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CONTENTS

Editorials

Can we deny patients expensive drugs?

Karen I Kaye, Executive Officer, NSW Therapeutic Advisory Group; Christine Y Lu, PhD student; and Richard O Day, Professor of Clinical Pharmacology, School of Medical Sciences, University of New South Wales, and Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney

Key words: cost of drugs, Pharmaceutical Benefits Scheme.

(Aust Prescr 2006;29:146–8)

A key principle of Australia's National Medicines Policy is that 'essential' medicines should be available for all patients who need them, at a price they and society can afford.[1] Decisions about which medicines will be nationally subsidised through the Pharmaceutical Benefits Scheme (PBS) are made by the Pharmaceutical Benefits Advisory Committee (PBAC) on the grounds of comparative safety and efficacy, as well as cost-effectiveness. These decisions challenge us all – patients, carers, the wider community, prescribers, government and the pharmaceutical industry.

Limits on public subsidy are increasingly inevitable. Negative decisions concerning expensive medicines are often contentious, providing material for the more sensationalist media. The impression is reinforced that the PBS is a government mechanism for limiting expenditure, rather than enabling equitable access to cost-effective medicines based on careful evaluation of evidence. Can we better balance an individual's right to optimal care and society's expectation of effective and efficient health services within the constraints of the health budget?

In this issue…

Dominic Barnes tells us it can take many years to develop a new drug. Drug companies aim to recover the cost of development during the period of patent protection. However, Paul Kubler questions whether strategies to extend this protection act against the policy of access to affordable medicines.

The affordability of highly specialised drugs is a particular problem in hospital practice. Karen Kaye, Cindy Lu and Ric Day ask how we can balance limited budgets with unlimited expectations for treatment.

Nick Pavlakis says that highly specialised drugs may improve the outcomes for patients with renal cancer. Drugs that alter the immune response inevitably have adverse effects, including accelerating periodontal disease, which Ivan Darby tells us can present as gingival bleeding.

For prescribers, whose duty and inclination is to provide optimal care for patients, denial of subsidised access in some circumstances raises clinical and ethical dilemmas. Australia's Quality Use of Medicines (QUM) framework can help. This means selecting the best treatment options for each patient (including using no medicines), choosing the most appropriate and cost-effective medicines, and using medicines safely and effectively with careful individualisation of regimens.

Restrictions on PBS access are increasingly applied, often because cost-effectiveness ('value for money') is only demonstrated in subsets of patients, such as those with more severe manifestations of disease. Patients with less severe disease may therefore be denied subsidised access to an effective medicine. The ethical dilemma here is to balance individual needs against the greater common good – to maximise the use of scarce resources for society and have everyone accept the decision as fair. Vested interests can encourage an expectation that treatment should be subsidised irrespective of cost. For example, intense lobbying led the government to subsidise trastuzumab (Herceptin) by creating a special program. This was outside the normal PBS mechanisms because the PBAC had advised against including trastuzumab in the PBS. Such decisions will inevitably fuel future lobbying efforts for other expensive drugs. If successful, they will no doubt benefit some individual patients, but may not represent best value for society and may undermine the PBAC process of evaluating cost-effectiveness.

Anomalies in the subsidies of drugs can undermine confidence in the system. In some cases, specific patient groups have different levels of access. For example, a drug that is not listed on the PBS may be subsidised for treatment of veterans. In other cases, a drug with proven efficacy may not be subsidised because data to support its cost-effectiveness have not been submitted to the PBAC. The cost of submitting an application for extension of indications or for an uncommon condition may not make economic sense to the drug company, particularly if the drug's patent is about to expire.

Evidence from small studies indicates that some tumour necrosis factor inhibitors, which are expensive biological drugs, are effective in patients with arthritis associated with Crohn's

disease. However, it is unlikely that a PBS submission will be made for this indication. Is it ethical that this patient group be denied access because of the rarity of their condition?

One option might be for the PBAC to specifically request submissions for 'essential' medicines for particular indications and consider ways to encourage such submissions. In the absence of a submission, an acceptable approach may be for the PBS to subsidise the use of these medicines for an indication after conventional therapies have proven ineffective, with an explicit requirement that an objective and subsequent clinically significant response would determine ongoing treatment subsidy. The financial risk to society would be small and patients with rare diseases would not be markedly disadvantaged or advantaged.

Sometimes patients needing expensive drugs are referred to a public hospital. Decision-making in hospitals allows more flexibility in prescribing, but unless the argument for using a drug is sound, and the evidence for efficacy and cost-effectiveness is rigorously evaluated in a consistent manner, our national system is undermined. This practice, unless carefully and responsibly undertaken, shifts costs from one sector of the health system to another. Hospital budgets are capped and the money spent on an expensive drug will not be available to treat other patients who may be equally or more deserving. A more consistent and equitable approach to the provision of expensive medicines to patients across all healthcare settings is worthy of exploration.[2,3,4]

Self-funding by patients is an option for registered, non-subsidised medicines. This option can be extremely challenging, particularly when patients and their families use their life savings to purchase a medicine. The patient has a right to be informed about such options, including the costs and why the medicine is not subsidised.[5] The clinician's role is critical in helping the patient come to a reasonable decision given the circumstances and the evidence for drug effectiveness and safety. It is important that the clinician's advice is not biased by competing interests. Information about PBAC decisions (regarding treatment subsidies) is helpful for patients who are considering paying for drugs. Efforts by the PBAC to communicate this information as public summary documents are very welcome.[6]

The concept of a 'worthwhile' response to treatment needs to be discussed explicitly with patients and their carers. There should be agreement about what constitutes an acceptable response before starting treatment, regardless of whether treatment is subsidised or not. The Cochrane Collaboration provides summaries for consumers that can sometimes assist.[7] Prescribers and patients have an obligation, both clinically and ethically, to monitor the effects of all medicines and be prepared to withdraw therapy if there is an inadequate response.

Clinicians have a responsibility to provide optimal care but to do so within the limits of our system (that is, without 'bending the law'), so that equity of access for all patients is preserved.[8,9] This balancing act is at times morally difficult. It would be made easier if the excessive manipulations of vested interests were not tolerated.

We want a health system that is transparent, accountable, and able to respond to both individual and societal needs. Demand for expensive drugs (and other therapies) will continue and funding for them will continue to be limited. Inevitably some patients will be denied access to some treatments. This will be better accepted if the community is educated and involved in open dialogue about priorities and values, and has confidence that the system is just – not only for access to medicines, but for all health services. This will require a continuing commitment to transparency by government[10] and the pharmaceutical industry, a willingness to consider continued improvements to the system, and a commitment by clinicians and consumers to work within the system.

The authors gratefully acknowledge guidance from members of the High Cost Drugs Working Group of the NSW Therapeutic Advisory Group.

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Professor Day is a member of the advisory boards to sponsors for adalimumab, infliximab and anakinra in Australia. He has

also been contracted to undertake clinical trials of etanercept, infliximab, adalimumab and anakinra. Recompense for these activities is placed in audited hospital trust funds for use in the research activities of the Clinical Pharmacology Department, St Vincent's Hospital, Sydney.

Christine Lu was supported by an Australian National Health and Medical Research Council postgraduate research scholarship (Grant No. 351040).

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New drugs for old

Paul Kubler, Clinical Pharmacologist/Rheumatologist, Royal Brisbane and Women's Hospital, Brisbane

Key words: evergreening, patent, perindopril.

(Aust Prescr 2006;29:148–9)

'Evergreening' is a strategy to extend the effective duration of a product's patent. Drug patent evergreening refers to filing 'new use' patent claims for a 'known' drug on the grounds of a change in formulation or method of administration rather than an alteration in the active chemical entity. Typically, these claims are made late in the life of the original patent. When successful, evergreening can delay the entry of generic products into the market while the originator company maintains the commercial advantage of a familiar, established brand. Multinational pharmaceutical companies have used evergreening to sustain the profitability of their 'blockbuster' (high sales volume) drugs for as long as possible.[1] Other strategies may have a similar effect.

'New' drugs have been developed which are single isomers of well-established chiral compounds.[2] Examples include esomeprazole (omeprazole) and escitalopram (citalopram). Despite the promise of potential benefits such as improved safety or enhanced efficacy because of different pharmacokinetic and pharmacodynamic properties, there is little evidence to suggest that these isomers offer clinically meaningful advantages.

Another strategy involves changing the pharmacokinetic properties of the drug. The creation of 'long-acting' or 'modified-release' formulations on the basis of altered absorption characteristics and/or extended plasma concentrations after administration is appealing, particularly if it helps patient compliance. However, there is often no significant benefit in terms of clinical efficacy or adverse events. In some cases (such as zolpidem for insomnia) the proposal appears to be counter-intuitive because the purpose of the drug is to create a short-term effect.

The recent regulatory approval of an alternative formulation of the 'blockbuster' ACE inhibitor, perindopril, is another example. The previous formulation contained perindopril erbumine in 2, 4 and 8 mg tablets. The new formulation contains an alternative salt, perindopril arginine, in different dose formulations of 2.5, 5 and 10 mg. According to an unreferenced statement from the manufacturer, the principal reason for the change is that the perindopril arginine formulation has improved stability which makes it 'better suited to the extremes of the Australian climate'. The new formulation offers no additional therapeutic benefit, however some problems with the changeover may arise. Compliance may be compromised by patient uncertainty about their therapy if prescribed and dispensed tablets in a 'higher' strength with different packaging without adequate counselling about the changes to the product. Busy general practitioners and pharmacists will be left with this burden of additional explanation.

Prescribing figures suggest that this 'salt change' may help the manufacturer maintain a significant commercial benefit. Perindopril erbumine was the seventh most prescribed pharmaceutical benefit in 2005–06 with over three million prescriptions (see page 167). Prescribing figures for general practitioners in August 2006 show that the new formulation (PBS-listed that month) entered in seventeenth place. This equates to an initial uptake of approximately 70% of the prescribing of the old formulation.[3]

There is an intriguing anomaly in the approved product information for the new formulation. Like its predecessor, the 'new' document contains pivotal clinical data from the EUROPA trial which used the original formulation, that is, 2, 4 and 8 mg doses of perindopril erbumine.[4] However, the new document portrays the original clinical data as dosing with 2.5, 5 and 10 mg of perindopril arginine. This is factually incorrect and the current product information does not explain the dosing conversion. We cannot be absolutely certain that the clinical trial would have had the same result if a different formulation had been used.

