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.

Bortezomib

Velcade (Janssen-Cilag)

vials containing 3.5 mg powder for reconstitution

Approved indication: multiple myeloma

Australian Medicines Handbook section 14.3.11

Multiple myeloma is a malignancy of plasma cells. Although modern treatments, such as bone marrow transplant, have improved the prognosis there is no cure and the median survival is 3–5 years. The options for patients whose cancers relapse after chemotherapy or transplantation are limited. Progression of the cancer may be related to dysfunction of an enzyme system (26S proteasome) that normally breaks down cellular proteins. Inhibiting this enzyme disrupts cell homeostasis and can cause apoptosis, particularly in proliferating cells.

Bortezomib is an inhibitor of the proteasome. It is a modified dipeptide related to the amino acids leucine and phenylalanine. Experimentally, bortezomib delays tumour growth in a variety of cancers including multiple myeloma.

A phase II trial recruited 202 people whose myeloma had relapsed and was refractory to therapy. They were given injections of bortezomib twice a week in two-week cycles with one treatment-free week between each cycle. Up to eight cycles were allowed and oral dexamethasone could be added to the regimen if there was a poor response. After a median treatment duration of 3.8 months myeloma protein could not be detected by electrophoresis in 19 patients. Overall 53 patients (27%) had at least a partial response to bortezomib.[1]

As high doses of dexamethasone can be used to treat relapsed myeloma it has been compared with bortezomib. The trial randomised 333 patients to eight cycles of intravenous bortezomib and 336 to oral dexamethasone. There was at least a partial response in 38% of the bortezomib group and 18% of the dexamethasone group. The myeloma protein disappeared in 6% of the bortezomib group but less than 1% of the dexamethasone group. This contributed to a higher rate of survival (80% vs 66%) when the patients were followed up after a year.[2]

Many patients will not complete eight cycles of therapy. In the phase III trial 37% of the patients given bortezomib stopped treatment because of adverse effects.[2] Common adverse reactions include gastrointestinal upsets, peripheral neuropathy, fever and hypotension. The patient's blood count should be checked before each dose as bortezomib can cause anaemia, neutropenia and thrombocytopenia.

Bortezomib is metabolised by several of the cytochrome P450 enzymes, but there are no drug interaction studies. It should probably not be used in patients with hepatic impairment, and the development of abnormal liver function may require treatment to be stopped.

As our understanding of the molecular biology of multiple myeloma improves new approaches to treatment are likely to emerge. For example, thalidomide can be used in refractory myeloma. Some of the patients in the trials had already been treated with thalidomide, so it seems that bortezomib can improve outcomes after a relapse. The size of the improvement is uncertain as there have been questions about the design of the comparison with dexamethasone[3], for example 99% of the dexamethasone group had already been treated with corticosteroids.[2] Assuming the results are valid, bortezomib only delays progression by about three months. The median time to progression with bortezomib was 189 days compared with 106 days with dexamethasone.[2] As the price of bortezomib will be much greater, the delay in progression will have a high cost and whether this improves the quality of the patient's remaining life is currently unclear.

[X] manufacturer did not respond to request for data

References *†

1. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348: 2609-17.
2. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487-98.
3. Dispenzieri A. Bortezomib for myeloma – much ado about something. N Engl J Med 2005;352:2546-8.

Disodium gadoxetate

Primovist (Schering)

pre-filled syringes containing 10 mL

Approved indication: liver imaging

Magnetic resonance imaging (MRI) can be enhanced by the use of contrast agents. Gadoxetate is a gadolinium containing contrast agent which can be used in the detection of focal hepatic lesions.

After intravenous injection gadoxetate concentrates in the liver and kidneys. Uptake into normal hepatocytes is more likely

than into abnormal areas such as metastases. As gadoxetate is eliminated in the bile, as well as in the urine, it may have a role in imaging the biliary system.

One of the clinical trials of gadoxetate involved 131 patients with known or suspected lesions in the liver. These patients had MRI before and 20 minutes after an injection of gadoxetate. Using the contrast agent increased the number of lesions identified by the researchers and by external radiological reviewers. Although the sensitivity of MRI was increased, the improvement was not statistically significant for all the radiologists.[1]

In other studies adding gadoxetate has increased the proportion of correctly characterised lesions from 81% to 88%. The combination of precontrast, dynamic and postcontrast MRI correctly characterises 89% of lesions compared to 80% with contrast-enhanced computed tomography (CT).

