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Editorial

Medicines and markets: the USA and Australia

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Key words: drug costs, drug therapy, Pharmaceutical Benefits Scheme.

(Aust Prescr 2009;32:90–1)

Among developed countries, the USA is virtually alone in its reluctance to intervene in response to market failure in pharmaceuticals. It was not until the introduction of the US Medicare Part D drug benefit in 2006 that millions of elderly and disabled Americans gained access to subsidised prescription drugs. After 40 years without any drug coverage, this controversial expansion of the Medicare program has been hailed as a triumph. It has also been described as complex, expensive and lacking in transparency.

Under Part D, benefits are provided through private insurance policies sold in federally-defined regional markets. Eligible enrollees (over 65s and the disabled) pay monthly premiums to participate in the drug plan of their choice. They may choose either a stand-alone drug plan (known as a PDP) or a managed care plan with integrated drug coverage (known as a Medicare Advantage PDP or MA-PDP), from a list of several dozen of each in any given region. Under Part D, the federal government contributes approximately 75% of the premium costs.[1]

Most Part D plans have tiered benefit structures, in which co-payments are varied to encourage patients towards the cheapest options. Plans typically have four tiers, with the first tier comprising generics, the second 'preferred brands', and the third 'non-preferred brands'. Plans may also place any drug costing $600* or more per month into a so-called specialty tier, and will usually apply a co-payment (or strictly speaking a co-insurance amount) of 25–33% of the drug price. Plan providers are largely free to determine which drugs are on their formularies (with the exception of drugs in certain 'protected' classes for which coverage is mandatory) and in which tiers those drugs are placed. They may also move drugs between tiers, or drop coverage of a drug during the plan year. In contrast, enrollees may switch plans only during a six-week 'open enrolment' window each November.[1]

In 2009 Part D premiums average $30.36 per month, but vary significantly across plans and regions, ranging from $10.30 to $136.80. This year under the standard benefit, enrollees face an annual excess of $295, after which 75% of their drug costs are covered, but only up to $2700. Once they have spent $4350 out-of-pocket in a calendar year (or a total of $6154 in drug costs), 95% of their costs are covered (the catastrophic coverage zone). Between $2700 and $4350 is the infamous 'doughnut hole' where enrollees are liable for 100% of their drug costs, even as they continue to pay their monthly premiums. These thresholds are indexed annually in accordance with Part D spending growth.[1]

In 2007, the 24.2 million Part D enrollees spent on average $461 out-of-pocket on prescription drugs, in addition to their monthly premiums. Fourteen percent fell into the doughnut hole; of these, about one-third were aged 85 or older and 15% stopped taking their medications as a result. For those who qualified for catastrophic coverage, average monthly out-of-pocket costs were still $285.[2]

Importantly, in designing Part D, Congress deliberately chose not to intervene in the pricing process and legislated to prohibit government intervention in drug price negotiations. Individual plan providers must each contract with drug companies to obtain discounts and rebates in return for favourable placement of their drugs on plan formularies. However, providers' capacity to negotiate is to some degree constrained, particularly for those drugs for which inclusion on plan formularies is mandatory. Consequently, Part D prices are high in comparison with Medicaid and other federally funded programs (which all have statutorily mandated discounts or rebates). In some cases prices are scarcely lower than retail.[3,4,5] In addition to concerns over high prices, the complexity of benefit structures, and the generous protections offered to induce the private sector to enter the Part D market, the program has been heavily criticised for its lack of transparency. Until recently there has been a dearth of data that would allow any formal scrutiny of its performance.[6,7]

The Obama administration faces unprecedented health policy challenges, with healthcare spending projected to reach $3.1 trillion in 2012, and rising unemployment likely to swell the ranks of the 47 million people currently uninsured (and the many underinsured).[8,9] The President has signalled lowering drug prices as a priority and has proposed legalising parallel importation of medicines from Canada and other countries with administered pricing systems, as well as increasing the use of generic medicines. Repealing the prohibition on direct price negotiation by government under Part D has also been mooted, but how negotiations would be undertaken, and for what, is

* All costs are expressed in US dollars

unclear. Without a formulary and a rational decision-making framework with the capacity to limit the use of or exclude a drug, it is difficult to see how savings could be achieved. Currently there is growing support in the US for the establishment of mechanisms to evaluate the comparative effectiveness of medical treatments, but there is little enthusiasm for evaluating their comparative cost-effectiveness. Taking into account costs when comparing treatments is widely disparaged as being 'not about medical discovery, but about bean counting'.[10]

In Australia there is at times frustration with the listing recommendations of the Pharmaceutical Benefits Advisory Committee, the time taken for drugs to be listed on the Pharmaceutical Benefits Scheme (PBS), the price of listed medicines, and the magnitude of out-of-pocket costs. While it is tempting to try to contrast Part D with the PBS, the heterogeneity of Part D makes assessments of the breadth and comprehensiveness of plan formularies and the metrics of costs, coverage and access particularly complex. Some Part D formularies may well be more extensive in the drugs they cover than the PBS, but the permutations arising from tiered benefit structures, variable cost sharing, and movements of drugs on and off the formularies and between tiers make it extremely difficult to determine the significance of the differences. Certainly Part D offers a great deal of choice for enrollees, but rather than conferring a sense of control, the nature and breadth of the choices offered has created complexity and confusion for many elderly and disabled Americans. Part D is arguably an example of a phenomenon that seems to be widespread in US health care – the design of the policy prioritises the act of choosing rather than the utility of the choice. Despite the emphasis on choice, enrollees cannot choose to have a stable benefit with constant coverage throughout the year.

By contrast, the PBS offers less choice, but is arguably simpler for both patients and prescribers, more equitable, and more transparent. It has a uniform national formulary, accessible information about prices and standard co-payments. Decision making is based on evidence of comparative effectiveness and comparative cost-effectiveness. This not only helps to determine the opportunity costs of new treatments, but also ensures value for money for the taxpayer and the healthcare system. It will be fascinating to see whether the imperative to rein in US healthcare expenditure will ever see Part D, or for that matter US Medicare, adopt a similar model.

Postscript

On 20 June 2009 the Pharmaceutical Research and Manufacturers of America announced its support for a plan to provide discounts of 50% to 'most beneficiaries on brand-name medicines' purchased in the Part D doughnut hole.[11] Although worth up to $80 billion over 10 years, some of the revenue foregone will nevertheless be recouped through increased sales of brand-name drugs to enrollees who would otherwise switch to generics in the doughnut hole. It may also be intended to lessen the impetus for introducing government drug price negotiations. While reported to have strong support from the President, the program will not help offset the cost of healthcare reform, as discounts will reduce out-of-pocket costs to enrollees but deliver no savings to government. These most significant changes to Medicare Part D could be argued as evidence that the program is failing to provide consumers with affordable drug coverage.

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Conflict of interest: none declared

Screening for multiple myeloma

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Summary

Patients with suspected multiple myeloma should be investigated with screening tests. They may have a paraprotein in the serum, Bence-Jones protein in the urine, or both. If these proteins are detected by a protein electrophoretogram, the patient requires further investigation to distinguish multiple myeloma from monoclonal gammopathy of uncertain significance. Identifying the paraprotein isotype assists in the diagnosis of multiple myeloma, but bone marrow biopsy is needed to show the percentage of plasma cells in the marrow.

Key words: Bence-Jones protein, monoclonal gammopathies, paraproteins.

(Aust Prescr 2009;32:92–4)

Introduction

Multiple myeloma has a wide range of clinical presentations. It should be considered as a possible underlying cause in patients presenting with anaemia associated with bone pain, vertebral crush fractures, unusually severe osteoporosis, susceptibility to recurrent bacterial infections, or renal failure.

In multiple myeloma there is a proliferation of abnormal plasma cells which produce a monoclonal protein. This protein is usually an immunoglobulin which consists of light and heavy polypeptide chains. The immunoglobulin can be deposited in the kidney tubules, reducing renal function, while the accumulation of plasma cells in the marrow leads to anaemia. The diagnosis of multiple myeloma therefore requires investigation of immunoglobulins in the blood and urine and plasma cells in bone marrow.