The regulatory events that have transpired appear to be in contrast to the intention of the Australian government to encourage greater use of generic medicines and to develop the generic drug industry in Australia. As the regulatory precedent has now been established, other companies with 'blockbuster' medicines reaching the end of their patent life may apply for the listing of an alternative formulation of their drug. The patents will soon expire on drugs such as amlodipine, atorvastatin and olanzapine.

When strategies are used to prolong the lifespan of 'blockbuster' drugs, prescribers should consider the rationale and trial evidence for minor variations before prescribing the 'new' drugs. It is difficult to give practical advice about how individual prescribers can respond. One proposal is that prescribers discuss the issue with their patients and consider changing therapy to a different drug in the same class. This is a possible action in the context of an ACE inhibitor because the drugs in the class have similar therapeutic effects.

Regulatory authorities need to respond to these strategies to encourage competition. The general community also needs to be better informed of this practice. Our focus must remain on access to affordable drugs for all Australians rather than prolonging patents for profit.

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Further reading

New drugs from old. Drug Ther Bull 2006;44:73-7.

Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Serotonin syndrome

Editor, – In the case report on serotonin syndrome precipitated by an over-the-counter cold remedy (Aust Prescr 2006;29:71), several mechanisms that may have caused this were proposed. I would like to add another contributing mechanism which relates to the patient taking methadone 70 mg daily. Although not a cytochrome P450 2D6 (CYP2D6) substrate, methadone is a potent CYP2D6 inhibitor.[1] It is possible that methadone is able to convert a CYP2D6 extensive metaboliser to a poor metaboliser. This process is known as phenocopying. There are very few data on methadone altering the pharmacokinetics of dextromethorphan in plasma. However, another CYP2D6 inhibitor, quinidine, can raise plasma dextromethorphan concentrations about 40-fold.[2] Hence, the combination of several drugs individually increasing the brain serotonin concentration and the likelihood of methadone increasing the dextromethorphan concentration may also have contributed in part to the patient developing serotonin syndrome.

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Assisting Aboriginal patients with medication management

Editor, – I agree with the letter from Dr Peter Lake regarding assisting Aboriginal patients with access to medicines (Aust Prescr 2006;29:59–60). I work in an Aboriginal Health Service in Port Augusta and we are often the first point of call of people coming down from Anungu Pitjantjatjara Lands. They often present with an empty dosette which is meant to be full of cardiovascular drugs. Sometimes there is no dosette at all. We then have to find, amongst other things, their Centrelink Health Care Card number before we can even think about prescribing.

They generally, and not surprisingly, have no idea as to the bureaucratic requirements of the Pharmaceutical Benefits Scheme. In the interests of compliance, our health service will pay for the drugs, provided they have their Health Care Card. We spend around $100 000 on this each year – none of which we receive funding for. Surely Section 100 should be attached to the patient and not to their address?

Jon Hunt
General practitioner
Pika Wiya Health Services
Port Augusta, SA

Managing painful paediatric procedures

Editor, – Further to the article 'Managing painful paediatric procedures' (Aust Prescr 2006;29:94–6), a recent Cochrane review[1] affirms what many breastfeeding mothers know instinctively: '…that neonates undergoing a single painful procedure should be provided either breastfeeding or supplemental breast milk for analgesia when available compared to positioning/pacifier/holding and swaddling. If it is not available/feasible to give breastfeeding or supplemental breast milk alternatives such as glucose or sucrose should be considered.'

Tricia Taylor
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Editor, –The methods and techniques outlined in the article 'Managing painful paediatric procedures' (Aust Prescr 2006;29:94–6) were excellent and relevant and are used on an almost daily basis in mixed and paediatric emergency departments. However, I feel that the minimisation of pain arising from the procedure of intravenous cannulation was inadequately covered. Intravenous cannulation of ill and injured children and adolescents is common and is often required as an emergency procedure within minutes of the patient presenting.

The use of subcutaneous local anaesthetic has been shown to significantly decrease the pain of intravenous cannulation[1,2,3], while not decreasing the success rate of intravenous cannulation attempts.[4] In children less than 24 months of age, the success rate with subcutaneous local anaesthetic was 73% versus 77% without subcutaneous local anaesthetic ($p = 0.5$).[5]

After skin preparation, the skin overlying the target vessel is pulled laterally and a small volume (approximately 0.2 mL) of 1% lignocaine is injected into the subcutaneous tissue using an insulin syringe. After allowing the skin to return to its former position, the cannula is inserted.

I would urge clinicians to investigate the use of subcutaneous local anaesthetic for intravenous cannulation in both adult and paediatric patients and to incorporate the technique into their practice.

Robert Douglas
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Adjunct Professor John Murtagh, author of the article, comments:

I do agree with the use of subcutaneous local anaesthetic to minimise the pain of intravenous cannulation. However, space precluded me from devoting more time to the issue. The use of this method also applies to the common emergency procedure of an intravenous cutdown. A combination of topical anaesthesia and subcutaneous injection is optimal, but not always practical.

Drug treatment of renal cancer

Nick Pavlakis, Medical Oncologist, Royal North Shore Hospital, Sydney

Summary

Renal cell cancer is best diagnosed early and treated by complete surgical excision. There is currently no standard effective drug therapy for advanced or metastatic renal cell cancer. Chemotherapy is ineffective, and immunotherapy has only modest activity and an uncertain effect on survival. Advances in the understanding of the biology of renal cell cancer have identified tumour angiogenesis as a target for drug therapy. New therapies have therefore emerged aimed at vascular endothelial growth factor and other growth factors mediating angiogenesis. These include bevacizumab, an antibody against vascular endothelial growth factor, and the oral drugs sunitinib and sorafenib.

Key words: angiogenesis inhibitors, bevacizumab, sorafenib, sunitinib.

(Aust Prescr 2006;29:151–3)

Introduction

In Australia, renal cell cancer is the eighth most common cancer in males and the ninth in females. In 2001 there were 2458 new cases (2.8% of all new cancers). The peak incidence occurs between 50 and 70 years. Renal cell cancers arising from the kidney epithelium account for 90–95% of all primary renal cell cancers and clear cell is the most common histology (75%).[1]

While patients may classically present with local symptoms and signs (flank pain, haematuria, abdominal mass), renal cell cancer is increasingly being diagnosed by the coincidental finding of a renal mass on imaging performed for other reasons. Despite this fortuitous presentation, 25–30% of patients will have advanced or metastatic disease.[1] Common metastatic sites include lung, soft tissue, bone, liver and central nervous system. Manifestations of advanced disease include fatigue (often with anaemia), fever, weight loss and hypercalcaemia.

Renal cell cancer is generally a very vascular tumour which is insensitive to chemotherapy and only modestly sensitive to immunotherapy. The best outcome for patients is with complete excision of localised disease. Some patients with limited metastatic disease may also benefit from surgical removal of metastases. About one in three patients will relapse following curative nephrectomy[1], hence the need for an effective systemic therapy remains.

Diagnosis and staging

The standard minimum evaluation of patients with a suspected renal cell tumour is a CT scan of abdomen and pelvis, a chest X-ray and urine analysis. A CT scan of the chest is more sensitive for small metastases.

The tumour stage is the most important prognostic factor. Patients with renal vein or vena cava involvement are still curable by complete resection. Hilar lymph node involvement is a worse prognostic sign. Patients with stage IV disease may have more distant local node involvement or distant metastases. Their five-year survival is less than 10%, but the prognosis can be somewhat variable. It is occasionally long and rarely (less than 1%) associated with spontaneous remission. Survival is dependent on histological grade, histological type, performance status, age, number and location of metastatic sites, time to appearance of metastases, and prior nephrectomy.

Treatment overview

Nephrectomy is the mainstay of treatment for patients with disease confined to the kidney, including those with involvement of local veins. Limited resection (partial nephrectomy) may be used in patients with small tumours (less than 4 cm), solitary kidneys or with tumours in both kidneys. Nephrectomy in patients with metastatic disease may be needed to alleviate haemorrhage or pain from the primary tumour.

Adjuvant therapy

The use of adjuvant systemic therapy following radical curative nephrectomy does not improve survival.[1] In selected patients with metastatic disease and good performance status at diagnosis, radical nephrectomy followed by interferon alfa may improve survival when compared with interferon alfa alone.[2]

Systemic therapy of advanced or metastatic disease

Until recently there was little evidence to support the routine use of systemic treatment. Chemotherapy has response rates (defined as a reduction of more than 50% in tumour size) of under 8% and is therefore of little value. This is because of the multidrug resistance protein found in proximal tubule cells, from which clear cell and papillary renal cell carcinoma are thought to originate.

A systematic review of immunotherapy has revealed little proven impact on the survival of patients with advanced renal cell cancer.[3] Interferon alfa alone is associated with only a modest tumour response rate (in approximately 15% of patients) and a median duration of response of approximately six months. High doses of interleukin-2 are associated with higher response rates (21%) and longer durations of response (up to 130 weeks) than lower doses, but with greater toxicity (nausea, vomiting, malaise and hypotension).[2] In view of these modest results, immunotherapy is not funded by the Pharmaceutical Benefits Scheme nor is it routinely used across Australia.

Combination immunotherapy and immunochemotherapy have been associated with greater tumour regression but at the cost of greater toxicity and without proven impact on survival. Other areas under study include tumour vaccines.

Biologic advances in renal cancer and angiogenesis

The greatest recent developments in renal cell cancer have involved improved understanding of its molecular pathogenesis, particularly the von Hippel-Lindau (VHL) tumour suppressor gene and its relationship to the angiogenesis mediated by vascular endothelial growth factor (VEGF).[1,4] VHL syndrome is an autosomal dominant disorder (germline mutation in one VHL gene allele) with inherited susceptibility to vascular tumours including clear cell renal cell cancer. Inactivation of the gene leads to overexpression of VEGF, which stimulates the angiogenesis that enables tumour growth. The lifetime risk of renal cell cancer in patients with the syndrome approaches 50%. Recently, the genetics underlying sporadic (non-hereditary) renal cell cancer have been shown to be similar with deletion of the VHL gene allele being found in 84–98% of patients with sporadic renal tumours.[1,4]

New treatments are focusing on gene products in the angiogenesis pathway. These include VEGF, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and transforming growth factor alpha (TGF-α).[1,3,4] VEGF exerts its biologic effect through interaction with transmembrane tyrosine kinase receptors found on the cell surface (VEGFR-1 to -4, with VEGFR-2 being most important for angiogenesis).[5] These angiogenic proteins are the targets of several drugs.

