Scottish Medicines Consortium

oxaliplatin 50mg, 100mg powder for intravenous infusion (Eloxatin®) No. (211/05)

Sanofi-aventis

New indication: adjuvant treatment of stage III (Dukes' C) colon cancer

4 October 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Oxaliplatin (Eloxatin®) is accepted for use within NHS Scotland, in combination with fluorouracil and folinic acid, for the adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of the primary tumour.

Addition of oxaliplatin to a standard regimen of fluorouracil and folinic acid increased disease-free survival in patients who had undergone complete resection of stage III (Dukes' C) colon cancer. An economic evaluation demonstrated that this is a cost-effective treatment option for these patients. Treatment with oxaliplatin (Eloxatin) should be under the supervision of an oncologist.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

oxaliplatin 50mg, 100mg power for intravenous infusion (Eloxatin®)

Indication

In combination with 5-fluorouracil and folinic acid, for the adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour.

Dosing information

85mg/m^2 by intravenous infusion every two weeks for 6 months.

UK launch date

September 2004

Comparator medications

Fluorouracil is licensed for treatment of colon cancer and is usually given in combination with folinic acid. Scottish Intercollegiate Guidelines Network (SIGN) guidelines, published in 2003, recommended bolus fluorouracil and low-dose folinic acid administered over five days every four weeks for six months (e.g. Mayo regimen) for the adjuvant treatment of Dukes' stage C colon cancer. They also note that a schedule of fluorouracil and folinic acid once weekly for 30 weeks may be an acceptable treatment option for certain patients. National Institute of Health and Clinical Excellence (NICE) guidelines, published in 2004, also recommend fluorouracil and folinic acid for adjuvant treatment of Dukes' stage C colon cancer. When SIGN guidelines were published data were awaited on use of the de Gramont regimen, which comprises twice monthly folinic acid and fluorouracil given by bolus and infusion over two days, in this indication. A trial published subsequently found that response rates with this regimen were similar to those with a monthly bolus regimen, which is similar to the Mayo regimen, in patients with resected Dukes' stage B2 or C colon cancer.

Capecitabine is also licensed post-surgery for the adjuvant treatment of Dukes' stage C colon cancer. When SIGN and NICE guidelines were published capeticabine was not licensed for this indication and the guidelines do not contain advice on it. The Scottish Medicines Consortium (SMC) issued advice in August 2005 that capecitabine is accepted for use within NHS Scotland for this indication. Scottish oncologists have advised that they expect capecitabine to be used in place of fluorouracil and folinic acid regimens for almost all patients with resected Dukes' stage C colon cancer.

Cost of relevant comparators

Regimen	Doses per cycle	Cost per cycle (£)	Cost per course (£)
Oxaliplatin Fluorouracil Folinic acid	**85mg/m^2 iv infusion 2-hour on D1 400mg/m^2 bolus, 600mg/m^2 iv infusion 22-hour D1, D2 200mg/m^2 iv infusion 2-hour on D1, D2**	**722[b]**	**8661[g]**
Fluorouracil[1] Folinic acid	400mg/m^2 bolus, 600mg/m^2 iv infusion 22-hour D1, D2 200mg/m^2 iv infusion 2-hour on D1, D2	227[b]	2721[g]
Capecitabine	1250mg/m^2 orally twice daily on D1 to D14	296[c]	2369[f]
Fluorouracil[3] Folinic acid	370mg/m^2 bolus on D1 50mg/m^2 bolus on D1	23[a]	704[h]
Fluorouracil[2] Folinic acid	425mg/m^2 bolus on D1 to D5 20mg/m^2 bolus on D1 to D5	93[d]	560[e]

Costs based on a body surface area of 1.7m^2 and prices in British National Formulary 49th edition; D = day of cycle; 1, 2, 3 = De Gramont, Mayo and QUASAR-once-a-week regimens, respectively; a, b, c, d, = 7-, 14-, 21- and 28-day cycles, respectively; e, f, g, h = 6-, 8-, 12- and 30-cycle courses, respectively

Summary of evidence on comparative efficacy

Oxaliplatin is a platinum-based antineoplastic drug that interacts with DNA to form inter- and intra-strand crosslinks, which disrupt DNA synthesis, leading to antitumour effects, although the mechanism by which it produces these effects is not completely elucidated.