Initial investigations

Patients suspected of having multiple myeloma first have screening tests and then more specialised tests to confirm the diagnosis. This sequence of investigations identifies the presence of a clonal plasma cell disorder, then differentiates whether it is behaving benignly (monoclonal gammopathy of uncertain significance) or malignantly (multiple myeloma) (Fig. 1). The basic tests include a full blood count, urea, creatinine, and electrolytes including calcium. All patients are screened with electrophoresis of serum and urine.

Serum and urine protein electrophoresis

Protein electrophoresis of serum and urine is a sensitive means of detecting the abnormal monoclonal proteins found in myeloma. The test can identify intact immunoglobulin or free light chains in about 98% of cases.

During electrophoresis of serum proteins, intact monoclonal immunoglobulin molecules will migrate as a sharply defined band. This is called a paraprotein, and is detected in about 80% of patients with myeloma. It is almost always found in association with Bence-Jones protein in the urine protein electrophoretogram. Bence-Jones protein is a homogeneous kappa or lambda free light chain.

In most of the remaining 20% of cases of myeloma where a paraprotein is not detected in the serum electrophoretogram, monoclonal light chains are readily detected by protein electrophoresis of concentrated urine. This form of myeloma is usually referred to as Bence-Jones myeloma.

Paraprotein heavy chain type isotype

Identification of the immunoglobulin isotype of a paraprotein by immunofixation of the paraprotein band enables it to be classified as an immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) molecule. Other isotypes are extremely rare. The identity of the isotype is important in differentiating whether production of the paraprotein is by a clonal plasma cell disorder, or by a clonal lymphoproliferative condition.

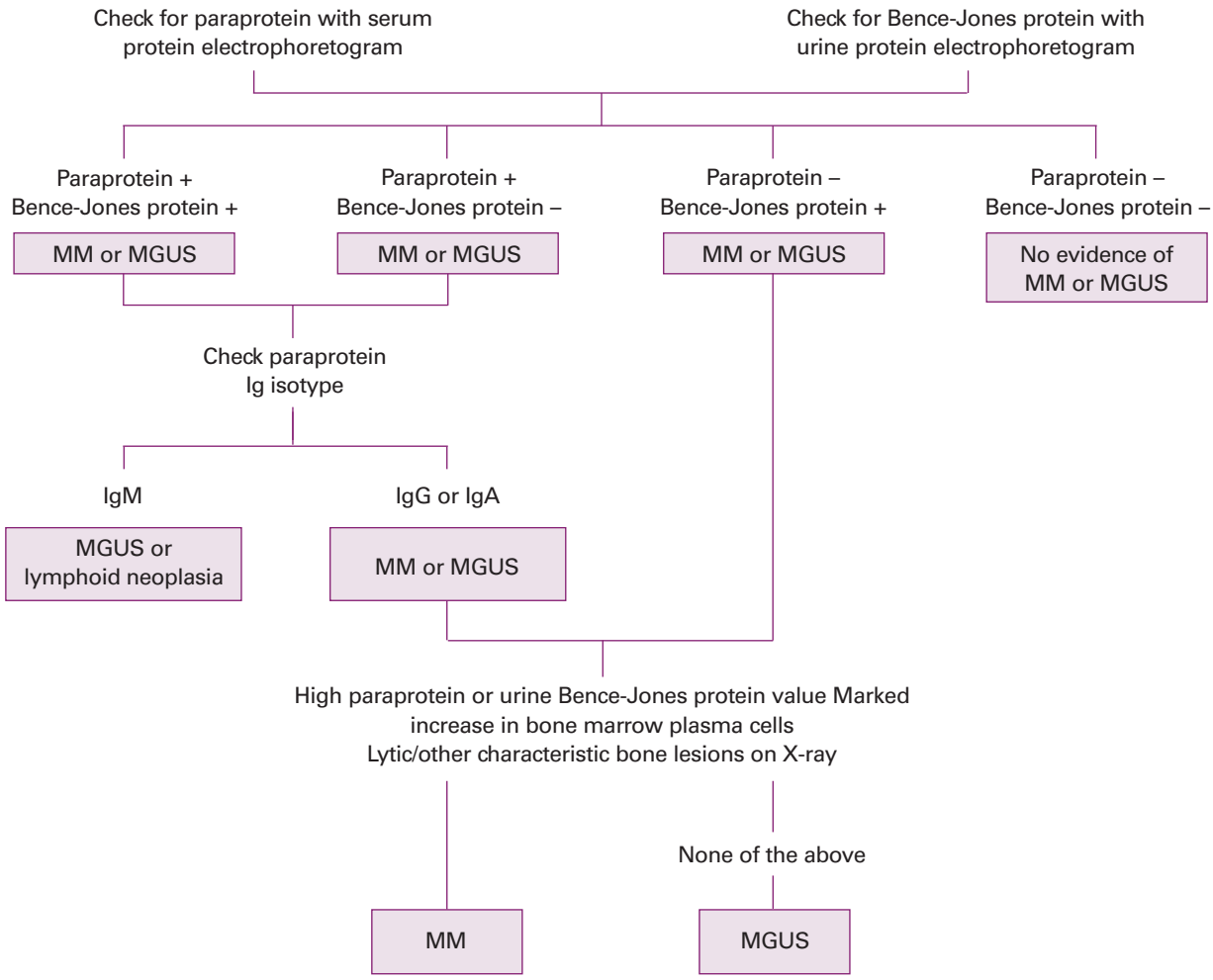
IgG and IgA paraproteins suggest a clonal plasma cell disorder. In myelomas which produce paraproteins, IgG paraproteins occur in approximately 75%, and IgA paraproteins in the remaining 25% of cases. An IgM paraprotein is extremely uncommon in myeloma. It is more indicative of a clonal lymphoproliferative disorder, such as low-grade non-Hodgkin's lymphoma. Waldenstrom's macroglobulinaemia is an example of one form of low-grade non-Hodgkin's lymphoma that is characteristically associated with a serum IgM paraprotein.

Serum immunoglobulin quantitation

Measuring total concentrations of IgG, IgA and IgM in serum can reveal elevation of a specific immunoglobulin isotype that is suggestive of the presence of a paraprotein. However, the test does not distinguish between the normal polyclonal and abnormal monoclonal forms of a particular immunoglobulin.

Fig. 1

Screening and diagnosis of multiple myeloma



MM multiple myeloma
MGUS monoclonal gammopathy of uncertain significance
Ig immunoglobulin

This test is therefore not a substitute for the serum electrophoretogram for identifying the presence of a paraprotein in screening for myeloma.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) was used in screening for myeloma before the ready availability of serum and urine protein electrophoresis. Very high values are often observed in association with a serum paraprotein, but there are many other causes of a very high ESR and it therefore lacks specificity. Another limitation is that typically the ESR is not significantly elevated in Bence-Jones myeloma.

Differentiation of monoclonal gammopathy of uncertain significance from multiple myeloma

Sometimes a patient has a monoclonal protein, but no other features of multiple myeloma. This is called monoclonal gammopathy of uncertain significance. It is relatively common and its prevalence in the community increases with age to about 3% in people aged 50–60 years, and about 5% in persons over 70 years old.[1] This clonal plasma cell or lymphoproliferative condition usually runs a non-progressive, clinically benign course and investigations fail to show a substantial tumour burden. Occasionally monoclonal gammopathy of uncertain significance transforms into clinically aggressive disease, although the rate of transformation is on average only about 1% per year. Transformation in a patient with an IgM paraprotein is usually to lymphoproliferative malignancy, while in patients with an IgA or IgG paraprotein the transformation is usually to myeloma.[1]

The detection of a paraprotein is often an incidental finding and insufficient to confirm a diagnosis of myeloma. Further information is required to establish whether the paraprotein disorder is monoclonal gammopathy of uncertain significance or myeloma.