The main adverse effects of gadoxetate are headache, nausea, vasodilatation, back pain and abdominal pain. Anaphylactoid reactions can occur and gadoxetate may prolong the QT_c interval on the ECG.

Other hepatobiliary contrast agents are available overseas, but the dilemma is whether the advantages of contrast-enhanced MRI are sufficiently superior to MRI and CT to make a difference to the patient's management.

[X] manufacturer declined to supply data

Reference

1. Huppertz A, Balzer T, Blakeborough A, Breuer J, Giovagnoni A, Heinz-Peer G, et al. Improved detection of focal liver lesions at MR imaging: multicenter comparison of gadoxetic acid-enhanced MR images with intraoperative findings. Radiology 2004;230:266-75.

Eflornithine hydrochloride

Vaniqa (Epitan)

11.5% cream in 30 g tubes

Approved indication: facial hair

Australian Medicines Handbook section 8.10

Eflornithine is an inhibitor of ornithine decarboxylase, an enzyme involved in cell proliferation and function. It was first studied in oncology, but was found to be active in trypanosomiasis. The drug's effectiveness in treating African sleeping sickness led to it being called 'the resurrection drug'.[1]

Unfortunately, parenteral eflornithine was too expensive for the countries that needed it. Commercial considerations therefore resulted in the manufacturer ceasing production in 1995.[1]

During treatment of trypanosomiasis it was noticed that some patients lost their hair. This led to the development of a topical formulation for slowing hair growth, opening up a more lucrative cosmetic market.[1] The Australian indication is for delaying the regrowth of unwanted facial hair, following depilation, in women.

The main clinical trials of eflornithine enrolled women who usually removed their facial hair at least twice a week. Compared to the 201 women randomised to apply the vehicle, the 393 who applied eflornithine twice daily had less hair growth. In the opinion of the treating doctors, after 24 weeks of treatment 32% of the women using eflornithine showed a marked improvement compared with 8% of those applying the vehicle. Secondary endpoints such as feeling 'uncomfortable at social gatherings' or 'uncomfortable in exchanges of affection' all showed that women given eflornithine no longer felt as bothered about facial hair as the women who had used the vehicle. The differences between the groups disappeared after treatment ceased.

Only a few of the women in the trials had polycystic ovary syndrome. Women who were using other treatments for hirsutism were excluded from the trials and published comparative studies are lacking.

Although a small proportion of the dose is absorbed into the systemic circulation, mainly local adverse reactions were reported during the trials. These included burning, stinging, itching, redness and tingling of the skin. Acne was reported in 21% of women using eflornithine or the vehicle and approximately 16% of both groups developed pseudofolliculitis barbae. The effects of long-term continuous use of eflornithine are unknown. Its safety in pregnancy has not been established, and it is contraindicated in severe renal impairment.

While women in developed countries can now access eflornithine to try to improve their appearance, access to eflornithine for sleeping sickness is less certain. Although the manufacturers reached an agreement with the World Health Organization to supply the drug, future production may not be assured.

[T][T] manufacturer provided some data

Reference †

1. Coyne PE. The eflornithine story. J Am Acad Dermatol 2001;45:784-6.

Posaconazole

Noxafil (Schering-Plough)

105 mL glass bottles containing 40 mg/mL suspension

Approved indication: specified fungal infections

Australian Medicines Handbook section 5.2.1

The increase in patients with disorders of the immune system or taking immunosuppressants has led to an increase in fungal infections. The drugs available to treat systemic fungal infections include amphotericin B and the triazole antifungals such as itraconazole and voriconazole.

Like other triazole antifungals, posaconazole inhibits the synthesis of ergosterol. This results in the breakdown of the

fungal cell membrane. *In vitro*, posaconazole is active against species of aspergillus and fusarium. It is also approved for use in chromoblastomycosis, coccidiodomycosis, mycetoma and zygomycosis.

Patients take the suspension twice a day. Doses are taken with meals as food more than doubles the absorption of posaconazole. The half-life is 35 hours so it takes at least a week for concentrations to reach a steady state. Most of the drug is excreted unchanged in the faeces. There is some metabolism, but cytochrome P450 is not extensively involved. Posaconazole does inhibit P450 3A4 so it may reduce the metabolism of drugs such as calcium channel blockers, midazolam, atorvastatin and simvastatin. Drugs which reduce plasma concentrations of posaconazole include phenytoin, rifabutin, H_2 receptor antagonists and, probably, proton pump inhibitors.