An open-label trial recruited 2246 adults, aged 18-75 years, who had undergone complete surgical resection of histologically proven stage II (T3 or T4, N0, M0) or stage III (T1, N1 or N2, M0) colon cancer, and had Karnofsky performance score ≥60 and carcinoembryonic antigen (CEA) levels <10ng/ml, but had not received chemotherapy, immunotherapy or radiotherapy. They were randomised within seven weeks of surgery, with stratification by tumour-node-metastasis (TNM) stage, treatment centre and presence of bowel obstruction or tumour perforation, to folinic acid 200mg/m^2 by 2-hour intravenous (iv) infusion followed by fluorouracil 400mg/m^2 by iv bolus then 600mg/m^2 by 22-hour iv infusion on day 1 and 2 of a 14-day cycle (de Gramont regimen) or to this regimen plus oxaliplatin 85mg/m^2 by 2-hour infusion concurrently with folinic acid on day 1. A course of treatment comprised 12 cycles. The primary endpoint was disease-free survival at three years, with second colorectal cancers considered relapses and noncolorectal cancers disregarded, in the intention-to-treat (ITT) population, analysed by two-sided log-rank test stratified by baseline disease stage. This was significantly greater with oxaliplatin plus fluorouracil and folinic acid compared to fluorouracil and folinic acid alone: 78.7% vs. 73.3%, with a hazard ratio (95% confidence intervals (CI)) of 0.76, (0.64, 0.89). Pre-specified subgroup analysis of three-year disease-free survival in the 40% and 60% of patients who had stage II and III disease, respectively, found that this was significantly greater with oxaliplatin plus fluorouracil and folinic acid compared to fluorouracil and folinic acid alone in patients with stage III disease: 72.8% vs. 65.8%; hazard ratio (95% CI) 0.75 (0.62, 0.90). There was no significant difference between the respective regimens for this outcome in patients with stage II disease: 87.4% and 84; hazard ratio: 0.79 (0.57, 1.09). Oxaliplatin is only licensed for adjuvant treatment of patients with stage III disease.

Analyses of further follow-up data from this trial have confirmed these results. In the most recent analyses at 56.2 months, when all patients had been followed-up for at least four years, disease-free survival rates with oxaliplatin in combination with fluorouracil and folinic acid and with fluorouracil and folinic acid alone in the ITT population were 75.2% and 69.3%, respectively. Probabilities of disease-free survival from Cox proportional-hazard models, with survival curves drawn according to Kaplan-Meier methods were 76.4% and 69.8%, with a hazard ratio (95% CI) of 0.77 (0.65, 0.90) and for patients with stage III disease the hazard ratio (95% CI) was 0.75 (0.62, 0.89).

There were no significant differences between treatment groups in overall survival rates in both the ITT population and the subgroup of patients with stage III disease in analyses conducted at median follow-ups of 37.9, 44.2, 48.6 and 56.2 months. Increases in survival with oxaliplatin in combination with fluorouracil and folinic acid compared to fluorouracil and folinic acid in the ITT population were 1.2%, 1.3%, 1.6% and 1.3% in the respective analyses and in patients with stage III disease were 2.2%, 2.3%, 2.6% and 3.2%, respectively. Analyses of survival data from further follow-ups are awaited.

An open-label trial recruited 2492 patients who had undergone complete surgical resection of stage II or III colon cancer (T3, 4; N0, 1, 2; M0), and had Eastern Co-operative Oncology Group (ECOG) performance status 0-2, but had not received chemotherapy or radiotherapy. They were randomised within six weeks of surgery to folinic acid 500mg/m^2 by iv 2-hour infusion followed one hour later by fluorouracil 500mg/m^2 by iv bolus once a week for the first 6 weeks of an 8-week cycle (Roswell Park regimen) or to this regimen plus oxaliplatin 85mg/m^2 by iv 2-hour infusion on the first day of weeks one, three and five. A course of treatment comprised 3 cycles. The primary endpoint was disease-free survival at three years, with relapses including recurrence of colorectal tumour and second primary. After median follow-up of 34 months rates of disease-free survival in the ITT population were 72.5% and 77.3% with the respective regimens. Probability of disease-free survival at 3 years was significantly greater with oxaliplatin in combination with fluorouracil and folinic acid compared to fluorouracil and folinic acid alone: 76.5% vs. 71.6%, with a hazard ratio (95% CI) of 0.79 (0.67, 0.93).

Summary of evidence on comparative safety

The most common adverse effect associated with oxaliplatin is peripheral neuropathy, which was experienced by almost all patients during treatment with oxaliplatin in the first trial described previously, with approximately 50% of patients having a mild neuropathy and 12.4% having a neuropathy of at least moderate severity that interfered with function. The majority of these resolved when treatment was completed, with 20%, 3.4% and 0.5% of patients having grade 1, 2 and 3 neuropathy, respectively, after 18 months follow-up.

The addition of oxaliplatin to fluorouracil and folinic acid (de Gramont regimen), in the first trial described previously, significantly increased the incidences of haematological and gastro-intestinal adverse effects. Rates of neutropenia (79% vs. 40%), thrombocythaemia (77% vs. 19%), anaemia (76% vs. 67%), neutropenia with infection or fever (1.8% vs. 0.2%), nausea (74% vs. 61%), vomiting (47% vs. 24%) and diarrhoea (56% vs. 48%) were significantly greater with oxaliplatin plus fluorouracil and folinic acid than with fluorouracil and folinic acid alone. With the exception of anaemia, rates of these adverse effects, which were of grade 3 or 4 severity, were also significantly greater with the oxaliplatin regimen.