Serum paraprotein concentration

The serum paraprotein concentration can be used for differentiating between the conditions. Concentrations below the threshold value are more likely to be monoclonal gammopathy of uncertain significance and those above are more likely to be myeloma. These values are:

- IgG paraprotein disorders 30 g/L
- IgA paraprotein disorders 20 g/L.

Patients with Bence-Jones myeloma have very low serum concentrations of the protein. However, they usually excrete more than 1 g of Bence-Jones protein in a 24-hour collection of urine.

Experience suggests that these values are only an approximate guide, especially in the case of borderline values.

Skeletal radiology

A major distinction between myeloma and monoclonal gammopathy of uncertain significance is increased lysis of bone resulting from the activation of osteoclasts by myeloma cells. In myeloma a skeletal X-ray survey commonly reveals abnormalities such as multiple, discrete lytic lesions, vertebral crush fractures, or even areas of diffusely reduced bone density. These findings are some of the most important means for detecting the malignant characteristics of myeloma.

Bone scan

Conventional bone scanning with technetium-99 labelled methylene diphosphonate measures localisation of the tracer in many tissues, including newly formed bone due to increased osteoblastic activity. The tracer is not selectively accumulated by myeloma tissue. While there may be quiescent osteoblast activity in myeloma, increased osteoblastic activity also occurs at sites of repair after fracture and sites affected by infection or inflammation. Bone scanning therefore lacks specificity for myeloma and is not a suitable alternative to radiological examination.

Bone marrow examination

A bone marrow aspirate and trephine biopsy is a key procedure in establishing a definitive diagnosis of myeloma. The procedure is usually performed when there is any suggestion from other screening tests of the possibility of underlying myeloma. It provides a direct measure of the degree of plasma cell infiltration in the bone marrow. In myeloma there is an abnormally high percentage of plasma cells (greater than 10%), compared to an approximately normal percentage in monoclonal gammopathy of uncertain significance.

Bone marrow biopsy may be unnecessary as part of initial screening if the patient has the typical features of monoclonal gammopathy of uncertain significance. An example would be the incidental detection of a very low paraprotein concentration in someone with an entirely normal blood count, normal renal function, absence of skeletal X-ray abnormalities, and no Bence-Jones protein in the urine.

Approximately 10–15% of patients, in whom the degree of plasma cell bone marrow infiltration and concentration of serum paraprotein fulfil the criteria for myeloma, have little or none of the skeletal, haematological or renal complications typical of clinically aggressive myeloma. They have a relatively protracted, indolent clinical course in the absence of therapy. This form of myeloma is designated as smouldering or indolent myeloma on the basis of its activity compared to that of the clinically aggressive form of the disorder.[2]

Newer tests

Assay of free light chains in the serum has become available relatively recently. While it does not supersede protein electrophoresis, it can detect a small but significant elevation of one or other free light chain in the very rare condition designated as non-secretory myeloma. This is characterised by the classical clinical and morphological features of myeloma, but lacks a paraprotein or urinary Bence-Jones protein on protein electrophoresis.

Conclusion

Multiple myeloma causes widely varied clinical manifestations. Early diagnosis will lead to the correct management. Screening tests to detect paraproteins are followed by biopsy to confirm the increased presence of plasma cells in the bone marrow.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 115)

1. Most patients with a low serum concentration of paraprotein will develop multiple myeloma.
2. An X-ray skeletal survey is the recommended investigation for assessing the effect of multiple myeloma on bone.

Patient support organisation: Myeloma Foundation of Australia
see p. 107

New drugs for multiple myeloma

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Summary

Multiple myeloma is a plasma cell neoplasm that is currently incurable. Older patients are managed with melphalan and prednisolone. Younger patients have induction chemotherapy followed by high-dose melphalan and autologous stem cell transplantation. Recent insights into the biological basis of myeloma have resulted in several new drugs becoming available. Thalidomide, bortezomib and lenalidomide have each improved the response to therapy, but they are expensive. Future challenges include optimising the sequence of these drugs, refining their combination with standard drugs and high-dose therapy, and identifying the subgroups of patients most likely to benefit from them.

Key words: bortezomib, lenalidomide, thalidomide, transplantation.

(Aust Prescr 2009;32:95–8)

Introduction

Multiple myeloma is a malignant proliferation of plasma cells that characteristically secrete a monoclonal protein. This is measured in the laboratory as paraprotein or free light chains in blood, or Bence-Jones protein in urine.[1] Clinically the disease is associated with a combination of hypercalcaemia, renal failure, anaemia and lytic bone lesions. While multiple myeloma remains incurable in the majority of cases, the considerable developments in our therapeutic armamentarium over recent years have significantly improved survival.

Treatment overview

Oral melphalan and prednisolone have been the backbone of myeloma therapy for many years. This combination, with or without newer drugs, remains the standard of care for older patients. Younger patients who are eligible for transplantation have induction chemotherapy followed by high-dose melphalan with autologous stem cell rescue. This approach has led to an improvement in median overall survival from 42 to 54 months.[2] While there are a number of induction regimens, the combination of vincristine, doxorubicin and dexamethasone has been most frequently used. An oral induction regimen containing cyclophosphamide, idarubicin and dexamethasone is increasingly being used.

Currently, the treatment approach for newly diagnosed myeloma is guided by the patient's eligibility for autologous haematopoietic stem cell transplantation (Fig. 1). Most Australian centres will consider transplantation in patients aged up to 65 years depending on their general health. Autologous stem cell transplantation for myeloma has a treatment-related mortality of 1–2%.

Supportive care

Both before and during treatment attention must be given to supportive care. This includes management of renal impairment, control of steroid-induced hyperglycaemia, transfusion support, aggressive management of febrile illnesses and effective pain relief to help maintain mobility. Cotrimoxazole is frequently used as prophylaxis against *Pneumocystis jirovecii* pneumonia throughout treatment. Prophylactic famciclovir or aciclovir, norfloxacin and often an antifungal drug are administered for the period of immunological compromise following autologous stem cell transplantation.

