combination is as safe as intravenous 5-FU/FA. If the effectiveness is established, this oxaliplatin combination has the potential to reduce the number of hospital visits by more than 60%,[23] which may have a further positive impact on the cost effectiveness of oxaliplatin in the adjuvant setting.

Conflict of interest statement

The study was supported by a research grant from Sanofi-aventis.

Acknowledgement

The original economic analysis was carried out by i3 Innovus.

REFERENCES

1. ISD Scotland National Statistics. Cancer incidence and mortality by site/type of cancer, sex and year of diagnosis/ registration of death: 1994–2003; 2004. <http:// wwwisdscotlandorg/isd/files/ cancer_incandmort_summaryxls> [cited 2006 Jun].
2. Northern Ireland Cancer Registry. Cancer incidence statistics; 2005. <http://wwwqubacuk/nicr/statspages/newtables/Colon-incidhtml>.
3. Welsh Cancer Intelligence and Surveillance Unit. Cancer incidence 2003 report; 2004. <http://wwwwalesnhsuk/sites3/ docmetadatacfm?orgid=242&id=49488> [cited 2006 Jun].
4. National Statistics. Cancer statistics registrations: registrations of cancer diagnosed in 2003, England. Series MB1 No. 34. Office for National Statistics, London; 2006.
5. CancerStats monograph 2004 – cancer incidence, survival and mortality in the UK and EU. Bowel cancer statistics. Cancer Research UK; 2004.
6. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol* 2004;**22**:1797–806.
7. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *New Engl J Med* 2004;**350**:2343–51.
8. De GA, Boni C, Navarro M, et al. Oxaliplatin/5-FU/LV in the adjuvant treatment of stage II and stage III colon cancer: efficacy results with a median follow-up of 4 years. In: *Proceedings ASCO-GI symposium*; 2005. p. 167.
9. Wolmark N, Wiehand H, Kuebler JP. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: results of NSABP Protocol C-07. In: *Proceedings of the ASCO Symposium*; 2005 [Abs. LBA3500].
10. US Food and Drug Administration. Colorectal cancer endpoints workshop summary; 2004 November. <http:// wwwfdagov/cder/drug/cancer_endpoints/ colonEndpointsSummaryhtm> [cited 2006 Jun].
11. Armitage P, Berry G, Matthews JNS. *Statistical methods in medical research*. 4th ed. Oxford: Blackwell Science; 2002.
12. Ramsey SD, Andersen MR, Etzioni R, et al. Quality of life in survivors of colorectal carcinoma. *Cancer* 2000;**88**:1294–303.
13. Health Survey for England 1996. The Stationery Office, London; 1996.
14. Cook J, Richardson J, Street A. A cost utility analysis of treatment options for gallstone disease: methodological issues and results. *Health Econ* 1994;**3**:157–68.
15. Grunberg SM, Srivastava A, Grunberg KJ, Weeks J. Intensity of chemotherapy-induced emesis and overall survival as determinants of a global utility score. *Support Care Cancer* 2002;**10**:624–9.
16. Launois R, Reboul-Marty J, Henry B, Bonneterre J. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. *Pharmacoeconomics* 1996;**10**:504–21.
17. Department of Health. NHS reference costs 2003. In: National Health Service; ed. 2004.
18. Joint Formulary Committee. *British national formulary*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2004.
19. Aballea S, Chancellor JV, Raikou M, et al. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/ leucovorin in adjuvant treatment of stage III colon cancer in the US. *Cancer* 2007;**109**:1082–9.
20. Aballea S, Chancellor J, Raikou M, et al. Cost-effectiveness analysis of oxaliplatin/5-FU/LV in adjuvant treatment of stage III colon cancer in the UK and Germany. *Value in Health*; 2005 [Abs. CN1].
21. Cassidy J, Douillard JY, Twelves C, et al. Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in Dukes' C colon cancer: the X-ACT trial. *Br J Cancer* 2006;**94**:1122–9.
22. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004;**13**:437–52.
23. Schmoll HJ, Tabernero J, Nowacki M. Initial safety findings from XeloxA: a randomised phase III trial of capecitabine plus oxaliplatin vs. bolus 5-FU/LV as adjuvant therapy for patients (pts) with stage III colon cancer. In: *Proceedings of the 13th European Cancer Conference, Paris*; 2005 [Abs. 617].