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 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.

Arcitumomab

CEA-Scan (Australian Radioisotopes)

vials containing 1.25 mg lyophilised arcitumomab for reconstitution with sodium-pertechnetate in saline

Approved indication: imaging of advanced colorectal cancer

Carcinoembryonic antigen (CEA) is found in the serum of patients with colorectal cancers. It can be used in monitoring these patients for local recurrences or metastases. Attaching a radioactive label to an antibody (arcitumomab) to CEA helps to localise where the tumour cells producing the CEA are.

Arcitumomab is made by exposing mouse spleen cells to human CEA. These cells produce an antibody from which the arcitumomab fragment is extracted. Arcitumomab is mixed with a technetium-containing radionuclide and diluted before being injected intravenously. The technetium disintegrates giving off gamma rays. It has a half-life of six hours and 28% of the radiolabel is excreted in the urine within 24 hours. Imaging should take place 2–5 hours after the injection.

In one trial, 40 patients with resected rectal cancer were followed up for five years with CEA immunoscintigraphy in addition to routine surveillance. Sixteen patients developed recurrent cancer. Although only six of these patients had increased serum CEA, immunoscintigraphy identified 82% of the tumours. The sensitivity for finding lesions was 94% and the specificity was 97%. This resulted in six patients having further surgery which could improve their survival. These patients had a mean survival of 35 months compared to 21 months in a group of historic controls.[1]

The adverse reactions to the injection have included itching, urticaria and other rashes. Some patients will develop antibodies to mouse protein.

Although CEA immunoscintigraphy can help to identify local recurrences, it may not give surgeons all the information they need. In a comparison with positron emission tomography (PET), CEA immunoscintigraphy did not detect all metastases in bone, lung and lymph nodes.[2] Another small study found that PET is better at predicting which patients have resectable recurrent disease. In 16 patients having resections, PET had predicted resectable tumours in 81% while CEA immunoscintigraphy identified only 13% as resectable. CEA immunoscintigraphy was unable to show which patients had unresectable disease whereas PET predictions were correct in 90% of patients with unresectable disease.[3]

REFERENCES

1. Lechner P, Lind P, Goldenberg DM. Can postoperative surveillance with serial CEA immunoscintigraphy detect resectable rectal cancer recurrence and potentially improve tumor-free survival? J Am Coll Surg 2000;191:511-8.
2. Willkomm P, Bender H, Bangard M, Decker P, Grünwald F, Biersack HJ. FDG PET and immunoscintigraphy with ^{99m}Tc-labeled antibody fragments for detection of the recurrence of colorectal carcinoma. J Nucl Med 2000;41:1657-63.
3. Libutti SK, Alexander HR, Choyke P, Bartlett DL, Bacharach SL, Whatley M, et al. A prospective study of 2-fluoro-2-deoxy-D-glucose/positron emission tomography scan, ^{99m}Tc-labeled arcitumomab (CEA-scan), and blind second-look laparotomy for detecting colon cancer recurrence in patients with increasing carcinoembryonic antigen levels. Ann Surg Oncol 2001;8:779-86.

Artemether and lumefantrine

Riamet (Novartis)

tablets containing 20 mg artemether and 120 mg lumefantrine

Approved indication: Falciparum malaria

Australian Medicines Handbook section 5.4.1

Plasmodium falciparum is the malaria parasite which causes most deaths. In many areas the parasite has developed resistance to chloroquine so there is a need to develop alternative treatments for malaria.

Artemisinin is a chemical found in the sweet wormwood (*Artemisia annua*), a Chinese herb used in the treatment of fever. Although artemisinin is effective against the parasite the symptoms rapidly recur unless high doses are used. To overcome the problems of monotherapy artemether, a derivative of artemisinin, has been combined with lumefantrine, an antimalarial drug developed in China. Compared to artemether, lumefantrine has a slower onset of action, but a more sustained effect against the parasite. The combination is more effective than either drug given alone.

Artemether is rapidly absorbed, but lumefantrine does not reach a peak plasma concentration until 6–8 hours after the combined tablet is swallowed. The tablets are taken after meals as food increases absorption. Artemether undergoes extensive first-pass metabolism and is mainly eliminated by the liver. It has a half-life of two hours whereas lumefantrine which is also eliminated by metabolism has a half-life of 4–6 days in infected patients.

As the metabolism of the drugs involves the cytochrome P450 system there are potential interactions with many drugs that are also metabolised by this system. The combination is contraindicated in patients taking drugs metabolised by CYP3A4 (e.g. erythromycin) or CYP2D6 (e.g. imipramine). It should also not be given with drugs, including other antimalarial drugs, that prolong the QT_c interval. Ideally all patients should have an electrocardiogram before and during treatment as prolongation of the QT_c interval is a contraindication to treatment.

Although palpitations can occur in 7.5% of patients the commonest adverse effects are headache and dizziness. Many

adverse events during treatment could be caused by malaria. They include fever, asthenia, anorexia and abdominal pain. The safety of artemether and lumefantrine in pregnancy is unknown and it is not approved for use in children less than 12 years old.