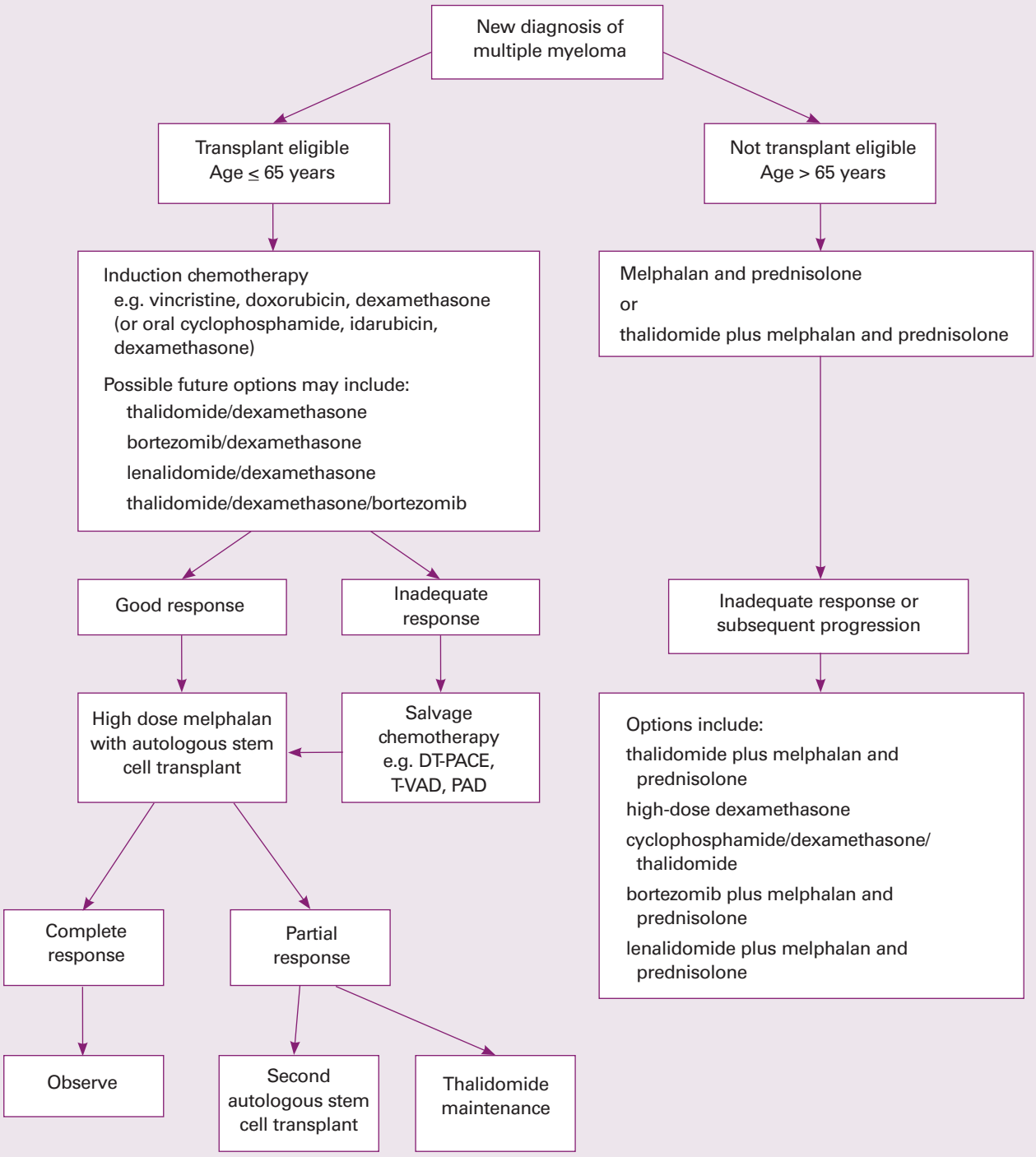
Radiotherapy and surgery, such as vertebroplasty, should be considered for established or imminent fractures and soft tissue plasmacytomas that pose an immediate threat (for example extradural plasmacytoma). Bisphosphonates can be given to patients with myeloma-related bone disease to reduce the risk of pathological fractures, hypercalcaemia and other skeletal-related events. While both intravenous and oral bisphosphonates are effective, the intravenous route is often preferred. Bisphosphonates have been associated with an increased incidence of osteonecrosis of the jaw. A dental review is therefore warranted before treatment and the bisphosphonate should be ceased if this complication develops.

New drugs

In recent years, evidence supporting a survival benefit for thalidomide, bortezomib and lenalidomide has resulted in their inclusion, in combination with older drugs, in the management of younger and older patients. Each of these new drugs has multiple mechanisms of action, targeting both intracellular signalling pathways and the tumour micro-environment. Their optimal sequence and combination is still being refined by ongoing clinical trials.

Fig. 1

A suggested approach to treatment of patients with newly diagnosed multiple myeloma



DT-PACE dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide
T-VAD thalidomide, vincristine, doxorubicin, dexamethasone
PAD bortezomib, doxorubicin, dexamethasone

Thalidomide

Despite its notorious history, thalidomide emerged as the first important new drug treatment for myeloma following recognition of its anti-angiogenic effects in the 1990s. It is given orally, but its precise mechanism of action is unclear. Thalidomide also has immunomodulatory and anti-inflammatory effects. Initial studies in patients with relapsed or refractory myeloma showed a response rate of 32% when thalidomide was used as a single drug, with a considerably higher response rate (41–65%) when it was combined with dexamethasone with or without cyclophosphamide.[3] Numerous subsequent studies have confirmed thalidomide's efficacy in a range of settings.

In elderly patients not eligible for transplant, randomised controlled trials show that the addition of thalidomide to melphalan and prednisolone results in response rates that are superior to melphalan and prednisolone alone. The partial response rate was 76% with melphalan, prednisolone and thalidomide compared with 48% in the melphalan and prednisolone group. However, an updated analysis found no survival advantage when thalidomide was added, probably because many of the patients in the control group later received thalidomide or other new drugs on relapse.[4]

In the younger patient group, thalidomide combined with dexamethasone is an effective pre-transplantation induction regimen.[3] It has also been used as 'maintenance' following high-dose therapy and autologous stem cell transplantation.[3] Maintenance therapy with thalidomide increased four-year overall survival from 77% to 87% in studies of patients after autologous stem cell transplantation.[3] The Therapeutic Goods Administration (TGA) has approved thalidomide in first-line treatment and for relapsed or refractory myeloma, but Pharmaceutical Benefits Scheme (PBS) funding is currently only available for relapsed or refractory myeloma.

Adverse effects

The most frequent adverse effects seen with thalidomide are constipation, fatigue, somnolence and peripheral neuropathy. As thalidomide significantly increases the risk of venous thrombosis, prophylaxis should be considered (aspirin, warfarin or low molecular weight heparin is recommended).

Thalidomide use is strictly regulated due to its teratogenicity. In Australia, patients, prescribers and dispensing pharmacists must be registered with the Pharmion Risk Management Program. They have to complete phone questionnaires emphasising the importance of effective contraception before receiving authority for each 28-day prescription. Distribution of the drug is carefully controlled and tracked.

Lenalidomide

Lenalidomide is an oral thalidomide analogue and acts by similar mechanisms, targeting both signalling pathways within the malignant plasma cell and the bone marrow micro-environment. After promising initial results as a single drug, trials comparing lenalidomide plus dexamethasone with dexamethasone alone found superior response rates (60% vs 24%) and improved median overall survival in relapsed myeloma.[5] Trials involving newly diagnosed patients have shown an 81% response rate when combined with melphalan and prednisolone in elderly patients, and a 91% response rate when combined with dexamethasone in younger transplant-eligible patients.[6,7] Lenalidomide is frequently effective even in patients whose myeloma is resistant to thalidomide.

Although approved by the TGA for relapsed disease, lenalidomide is not presently subsidised by the PBS. Haematologists can currently access lenalidomide through a temporary expanded access program established by the drug company.

Adverse effects

Unlike thalidomide, lenalidomide is not associated with somnolence, constipation or peripheral neuropathy, but causes neutropenia and thrombocytopenia. Thromboembolic events occur at an increased rate, hence antithrombotic prophylaxis is recommended. Effective contraception is also required given its teratogenic potential.

Bortezomib

Just as the use of thalidomide arose from an understanding of the importance of angiogenesis in myeloma, the development of bortezomib followed new insights into the importance of the proteasome. This is the intracellular structure responsible for orderly degradation of intracellular proteins. Proteasomal inhibition by bortezomib results in cellular apoptosis, particularly in malignant and proliferating cells.

Early studies showed that intravenous bortezomib had a higher response rate and a six-month survival advantage over high-dose dexamethasone in relapsed myeloma. The median overall survival was 29.8 months with bortezomib versus 23.7 months with dexamethasone.[8] In newly diagnosed elderly patients, bortezomib used with melphalan and prednisolone resulted in a response rate of 89%, with overall survival being 90% at 16 months versus 62% in those treated with melphalan and prednisolone alone.[9] Younger transplant-eligible patients had similarly impressive response rates when bortezomib was included in induction regimens.[10]

In Australia, bortezomib is currently subsidised by the PBS for patients who have progressive disease after at least one prior treatment, who have undergone or are ineligible for stem cell transplant and who have failed thalidomide. Ongoing therapy requires documentation of an adequate response. In contrast, for newly diagnosed patients its use is currently limited to those enrolled in clinical trials.

Adverse effects

The major adverse effects of bortezomib include fatigue, gastrointestinal upset, painful peripheral neuropathy, anaemia, thrombocytopenia and neutropenia. There is also an increased incidence of herpes simplex and herpes zoster infections.

Related conditions

Monoclonal gammopathy of undetermined significance is an asymptomatic clonal plasma cell proliferation, but 1% of patients progress to myeloma every year. These patients require careful monitoring, but treatment is not indicated.

Smouldering myeloma refers to an intermediate pre-malignant phase with no end-organ damage. Although these patients have a greater risk of progression to myeloma, treatment may still be reserved until there is evidence of systemic effects.

