Scottish Medicines Consortium

Re-Submission

bevacizumab 100mg/4ml and 400mg/16ml solution for intravenous infusion (Avastin®) No. (221/05)

Roche

5 May 2006

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 re-submission

Bevacizumab (Avastin®) is not recommended for use within NHS Scotland in combination with intravenous fluorouracil/folinic acid or intravenous fluorouracil/folinic acid/irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Bevacizumab, in combination with standard regimens containing fluorouracil and folinic acid or fluorouracil, folinic acid and irinotecan, improved overall and disease-free survival times compared to these standard regimens. However, the economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

bevacizumab 100mg/4ml and 400mg/16ml solution for intravenous infusion (Avastin®)

Indication

In combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Dosing information

5mg/kg by intravenous infusion every 14 days. It is recommended that treatment continues until progression of the underlying disease.

UK launch date

14th March 2005

Comparator medications

The 2005 guidance from the National Institute for Health and Clinical Excellence (NICE) recommends irinotecan and oxaliplatin, within their licensed indications, as treatment options for people with advanced colorectal cancer. Irinotecan may be used in combination with fluorouracil and folinic acid as first-line therapy or irinotecan alone may be used in subsequent therapy. Oxaliplatin in combination with fluorouracil and folinic acid may be used as first-line or subsequent therapy. NICE guidance in 2003 recommended capecitabine and tegafur with uracil as first-line treatment options for people with metastatic colorectal cancer. Raltitrexed was not recommended for patients with advanced colorectal cancer, except in appropriately designed clinical studies.

Cost of relevant comparators

Bevacizumab is used in addition to standard chemotherapy and therefore increases overall drug acquisition costs. A dose of bevacizumab costs £728 and £924 for patients with body weights of 60kg and 80kg, respectively. Treatment is recommended to continue until progression of the underlying disease. In the clinical trials described below, the median time to disease progression with a bevacizumab-containing regimen was approximately 9 to 10 months. The costs of 10-months' treatment with bevacizumab are £14,560 and £18,488 for patients with body weights of 60kg and 80kg, respectively. Costs per cycle of the bevacizumab-containing regimens used in the clinical trials and other chemotherapy regimens for first-line treatment of metastatic colorectal cancer are detailed in the table.

Regimen	Doses per cycle (where D1 = Day 1)	Cycle length	Cost (£) per	
			cycle	6 mths*
Bevacizumab Fluorouracil/ Folinic acid Irinotecan	**5mg/kg iv infusion D1, 15 and 29 500mg/m^2 iv bolus D1, 8, 15 and 22 20mg/m^2 iv bolus D1, 8, 15 and 22 125mg/m^2 iv infusion D1, 8, 15 and 22**	**6 weeks**	**4113**	**16452**
Bevacizumab Fluorouracil/ Folinic acid	**5mg/kg iv infusion D1, 15, 29 and 43 500mg/m^2 iv infusion D1, 8, 15, 22, 29 and 36 500mg/m^2 iv infusion D1, 8, 15, 22, 29 and 36**	**8 weeks**	**5287**	**15861**
Fluorouracil/ Folinic acid Irinotecan[A]	500mg/m^2 iv bolus D1, 8, 15 and 22 20mg/m^2 iv bolus D1, 8, 15 and 22 125mg/m^2 iv infusion D1, 8, 15 and 22	6 weeks	1340	5360
Fluorouracil Folinic acid[B]	500mg/m^2 iv infusion D1, 8, 15, 22, 29 and 36 500mg/m^2 iv infusion D1, 8, 15, 22, 29 and 36	8 weeks	1590	4770
Tegafur/uracil Folinic acid	100mg/m^2/224mg/m^2 three times daily D1-28 30mg three times daily D1 to D28	5 weeks	1119	5595
Oxaliplatin Fluorouracil Folinic acid[E]	85mg/m^2 iv infusion D1 400mg/m^2 bolus, 600mg/m^2 iv infusion D1 and 2 200mg/m^2 iv infusion 2-hour D1 and 2	2 weeks	728	9464
Capecitabine	1250mg/m^2 orally twice daily on D1 to D14	3 weeks	317	2536
Fluorouracil Folinic acid[C]	400mg/m^2 bolus, 600mg/m^2 iv infusion D1 and 2 200mg/m^2 iv infusion 2-hour D1 and 2	2 weeks	233	3029
Fluorouracil Folinic acid[D]	425mg/m^2 bolus daily on D1 to D5 20mg/m^2 bolus daily on D1 to D5	4 weeks	94	564

Costs from 50th edition of the British National Formulary based on a patient with body weight of 80kg and body surface area of 1.8m^2; A = IFL, Saltz regimen; B = Roswell Park regimen; C = de Gramont regimen; D = Mayo regimen; E = FOLFOX4; * cost per 6 months is costs of complete cycles, which would be administered during a 26-week period.