A regimen of six doses given over 60 hours has been compared with a mefloquine-based regimen in Thailand. Mefloquine was given to 55 patients with acute uncomplicated falciparum malaria and 164 were given artemether and lumefantrine. All the patients given the mefloquine-based regimen were cured within a month, while the cure rate with the combination was 95.5%. There was no significant difference between the treatments in the clearance of parasites from the blood; more than 90% of patients had a reduction in parasites by the third day of treatment.[1]

People travelling to areas where malaria is endemic need to take precautions to reduce the risk of infection (see 'Malaria prevention in the expatriate and long-term traveller' Aust Prescr 2002;25:66–9). Although artemether and lumefantrine tablets are not approved for prophylaxis they may have a role in emergency 'standby' treatment, however this use has not been evaluated. The future of malaria treatment may lie in combination regimens as they can slow the development of resistance. Artemether and lumefantrine tablets are therefore likely to be used for treatment, particularly as the manufacturer will supply the drug to developing countries at a reduced cost.

REFERENCE

1. Lefèvre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I, et al. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 2001;64:247-56.

Bosentan

Tracleer (Actelion)

62.5 mg and 125 mg film-coated tablets

Approved indication: pulmonary hypertension

Australian Medicines Handbook section 6.7.2

Primary pulmonary hypertension is a rare disease of unknown aetiology. Secondary causes of pulmonary hypertension include systemic sclerosis. Patients become dyspnoeic on exertion and the high pulmonary arterial pressure eventually leads to right ventricular failure. Most patients die within a few years of diagnosis.

Research into the cause of primary pulmonary hypertension has found that patients have increased amounts of endothelin-1. This is a peptide which causes vasodilatation or vasoconstriction depending on which receptors it activates.

Bosentan acts as an antagonist at the endothelin receptors. This reduces the pulmonary artery pressure in rats, so bosentan has been studied as an oral treatment for patients with pulmonary hypertension.

A double-blind study randomised 32 patients to take bosentan or a placebo for 12 weeks in addition to their usual therapy. Bosentan reduced dyspnoea and patients were able to walk further.[1] Similar improvements were seen in a larger study which randomised 213 patients.[2]

Patients take 62.5 mg twice daily for four weeks then increase to a maintenance dose of 125 mg twice daily. The bioavailability of the tablets is 50% and this is not changed by food. Plasma concentrations decrease during treatment probably because bosentan induces its own metabolism. This metabolism involves cytochrome P450 2C9 and 3A4 so bosentan will alter the plasma concentrations of drugs such as warfarin, glibenclamide and simvastatin. Bosentan also interacts with digoxin and ketoconazole.

Moderate to severe liver disease is a contraindication to bosentan and it can have serious adverse effects on the liver. Patients must therefore have regular tests of liver function during treatment. In clinical trials, 11% of patients had a more than three-fold increase in liver enzymes.

Adverse events that occur more frequently in patients taking bosentan, than in those taking placebo, include headache, flushing, palpitations and hypotension. Nearly 6% of patients will develop anaemia. Bosentan is teratogenic.

While bosentan has statistically significant effects, their clinical importance can be questioned. In the large trial, the mean treatment effect on dyspnoea, using a scale of 1–10, was 0.6.[2] After 16 weeks of treatment the patients could walk an extra 36 metres in six minutes. It is not clear how long these effects will last or if they make any difference to survival. If a patient's condition deteriorates consideration should be given to withdrawing bosentan as its efficacy in severe pulmonary hypertension is unknown. Its approval is limited to primary pulmonary hypertension and pulmonary hypertension associated with scleroderma.

Bosentan is an adjunctive treatment, but the best combination of therapies is yet to be defined.

REFERENCES

1. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119-23.
2. Bosentan Randomized Trial of Endothelin Antagonist Therapy Study Group. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.

Deferiprone

Ferriprox (Orphan)

500 mg tablets

Approved indication: iron overload in thalassaemia

Australian Medicines Handbook section 4.2

Patients with thalassaemia major develop anaemia and require blood transfusions. As the body has a limited capacity to excrete iron, frequent transfusions cause iron overload. This can lead to complications such as cirrhosis, heart failure and diabetes.

To prevent the complications of iron overload patients are treated with desferrioxamine. This is a chelating agent which forms water-soluble complexes in a 1:1 ratio with iron atoms.

These complexes can then be excreted by the kidney. Unfortunately desferrioxamine can only be given by injection and children may require prolonged subcutaneous infusions several times a week. As desferrioxamine is expensive to administer and can have serious adverse effects, there is a need for an oral iron-chelating agent.

Deferiprone is a chelating agent which is rapidly absorbed from the gut. Three molecules of deferiprone will form a complex with one iron atom. This complex is then excreted in the urine. Up to 90% of the dose is excreted within 24 hours. Deferiprone is also metabolised, but its metabolite has no chelating activity.