Challenges for the future

Thalidomide, lenalidomide and bortezomib are advances in the treatment of myeloma, but their exact place in therapy is yet to be fully defined. While these drugs have survival benefits, the challenge is to determine their optimal sequence and combination with other drugs. Another important challenge is to determine which subgroups of patients would benefit most from these drugs. Debate continues as to whether these new drugs ought to be used as part of initial therapy to improve the initial response, or whether equivalent survival benefits and quality of life can be obtained, with less toxicity, by deferring them until disease progression occurs. Until these questions are answered by future clinical trials, PBS restrictions dictate that most Australian patients will receive these drugs only when their disease progresses.

The efficacy of these new drugs has also challenged some of the paradigms of myeloma treatment. For example, while maintenance therapy has not previously been used in myeloma, it may have a role in future. Furthermore, regimens containing the new drugs might provide the same benefits as an autologous transplant, thus obviating the need for transplantation. However, if the two approaches are found to be equally efficacious, the high cost of the new drugs and the low transplant-related mortality may ensure that autologous transplantation still has a role.

Allogeneic stem cell transplantation has been trialled in myeloma with both myeloablative and reduced intensity conditioning. A plateau in long-term survival has been demonstrated suggesting that this may be a potentially curative approach. Nonetheless, it is associated with considerable transplant-related mortality and morbidity, and currently should be regarded as an experimental treatment.

While myeloma remains incurable, these new therapies are substantially changing our approach to this disease. More importantly, they have the potential to further improve survival as we continue to determine their optimal place in the management of this common haematological malignancy.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 115)

3. Thalidomide increases the risk of venous thrombosis in patients with multiple myeloma.
4. Bisphosphonates are ineffective for the treatment of the hypercalcaemia associated with multiple myeloma.

Patient support organisation: Myeloma Foundation of Australia

see p. 107

The management of hepatitis B

Sally J Bell *and* ***Tin Nguyen****, Department of Gastroenterology, St Vincent's Hospital, Melbourne*

Summary

Chronic hepatitis B affects almost 1% of Australians, many of whom are born in endemic areas outside Australia. This infection can shorten lifespan, usually because of cirrhosis or hepatocellular carcinoma. Most patients acquire the infection perinatally or in childhood before migration. A small number of people acquire infection as adults via injecting drug use or sexual contact. Hepatitis B infection is usually asymptomatic, and screening using hepatitis B surface antigen should be considered for all patients from endemic countries and those with percutaneous or sexual risk factors. Improved laboratory testing for viral DNA can help identify the need for treatment and long-term risk of liver damage. Treatment is with nucleos(t)ide analogues (usually long-term) or pegylated interferon (for 12 months). This reduces inflammation, can improve liver injury and reduces progression to cirrhosis and hepatocellular carcinoma. Long-term monitoring is recommended to detect reactivation of infection and hepatocellular carcinoma.

Key words: antiviral drugs, cirrhosis, hepatocellular carcinoma, liver.

(Aust Prescr 2009;32:99–104)

Introduction

Although Australia has traditionally been regarded as having a low prevalence of chronic hepatitis B, recent estimates suggest that 160 000 people are infected.[1,2] The majority of these patients are born in an endemic area such as Asia, Africa, the Middle East, Central and South America, Eastern Europe (except Hungary), Mediterranean Europe (Greece, Italy, Malta, Portugal and Spain), the South Pacific and the Caribbean. High rates of infection also exist in indigenous populations.[1]

Routes of transmission

Hepatitis B transmission can occur via a number of routes including percutaneous or parenteral, horizontal transmission through mucosal contact with infected blood or bodily secretions, and during the perinatal period (see Table 1). Transmission during the perinatal period is more common in patients born in endemic areas. Blood transfusions or organ transplantation are now extremely rare routes of transmission due to the rigorous screening protocols in Australia.

Natural history of infection

Chronic hepatitis B shortens the lifespan in 45% of infected men and 15% of infected women usually due to the development of cirrhosis or hepatocellular carcinoma. Following exposure, acute hepatitis B infection has an incubation period of 6–12 weeks. Adults who acquire infection commonly develop symptoms of jaundice, anorexia, nausea, right upper quadrant discomfort and fatigue. In the perinatal setting asymptomatic subclinical hepatitis is common. While over 95% of people infected as adults will spontaneously clear the virus, this reduces to 30% in children, and 5% in infants.

Diagnosis

It is important to distinguish between patients with newly acquired hepatitis B and those with chronic infection. This may be difficult because both groups may have the hepatitis B surface antigen (HBsAg) in their blood, and may be clinically well.

Acute hepatitis B

Newly acquired infection is more likely if the patient has:

- recent risk factors
- negative HBsAg in last 1–2 years
- high levels of specific immunoglobulin (Ig) M antibody to hepatitis B core protein in the absence of previous evidence of infection.

Table 1

Routes of transmission of hepatitis B

Route	Example
Percutaneous	Injecting drug use Needlestick injury Tattooing/body piercing
Horizontal	Sexual contact with an infected individual (higher risk with anal intercourse) Child to child (usually through open sores of infected individual)
Perinatal	Mother to neonate at or around time of birth

Chronic hepatitis B

Chronic infection is classically based on the detection of HBsAg on two occasions six months apart with no clinical or laboratory evidence of acute disease. IgG antibodies to hepatitis B core protein are present in chronic infection, and patients may be either positive or negative (depending on the phase of infection) for the hepatitis B e antigen (HBeAg).

In general practice, it is common to detect HBsAg in clinically well patients born in endemic areas. If there are no recent percutaneous or sexual risk factors for acquisition, these patients are likely to have chronic infection.

Baseline evaluation

This should include a thorough history to identify the country of birth of the patient and their parents, family history of hepatitis B or hepatocellular carcinoma, cofactors for liver disease such as alcohol abuse, and risk factors for co-infection with hepatitis C virus or HIV. It is also important to get information about the patient's sexual contact(s), as well as their vaccination status. A physical examination should be carefully performed for evidence of chronic liver disease.

Initial blood tests should include liver function tests, full blood examination, prothrombin time, as well as the presence of HBeAg and HBeAg-specific antibodies, viral DNA load, antibodies to hepatitis C, HIV antibody, hepatitis A-specific IgG, and alfa-fetoprotein. A baseline ultrasound of the liver should be performed to screen for hepatocellular carcinoma and identify any features of cirrhosis. If there is significant deterioration in liver function, testing for hepatitis D co-infection (by measuring hepatitis D antigen and antibody) should be considered as it can affect choice of therapy.

Managing acute infection

Treatment of acute hepatitis B is supportive for most cases. However, acute liver failure can develop in up to 1%, and can be recognised clinically by the presence of encephalopathy, abnormal prothrombin time and renal impairment. These patients should be referred to a liver transplant unit.

Managing the different phases of chronic infection

Patients with chronic hepatitis B can progress through up to four phases of disease (Table 2). Understanding these phases is critical to determining the risk of liver damage and need for treatment.

Table 2

Recognising and managing the phases of chronic hepatitis B infection

	Phase 1 Immune tolerance	Phase 2 Immune clearance	Phase 3 Immune control	Phase 4 Immune escape
HBeAg	Positive	Positive	Negative	Negative
Antibodies to HBeAg	Negative	Negative	Positive	Positive
Viral DNA (IU/mL)	>20 000	>20 000	<2 000	>2 000
Alanine aminotransferase	Persistently normal	Elevated (1–2 x) and fluctuating	Normal	Elevated or fluctuating
Liver histology	Normal or mild hepatitis	Moderate to severe hepatitis	Normal to mild hepatitis May have cirrhosis	Moderate to severe hepatitis May have cirrhosis
General recommendations	Monitor HBeAg and liver function annually	Liver biopsy Consider antiviral treatment Monitor liver function and viral load every 3 months if on drug treatment	Monitor liver function annually Check for signs of cirrhosis and biopsy if > 40 years of age	Liver biopsy Consider antiviral treatment Monitor liver function and viral load every 3 months if on drug treatment

HBeAg hepatitis B e antigen

Phase 1 – immune tolerance

In this phase, which usually lasts for 20–40 years, the host immune system is 'tolerant' to the virus, resulting in high levels of viral replication and persistently normal alanine aminotransferase. Patients also have hepatitis B e antigen (HBeAg) (a protein which is secreted during viral replication), but no antibodies to this antigen.