Bevacizumab

This humanised VEGF neutralising monoclonal antibody was the first of the anti-angiogenic drugs to show efficacy in renal cell cancer.[4,6] In a randomised, double-blind, phase II study in 116 patients with metastatic clear cell renal cell cancer, the time to progression of disease was significantly prolonged with high-dose bevacizumab (10 mg/kg intravenously fortnightly) compared with placebo (4.8 vs 2.5 months, $p < 0.001$). The trial was stopped after the interim analysis. Adverse drug reactions included reversible hypertension (8% needed treatment) and asymptomatic proteinuria (25% of patients).

Bevacizumab is approved in Australia for treatment of advanced colorectal cancer. The results of an international phase III trial of first-line interferon alfa with either bevacizumab or placebo in patients with metastatic renal cell cancer are awaited.

Tyrosine kinase inhibitors

In almost all cancers, overexpression of the epidermal growth factor receptor (EGFR) has been shown to correlate with a poorer prognosis and a more malignant phenotype. Erlotinib is a small molecule which inhibits the tyrosine kinase associated with EGFR. As 80–90% of patients with renal cell cancer have EGFR overexpression, trials of erlotinib with bevacizumab are in progress. Erlotinib's main adverse reactions are an acneiform skin rash and diarrhoea.

Sunitinib

Sunitinib is an oral tyrosine kinase inhibitor acting on, at least, PDGF and VEGFR-2. The activity of sunitinib (50 mg/day for 4–6 weeks) was recently reported in 63 patients with metastatic renal cell cancer who had previously been treated with either interferon alfa or interleukin-2.[6] There was a partial response in 25 patients and 17 had stable disease for three months or more. Median time to progression in the 63 patients was 8.7 months. Treatment was generally tolerated but was associated with fatigue, diarrhoea, stomatitis and leucopenias. A randomised trial comparing first-line interferon alfa and sunitinib has just been completed.[7] In this trial of 750 patients the response rate was significantly greater with sunitinib (24.8% vs 4.9%, $p < 0.001$), as was progression-free survival (47.3 weeks vs 24 weeks, $p < 0.001$).

Sorafenib

Sorafenib inhibits a variety of receptor kinase molecules that are involved in tumour growth and angiogenesis. Oral sorafenib has been evaluated in patients with advanced renal cell cancer who have previously received one systemic therapy, usually interleukin-2. A prospective randomised multicentre trial compared sorafenib (400 mg twice daily) to placebo in 769 patients.[6] Progression-free survival was doubled with sorafenib (24 compared to 12 weeks for placebo, $p < 0.000001$). The effect of sorafenib was seen across different risk groups and was unaffected by the prior therapy being interleukin-2 or interferon alfa. Sorafenib's effect on progression-free survival was mainly due to disease stabilisation as the tumour response rate was only 2%. Its effect on survival awaits further follow-up. The most common adverse effects were a hand-foot reaction (40%), rash and hypertension (requiring treatment in 17%).

Future directions

The plethora of new drugs in renal cell cancer has raised hope for patients. As the data from clinical trials are published, a number of options may emerge for treating patients to prolong disease-free and/or overall survival, with relatively mild toxicity. Sorafenib and sunitinib have just completed randomised

phase III trials in Australia. Ongoing research into molecular profiling and biomarkers may assist in identifying which patients will get the greatest benefit from these new treatments.

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[R] randomised controlled trial

Dr Pavlakis has served on advisory boards for Roche (bevacizumab in colon cancer and non-small cell lung cancer) and Pfizer (sunitinib for non-small cell lung cancer).

Self-test questions

The following statements are either true or false (answers on page 171)

1. Only 2–3% of patients with asymptomatic renal cell cancer have metastatic disease.
2. Adjuvant chemotherapy of renal cell cancer improves the survival of patients after radical curative nephrectomy.

Medicinal mishap

Brand confusion with digoxin

Prepared by John Balassa, General practitioner, Marrickville, New South Wales

Case

A 74-year-old retired man attended our surgery with a five-day history of upset stomach, nausea, an aversion to food, but no diarrhoea. He blamed some takeaway chicken for his problem.

His past history included valvular heart disease (mitral and aortic), myocardial infarction, chronic atrial fibrillation and partial thyroidectomy. The patient's usual medications were:

- Lanoxin PG (digoxin 62.5 microgram) three times a day
- Coumadin (warfarin)
- Lasix (frusemide)
- Neo-Mercazole (carbimazole).

On examination the physical findings were non-specific. The patient was given a proton pump inhibitor.

The patient returned 12 days later as he was still unwell. His pulse rate was 38 and irregular. He was having visual problems and he described blurred vision with honey coloured 'lakes' in his visual field, surrounded by yellow beads and dragonfly wing coloured areas.

Xanthopsia can be a sign of digoxin toxicity so his serum digoxin was checked. It was 6.2 nanomol/L which is a toxic concentration (therapeutic range 0.6–2.6 nanomol/L).

The patient's medications were reviewed and I found that a different brand of digoxin from his Lanoxin PG had been recommended. The box had a label of Sigmaxin PG, but it contained digoxin 250 microgram tablets. The patient had therefore been taking four times his usual dose. The digoxin was stopped and the concentration returned to normal. His pulse rate increased to 48 and gradually his xanthopsia disappeared. He developed marked oedema while off digoxin.

Comment

Any person with stomach upsets needs to have their medications checked. Loss of appetite is an early sign of digoxin toxicity. It may also cause nausea, vomiting, diarrhoea and abdominal pain. Xanthopsia (yellow vision) is a rare symptom.

The proliferation of new brands for old drugs can cause confusion. The patient took the new tablets but probably would have realised that he had not received his usual 'little blue' tablets. It is therefore important to explain to patients when there is going to be a change in their brand of medication. They need to understand why the substitution is being made and that they are not being given an additional medicine.

The different brands of digoxin are marketed by different companies, however these companies seem to belong to the same corporation. The need for different brands therefore appears to be unnecessary.

Drugs and gingival bleeding

Ivan Darby, Senior Lecturer and Head of Periodontics, School of Dental Science, University of Melbourne

Summary

Gingival bleeding is an uncommon adverse effect, but some drugs may directly or indirectly cause bleeding gums. The gums may bleed spontaneously or following oral hygiene procedures or eating. Bleeding may result from anticoagulants and drug interactions which increase the bleeding time. Adverse effects such as gingival enlargement, oral ulceration, xerostomia and immune suppression are known to increase the likelihood of bleeding gums.

Key words: anticoagulants, gingival enlargement, periodontitis.

(Aust Prescr 2006;29:154–5)

Introduction

Bleeding gums are usually the result of plaque-induced gingival inflammation and swelling. The tissues bleed when traumatised by cleaning or eating. Occasionally bleeding may result from direct trauma, viral, fungal or bacterial infection, dermatoses, or as a manifestation of a systemic condition such as erythema multiforme or lupus erythematosus. Although it is a relatively uncommon reaction, a number of drugs have adverse effects that may directly or indirectly cause gingival bleeding. They may affect the oral mucosa, teeth, periodontium (supporting structures of the teeth) or salivary glands and impair or change taste. The adverse effects on the periodontal tissues may result in gingival bleeding.

Anticoagulant therapy

Patients taking anticoagulants such as warfarin or heparin may develop gingival bleeding. Those taking a combination of anticoagulants and antiplatelet drugs, for example warfarin and clopidogrel after cardiac surgery, have an increased risk of spontaneous and prolonged gingival bleeding. Patients on warfarin should have their INR checked.

The bleeding usually results from toothbrushing, interdental cleaning such as flossing, or eating, but it can also occur spontaneously, such as at night onto the pillow. This bleeding is usually easy to control.

Gingival enlargement

One of the most common adverse effects of drugs on the periodontium is overgrowth of the gingival tissues.[1] The three main groups of drugs that cause gingival enlargement are the calcium channel blockers, anticonvulsants and immunosuppressants. The effect varies between patients and is influenced by age, gender, concomitant medication and genetic factors. It is somewhat dependent on the level of oral hygiene and the length of time the patient has been taking the drug.

The three most frequently implicated drugs are phenytoin, cyclosporin and nifedipine.[2] Phenytoin may cause overgrowth in 50% of dentate patients, cyclosporin in 30% and calcium channel blockers in 10%.[2] The three major drugs are usually prescribed with other medications, and expression of overgrowth may be affected by these other drugs. For example, nifedipine may be prescribed in transplant patients taking cyclosporin.[2]

Children and teenagers are more susceptible to phenytoin and cyclosporin-induced overgrowth than adults, suggesting that hormones, especially androgens, are important contributing factors. Males taking nifedipine are three times more likely to develop overgrowth than females, and men are also more prone to overgrowth when taking cyclosporin.

Other drugs may cause overgrowth, but only rarely. Tacrolimus seems to cause overgrowth in roughly 5% of kidney transplant patients, but in fewer liver transplant patients. Oral contraceptives have also been associated with some gingival overgrowth and bleeding mimicking the effects of pregnancy. This is probably a secondary reaction to irritation from plaque rather than a direct effect.

Clinical features

The overgrowth generally starts as painless enlargement of the papilla and proceeds to include the gingival margin, eventually developing to cover a substantial portion of the crown of the tooth. Histologically, the features of a drug-induced overgrowth are a fibrotic or expanded connective tissue and an enlarged gingival epithelium. It is thought that fibroblasts are primarily responsible. The gingival enlargement can be localised around one tooth, but is more commonly generalised throughout the whole mouth. It tends to affect the anterior teeth more severely.

While the overgrowth itself does not bleed, it is easily traumatised by the patient and will prevent adequate oral hygiene thus allowing the build-up of plaque. This accumulation will result in an inflammatory reaction with consequent bleeding. In addition, when the overgrowth reaches a large enough size it can be traumatised by biting.

Treatment

The treatment of overgrowth is initially by professional cleaning, but may require surgery to remove the overgrown tissue and restore normal architecture. If the patient remains on the causative drug then the problem will recur, possibly requiring re-treatment a couple of years later. The adverse effect may have to be accepted if the drug cannot be changed (Fig. 1).

