New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Balsalazide sodium

Colazide (Pharmatel)

750 mg capsules

Approved indication: ulcerative colitis

Australian Medicines Handbook section 12.6.2

Mesalazine is an aminosalicylic acid derivative which has been used in the treatment of inflammatory bowel disease. Balsalazide is the prodrug of mesalazine. The active drug is released from balsalazide by bacterial enzymes in the colon.

Very little balsalazide is absorbed after oral administration. Mesalazine is absorbed, but is rapidly metabolised and excreted in the urine.

Balsalazide has been compared with mesalazine in a double-blind trial. Patients with acute ulcerative colitis were treated for up to 12 weeks. More patients taking balsalazide went into remission. At the end of the study 62% were in remission compared to 37% of the patients taking mesalazine.[1]

This trial continued as a study of balsalazide and mesalazine in maintenance treatment. Although 58% of both treatment groups were in remission after a year, fewer patients taking balsalazide relapsed in the first three months. They also had more symptom-free days and nights.[2]

The adverse effects of balsalazide and mesalazine are similar. During the study of acute ulcerative colitis only half the patients treated with balsalazide experienced adverse effects compared to 70% of the patients taking mesalazine.[1] However, during maintenance treatment both drugs were associated with adverse effects in more than 60% of patients.[2]

Adverse effects include headache, diarrhoea, nausea and vomiting. Balsalazide should not be given to patients who are allergic to salicylates. Any unexplained bleeding or bruising is an indication for a blood test to look for a blood dyscrasia.

The newer aminosalicylic acid derivatives were designed to overcome the problems associated with drugs such as sulfasalazine. A Cochrane review has, however, questioned if the newer drugs have a clinical advantage over sulfasalazine for inducing remission.[3] Another Cochrane review has found that the newer drugs are inferior to sulfasalazine for maintenance treatment.[4] The use of balsalazide is therefore restricted to patients who are intolerant of sulfasalazine.

References

1. Abacus Investigator Group. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. Gastroenterology 1998;114:15-22.
2. Abacus Investigator Group. Maintenance of remission of ulcerative colitis: a comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months. Aliment Pharmacol Ther 1998;12:1207-16.
3. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for inducing remission in ulcerative colitis. *The Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD000543. DOI: 10.1002/14651858.CD000543.
4. Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for maintaining remission in ulcerative colitis. *The Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD000544. DOI: 10.1002/14651858.CD000544.

Bevacizumab

Avastin (Roche)

100 mg/4 mL and 400 mg/16 mL in single-dose vials

Approved indication: metastatic colorectal cancer

Australian Medicines Handbook section 14.3.4

Many patients with colorectal cancer will develop metastatic disease. This is difficult to treat and has a very poor prognosis, so new therapies are being studied. One approach is to inhibit the new vessels the tumours need to grow. This can be attempted by inhibiting vascular endothelial growth factor, which is increased in metastatic disease.

Bevacizumab is a genetically engineered humanised monoclonal antibody against vascular endothelial growth factor. By binding to the growth factor, bevacizumab prevents it from binding to endothelial receptors.

In a study of 104 untreated patients with metastatic colorectal cancer bevacizumab was used in combination with fluorouracil and folinic acid. High and low doses of bevacizumab were tested in this study. The response rate, as judged by changes in tumour size, was 24% with the high-dose regimen and 40% with the low-dose regimen. This gave the low-dose regimen a statistically significant advantage over the 17% response rate seen in a control group of patients who received fluorouracil and folinic acid alone. Compared to the control group, patients given the combination containing the low dose of bevacizumab also had a significantly longer median time before their cancers

progressed (9 versus 5.2 months). Their median survival was 21.5 months compared to 13.8 months in the control group.[1]

Following this trial, the low dose of bevacizumab (5 mg/kg) was studied in addition to a regimen containing irinotecan, fluorouracil and folinic acid. The four drugs were given to 402 patients with previously untreated metastatic disease and the results were compared with those of 411 patients given the three-drug regimen plus a placebo. Overall the response rate was 44.8% in the bevacizumab group and 34.8% in the control group. The progression-free survival was 10.6 months with bevacizumab compared with 6.2 months. There was also a significant difference in median survival time; 20.3 months in the bevacizumab group versus 15.6 months in the control group.[2]

Bevacizumab has to be diluted and given as a slow intravenous infusion once every 14 days. The antibody has a half-life of approximately 20 days.

Although bevacizumab improves survival by a few months it increases the risks of adverse effects. In the phase 3 trial there were significantly more serious adverse events in the patients taking the bevacizumab regimen than in those taking irinotecan, fluorouracil and folinic acid (84.9% versus 74%). Bevacizumab was associated with increased leucopenia, diarrhoea and hypertension.[2] Although there is a risk of venous and arterial thrombosis, including stroke and myocardial infarction, there is also a risk of fatal haemorrhage in patients taking regimens that include bevacizumab. The gut perforations which can occur with bevacizumab[2] may also be fatal. As wound healing may be affected, treatment should not begin until at least a month after surgery. Proteinuria is another problem and if the nephrotic syndrome develops treatment should be stopped. Congestive cardiac failure has also been reported.

Bevacizumab is approved for use with fluorouracil and folinic acid, or with fluorouracil, folinic acid and irinotecan.