Recommendation

During this phase there is minimal damage and so a liver biopsy and antiviral treatment are not required. However, the majority of patients will eventually progress to phase 2 and develop active disease. Patients should therefore be advised that periodic monitoring of liver function is important to detect a rise in alanine aminotransferase.

Phase 2 – immune clearance

This phase is characterised by a more vigorous immune response resulting in liver damage with intermittently elevated alanine aminotransferase and elevated viral DNA. Repeated episodes of inflammation lead to fibrosis, and the duration and severity of this phase determines the degree of long-term liver damage. Approximately 30–40% of patients emerge from this phase with established cirrhosis.[3]

During this phase, approximately 5–10% of patients each year will spontaneously lose HBeAg and develop antibodies to HBeAg. This is called seroconversion and is usually associated with reduced viral replication. The median age for seroconversion is 30–32 years.

Recommendation

It is common practice to initially observe patients with high alanine aminotransferase concentrations (greater than 2–5 times upper limit of normal) for three months to assess whether spontaneous HBeAg seroconversion will occur.

All patients with a persistently abnormal alanine aminotransferase should therefore be referred to a hepatologist for consideration of a liver biopsy and treatment.

Phase 3 – immune control

In this phase the immune response suppresses viral replication to low or undetectable levels. Inflammation reduces and serum alanine aminotransferase normalises. The establishment of immune control is associated with HBeAg seroconversion, and these patients are thought not to have ongoing damage. Once seroconversion occurs, patients may stay in this phase indefinitely.

Recommendation

Although most patients in this phase do not require antiviral treatment, a significant proportion will already have established cirrhosis and require regular careful assessment (Table 3).

Carefully performed ultrasound can reveal coarse echo texture suggestive of cirrhosis. Low albumin and elevated prothrombin time are markers of synthetic dysfunction seen in advanced disease, and low platelets (150 x 10^9/L) may be due to portal hypertension. If any of these features are detected, a liver biopsy should be considered, and treatment is recommended for patients with confirmed cirrhosis and detectable viral DNA.

Patients in this phase can reactivate at any time and should still undergo regular monitoring with at least annual liver function tests. Prophylactic treatment is recommended if patients require immunosuppressive therapy, for example cancer chemotherapy.

Phase 4 – immune escape

In this phase the virus mutates and loses its ability to make the HBeAg protein. Despite this, it can still replicate, resulting in recurrence of active liver disease and progressive fibrosis. This phase is characterised by persistently elevated or fluctuating levels of alanine aminotransferase, HBeAg negativity, but elevated viral DNA. Patients in this phase are usually older than 40 years.

Recommendation

Patients in this phase are at high risk of cirrhosis (8–10% per year) and require long-term treatment to suppress viral replication.

Referral

Drug treatment is primarily undertaken at a liver clinic under the supervision of specialist hepatologists. Non-urgent referrals should be directed to the liver clinic. Patients presenting with an alanine aminotransferase greater than 200 U/L, or decompensated liver disease (muscle wasting, ascites, jaundice, encephalopathy or bleeding) should be discussed with a specialist to expedite referral.

Table 3

Signs and symptoms of liver cirrhosis

Clinical	Fatigue Muscle wasting Dupuytren's contracture Palmar erythema Spider naevi Splenomegaly
Radiological	Coarse echotexture Features of portal hypertension - dilated portal vein - recanalisation of para-umbilical vein - varices
Laboratory	Synthetic dysfunction - low albumin - elevated prothrombin time Portal hypertension - thrombocytopenia

Treatment options

Short-term treatment goals include suppression of viral replication, normalisation of serum alanine aminotransferase and improvement in liver histology. In HBeAg positive patients, seroconversion is a therapeutic end point because it is associated with an improved prognosis. The aim of long-term treatment is to prevent or delay the onset of complications including cirrhosis, hepatic decompensation and hepatocellular carcinoma.

The two major options for chronic hepatitis B are pegylated interferon or nucleos(t)ide analogue therapy. There are advantages and disadvantages with both treatments (Table 4).

Interferons

Pegylated interferon therapy consists of weekly subcutaneous injections usually given for 12 months. This treatment stimulates the immune system to eradicate the virus from infected hepatocytes. The benefits of pegylated interferon can persist even after treatment, and relapse rates appear to be less than with non-pegylated interferon.[4]

Adverse effects include neutropenia and thrombocytopenia which require monthly blood monitoring, and dose reduction if necessary. Fever after injection, fatigue, myalgia and headache are common in the first month and can be treated with standard dose paracetamol.

Interferons affect serotonin concentrations and can cause mood disturbance. It is therefore important to ensure that the patient is euthymic at the start of treatment and that their mood is monitored regularly. A past history of depression or anxiety, or antidepressant use is not a contraindication to interferon therapy. Mood disturbances respond to low-dose selective serotonin reuptake inhibitors and do not usually require interruption of interferon treatment.

Table 4

Pros and cons of drug treatments for hepatitis B

	Pegylated interferon	Nucleos(t)ide analogues
Example	Pegylated interferon alfa-2a	Entecavir – currently available Adefovir – second-line therapy Lamivudine – resistance problems Emtricitabine Telbivudine Tenofovir
Advantages	Defined treatment duration No antiviral resistance Durability of HBeAg seroconversion	Easy to administer and monitor Safe in cirrhosis and decompensated liver disease Well tolerated
Disadvantages	Subcutaneous injection Significant adverse effects Less effective than nucleos(t)ide analogues in patients with high HBV DNA and low alanine aminotransferase	Prolonged duration of therapy Risk of antiviral resistance with long-term use

HBeAg hepatitis B e antigen
HBV hepatitis B virus

Nucleos(t)ide analogues [4]

Conversely, treatment with nucleos(t)ide analogue therapy is usually a once-daily oral treatment. While a number of different oral drugs are available, they all inhibit the viral polymerase enzyme to suppress viral replication. Unlike pegylated interferon, oral nucleos(t)ide analogues do not induce a strong immune response and thus often require long-term administration to prevent relapse.

Approximately 20% of HBeAg positive patients per year will achieve the therapeutic end point of HBeAg seroconversion on oral nucleos(t)ide analogue therapy. Consolidation treatment is recommended for 12 months after seroconversion. However, longer-term treatment may be needed if the patient does not seroconvert, has immune escape (HBeAg negative at the start of treatment) or is cirrhotic.

Pregnancy

It is important to note that telbivudine is a category B1 drug whereas all the other nucleos(t)ide analogues are category B3. However, experience with drugs such as lamivudine is far greater than with telbivudine so many doctors would use lamivudine in pregnancy.