Suppression of the natural flora

The use of antibiotics (both systemically and topically as a mouthwash), oral steroids and other drugs which allow the overgrowth of organisms such as *Candida albicans*, may occasionally cause an erythematous reaction which can result in gingival bleeding. This may be exaggerated by the presence of an upper denture, as some patients get a candidal infection underneath the plate.

Xerostomia

Many drugs cause a dry mouth or reduce the salivary flow, especially in elderly patients whose salivary flow is already diminished by age. These include antidepressants, antihypertensives, amphetamines, antihistamines, anticholinergics and drugs for Parkinson's disease. The effect of a dry mouth will increase both dental caries and periodontal disease due to decreased flushing of the mouth by the saliva and a reduced buffering capacity. The gingival inflammation from the periodontal disease may result in bleeding gums.

Immunosuppression

Drugs that suppress the immune response, such as methotrexate, can cause aplastic anaemia, agranulocytosis and thrombocytopenia. These conditions can result in a much more rapid destruction of periodontal tissues, excessive bleeding, a prolonged gingival bleeding time, oral ulceration, swollen gingiva or opportunistic infections. The patient may notice gingival bleeding spontaneously or following oral hygiene procedures and eating. Patients who develop gingival bleeding while taking these drugs need a full blood count.

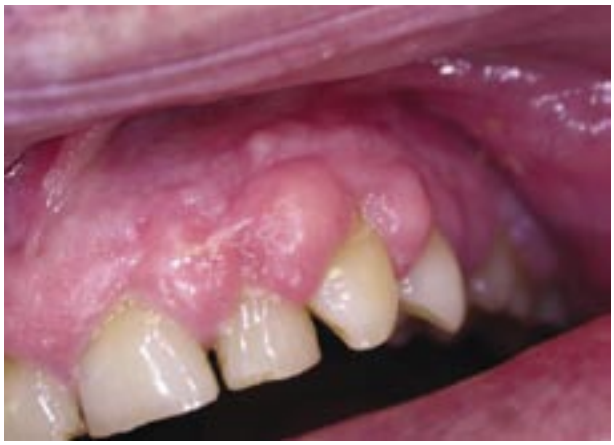
Drug interactions

Drug interactions are especially common in elderly patients who may require treatment for several medical conditions. For example, patients taking non-steroidal anti-inflammatory drugs with anticoagulants such as warfarin, could have excessive and prolonged gingival bleeding because of the interaction. The interactions of warfarin and antiplatelet drugs are particularly problematic.[3] The role of complementary medicines in increasing bleeding time is uncertain. However, a number of herbal preparations may interact with warfarin to increase its anticoagulant effect, including garlic and those containing coumarins such as arnica.[4]

Fig. 1

Gingival overgrowth as an adverse effect of nifedipine

Although this tissue is healthy, the patient complained that he was biting on the lower anterior gingival enlargement (not shown). The patient's doctor and periodontist changed his antihypertensive medication four times, but nifedipine was found to be the best for controlling his blood pressure. The patient accepted that he would continue to have gingival enlargement while on nifedipine. The tissue was surgically resected, but this procedure may need to be repeated in a few years.



Conclusion

Considering the large number of drugs prescribed, bleeding from the gums is an infrequent adverse effect. However, a number of medications can directly or indirectly result in bleeding from the gingival tissues. Patients presenting with excessive or prolonged gingival bleeding need to be thoroughly examined, and have a complete medical and medication history taken. Referral to a dentist or periodontist should be considered.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 171)

3. Up to 50% of patients taking phenytoin may develop gingival enlargement.
4. Nifedipine is responsible for most of the gingival enlargement associated with calcium channel blockers.

Spider bite: a current approach to management

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Summary

Although spider bite is common, most spider bites cause minor effects and do not require treatment. More significant effects result from redback and, less commonly, from funnel-web spider bites. Redback spider envenoming causes local, radiating and regional pain, sometimes associated with local or regional diaphoresis, non-specific systemic features, and less commonly, other autonomic or neurological effects. Antivenom is recommended for severe or persistent pain and systemic effects. Funnel-web spider envenoming can rapidly cause life-threatening effects, but it can be treated effectively with antivenom. Envenoming is characterised by excessive autonomic activity, neuromuscular excitation and pulmonary oedema. Clinical effects attributed to suspected spider bites such as ulcers, should be thoroughly investigated for other causes including infectious, inflammatory, vascular and neoplastic conditions.

Key words: antivenom, envenoming, funnel-web, necrotic arachnidism, redback.

(Aust Prescr 2006;29:156–8)

Introduction

Spider bites are a common problem with numerous calls being made to poisons information centres annually. There is ongoing misinformation about the effects of suspected spider bites, because past information has been based on circumstantial evidence. A definite spider bite is where there is evidence of a spider biting (effects), the spider is seen at the time and it is then identified by an expert. In a study of 750 definite spider bites the majority caused only minor effects and did not require treatment in a healthcare facility. Moderate to severe envenoming resulted almost exclusively from redback spiders and rarely funnel-web spiders.[1] Pain or discomfort occurs in all spider bites. Other local effects include fang marks or bleeding (larger spiders), erythema or red marks (about two-thirds of cases) and itchiness.

Spider bites are best considered in three medically relevant groups: big black spiders, redback spiders and all other spiders. Big black spiders are any large black-looking spiders that may be a funnel-web spider. Patients bitten by big black spiders must be managed as having suspected funnel-web spider bites until there are no signs of envenoming after four hours. Redback spiders are fairly easy to identify and their bites do not cause rapidly developing or life-threatening effects but many cause significant pain and systemic effects. All other spiders in Australia cause minor effects. If the patient has not been bitten by a big black spider or a redback spider they can be reassured and no further treatment is required.

Necrotic arachnidism and white-tail spider bite

Necrotic arachnidism, or more commonly in Australia white-tail spider bite, has become an entrenched diagnosis despite the lack of evidence that spider bites cause necrosis or ulcers in Australia. In a prospective study of definite white-tail spider bites there were no cases of necrotic ulcers. The bites caused pain in only 21% of patients, pain and a red mark for 24 hours in 35%, or a persistent red mark and associated itchiness, pain or lump lasting for about seven days in 44%.[2] Current evidence suggests that spider bites are very unlikely to cause necrotic lesions and such cases presenting as suspected spider bites should be thoroughly investigated for other causes. A recent series of suspected white-tail spider bites found other causes when appropriately investigated.[3]

> Spider bites are very unlikely to cause necrotic lesions

It is important to distinguish patients presenting with clinical effects (usually skin lesions or ulcers) that have been attributed to a spider bite and patients with a clear history of a definite spider bite. Diagnosis and investigation in patients with ulcers must focus on important causes of necrotic ulceration including infectious, inflammatory, vascular and neoplastic conditions.[3]

Redback spider bites

Redback spider bites are the commonest cause of significant envenoming in Australia. Severe and persistent pain occurs in a half to two-thirds of cases and may be severe enough to prevent sleep in about a third of cases.[4] Redback spiders live in dry or dark areas and commonly cause bites when people put on shoes or when they move outdoor furniture, bike helmets, firewood or pot plants. Most bites are by the larger female spider and in most cases the spider is recognised by the patient if it is seen. Redback spider bites occur in the warmer months and peak between January and April.

Envenoming by redback spiders is characterised by local, radiating and regional pain which may be associated with local and regional diaphoresis, non-specific systemic features, and less commonly other autonomic or neurological effects (see box). The bite may not be felt or may only be an initial irritation or discomfort. Pain increases over about an hour and may radiate proximally to the limb or less commonly the trunk. These spiders are small and rarely leave fang marks or cause local bleeding. Local erythema is common and local diaphoresis occurs in about a third of cases. Common non-specific effects include nausea, lethargy, malaise and headache. Numerous other systemic effects are reported less commonly (see box). The effects last about 1–4 days with almost all cases resolving within one week. There have been no deaths since the 1950s. The diagnosis is based on the history, but can be difficult in young children and infants who may present with undifferentiated pain or distress.

Treatment

There has been controversy over the management of redback spider bites, particularly who should be treated with antivenom and the route of administration. Pressure bandaging is contraindicated in redback spider bites. A recent prospective study has suggested that many patients would benefit from antivenom treatment because untreated patients had persistent pain and many were unable to sleep because of it.[4] Although intramuscular antivenom has been recommended and used for over 40 years there are concerns that it is less effective than intravenous antivenom. A recent randomised controlled trial was unable to demonstrate a difference between intramuscular and intravenous routes, but the trial was small and many patients were lost to follow-up.[5] A larger ongoing randomised controlled trial hopes to determine the more effective route. Despite concern about the safety of intravenous antivenom, diluted intravenous antivenom appears to have a similar low reaction rate to intramuscular antivenom.

Symptomatic relief is probably only effective in the most minor cases and even parenteral opiates are ineffective in many cases. Antivenom is recommended for systemic envenoming and for severe local or radiating pain. The current recommendation is an initial dose of two vials of antivenom given as an intramuscular injection or as a slow intravenous infusion over 15 minutes. Intravenous antivenom may be preferred for severe envenoming, in children or if there is a poor response to intramuscular antivenom. Antivenom has been safely used in breast-feeding and pregnant women. The use of antivenom 24–96 hours after the bites is reasonable based on the natural course of envenoming and reported response in these cases.

Redback spider bite: clinical effects

Local and regional effects

- increasing pain at the bite site over minutes to hours, which can last for days
- pain radiating from the bite site to the proximal limb, trunk or local lymph nodes
- local sweating
- regional sweating with unusual distributions of diaphoresis, e.g. bilateral below knee diaphoresis
- less common effects include piloerection, local erythema, fang marks (5%)

Systemic effects

- nausea, vomiting and headache
- malaise and lethargy
- remote or generalised pain
- abdominal, back or chest pain
- less common effects include hypertension, irritability and agitation (more common in children), fever, paraesthesia or patchy paralysis, muscle spasms, priapism

Adverse effects

Early allergic reactions to redback spider antivenom are rare (less than 2%) and premedication is not recommended. Serum sickness is uncommon, but all patients should be warned about it. For moderate to severe cases of serum sickness a short course of prednisone is recommended. Patients who do not require treatment with antivenom can be discharged and told to return if they require treatment for the pain or systemic effects.