Summary of clinical effectiveness issues

In the first trial described previously 35% and 65% of patients were aged 65-75 years and less than 65 years, respectively. In these respective subgroups the hazard ratios (95% CI) for disease-free survival with oxaliplatin plus fluorouracil and folinic acid compared to fluorouracil and folinic acid were 0.95 (0.72, 1.26) and 0.68 (0.55, 0.84). Cancer registration data indicate that 75% and 42% of patients diagnosed with colon cancer in Scotland in 2001 were aged more than 65 and 75 years, respectively. Patients in the clinical trial were generally younger than the Scottish population who have colon cancer. The benefits with oxaliplatin in practice within Scotland may be different, possibly lower, than those observed in the clinical trial.

Scottish oncologists advise that capecitabine, which is administered orally, is likely to replace parenteral fluorouracil and folinic acid regimens for the adjuvant treatment of patients with Dukes' stage C colon cancer. There are no trials comparing oxaliplatin plus fluorouracil and folinic acid with oxaliplatin plus capecitabine, therefore relative efficacy and safety are unclear.

Summary of comparative health economic evidence

The submission included a cost-utility analysis comparing oxaliplatin in combination with the de Gramont fluorouracil and folinic acid regimen compared to the de Gramont regimen alone. The main data source was the first trial described previously with survival trends extrapolated over the lifetime of the patient sample. On this basis the cost per QALY at the end of follow-up in this trial was estimated to be £56k but over the lifetime of the patient sample it is estimated to be just below £5k.

In terms of its design the economic evaluation used an appropriate comparator, perspective and time horizon.

The clinical benefits were estimated in a plausible and transparent way, although the method used could have been subject to a sensitivity analysis. The calculation of QALYs used plausible methods and values, although the assumptions used slanted the estimates slightly against oxaliplatin.

The handling of resource use covered all the main cost headings, counted resource use in a plausible way and used appropriate sources to value the resources used.

The data were analysed in an acceptable way and the deterministic sensitivity analysis was helpful in establishing that, once the principle of extrapolation of trial findings is accepted, the results seem robust to changes in the other assumptions.

The economic case for the use of oxaliplatin has been demonstrated.

Budget impact

The manufacturer estimates that, including the impact on treatment of relapsed disease, the net NHS budget impact will be £327k in year 1 rising to £1.6M by year 5. The manufacturer has not estimated the drug budget impact separately but a reasonable proxy is to use the additional cost of oxaliplatin combination of £4,500 per patient before relapse. Using the manufacturer's assumed growth in patient numbers and market share would imply the drugs budget impact would be £338k in year 1 and £1.9M in year 5.

Guidelines and protocols

The March 2003 SIGN publication number 67 on the management of colorectal cancer notes that there is evidence showing absolute survival benefit of 4% to 13% from adjuvant chemotherapy for patients with Dukes' C colon cancer.

The May 2004 NICE guidance on cancer services: improving outcomes in colorectal cancers manual update notes that systemic chemotherapy should be offered to all patients who, after surgery for Dukes' stage C colon cancer, are fit enough to tolerate it and that this should be scheduled to begin within six weeks of surgery. The standard treatment has been a course of fluorouracil and folinic acid given iv over six months. The absolute increase in five-year survival rates achieved by fluorouracil and folinic acid is between 4% and 13%.

NICE is conducting technology appraisals of three drugs for adjuvant treatment of colorectal cancer and expects to issue advice for oxaliplatin and capecitabine in May 2006 and for irinotecan in June 2007.

Association of Coloproctology for Great Britain and Ireland guidelines for the management of colorectal cancer, published in 2001, recommend that patients with Dukes' C colon cancer should be considered for adjuvant chemotherapy.

Additional information

After review of a full submission SMC issued advice on 8th August 2005 that capecitabine is accepted for use within NHS Scotland for adjuvant treatment of patients following surgery for stage III (Dukes' C stage) colon cancer. Oral capecitabine appears to be at least as effective as standard IV 5-FU/FA chemotherapy with the convenience of oral administration. It should only be prescribed by oncologists. It is more expensive than IV chemotherapy regimens. However, its use may allow changes to service delivery that have individual patient or organisational benefits.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 September 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Andre T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; 350: 2343-51

Wolmark N, Wieand HS, Kuebler JP et al. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07. Abstract number LBA 3500 at the 2005 ASCO annual meeting

De Gramont A, 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. Abstract number 167 at the 2005 ASCO-GI Symposium

De Gramont A, Boni C, Navarro M, et a. 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. Abstract number 3501 at the 2005 ASCO annual meeting

Scottish Intercollegiate Guidelines Network (SIGN) publication number 67: management of colorectal cancer. March 2003. http://www.sign.ac.uk/pdf/sign67.pdf

National Institute of Clinical Excellence (NICE) guidance on cancer services: improving outcomes in colorectal cancers manual update. May 2004. http://www.nice.org.uk/pdf/CSGCCfullguidance.pdf