Summary of evidence on comparative efficacy

Bevacizumab is a recombinant humanised monoclonal IgG1 antibody that binds to human vascular endothelial growth factor (VEGF), inhibiting its binding to receptors on endothelial cells and thereby neutralising the physiological activity of VEGF. This reduces development of blood vessel within tumours and inhibits tumour growth.

A double-blind trial recruited 923 adults with histologically confirmed metastatic colorectal cancer with bidimensionally measurable disease, an Eastern Co-operative Oncology Group (ECOG) performance status of 0-1 and life expectancy of more than 3 months, who had no central nervous system (CNS) metastases or previous chemotherapy for metastatic disease. They were randomised, with stratification for centre, ECOG performance status, number of metastatic sites and primary tumour site to one of three regimens: (1) irinotecan 125mg/m^2 intravenous (iv) 1.5 hour infusion, folinic acid 20mg/m^2 iv bolus and fluorouracil 500mg/m^2 iv bolus weekly for the first 4 weeks of a 6-week cycle (IFL; Saltz Regimen) plus placebo every 2 weeks; (2) IFL regimen plus bevacizumab 5mg/kg iv 0.5-1.5 hour infusion every 2 weeks; or (3) folinic acid 500mg/m^2 iv 2 hour infusion plus fluorouracil 500mg/m^2 iv bolus weekly for the first 6 weeks of an 8-week cycle (Roswell Park regimen) plus bevacizumab 5mg/kg iv 0.5-1.5 hour infusion every 2 weeks. Enrolment in the latter treatment arm was discontinued, as per protocol, after 313 patients had been enrolled to the study and the adverse effect profile of IFL plus bevacizumab regimen was found to be acceptable. Patients in this arm continued their assigned treatment, but the study focused on the comparison of the other two

groups. Treatment was continued until disease progression or 96 weeks. Patients on bevacizumab who had not experienced disease progression at 96 weeks were allowed to continue this drug in an extension study. At the time of disease progression patients were offered additional chemotherapy, which could include bevacizumab for patients who had received this drug during the study. However, those who had received placebo were not permitted to receive bevacizumab in their chemotherapy after disease progression. The primary endpoint, overall survival time from randomisation, was analysed via log-rank test with stratification for ECOG performance status, number of organs with disease, and site of the primary tumour. Median overall survival was significantly greater with bevacizumab plus IFL than with IFL alone: 20.3 vs. 15.6 months, with a hazard ratio (95% confidence intervals (CI)) for death of 0.66 (0.54, 0.81). The median progression-free survival was significantly improved with bevacizumab plus IFL than with IFL: 10.6 vs. 6.2 months, hazard ratio (95% CI) for progression of 0.54 (0.45, 0.66). Quality of life was assessed via the functional assessment of cancer therapy-colorectal (FACT-C) questionnaire, which includes the colorectal cancer subscale (CCS). Data from the CSS, functional and physical subscales of FACT-C comprise the trial outcome index (TOI-C). Baseline data for these were available for approximately 122 and 125 patients in the bevacizumab plus IFL and IFL alone groups, respectively. Median times to deterioration in quality of life by pre-specified amounts (9, 3 and 7 points on FACT-C, CSS and TOI-C scores, respectively) were not significantly different in the bevacizumab plus IFL and IFL alone groups: 4 vs. 4 months (FACT-C), 2.9 vs. 2.7 months (CCS), 2.8 vs. 3.3 months (TOI-C).

An open-label trial recruited 104 patients similar to those included in the study described previously. They received folinic acid 500mg/m^2 iv 2 hour infusion and fluorouracil 500mg/m^2 iv bolus weekly for the first 6 weeks of an 8-week cycle (Roswell Park regimen) and were randomised to no additional chemotherapy, bevacizumab 5mg/kg or 10mg/kg iv 0.5-1.5 hour infusion every 2 weeks. Treatment was continued until disease progression or for 48 weeks. There were imbalances in baseline demographics across the treatment groups, which generally favoured a better prognosis in the control group. The primary outcomes, objective tumour response (complete or partial, confirmed after $\geq$4 weeks) and progression-free survival were assessed via ECOG tumour response criteria by investigators and verified by an independent review facility. The respective outcomes were compared between each bevacizumab group and placebo using chi-squared and log-rank tests. Median progression-free survival times were greater in the bevacizumab 5mg/kg and 10mg/kg groups compared to the control group, 9.0 and 7.2 vs. 5.2 months, respectively, with hazard ratios for progression of 0.44 and 0.69 in the respective comparisons to the control. Objective tumour response rates were greater with bevacizumab 5mg/kg and 10mg/kg compared to the control group: 40% and 24% vs. 17%. For both outcomes the differences between bevacizumab 5mg/kg, but not 10mg/kg, and the control group were significant. In analyses submitted to the regulatory authorities, median overall survival times in the bevacizumab 5mg/kg and 10mg/kg groups were greater than in the control group: 17.7 and 15.2 vs. 13.6 months, with no significant differences between either group and the control group. Survival data were limited by lack of follow-up data and cross-over of 22 patients from the control group to treatment with bevacizumab 10mg/kg monotherapy after disease progression.