Funnel-web spider bites

Funnel-web spiders (Hexathelidae, Atracinae: *Atrax* and *Hadronyche* species) are the most dangerous spiders in Australia. Severe envenoming has only been reported from southern Queensland to southern New South Wales, but it is rare (5–10 cases annually requiring antivenom).[6] However, funnel-web spider envenoming is an important clinical condition because of the life-threatening effects, rapid onset and the availability of effective antivenom.

Funnel-web spider bites cause immediate local pain, and usually puncture marks and local bleeding. In many cases this is the only effect because severe envenoming develops in only a proportion of cases. In some cases mild envenoming occurs with local neurotoxicity (paraesthesia, numbness or fasciculations) and/or non-specific systemic effects. Severe envenoming is characterised by:

- autonomic excitation – generalised diaphoresis, hypersalivation, lacrimation, piloerection, hypertension, bradycardia or tachycardia, miosis or mydriasis
- neuromuscular excitation – paraesthesia (local, distal and oral), fasciculations (local or generalised, commonly tongue fasciculations), muscle spasms
- non-specific systemic effects – abdominal pain, nausea, vomiting, headache
- pulmonary oedema and less commonly myocardial injury
- central nervous effects – agitation/anxiety, and less commonly drowsiness or coma.

Severe envenoming has been reported for six species, including the Sydney funnel-web spider (*Atrax robustus*), the southern tree funnel-web spider (*Hadronyche cerberea*) and northern tree funnel-web spider (*Hadronyche formidabilis*). The Sydney funnel-web spider causes severe envenoming in 17% of cases, but the two tree funnel-web spiders cause severe envenoming in over half of cases.[6]

Treatment

First aid for funnel-web spider bite is a pressure immobilisation bandage and rapid transport to hospital. The mainstay of treatment is funnel-web spider antivenom, admission to a critical care area and monitoring for 12–24 hours until all evidence of envenoming has resolved. Funnel-web spider antivenom appears to be effective in bites by *Atrax* and *Hadronyche* species. Premedication is not required and early allergic reactions and serum sickness are rare.[6] The initial dose of antivenom is two vials which can be repeated every 15–30 minutes until envenoming has resolved.

Patients with funnel-web spider bites without symptoms of severe envenoming, or bites by unidentified big black spiders in eastern Australia, should initially be treated as suspected cases of envenoming. These patients should be observed for 2–4 hours and the pressure immobilisation bandage can be removed once funnel-web spider antivenom is available. If there is no evidence of severe envenoming after two hours, it is unlikely to occur[6], but it is prudent to observe the patient for four hours.

Mouse spider bites can cause local neurotoxic effects (paraesthesia, numbness) and non-specific systemic effects in some cases. However, because they are large black spiders, the bites should be treated as suspected funnel-web spider bites.

A clinical toxicologist can be contacted for advice on managing severe envenoming through the Poisons Information Centre (phone 13 11 26).

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For images of spiders: see Clinical Toxinology Resources website. http://www.toxinology.com [cited 2006 Nov 9]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 171)

5. Most patients bitten by redback spiders only need analgesia and do not require antivenom.
6. Pregnant women should not be given spider antivenom.

Message to all 2006 graduates in medicine, pharmacy and dentistry

If you are graduating in Australia this year and wish to continue receiving *Australian Prescriber*, please complete and send in the distribution form on the inside back cover of this issue, or register online at www.australianprescriber.com You can also request a new issue email alert by visiting the website.

How prescription drugs are developed

Dominic Barnes, Vice President, Medical and Scientific Affairs, Janssen-Cilag Australia, and part-time General Practitioner, Sydney

Summary

Modern drug development is a risky business both for pharmaceutical companies and patients. Many thousands of promising compounds need to be tested. Following discovery of a promising compound, extensive animal and human trials are undertaken in consultation with government regulators under strict ethical conditions to provide evidence that the new drug works, is safe and is manufactured using the highest quality standards. This evidence is evaluated by the regulatory authorities and, if acceptable, leads to the registration of the new medicine. Once registered the new medicine may be submitted for government subsidy. In Australia, if the drug demonstrates cost-effectiveness it may become available on the Pharmaceutical Benefits Scheme.

Key words: clinical trials, drug evaluation, drug industry.

(Aust Prescr 2006;29:159–61)

Introduction

In April 2006 six healthy young male volunteers required intensive care following administration of a new experimental compound. The investigational drug TGN1412 was a monoclonal antibody specific for a membrane receptor present on the surface of white blood cells. It was developed by TeGenero, a pharmaceutical company, and had been trialled in monkeys at 500 times the dose initially administered to humans in the phase I safety trial. Despite this, a reaction occurred that had not been seen or suspected from the animal trials, and all six volunteers very nearly died. Subsequent investigations have suggested that the non-binding tail of the antibodies formed multiple cross-linkages and induced a massive flood of inflammatory mediators, referred to as a cytokine storm, resulting in an overwhelming systemic inflammatory reaction and multiple organ failure. This tragedy illustrates the hazards of drug development.

Drug development has moved from its origins of simple empiricism and serendipitous use of plant-derived alkaloids, to a highly complex systematic process. It starts with basic research, which can involve molecular biology and genetic manipulation, vast molecular libraries and automated screening, and computer-assisted drug design. From this, promising compounds are tested in animal studies before going on to human trials.

Drug discovery

In an ideal world, a new drug is discovered in a purposeful way in response to an unmet clinical need. Drugs are mainly developed by pharmaceutical companies, although the early research, which leads to identification of either a biological target such as a new cell membrane receptor, or a new compound that interacts with a biological target, may also be performed in government-funded research institutions.

Techniques such as computer-assisted drug design are employed to elucidate the three-dimensional structure of a particular biological target and to design a molecule that interacts specifically with that target. Drug researchers also have access to libraries containing large numbers of molecules which are screened against multiple *in vitro* biological targets using high-throughput computerised processes looking for a significant receptor-ligand reaction.

More recent advances in biotechnology have provided drug researchers with new biological targets such as cell membrane channels, as well as active complex biological proteins such as hormones. An example of this is the discovery that erythropoietin is a key regulator of red blood cell production. The identification of the gene encoding its amino acid sequence, and the subsequent insertion of this human gene into a non-human mammalian cell, allowed erythropoietin to be mass-produced for the treatment of anaemia in patients with renal failure.

Despite these technological advances, serendipity has been responsible for many of today's medicines. Sildenafil, for example, was initially investigated in clinical trials as a proposed anti-anginal drug, but was noted to have a particular adverse effect. This led to a re-evaluation of its development plan, and its subsequent commercialisation as an erectile dysfunction treatment.

Once a promising new compound has been identified, it needs to undergo thorough testing to ensure that it works and is safe. Usually only a handful of the thousands of compounds tested make it through this testing to be available in pharmacies as new drugs.

Animal studies

Toxicology studies in animals are conducted before a compound can be used in humans, and government medicines regulatory

agencies such as the US Food and Drug Administration (FDA) are closely consulted in the design of these trials. Usually two mammalian species are tested, such as rats and guinea pigs, using single and repeated dose administration regimens. Depending on the type of drug being tested, specific strains of purpose-bred animals are also used, such as rats with diabetes for new hypoglycaemic drugs, or guinea pigs with a predisposition to osteoarthritis for testing of non-steroidal anti-inflammatory drugs. Reproductive toxicology tests on male and female animals with dosing commencing four weeks prior to mating are conducted to determine effects on fertility in both sexes, on embryogenesis, and on fetal malformation.

Clinical trials

Once the animal studies have suggested an appropriate dose and have provided adequate evidence that the drug candidate has some efficacy and appears to be safe, human studies may be started. Clinical trials must be conducted according to Good Clinical Practice, which defines a set of very strict conditions developed by international regulatory bodies in agreement with the principles espoused in the Declaration of Helsinki. The design of these trials is determined in consultation with one of the major drug regulators such as the FDA in the USA. Classically, there are four phases of trials in the development of a new medicine.

Phase I

Phase I trials are typically conducted in healthy young male volunteers in groups of about 10–20. They are designed to assess how the drug is absorbed, distributed, metabolised and excreted by the body (that is, pharmacokinetics) and to establish the safe dose for phase II trials.

Phase II

Phase II trials are designed to examine what effect the drug has on the body (that is, pharmacodynamics) such as heart rate, blood pressure and cognitive effects, depending on the disease the drug is being developed to treat. These studies are usually conducted in 50–100 patients with the disease rather than healthy volunteers as in phase I.

In phase I and II trials a very low dose of the investigational drug is usually given to a small number of people who are then monitored closely in a purpose-designed early phase unit. An early phase unit is similar to an intensive care ward with about 10 beds, each with sophisticated monitoring and emergency treatment facilities such as electrocardiograms, electroencephalograms, blood chemistry and haematology analysers, oxygen, intravenous fluids and resuscitation equipment. These units are often located within a hospital. If the first participants show no ill effects the dose is increased in the next group. This process is repeated several times until a minimum effective and maximum tolerated dose is established. The maximum tolerated dose is reached when a specified percentage of participants experience adverse events as predefined in the study protocol.

Phase III

Phase III trials involve larger numbers of patients with a particular disease or condition and are usually randomised comparative double-blinded studies. The comparator is either placebo or an active drug already well established as treatment for the disease under investigation, or both. Typically, several hundred patients are exposed to the investigational drug in these trials, which are designed to show efficacy and safety and to better determine the appropriate dose range. The cost-effectiveness of a drug is sometimes analysed during the phase III trial stage. In a typical development program for a new medicine, several phase III trials are required by the regulatory authorities. Unfortunately, even with a large-scale phase III program, uncommon adverse events may not be detected until the new medicine is used widely in the community. As a rule of thumb, you need to expose about three times as many patients to a drug to reliably detect an adverse event that has a particular incidence; for example, to detect a 1 in 1000 event, 3000 patients need to be exposed.

Phase IV

Phase IV (post-registration) trials are those undertaken after the new medicine has been registered and are usually randomised controlled trials. They are designed to answer important questions which help determine its clinical position (for example first-, second-, or third-line use), cost-effectiveness, and safety profile in certain patient populations.

Phase IV trials may be very large studies involving thousands of patients for several years. They are very expensive but often more useful than the earlier registration studies because they allow broader, more realistic patient groups to be studied.

Publication of study results

Timely publication of study results is critically important to allow free and rapid dissemination of new research. However, studies with negative or unfavourable outcomes are sometimes not submitted for publication, a practice frowned upon by industry, clinicians and academia. Acceptance of a proposed publication by a medical journal is dependent on many factors such as its accuracy and quality, as well as its relevance and interest to readers. Failings in any of these areas may mean a study is not published.