A prospective trial of deferiprone involved 21 patients who were unwilling or unable to take desferrioxamine. During an average of three years of treatment the patients' hepatic iron concentrations fell from a mean of 80.7 to 46.8 micromol/g. There was also a significant reduction in serum ferritin.[1]

Nineteen of the patients in the trial continued treatment. This enabled the researchers to review the efficacy of deferiprone after 4.6 years (mean duration of treatment). They found that the average concentration of hepatic iron had not decreased significantly. In some patients hepatic iron concentrations had increased.[2]

The researchers also reported that long-term treatment was associated with hepatic fibrosis. This conclusion was controversial and led to lawsuits against the principal researcher.[3]

While there is an argument about the risk of hepatic fibrosis, there is an association between deferiprone and severe neutropenia and agranulocytosis. The patient's neutrophil count should therefore be monitored weekly. More common adverse events include discolouration of the urine, nausea, vomiting and arthralgia.

While desferrioxamine treatment is inconvenient, compliance with deferiprone is also demanding. To maintain concentrations high enough to form the 3:1 complexes with iron, patients must take a daily dose of deferiprone of 75 mg/kg. This will often equate to several tablets three times a day.

It will take years before we know if deferiprone safely prevents the complications of iron overload. There are no data on the use of the drug in young children. Until there is a good quality study comparing it with desferrioxamine, deferiprone should only be used in patients who cannot tolerate desferrioxamine.

REFERENCES

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2. Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med 1998;339:417-23.
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Rasburicase

Fasturtec (Sanofi-Synthelabo)

glass vials containing 1.5 mg freeze-dried powder

Approved indication: treatment and prophylaxis of acute hyperuricaemia

Australian Medicines Handbook section 15.3

Rapidly proliferating tumours increase the production of uric acid. If the tumour cells are damaged by chemotherapy the resulting hyperuricaemia can cause acute renal failure.

Humans lack the enzyme (urate oxidase) which, in other mammals, converts uric acid to a more soluble molecule. A genetically engineered form of the enzyme (rasburicase) has been developed. This can be used when there is a risk of rapid tumour lysis in a patient with a haematological malignancy.

Rasburicase is infused when the patient starts chemotherapy. The daily infusion is given over 30 minutes for 5–7 days. Ideally, it should not be given through the same line as the patient's chemotherapy. The half-life of rasburicase is approximately 19 hours and like other proteins it is broken down by hydrolysis.

Allopurinol (which reduces uric acid production by inhibiting xanthine oxidase) can be used as prophylaxis against hyperuricaemia. An open-label randomised trial has therefore compared rasburicase to oral allopurinol in 52 children starting chemotherapy for leukaemia or lymphoma. Rasburicase reduced the concentration of uric acid significantly faster than allopurinol during the first four days of chemotherapy. Uric acid concentrations fell by 86% within four hours of a dose of rasburicase, compared to 12% after allopurinol. This more rapid reduction resulted in patients having 2.6 times less exposure to uric acid in the first four days of therapy.[1]

Attributing adverse effects, such as fever, nausea and vomiting, to rasburicase in patients receiving chemotherapy can be difficult. There is a problem in patients with a deficiency of glucose-6-phosphate dehydrogenase as the oxidation of uric acid may precipitate a haemolytic anaemia. As rasburicase is a protein it has the potential to cause allergic reactions. Some patients will develop antibodies to rasburicase.

Clinical experience with rasburicase is limited and it is not approved for use in subsequent courses of chemotherapy. An intravenous drug may be expected to have a more rapid effect than an oral drug so some caution is needed when interpreting the comparative study. This study was also too small to show any significant differences in renal failure or the need for dialysis.[1]

REFERENCE

1. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001;97:2998-3003.

Vardenafil

Levitra (Bayer Australia)

5 mg, 10 mg and 20 mg tablets

Approved indication: erectile dysfunction

Australian Medicines Handbook section 13.3

Vardenafil is the third inhibitor of phosphodiesterase type 5 to be marketed in Australia. Like sildenafil and tadalafil it raises concentrations of cyclic guanosine monophosphate in the corpus cavernosum of the penis. This increases the likelihood of an erection in response to sexual arousal.

Patients take vardenafil 25 to 60 minutes before attempting intercourse. Although nearly 50% of men with erectile dysfunction will respond to a placebo, vardenafil will produce an erection in 68–80% depending on the dose. Response rates are lower in men with diabetes and those who have had their prostate removed.

Vardenafil and sildenafil have similar half-lives (approximately four hours). Like the other phosphodiesterase inhibitors, vardenafil is metabolised by cytochrome P450 3A4. This results in potential interactions with drugs such as erythromycin. Vardenafil should not be prescribed for patients taking potent CYP3A4 inhibitors such as ketoconazole and ritonavir. A low dose is recommended for people with reduced hepatic function. The drug is contraindicated in patients taking nitrates.

As vardenafil has vasodilatory effects it can cause headache, flushing and reduced blood pressure. It is contraindicated in patients with severe cardiovascular disorders, including unstable angina and a recent history of myocardial infarction.

Studies comparing the three oral treatments for erectile dysfunction are needed. A literature review found that there are no relevant differences in their selectivity for phosphodiesterase type 5 and they have similar efficacy in helping patients achieve an erection.[1]

REFERENCE

1. Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil. Eur J Med Res 2002;7:435-46.

Answers to self-test questions

1. True
2. False
3. True
4. False
5. True
6. False
7. False
8. True

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