A double-blind study conducted concurrently with the first trial described previously recruited 209 patients with untreated measurable metastatic colorectal cancer who were considered by the investigator to be non-optimal candidates for treatment with an irinotecan-containing chemotherapy regimen and met at least one of the following criteria: age at least 65 years, ECOG performance status 1 or 2, albumin $\leq$3.5g/dL, or prior radiotherapy to the pelvis or abdomen. They received folinic acid 500mg/m^2 iv 2 hour infusion and fluorouracil 500mg/m^2 iv bolus weekly for the first 6 weeks of an 8-week cycle (Roswell Park regimen) and were randomised with stratification for centre, ECOG performance status, site or primary cancer and number of metastatic sites, to bevacizumab 5mg/kg iv 0.5-1.5 hour infusion or placebo every 2 weeks. The primary endpoint, overall survival from randomisation, was analysed via

log-rank test with stratification for ECOG performance status, number of organs with disease, and site of primary tumour. Median overall survival time was greater with bevacizumab plus fluorouracil and folinic acid than with fluorouracil and folinic acid alone: 16.6 vs. 12.9 months, with a hazard ratio (95% CI) for death of 0.79 (0.56, 1.1). The difference between the groups was not significant. Median progression-free survival was significantly increased with bevacizumab plus fluorouracil and folinic acid compared to fluorouracil and folinic acid alone: 9.2 vs. 5.5 months, with a hazard ratio (95% CI) for progression of 0.50 (0.34, 0.73). In analyses of median times to deterioration in quality of life similar to those conducted in the first trial described previously, this was significantly longer with bevacizumab plus fluorouracil and folinic acid than with fluorouracil and folinic acid alone for FACT-C: 3.6 vs. 2.6 months; was of borderline significance (p=0.048) for TOI-C: 3.2 vs. 2.3 and was not significant for CSS: 3.1 vs. 3.0.

Summary of evidence on comparative safety

Bevacizumab is associated with adverse effects on the vascular system. In colorectal cancer trials, it was associated with hypertension in 22-32% of patients, which was grade 3 severity (requiring anti-hypertensive medication) in 11-16% of patients. Proteinuria was reported by 22-38% of bevacizumab-treated patients in these trials, which was mainly of grade 1 severity. Rates of arterial thrombotic events (including cerebrovascular accident, transient ischaemic attack and myocardial infarction) were greater in bevacizumab-treated patients than with those receiving only chemotherapy: 3.3-10% vs. 1.3-4.8%. In a pooled analysis of data from five clinical trials of bevacizumab including the colorectal cancer trials, age >65 years was associated with an increased risk of arterial thromboembolic events when treated with bevacizumab. In metastatic colorectal cancer trials bevacizumab was associated with haemorrhage, particularly epistaxis and intratumoural haemorrhage, which were reported by 22-34% and 1-3% of patients, respectively.

In trials of bevacizumab in other types of cancer, CNS bleeding was observed in a patient with CNS metastases. Its use is contra-indicated in patients with untreated CNS metastases. In colorectal cancer trials bevacizumab was associated with gastro-intestinal perforation in 1.4-2.0% of patients, and had a fatal outcome in 0.4-1.0% of patients. Many of these patients had previous intra-abdominal inflammation resulting from gastric ulcer disease, tumour necrosis, diverticulitis or colitis and caution is advised when administering it to patients with these conditions. Bevacizumab's effects on the vasculature may interfere with wound healing and it is contra-indicated in patients who have undergone surgery within the preceding month.

Summary of clinical effectiveness issues

In a review by the European Medicines Agency it is noted that the patients included in the first two trials described previously had overall good performance status, were relatively young (mean age 59 years) and close to 38% had only one metastatic site. The population included may thus have a more favourable prognosis than the general population with metastatic colorectal cancer. 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. It is possible that the benefits observed with bevacizumab in these two trials may be different to those observed in many Scottish patients.