The pharmaceutical industry has adopted a global standard proposed by the International Committee of Medical Journal Editors whereby a study must be registered on a public website (such as the FDA's www.ClinicalTrials.gov, or the National Health and Medical Research Council's www.actr.org.au) before

the enrolment of the first patient, if it is to be published in any of the major medical journals.[1] This allows doctors and patients to easily see what studies are being conducted with particular drugs for any given therapeutic area or disease state.

Drug approval and commercialisation

Once the phase I to III program is complete the pharmaceutical company sponsor compiles all the data about the new medicine which are then assessed by the government regulatory authorities (such as the FDA in the USA, the Therapeutic Goods Administration (TGA) in Australia and Medsafe in New Zealand). The regulators examine the evidence relating to the chemistry and manufacture of the new drug, the animal toxicology, and the clinical studies. They specifically evaluate the methodological quality of the trials, as well as the efficacy and safety of the drug (the first three 'hurdles'). A new medicine must have an acceptable benefit:harm ratio in a well-defined patient group to allow it to be registered for that specific indication. Once the regulator has approved the new medicine, which can take around 14 months in Australia, the sponsoring pharmaceutical company can begin to sell and promote it.

In Australia, and increasingly in other countries, a 'fourth hurdle' for wider public access to new drugs exists – demonstration of cost-effectiveness relative to current management. After registration by the TGA, a pharmaceutical company can apply to have the drug considered for government subsidy under the Pharmaceutical Benefits Scheme. This will only be granted if the sponsor company can show that the new medicine is cost-effective compared to currently used medicines.

Conclusion

Drug discovery, development and commercialisation is a long, expensive and risky process both for the sponsoring company and the trial participants involved. For each successful entrant to the market, thousands of compounds fail to survive the testing and regulatory review process, however, the rewards for successful innovation can be substantial.

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Dr Barnes is the local medical director for a pharmaceutical company, Janssen-Cilag. He has also worked full-time in the past for Bayer and Pfizer, and has provided consulting services to several biotechnology companies, contract research organisations, and the National Prescribing Service.

Self-test questions

The following statements are either true or false (answers on page 171)

7. Phase I trials are usually conducted in healthy volunteers.
8. Uncommon adverse events are mainly identified before a drug is approved.

'Guiding principles for medication management in the community'

The Australian Pharmaceutical Advisory Council has published new guidelines for the management of medicines for people who follow complex medication regimes in their own homes. Launched in August 2006, the 'Guiding principles for medication management in the community' will be of benefit for older people with complex medication management. The guidelines recognise the importance of partnerships between a variety of health and community care providers. An electronic version of the principles is at http://www.health.gov.au/internet/wcms/publishing.nsf/content/nmp-guiding. The paper version of the book can be ordered from the online address or from (02) 6289 7753.

Antibodies to cyclic citrullinated peptides: how they assist in the diagnosis of rheumatoid arthritis

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Summary

New assays for antibodies against artificially generated cyclic citrullinated peptides are of importance in the assessment of patients with suspected rheumatoid arthritis, especially during the early stages of the disease. These assays have similar sensitivity but are more specific for rheumatoid arthritis than the traditional rheumatoid factor test. The combined use of these assays and tests for rheumatoid factor provides more information than either test alone, particularly with respect to differentiating potential cases of rheumatoid arthritis from early cases of undifferentiated arthritis.

Key words: anti-keratin antibodies, rheumatoid factor.

(Aust Prescr 2006;29:162–4)

Introduction

Around 80% of patients with rheumatoid arthritis have a positive test for rheumatoid factor, but the test may take many years to become positive. The test for rheumatoid factor therefore has a low sensitivity in the early stages of rheumatoid arthritis. Furthermore, tests for rheumatoid factor may be positive in some patients with other inflammatory diseases (including Sjogren's syndrome), infections (bacterial or chronic viral, such as viral hepatitis) and haematological disorders (including cryoglobulinaemia and some plasma cell disorders). Rheumatoid factor therefore also has a relatively low specificity so it is not an ideal test in the early detection and confirmation of rheumatoid arthritis.

Alternatives to rheumatoid factor

In view of the limitations in interpreting rheumatoid factor results, there has been interest in developing better tests for the diagnosis of rheumatoid arthritis. It has been known for many years that senescent (ageing) cells display antigens that are not present on other cells, and that patients with rheumatoid arthritis may generate antibodies against these antigens. This was first reported in 1964 with the test for anti-perinuclear factor antibodies that were directed against senescent buccal mucosal cells. However, this test was challenging to perform and interpret. Buccal mucosal cells were later found to express filament aggregating protein (filaggrin) and in 1979, antibodies directed against keratin (anti-keratin antibodies) in senescent oesophageal cells were identified.

It now appears that anti-perinuclear factor, anti-filaggrin and anti-keratin antibodies are essentially the same antibody detected by different assays. Of these, only assays for anti-keratin antibodies are currently performed by a limited number of Australian pathology laboratories.

Antibodies to citrullinated peptides

As cells age, some of their structural proteins undergo 'citrullination' under the direction of cellular enzymes. Arginine residues undergo deimination to form the non-standard amino acid citrulline. Citrullinated peptides fit better into the HLA-DR4 molecules that are strongly associated with rheumatoid arthritis development, severity and prognosis. It is also known that many types of citrullinated peptides are present in the body, both in and outside joints.

In the late 1990s, antibodies against citrullinated peptides were 'discovered'. Sera from patients with rheumatoid arthritis contain antibodies that react against different citrullinated peptides, however the antibodies from each individual do not react against all possible citrullinated peptides. Artificial cyclic citrullinated peptides (CCP) have therefore been developed to mimic the range of conformational epitopes present *in vivo*. These artificial peptides are used in the current assays for antibodies against CCP (anti-CCP assays). The patient's serum is mixed with these peptides and if it contains anti-CCP antibodies they will bind together. This binding can be detected by an enzyme-linked immunosorbent assay.

Anti-CCP assays can be considered as alternatives to assays for anti-keratin antibodies. Table 1 compares assays for anti-CCP antibodies, anti-keratin antibodies and rheumatoid factor.

Table 1

Comparison of antibody assays for rheumatoid arthritis

	Assay type		
	Anti-CCP* antibodies	**Rheumatoid factor**	**Anti-keratin antibodies**
Sensitivity (%) †	39–94% (64%)	25–95% (60%)	23–47% (42%)
Specificity (%) †	89–98% (94%)	31–95% (79%)	94–97% (96%)
Availability	Offered by many laboratories in Australia	Widely available	Limited availability
Comments	Results (including numerical values) may vary between different laboratories depending on assay used	False positive results occur in a range of inflammatory, infectious and haematological diseases	Less sensitive than anti-CCP assays which can be considered as a replacement for this test

* CCP cyclic citrullinated peptides

† range of values from various studies (mean value)

Clinical utility of anti-CCP assays

Anti-CCP assays are offered by many, if not the majority, of private and public pathology services in Australia. The assay requires 5 mL of clotted serum which can also be used to test for rheumatoid factor. The turnaround time from these laboratories is generally less than two weeks.

Diagnosis of rheumatoid arthritis and prediction of disease severity

Anti-CCP assays have a sensitivity of 39–94% (mean 64%) in patients with established rheumatoid arthritis, with a specificity of 89–98% (mean 94%).[1] This means that anti-CCP antibodies are more specific than rheumatoid factor for the presence of rheumatoid arthritis but have similar sensitivity (Table 1). A positive result for anti-CCP antibodies also appears to be a better predictor of greater disease severity than a positive result for rheumatoid factor. The combined use of anti-CCP assays and rheumatoid factor tests also provides better prognostic information than using anti-CCP assays alone.

The anti-CCP assays appear to be of particular value in the evaluation of patients with early-onset arthritis. They have a sensitivity of 50–60% and specificity of 95–98% for the development of rheumatoid arthritis. This is useful during the early phase of rheumatoid arthritis, when patients may have milder and non-specific symptoms which make a definitive clinical diagnosis difficult. Making a definitive diagnosis of rheumatoid arthritis during this early phase is important, as early aggressive therapy within the first three months of the development of joint symptoms may decrease the probability of developing severe joint disease. A prospective study of 318 patients with early undifferentiated arthritis reported that within one year 83% and within three years 93% of patients who were positive for anti-CCP antibodies developed symptoms and signs that enabled a diagnosis of rheumatoid arthritis, compared with 25% of patients who were negative for anti-CCP antibodies.[2]

Anti-CCP antibodies have been shown to pre-date the development of clinical disease. However, neither rheumatoid factor nor anti-CCP assays should be used to screen for rheumatoid arthritis in healthy individuals in the absence of clinical symptoms.

Several studies have shown that while the majority of patients with rheumatoid arthritis will be positive for rheumatoid factor and anti-CCP antibodies at some point during their disease, these tests may not be positive at the same time. For example, while patients may initially have a positive anti-CCP assay, it may take many years to become rheumatoid factor positive. In addition, a minority of patients will only be positive for either rheumatoid factor or anti-CCP antibodies. This is another reason why, ideally, both tests should be performed in the assessment of a patient with suspected rheumatoid arthritis, including all patients with persistent arthritis of more than six weeks duration.

Uncertain role in monitoring disease activity

At present, there are conflicting data regarding the utility of serial anti-CCP assays to monitor the activity of rheumatoid arthritis and its response to therapy. Some studies have suggested that the correlation between anti-CCP antibodies and disease activity was stronger than for rheumatoid factor, but at least one study found the reverse. Furthermore, studies looking at patients who have responded to disease-modifying antirheumatic drugs or tumour necrosis factor inhibitors have not shown a consistent fall in concentrations of anti-CCP antibodies or rheumatoid factor. Based on the available data, serial monitoring of anti-CCP antibodies is not currently recommended. Clinical assessment and serial measurements of inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, are better established methods of monitoring.

Comparison of results between different laboratories

While the majority of currently available anti-CCP assays are based on one particular manufacturer's assay (for patent reasons), other manufacturers are actively developing their own anti-CCP assays (likely to be marketed as 'third or subsequent' generation assays). Such assays will probably produce different results and numerical values from the currently available assays. We therefore recommend caution when comparing the results (particularly numerical values) of anti-CCP antibody testing from different laboratories.