Further studies are investigating the addition of bevacizumab to regimens containing oxaliplatin. Although genetic engineering is increasing treatment options, the best regimen is not yet clear.

T T T manufacturer provided all requested information

References * †

1. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, 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.
2. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

Cetuximab

Erbitux (Alphapharm)

2 mg/mL in 50 mL vials

Approved indication: metastatic colorectal cancer

Australian Medicines Handbook section 14.3.4

Antineoplastic antibodies such as rituximab and trastuzumab act on cancer cells by binding to target antigens.[1] Cetuximab is a genetically engineered chimeric monoclonal antibody which binds the epidermal growth factor receptor. The gene for this receptor is overexpressed in many patients with colorectal cancer and is associated with a poor prognosis. By binding to the receptor, cetuximab blocks the action of epidermal growth factor with the aim of reducing the growth and viability of tumour cells.

Cetuximab is given by a slow intravenous infusion once a week. The pharmacokinetics of cetuximab vary with the dose. At higher doses there is a decreased clearance and increased half-life. At the recommended doses cetuximab has a half-life of 80–120 hours.

A randomised, open-label trial compared cetuximab alone or in combination with irinotecan in 329 patients with metastatic colorectal cancer. All the patients had tumours with epidermal growth factor receptors and their tumours had progressed despite previous treatment with irinotecan. Approximately 11% of the patients given cetuximab and 23% of the patients given the combination had some response to treatment, as judged by imaging studies. Although the median time for the disease to progress was longer with the combination (4.1 months versus 1.5 months), this therapy had no significant survival advantage over cetuximab alone. The median survival was 8.6 months with combination therapy and 6.9 months with monotherapy.[2]

During the study 80% of the patients developed an acne-like skin reaction. This was severe in 5.2% of the patients taking cetuximab and in 9.4% of those taking cetuximab with irinotecan.[2] Premedication with an antihistamine is recommended because of the risk of a hypersensitivity reaction to an infusion of cetuximab. Dyspnoea has developed in 25% of patients given cetuximab. This has been severe in approximately 10% of patients. Those given cetuximab in combination with irinotecan are prone to diarrhoea and neutropenia. Blocking the epidermal growth factor receptor may delay wound healing.

After irinotecan has failed adding cetuximab induces a greater response than giving cetuximab alone. This suggests that cetuximab somehow enhances the effect of irinotecan. There is therefore a need to compare cetuximab with other drugs, such as oxaliplatin, which can be given to patients with irinotecan-refractory disease.

Although cetuximab has been approved for monotherapy and for use in combination with irinotecan, combined therapy is more likely to be useful for metastatic disease that has

progressed. Cetuximab should not be prescribed for patients whose colorectal tumours do not have overexpression of the epidermal growth factor receptor.

[X] manufacturer did not respond to request for data

References †

1. Ward R. Antineoplastic antibodies – clinical applications. Aust Prescr 2003;26:141-3.
2. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45.

Ciclesonide

Alvesco (Altana Pharma)

metered dose inhalers delivering 80 microgram or 160 microgram per actuation

Approved indication: asthma prophylaxis

Australian Medicines Handbook section 19.2

Inhaled corticosteroids can have an important role in helping patients with asthma achieve their best lung function. Ciclesonide is a non-halogenated glucocorticosteroid which is claimed to have a finer aerosol than other drugs, so less of the dose is deposited in the oropharynx. In the lung, ciclesonide is metabolised to its active metabolite which has a higher affinity for glucocorticoid receptors. Although ciclesonide has a different structure, it still acts like other inhaled corticosteroids by reducing bronchial hyperreactivity and inflammation in the airways.

The active metabolite is metabolised by cytochrome P450 3A4, so drugs which inhibit this enzyme may increase plasma concentrations of the metabolite. The clinical significance of this interaction with inhaled ciclesonide is unclear. Ciclesonide and its metabolites are mainly excreted in the faeces.

The effect of ciclesonide has been compared with placebo in a double-blind crossover trial of 13 asthmatic patients given an allergen challenge. After inhaling powdered ciclesonide for a week before the challenge the patients' forced expiratory volumes (FEV_1) decreased significantly less than they did after one week of placebo.[1]

Although ciclesonide is more active than placebo it is unclear if it has any greater efficacy than other drugs such as budesonide. The product information says there have been 16 trials of ciclesonide, but few of them seem to have been published in full by peer-reviewed journals. As only five studies of 12 weeks' duration are briefly summarised in the product information, it is difficult to assess the long-term effectiveness of ciclesonide in asthma.

In theory, the deposition of most of the dose in the lung and ciclesonide's lower affinity for the glucocorticoid receptors should reduce some of the problems associated with inhaled corticosteroids. The common adverse effects of ciclesonide include hoarseness and bronchospasm, but the incidence of long-term adverse effects such as adrenal suppression and cataracts is unknown. It is not approved for use by children under 12 years old.

Although ciclesonide has the convenience of a once-daily dose, its place in therapy is unclear. Until more data are made available for scrutiny, there seems to be little justification for doctors to add ciclesonide to their choice of inhaled corticosteroids.

[X] manufacturer did not respond to request for data

Reference

1. Larsen BB, Nielsen LP, Engelstätter R, Steinijans V, Dahl R. Effect of ciclesonide on allergen challenge in subjects with bronchial asthma. Allergy 2003;58:207-12.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int)