In the largest trial patients who had received bevacizumab as first-line therapy could continue to receive it as part of their second-line chemotherapy after disease progression. This second-line use of bevacizumab is not licensed and would not occur in practice. Median survival time from time of first disease progression in 170 patients initially treated with IFL

alone then second-line chemotherapy was 10 months. In 52 and 94 patients initially treated with IFL plus bevacizumab then second-line chemotherapy without and with bevacizumab, respectively, median survival times from first disease progression were 9.4 and 10 months, respectively.

Summary of comparative health economic evidence

A cost utility analysis was provided showing bevacizumab compared to an IFL regimen and also bevacizumab compared to fluorouracil and folinic acid alone. The model comprised three states; pre-progression, post-progression and death. Survival data were obtained by applying a Weibull distribution to the survival data from the two trials described previously, which primarily assess survival, in order to estimate mean survival. Utility values were taken from published sources and valued the pre-progression state at 0.8 and the post-progression state at 0.5. No additional disutility was assumed when bevacizumab was added to the treatment regimens. Resource use information was estimated using a combination of trial-level data and data from a published study involving second-line irinotecan chemotherapy.

The results of the model indicated that the cost per QALY of adding bevacizumab to IFL was £78,000 to £93,000 per QALY. The addition of bevacizumab to a fluorouracil and folinic acid regimen gave a cost per QALY of £24,000 to £60,000.

The economics submission was well conducted and adequately described. However, a few points of concern were noted. The quality of life data provided in the submission do not exclude the possibility that bevacizumab treatment could be associated with a small reduction in utility. The method used to estimate resource use was slightly confusing and the appropriateness of using a study in patients receiving second-line treatment to reflect on first-line patients was not adequately justified in the submission. In addition, feedback from clinical experts suggests that the comparator treatments in the economic evaluation are used in only a small percentage of patients. Aside from these issues, the cost-effectiveness ratio remains high for this new therapy.

The manufacturer also submitted a proposal for a patient registry programme which SMC could not consider at this stage.

Patient and public involvement

Patient Interest Group Submission: Bowel Cancer UK

Budget impact

The manufacturer has estimated an annual budget impact of £5.5 million.

Guidelines and protocols

NICE is conducting a technology appraisal of bevacizumab and cetuximab for advanced colorectal cancer that is expected to be published in November 2006.

The August 2005 NICE review of technology appraisal number 33, guidance on the use of irinotecan, oxaliplatin and raltitrexed for treatment of advanced colorectal cancer, notes that irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer. Irinotecan may be used in combination with fluorouracil and folinic acid as first-line therapy, or irinotecan alone may be used in subsequent therapy. Oxaliplatin in combination with fluorouracil and folinic acid may be used as first-line or subsequent therapy. Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. It use for this patient group should be confined to appropriately designed clinical studies.

The May 2003 NICE technology appraisal number 61, guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer, notes that oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer. The choice of regimen (intravenous fluorouracil/folinic acid or one of the oral therapies) should be made jointly by the individual and the clinician(s), taking account of contra-indications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.

The March 2003 Scottish Intercollegiate Guidelines Network (SIGN) publication number 67 on the management of colorectal cancer notes that all patients with metastatic colorectal cancer should be considered for chemotherapy. Recommended initial treatment regimens include continuously infused fluorouracil (Lokich regimen), intermittently infused fluorouracil plus folinic acid (de Gramont regimen) or capecitabine. Initial combination chemotherapy with oxaliplatin plus fluorouracil and folinic acid, should be considered in patients fit for hepatic resection but who have inoperable hepatic metastases that might become resectable on treatment. Raltitrexed is not recommended as a first-line therapy but may be considered as an alternative in those patients intolerant of fluorouracil regimens or in whom fluorouracil is contra-indicated due to cardiotoxicity. Although as efficacious as alternative regimens, raltitrexed is associated with significantly greater toxicity and its benefit to patients who are intolerant to fluorouracil or with coronary heart disease should be carefully weighted against the potential harms.

Additional information

Following a review by an independent review panel, the Scottish Medicines Consortium (SMC) issued advice on 9th September 2005 that cetuximab is not recommended for use within NHS Scotland in combination with irinotecan for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

After review of a full submission, SMC issued advice in in January 2006 that bevacizumab is not recommended for use within NHS Scotland in combination with intravenous fluorouracil/folinic acid or intravenous fluorouracil/folinic acid/irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

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 13 April 2006.

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

The undernoted references were supplied with the submission.

Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. New Engl J Med 2004; 350: 2335-42.

Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21: 60-5.

Kabbinavar FF, Schulz J, McLeod M et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005; 23: 3697-705.

Kabbinavar FF, Hambleton J, Mass RD et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol 2005; 23: 3706-12.