Conclusion

Assays that detect antibodies to CCP are a new and important development in the diagnosis of patients with rheumatoid arthritis, particularly during the early phases of the disease when making a definitive diagnosis on clinical grounds may be difficult. The use of anti-CCP assays and rheumatoid factor in combination provides better diagnostic and prognostic information than either test alone.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 171)

9. Some patients with rheumatoid arthritis do not have a positive test for antibodies to cyclic citrullinated peptides.
10. The response to treatment of patients with rheumatoid arthritis is best assessed by serial assays of antibodies to cyclic citrullinated proteins.

Medicines Australia Code of Conduct: breaches

Medicines Australia has a code of conduct to guide the promotion of prescription drugs by pharmaceutical companies in Australia.[1] Complaints are reviewed by the Code of Conduct Committee and the results are published in its annual report. The report for 2005–06 is available on the Medicines Australia website.[2]

There were 27 new complaints in 2005–06. Seven are unresolved, but the report includes three complaints held over from the previous year. The Code of Conduct Committee found breaches in 11 of the complaints it finalised (Table 1).

The number of complaints coming from health professionals almost equalled the number made by companies about their competitors. In one case eight pharmaceutical companies were alleged to have breached the Code of Conduct with their advertisements in electronic prescribing software.[3] The Code of Conduct Committee required six of these companies to revise their advertising.

During the year the Code of Conduct Committee had to consider whether a venue was of more than 'reasonable quality'. It also judged if the hospitality offered to specialists was 'sumptuous' or 'simple and modest'. Probably for the first time the Code was applied across the Tasman. A cruise vessel on Auckland harbour was not considered to be an appropriate place for an educational event.

In total 11 complaints were found to have identified breaches of the Code of Conduct. Details of the complaints can be found in the annual report.[2] Analysis of these complaints should lead to improvements in the Code. The 15th edition of the Code of Conduct should be available in 2007.

References

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Table 1

Breaches of the Medicines Australia Code of Conduct July 2005 – June 2006

Company	Complaint		Sanction imposed by Code of Conduct Committee
	Drug – brand name	Drug – generic name	
Alcon	Patanol	olopatadine	Advertisement in prescribing software to be revised
Boehringer Ingelheim	Asasantin	aspirin/dipyridamole	Advertisement in prescribing software to be revised
GlaxoSmithKline	Avandia	rosiglitazone	Advertisement in prescribing software to be revised
Pfizer	Norvasc	amlodipine	Advertisement in prescribing software to be revised
	Celebrex	celecoxib	Advertisement in prescribing software to be withdrawn
Sanofi-Aventis	Actonel	risedronate	Advertisement in prescribing software to be revised
Solvay	Zanidip	lercanidipine	Advertisement in prescribing software to be revised
Abbott	Sevorane	sevoflurane	Withdrawal of detail aid Corrective letter to everyone who received the detail aid $25 000 fine
AstraZeneca	Symbicort	budesonide/ eformoterol	Withdrawal of promotional material Corrective letter to general practitioners and respiratory physicians $50 000 fine
Baxter	Sponsored educational meeting during harbour cruise		No further educational meetings to be held at same or similar venue as the harbour cruise
Bayer	Levitra	vardenafil	Withdrawal of promotional material from website, and patient brochure Corrective letter to doctors invited to join register of doctors interested in men's health
Douglas	Estelle-35ED *	cyproterone/ ethinyloestradiol	Withdrawal of promotional material Corrective advertisement (same size as original) in Australian Journal of Pharmacy and other journals
GlaxoSmithKline	Seretide	fluticasone/salmeterol	Withdrawal of promotional material Corrective letter to general practitioners and respiratory physicians $15 000 fine
Merck Sharp & Dohme	Zocor	simvastatin	Withdrawal of promotional material Corrective letter to medical practitioners $20 000 fine
Pfizer	Somac	pantoprazole	Withdrawal of promotional material previously found in breach of the Code $100 000 fine
Pfizer	Vfend	voriconazole	Withdrawal of promotional material $20 000 fine
Solvay	Zanidip	lercanidipine	Withdrawal of promotional material $30 000 fine

* See also: She needs safe and reliable contraception, not a treatment for severe acne! Estelle™-35ED (cyproterone-oestradiol) (Douglas). Healthy Skepticism. AdWatch 2006 Apr. http://www.healthyskepticism.org/adwatch.php [cited 2006 Nov 9]

Medicinal mishap

Fenofibrate–warfarin interaction

Prepared by Razvan A Ghiculescu, Clinical pharmacology advanced trainee, Department of Clinical Pharmacology, Royal Brisbane and Women's Hospital, Brisbane

Case

A 65-year-old woman taking warfarin was admitted to hospital because she had melaena and an INR greater than 10. She also had a painful left ankle due to a large atraumatic haemarthrosis which had left her unable to weight bear. The patient had a history of type 2 diabetes mellitus complicated by chronic renal failure, peripheral vascular disease, hypertension, dyslipidaemia and hypothyroidism.

She had been treated with warfarin for 16 years for two indications, paroxysmal atrial fibrillation and a mitral valve xenograft, and her INR was usually stable. Her dyslipidaemia was managed with simvastatin, but four weeks before admission she was changed to fenofibrate. This was because she had mixed dyslipidaemia with predominant hypertriglyceridaemia. She was found to have normocytic normochromic anaemia and acute-on-chronic renal failure (estimated glomerular filtration rate of 17 mL/min).

Initial management included correction of coagulation factor deficiency with fresh frozen plasma, daily INR monitoring and withdrawal of warfarin for three days. The gastrointestinal bleeding was managed with a proton pump inhibitor given parenterally and transfusions of packed red blood cells.

While in hospital, she developed paroxysmal atrial fibrillation with rapid ventricular response rate and myocardial damage as evidenced by a small rise in troponin I. She was discharged after seven days with an INR of 2.8, in rate-controlled atrial fibrillation, and with no evidence of ongoing gastrointestinal blood loss. She was also able to weight bear.

Comment

The patient's presentation was probably caused by the interaction between fenofibrate and warfarin. Fenofibrate is a fibric acid derivative that is approved as an adjunct to diet in the treatment of dyslipidaemia when hypertriglyceridaemia is the predominant abnormality.

There are two possible explanations why fenofibrate can amplify the anticoagulant effect of warfarin. Fenofibrate is highly protein bound *in vivo* and so has the potential to displace warfarin from its binding protein and lead to an enhanced hypoprothrombinaemic effect. In addition, fenofibrate is a mild to moderate inhibitor of CYP2C9, which is the major enzyme system responsible for warfarin metabolism.[1]

The product information warns that anticoagulant doses should be reduced to prevent bleeding complications. Frequent monitoring is recommended when starting treatment with fenofibrate until the INR is stabilised.

Most clinicians do not suggest a pre-emptive change in warfarin dose, although some authors recommend an empiric 20% reduction in warfarin dose when fenofibrate is initiated.[1] The INR should be checked 48–72 hours after the first dose of fenofibrate.

Conclusion

Clinicians need to be aware of a potential interaction between fenofibrate and warfarin. Whenever starting fenofibrate for patients receiving concurrent warfarin, the INR should be checked 48–72 hours as the warfarin dose may need to be reduced.

Reference

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Top 10 drugs

These tables show the top 10 subsidised drugs in 2005–06. The tables do not include private prescriptions.

Table 1

Top 10 drugs supplied by DDD*/1000 pop/day †

Drug	PBS/RPBS ‡
1. atorvastatin	116.088
2. simvastatin	58.702
3. ramipril	35.897
4. diltiazem hydrochloride	26.970
5. omeprazole	19.531
6. frusemide	18.420
7. salbutamol	18.073
8. aspirin	18.047
9. sertraline	18.039
10. irbesartan	17.971

Table 2

Top 10 drugs by prescription counts †

Drug	PBS/RPBS ‡
1. atorvastatin	9 045 273
2. simvastatin	6 355 305
3. paracetamol	4 205 023
4. omeprazole	4 180 429
5. esomeprazole	3 715 500
6. atenolol	3 259 401
7. perindopril	3 124 409
8. irbesartan	3 025 037
9. ramipril	3 024 099
10. irbesartan with hydrochlorothiazide	2 962 120

Table 3

Top 10 drugs by cost to Government †

Drug	Cost to Government ($A)	DDD*/1000/day PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1. atorvastatin	522 357 695	116.088	9 045 273
2. simvastatin	330 247 669	58.702	6 355 305
3. esomeprazole	169 953 743	14.265	3 715 500
4. clopidogrel	169 947 052	8.485	2 179 960
5. salmeterol and fluticasone	165 917 558	— §	2 839 015
6. olanzapine	154 623 092	3.016	745 603
7. omeprazole	149 094 755	19.531	4 180 429
8. alendronic acid	113 917 837	9.177	2 297 414
9. pantoprazole	103 564 509	11.603	2 733 589
10. pravastatin	102 445 719	13.934	2 018 695

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† Based on date of supply

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

§ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Drug Utilisation Database, as at 9 October 2006. © Commonwealth of Australia.

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.

Alemtuzumab

MabCampath (Schering)

glass vials containing 30 mg/mL

Approved indication: chronic lymphocytic leukaemia

Australian Medicines Handbook section 14.3.4

The treatment of chronic lymphocytic leukaemia is changing with increasing use of multidrug regimens including fludarabine (see 'Treatment of adult leukaemias', Aust Prescr 2006;29:76–9). Although response rates have improved, some patients do not respond and in others the disease progresses within a few months. The median survival for these patients with refractory

disease is only eight months.

Alemtuzumab is a humanised monoclonal antibody that has been studied in chronic lymphocytic leukaemia because it binds to a glycoprotein (CD52) on the surface of lymphocytes. By binding to this antigen alemtuzumab induces lysis of the cell.

In a phase II study, 29 patients with relapsed or refractory disease were given intravenous infusions of alemtuzumab three times a week for up to 12 weeks. Although adverse reactions were common, 11 patients had a partial response and one had a complete response to alemtuzumab.[1]

Another phase II study enrolled 24 patients who had previously been treated with fludarabine. There were no complete responses, but eight patients had a partial response. Overall, median survival was approximately 28 months, but in the responders it was 36 months.[2]

A larger study included 93 patients in whom previous treatment including fludarabine had failed. The aim was to give patients infusions of alemtuzumab three times a week for up to 12 weeks. This regimen resulted in two patients having a complete response and 29 having a partial response. Overall median survival was 16 months. Approximately 10% of the patients died during the study or within 30 days of treatment.[3]

The infusions of alemtuzumab are given over two hours. The pharmacokinetics of alemtuzumab are not linear as clearance declines during treatment. At the start of treatment the mean half-life is eight hours, but increases to six days.