Treatment initiation

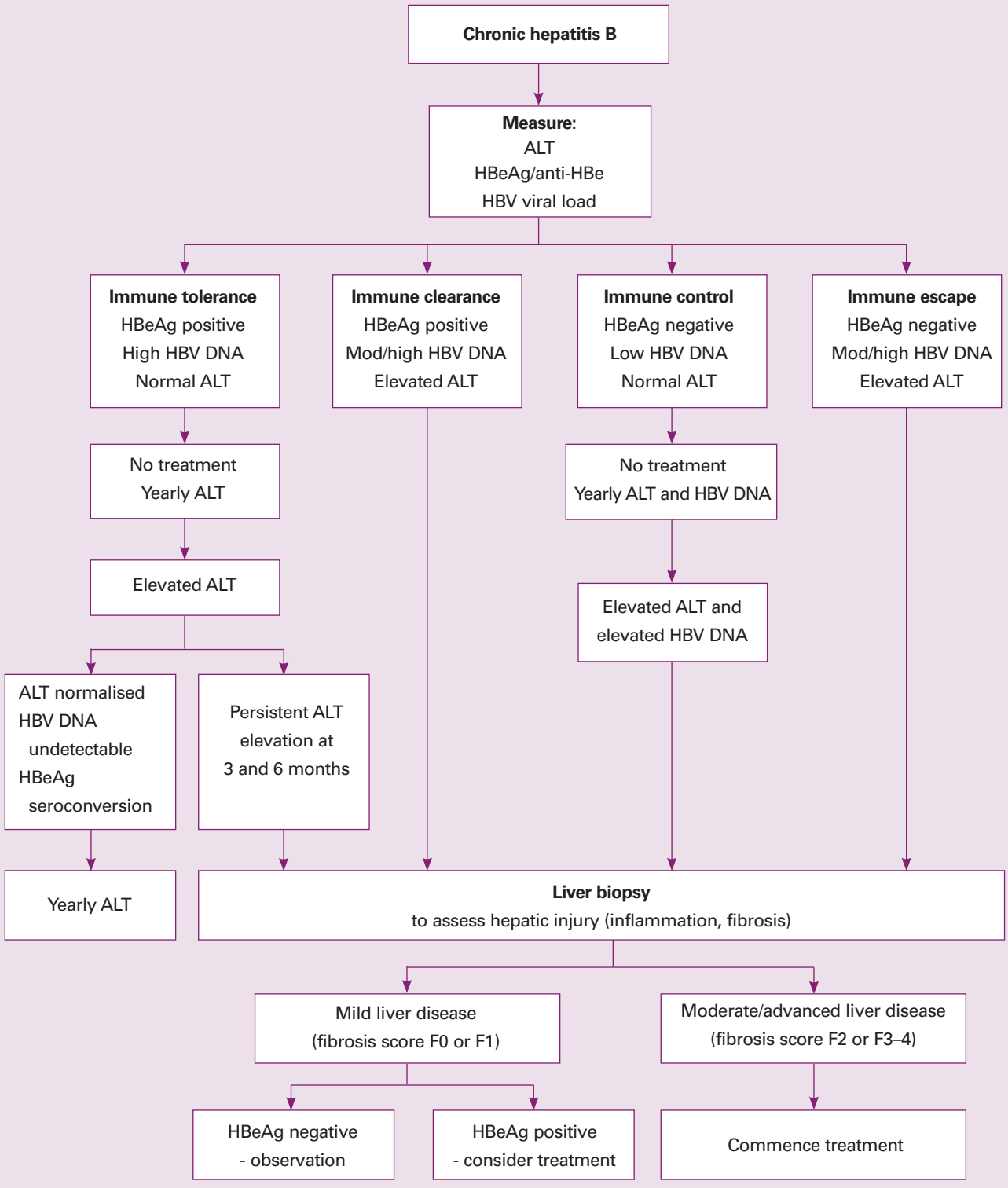
In general, patients who are offered treatment have active viral replication and liver damage. Important considerations before treatment include:

- patient choice
- timing of pregnancy (oral drugs are not licensed for use in pregnancy)
- risk of progression without treatment (highest in those with high alanine aminotransferase, repeated flares or significant fibrosis already)
- potential need for indefinite therapy (immune escape/HBeAg negative disease and cirrhosis)
- risk of antiviral resistance with oral nucleos(t)ide analogues
- potential treatment-related adverse effects.

A general approach in treatment-naïve patients with chronic hepatitis B is outlined in Fig. 1.

Fig. 1

General approach to treatment-naïve patients with chronic hepatitis B infection



ALT alanine aminotransferase
HBeAg hepatitis B e antigen
HBe hepatitis B e
HBV hepatitis B virus

Follow-up

Ongoing monitoring is recommended even in patients for whom antiviral treatment is not currently indicated. Patients in the immune tolerant phase should have yearly liver function tests and those in the immune control phase should also have yearly tests for viral DNA. All patients with an abnormal alanine aminotransferase should be referred to a specialist or hepatology clinic for consideration of therapy.

Surveillance for hepatocellular carcinoma is recommended in high-risk patient groups and consists of an abdominal ultrasound and serum alfa-fetoprotein every six months. High-risk groups include patients with cirrhosis, family history of hepatocellular carcinoma, Asians older than 35 years (if infected early in life) and Africans older than 20 years.

Conclusion

Chronic hepatitis B is a common health problem in Australia. Treatment options include either oral nucleos(t)ide analogue drugs or pegylated interferon. Therapy reduces inflammation, can improve liver injury and reduces progression to cirrhosis and hepatocellular carcinoma. Long-term monitoring is recommended even in patients not currently on antiviral therapy. Patients at increased risk of hepatocellular carcinoma should undergo surveillance with six-monthly liver ultrasound and serum alfa-fetoprotein tests.

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Conflict of interest: Dr Bell is on an advisory board for Bristol-Myers Squibb (makers of entecavir) and is a speaker for Gilead (makers of tenofovir) and Roche (makers of pegylated interferon).

Self-test questions

The following statements are either true or false (answers on page 115)

5. The hepatitis B virus can develop resistance to nucleos(t)ide analogues.
6. Pegylated interferon is usually the best treatment for patients with high levels of hepatitis B virus DNA.

NPS RADAR
Rational Assessment of Drugs and Research

NPS RADAR update

The latest issue of *NPS RADAR* reviews rivaroxaban listed on the Pharmaceutical Benefits Scheme on 1 August 2009. Rivaroxaban is the first of a new class of oral anticoagulants for preventing venous thromboembolism after elective hip or knee replacement surgery. The 10 mg tablet should be taken once daily for 35 days after hip surgery and for 14 days after knee surgery. Neither monitoring of prothrombin time nor dose adjustment is required but, as with other drugs for this indication, managing the risk of bleeding is a primary concern.

Also included in *NPS RADAR* are *In Brief* items covering:

- oxybutynin patches as an alternative for patients with overactive bladder who cannot tolerate or swallow oral oxybutynin. Dry mouth and constipation are less likely with transdermal oxybutynin than oral formulations, but application site reactions are common
- praziquantel for people with schistosomiasis.

For more information about rivaroxaban, oxybutynin patches and praziquantel, see the *NPS RADAR* website (www.npsradar.org.au) or your mailed copy from 1 August.

Visit www.npsradar.org.au to register for your free email updates to keep track of the latest *NPS RADAR* news and reviews.

Thoracic computed tomography: principles and practice

Graham Simpson, *Director, Thoracic Medicine, Cairns Base Hospital, Cairns, and Adjunct Associate Professor, James Cook University Medical School, Townsville, Queensland*

Summary

Computerised tomography of the chest has revolutionised thoracic imaging. It can provide important information in the diagnosis and management of pulmonary masses and malignancy, mediastinal disease, bronchiectasis, interstitial lung disease and pleural abnormalities. However, it is a relatively expensive technique and carries a risk of inducing malignant disease due to radiation exposure. To improve current practice, requesting doctors need a greater understanding of the indications for computerised tomography scanning and its different forms (conventional vs high resolution). A greater involvement of specialist radiologists in vetting requests and advising on the most appropriate investigation is also needed.

Key words: chest X-rays, imaging, lung cancer, lung diseases.

(Aust Prescr 2009;32:105–7)

Introduction

Since its development, computerised tomography (CT) scanning has revolutionised medical imaging, paving the way for techniques such as magnetic resonance imaging and positron emission tomography. It is however a relatively expensive investigation – the Medicare rebate for a chest CT scan is $340 compared to $40.10 for a chest X-ray. Chest CT is also associated with high radiation exposure. There is evidence that in general practice and hospitals the investigation is inappropriately used, causing unnecessary expense and risk of adverse events.[1,2]

Principles of CT scanning

Medical CT produces cross-sectional imaging data of internal structures of the body based on their ability to block an X-ray beam. Single or multiple X-ray tubes rotate around the patient with an opposed array of detectors picking up the transmitted radiation. The digitised data are then used to calculate the radiological absorption characteristics of individual volume elements (voxels) of the body parts scanned. These can then be used to generate images with each voxel displayed as a two-dimensional pixel. The usual images are cross-sectional (axial), but can also be reformatted in newer scanners to provide coronal, sagittal or three-dimensional images.