Posaconazole has mainly been studied in infections that were resistant to other drugs. Its approval is therefore limited to patients who cannot tolerate other antifungals or have a refractory infection. In a study of fungal infections of the central nervous system, patients were treated with posaconazole for up to a year. Most patients had already been treated with amphotericin. Treatment with posaconazole was successful in 14 of the 29 patients with cryptococcal meningitis and five of the 10 patients with other infections.[1]

During the trials of posaconazole the most frequently reported problems were fever, gastrointestinal upsets and headache. Other adverse effects included neutropenia, anorexia, dizziness, fatigue and rash. Posaconazole can alter liver function and may also potentially prolong the QT_c interval in the ECG.

Refractory fungal infections are difficult to treat so there is a need for new antifungal drugs, but already organisms with reduced susceptibility to posaconazole have been identified. There is limited published information about the clinical effectiveness of posaconazole so it is not possible to evaluate if it has any advantage over other antifungals such as voriconazole.

T T manufacturer provided some data

Reference †

1. Pitisuttithum P, Negroni R, Graybill JR, Bustamante B, Pappas P, Chapman S, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. J Antimicrob Chemother 2005;56:745-55.

Tazarotene

Zorac (EpiPharm)

0.1% and 0.05% cream in 30 g tubes

Approved indication: psoriasis, acne

Australian Medicines Handbook section 8.2.1

Topical treatments are first-line therapy for acne and plaque psoriasis. The options for acne include the retinoids such as adapalene and tretinoin. Tazarotene is a retinoid which has been available overseas for several years. As tazarotene modulates the proliferation and differentiation of keratinocytes it has been studied in psoriasis and acne.

Early clinical trials compared a gel formulation with applications of inactive vehicle. Tazarotene reduced the severity of psoriasis in 45–63% of lesions depending on the concentration of the gel and whether it was applied once or twice a day. Only 13% of lesions responded to the vehicle.[1] Over 12 weeks the cream formulation produced a clinical improvement in the skin of 49% of patients with facial acne compared with 33% of those given the vehicle.[2]

The efficacy of a once-daily application of gel was compared with that of twice-daily fluocinonide, a potent topical corticosteroid for psoriasis. After 12 weeks there was no significant difference between the treatments. Patients who responded to tazarotene were less likely to relapse in the 12 weeks after treatment stopped.[3]

A retrospective study evaluated the effect of topical retinoids in inflammatory facial acne. Clinically significant improvements were judged to have occurred in 36% of the evaluations of patients given tazarotene, 34% of the evaluations of adapalene and in 28% of the evaluations of tretinoin. Only 17% of the evaluations considered that there had been a response to a vehicle.[4]

Tazarotene is a prodrug which is converted to tazarotenic acid. Some of this is absorbed into the systemic circulation then excreted in the urine and faeces. As retinoids are teratogenic, tazarotene should not be used in pregnancy or in women who could become pregnant during treatment.

Common complaints reported in trials of tazarotene include a burning or stinging sensation, itching, irritation, redness and dry skin. Patients should be advised to use sunscreens. Those with acne are likely to develop desquamation. The safety and efficacy of tazarotene have not been established beyond 12 weeks of treatment.

There have been studies of tazarotene in combination regimens, but there do not appear to have been many published comparisons with other treatments. In acne tazarotene is an alternative to the other retinoids and it can probably be considered in psoriasis for patients who have not tolerated or not responded to other topical treatments.

T T manufacturer provided some data

References

1. Krueger GG, Drake LA, Elias PM, Lowe NJ, Guzzo C, Weinstein GD, et al. The safety and efficacy of tazarotene gel, a topical acetylenic retinoid, in the treatment of psoriasis. Arch Dermatol 1998;134:57-60.

2. Shalita AR, Berson DS, Thiboutot DM, Leyden JJ, Parizadeh D, Sefton J, et al. Effects of tazarotene 0.1% cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. Clin Ther 2004;26:1865-73.
3. Lebwohl M, Ast E, Callen JP, Cullen SI, Hong SR, Kulp-Shorten CL, et al. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. J Am Acad Dermatol 1998;38:705-11.
4. Leyden JJ, Shalita A, Thiboutot D, Washenik K, Webster G. Topical retinoids in inflammatory acne: a retrospective, investigator-blinded, vehicle-controlled, photographic assessment. Clin Ther 2005;27:216-24.

The T-score (T) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

* 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)

Answers to self-test questions

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

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