The dose of the infusion has to be increased gradually as alemtuzumab may be poorly tolerated. Infusion-related reactions include fever, hypotension and gastrointestinal upsets. Nearly 90% of patients have rigors. There have been fatal cardiovascular adverse events. Premedication with steroids, an analgesic and an antihistamine is recommended.

Most patients will develop a cytopenia.[3] Transfusions of blood or platelets may be needed.

The action of alemtuzumab means that infections are common[4] and can be fatal. They include pneumonia, and viral and fungal infections. Antibiotic prophylaxis may reduce the risk of pneumocystis pneumonia.

Although alemtuzumab has a clinical benefit for some patients[3], its role will be limited by its toxicity. At present it is only approved for use after at least two other therapies have failed.

[X] manufacturer did not respond to request for data

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Rosuvastatin

Crestor (AstraZeneca)

5 mg, 10 mg, 20 mg and 40 mg tablets

Approved indication: hypercholesterolaemia

Australian Medicines Handbook section 6.6.1

When patients have hypercholesterolaemia that fails to respond to diet and exercise they may require treatment with an HMG-CoA reductase inhibitor. These drugs are widely prescribed and the approval of rosuvastatin adds to the choice of 'statins'.

Rosuvastatin is taken once a day. Although the tablet's bioavailability is only 20% it does not have to be taken on an empty stomach or at a particular time of day. While most of the dose is excreted unchanged in the faeces approximately 10% is metabolised in the liver by cytochrome P450 2C9. Rosuvastatin is contraindicated in people with liver disease. Other patients should have liver function tests before and during treatment.

Rosuvastatin has been compared with atorvastatin, pravastatin and simvastatin in an open-label randomised trial involving 2431 patients. After six weeks rosuvastatin had reduced total cholesterol concentrations significantly more than the other drugs had. It also produced larger increases in concentrations of high density lipoprotein (HDL) cholesterol. A 10 mg dose of rosuvastatin will reduce low density lipoprotein (LDL) cholesterol by 46% compared to 37% with 10 mg atorvastatin, 35% with 20 mg simvastatin and 30% with 40 mg pravastatin.[1] (The approximate equivalent doses are rosuvastatin 5 mg = atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg and fluvastatin 80 mg.[2])

The effect on LDL cholesterol may assist patients who are having trouble meeting their targets for risk reduction. In a retrospective study of 8251 patients starting statins, patients taking rosuvastatin were more likely to attain the target concentration of LDL cholesterol. However, the differences in HDL concentrations between statins were not significant.[3]

High doses can reduce the volume of atheroma in coronary vessels, but it is not known if this will improve the clinical outcomes. The doses used in this trial were above the usual maximum daily dose of 20 mg.[4] Higher doses are likely to cause a higher frequency of adverse reactions.

Adverse effects resulted in 3.7% of patients in trials discontinuing treatment. These adverse effects include nausea, asthenia, diarrhoea and myalgia. There is a risk of

rhabdomyolysis which may be increased if the patient is also taking drugs such as gemfibrozil. There are also clinically significant interactions with warfarin and cyclosporin. A few patients develop proteinuria or haematuria while taking rosuvastatin. Asian patients could be at greater risk of adverse effects because they tend to have higher plasma concentrations of rosuvastatin than Caucasians.

Dose for dose, rosuvastatin has a greater effect than other statins on cholesterol concentrations, but it should not become the first choice until data about its longer-term safety and effect on cardiovascular outcomes are available. An American drug bulletin has advised its readers not to use rosuvastatin at all.[5,6] Although there has been criticism that the data supporting rosuvastatin is weak, the company is alleged to have spent an estimated US$1 billion to persuade doctors to prescribe.[6,7]

T T T manufacturer provided all requested information

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Sorafenib tosylate

Nexavar (Bayer)

200 mg tablets

Approved indication: renal cell cancer

Australian Medicines Handbook section 14.3.9

Sorafenib (BAY 43-9006) is a tyrosine kinase inhibitor. Its action on multiple receptors reduces tumour proliferation and angiogenesis. In animal studies it reduced the growth of renal cell carcinoma in mice.

A phase II trial of sorafenib included 202 patients with metastatic refractory renal cell cancer. All the patients took 400 mg sorafenib twice daily for 12 weeks. After 12 weeks 73 patients whose tumours had shrunk by at least 25% continued treatment. A group of 65 patients whose tumours had not shrunk by 25% were randomised to continue sorafenib or a placebo. (Patients whose tumours had progressed were withdrawn from the study.) Twelve weeks after randomisation 16 of the 32 patients taking sorafenib were progression free, compared with 6 of the 33 patients taking placebo.[1]

A phase III trial randomised 769 patients with advanced renal cell cancer that had progressed despite a previous systemic therapy, such as interferon. The median time from randomisation to disease progression was 167 days for patients taking sorafenib and 84 days for those taking a placebo.

Patients should probably take sorafenib on an empty stomach as food can reduce bioavailability. Sorafenib is metabolised in the liver by glucuronidation and cytochrome P450 3A4, but no dose adjustment is recommended for patients with mild to moderate liver impairment. Sorafenib has not been studied in patients with severe renal impairment, but only 20% of a dose is excreted in the urine.

Adverse events are common. In the phase II trial many of the patients developed rashes or a hand-foot skin reaction. Most were able to continue treatment. Nausea, diarrhoea and fatigue were also common. Approximately 17% of the patients in the phase III study developed hypertension while taking sorafenib, so regular monitoring of blood pressure is needed. Myocardial ischaemia was more frequent with sorafenib than with placebo (2.9% vs 0.4%). Consider discontinuing treatment if myocardial ischaemia develops. Bleeding occurred in 15% of the patients taken sorafenib and in 8% of the placebo group. Particular caution is needed if the patient is taking sorafenib and warfarin. Common laboratory abnormalities include lymphopenia, neutropenia, hypophosphataemia and elevated lipase.

Although sorafenib can reduce tumour size, only 2% of the patients in the phase III trial had an objective response. The drug therefore seems to keep the disease stable. At the time of writing the effect on survival was uncertain. An interim analysis reported that the median survival was 19.3 months with sorafenib and 15.9 months with placebo.

T T manufacturer provided some data

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Sunitinib malate

Sutent (Pfizer)

12.5 mg, 25 mg and 50 mg capsules

Approved indications: gastrointestinal stromal tumour, renal cell carcinoma

Australian Medicines Handbook section 14.3.9

Tyrosine kinase inhibitors, such as imatinib, interfere with the angiogenesis that is required for tumour growth (see 'Angiogenesis inhibitors in cancer', Aust Prescr 2006;29:9–15). Sunitinib (SU11248) acts on multiple receptor tyrosine kinases, including a tyrosine kinase which is associated with gastrointestinal stromal tumours. Its anti-angiogenic effects may give it a role in vascular tumours such as renal cell carcinoma.

In an open-label phase II trial, 63 patients were treated with sunitinib after their metastatic renal cell carcinoma had progressed despite immunotherapy. The median duration of treatment was nine months. The investigators' assessment of tumour images found that 25 patients had a partial response to treatment. The median time to further progression of the tumours was 8.7 months with a median survival of 16.4 months.[1]

Another open-label phase II study included 106 patients with metastatic clear cell renal cell carcinoma after immunotherapy had failed. They were treated for about seven months. Independent assessments found that 36 patients achieved a partial response. The median duration of response and median survival had not been reached when the data were analysed. After six months 79% of the patients were still alive.[2]

Gastrointestinal stromal tumours are sarcomas that usually occur in the stomach or small bowel. Before the development of imatinib, surgery was the only effective treatment but was not always possible. A placebo-controlled trial has investigated giving sunitinib after treatment with imatinib fails. Interim analysis showed a partial response in 14 of the 207 patients randomised to take sunitinib and none of the 105 patients in the placebo group. The time to disease progression was 27.3 weeks with sunitinib and 6.4 weeks with placebo. As this difference could contribute to improved survival all the patients in the placebo group were switched to sunitinib.

The recommended regimen for sunitinib is a daily dose of 50 mg for four weeks followed by a two-week break before repeating the cycle. The dose can be taken with or without a meal as food has no effect on bioavailability. Sunitinib and its active metabolite are metabolised by cytochrome P450 3A4. Dose reductions should be considered if the patient is taking an inhibitor of this enzyme. The dose of sunitinib may need to be increased if an enzyme-inducing drug is prescribed. Patients taking sunitinib should not take St John's wort because of this interaction. The half-life of sunitinib is 40–60 hours with most of the metabolites being excreted in the faeces. There have been no studies of sunitinib in patients with impaired hepatic or renal function.

In the trials, fatigue, diarrhoea, dyspepsia, nausea and vomiting were common adverse events. Discolouration of the skin or hair, and rashes, particularly on the palms and soles, were also frequently reported. Hypertension developed in 25% of previously untreated patients with renal cancer and 33% reported bleeding. Reductions in platelets and blood cell counts are very common. Many patients will also develop abnormal biochemical and liver function tests. Sunitinib can prolong the QT interval and cause left ventricular dysfunction. Deep venous thrombosis and pulmonary embolism have also been reported. As sunitinib has been associated with adrenal toxicity in animal studies, patients experiencing stress, such as surgery, should be monitored for adrenal insufficiency. Approximately 4% of patients develop hypothyroidism.

The evidence shows that sunitinib is likely to be of benefit to some patients with gastrointestinal stromal tumours who have not responded to imatinib or cannot tolerate it. However, these tumours are uncommon so only a limited number of people will benefit.

Advanced renal cell carcinoma has a poor prognosis. Sunitinib may improve this, but the results need to be confirmed in randomised phase III studies. Preliminary data suggest that there may be a greater response to sunitinib than to immunotherapy with interferon alfa.[3]

T T T manufacturer provided all requested information

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Further reading

Pavlakis N. Drug treatment of renal cancer. Aust Prescr 2006;29:151-3.

The T-score (T) is explained in 'Two-way transparency', Vol 28 No 4, 2005 (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.europa.eu)

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

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