The older CT scanners used axial rotation of the X-ray tube around the patient who would be progressively moved through the X-ray scanning tube, usually in 1 cm increments, and then rescanned. Newer CT scanners allow continuous rotation of the X-ray tube as the patient moves by the use of slip rings. These transmit the high voltages necessary for imaging and the acquired data in the reverse direction without the use of cabling. This is helical (sometimes incorrectly called spiral) CT scanning and has shortened data acquisition time. The development of multi-slice CT with multiple detector rows has further increased the speed of scanning and improved spatial resolution in the longitudinal (z) axis.

Different types of CT scanning

There are two types of CT scanning: conventional scanning (with or without contrast media) and high resolution scanning. It is useful to distinguish between the two as an inappropriately worded request may still lead to the wrong type of image being produced. Newer techniques such as helical multi-slice scanning have slightly blurred the distinction between these investigations. Most chest CT scans are taken supine at full inspiration.

Conventional CT with or without contrast

A conventional chest CT provides continuous axial cross-sectional images of the chest. These correspond to 7–10 mm slices of the chest so there is some potential for loss of detail due to signal averaging. However, the full volume of the lungs is scanned.

By altering the processing algorithms, two sets of images can be obtained – lung windows and mediastinal windows. In the mediastinal windows the lungs are overexposed and simply appear black. This algorithm is used to assess chest wall and mediastinal structures, usually with intravenous contrast so that vascular structures in the mediastinum can be distinguished

from enlarged lymph nodes or other masses. These mediastinal windows are also appropriate to look at the chest wall and pleura and in particular for pleural plaques such as calcium-containing asbestos pleural plaques. In the lung windows the mediastinal and chest wall structures are essentially whited out and the lung tissue can be seen in detail including areas of consolidation, and pulmonary vascular structures.

In staging of lung cancer a contrast CT is needed and should include the upper abdomen to assess the liver and adrenal glands.

High resolution CT

In a typical high resolution chest CT scan the patient's lungs are scanned at 1 cm intervals, but only a 1 mm slice is taken. Thus, only 10% of the lung tissue is sampled and small lesions may be missed. A high resolution CT scan is **not** simply a 'better' CT scan. It is designed to look at fine detail of lung anatomy and is important in detection and assessment of diseases such as bronchiectasis, interstitial lung diseases (such as sarcoidosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis) and in the assessment of emphysema and bullous lung disease. It is usually performed without contrast, and mediastinal and chest wall structures are not examined.

Common clinical scenarios – where does CT fit in?

In many clinical situations, simpler, cheaper and safer tests may be more appropriate. If a request for CT chest scan is being considered then it may be useful to discuss this with a consultant radiologist to see if it is the appropriate test.

Masses on chest X-ray

The most common reason for a general practitioner to request a CT scan of the chest is a mass visible on a chest X-ray. There are two common patterns:

- the mass is clinically likely to be lung cancer (for example, the patient is a smoker with suspicious symptoms such as increased cough, weight loss or haemoptysis)
- a usually smaller mass or nodule is found on an X-ray performed for some other reason.

In the first scenario, it is essential to obtain a histological diagnosis which scanning cannot provide. These patients are going to need some form of biopsy, usually bronchoscopic. Performing a CT scan may delay diagnosis. CT in lung cancer is essentially a staging investigation and should only be done after other appropriate investigations such as lung function testing, and after consideration of comorbidities and clinical findings which may render the patient inoperable. Patients who may be considered for radiotherapy or other treatment will have to have radiotherapy-planning CT scans even if they have had a previous diagnostic CT scan.

Incidentally found pulmonary nodules can present a considerable management challenge. Calcification (which is usually detectable on plain chest radiographs) is very reassuring and implies that the lesion is both chronic and benign. However, a specialist referral is almost always indicated and CT scanning is unlikely to alter this requirement.

Pneumonia

All pneumonias should be followed radiologically with repeat plain chest radiographs until they clear or any abnormalities stabilise. Recurrent pneumonias in the same area require investigation by bronchoscopy.

Pleural effusion

Pleural effusions occurring in association with pneumonia require aspiration and not further imaging to assess whether an empyema is present. If there is no evidence of infection, obvious heart failure or nephrotic syndrome, the vast majority of pleural effusions are malignant. Diagnosis rests on aspiration of pleural fluid or thoracoscopy rather than imaging.

Haemoptysis

Patients with haemoptysis should have a plain X-ray and be referred for bronchoscopy.

Non-specific shadowing on chest X-ray

When there is ill-defined abnormality on a chest X-ray (old fibrosis, atelectasis) then the best investigation is to track down any old X-rays. CT may be helpful, but if the clinical suspicion for malignancy is low then a repeat chest X-ray in three months is probably a better test.

Shortness of breath

CTs are almost never helpful for diagnosing respiratory causes of breathlessness. Initial investigations should involve plain chest X-ray and spirometry. A small number of patients with interstitial lung disease will have a normal plain radiograph. However, almost all of these will have abnormal physical signs or respiratory function tests suggesting the diagnosis and require referral. If CT is considered then a high resolution CT should be requested.

Cough

If imaging is being considered in patients with chronic cough, the initial investigation should be a plain chest radiograph. If this is normal then a CT is extremely unlikely to show the cause of the cough, which is likely to represent upper airway disease, asthma or gastro-oesophageal reflux.

Asbestos exposure

Many patients are concerned by minor asbestos exposure in the past. If physical examination, spirometry and plain chest X-ray are normal, CT is very unlikely to show any significant pathology and should be avoided. CTs may well reveal benign asbestos pleural plaques but as these are of no clinical significance, there seems little point in finding them.

Patients with significant asbestos exposure and symptoms present a different clinical problem and high resolution CT may well be indicated. However, these patients will have abnormal physical findings, spirometry and chest X-rays.

Safety

In Australia it is estimated that CT scans account for 65% of the population's medical radiation exposure.[3] Chest or abdominal CT scans deliver an average dose of 8–10 mSv (compared to a chest X-ray which is 0.02 mSv) and the dose to the breast tissue during a chest CT might be over 30 mSv.[4,5,6] The International Commission on Radiological Protection estimates the risk of inducing a fatal cancer as 6% per Sievert which means that the doses involved in chest CT examination would lead to a fatal tumour in one per 2500 scans. This risk is age-related and in children it may be as high as one in a few hundred.[7] Clearly, chest CT scans need to be ordered with a careful analysis of the risk-benefit ratio.

Conclusion

Although CT of the chest is an extremely valuable investigation, it is much overused and is not without adverse effects. Being familiar with the different types of CT scans – conventional and high resolution – is important for doctors who order these tests as the two techniques have entirely different uses and indications. For example, high resolution CT scan may well miss a small pulmonary mass, but a conventional CT scan even on lung windows cannot reliably detect or assess interstitial lung disease or bronchiectasis.

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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 115)

7. Conventional CT scanning is the most appropriate technique for assessing bronchiectasis.
8. Small lesions in the lung are best detected using high resolution CT.

Patient support organisation

Myeloma Foundation of Australia

See articles on multiple myeloma on pages 92–4 and 95–8

The Myeloma Foundation is a volunteer-driven, non-profit organisation which supports and informs those living with the disease and educates those involved in its care and treatment. A telephone support line is staffed by myeloma support nurses. The Foundation runs seminars and workshops, support groups and health professional education. The website contains informative videos and fact sheets, links to a patient guide and a newsletter, and resources for health professionals such as the myeloma nurses' learning program.

Website	www.myeloma.org.au
Myeloma support line	1800 693 566 (free call, Mon–Fri working hours)

eAudit – Proton pump inhibitors

An electronic clinical audit (eAudit) from the National Prescribing Service will soon be available to assist general practitioners in reviewing patients taking proton pump inhibitors (PPIs). This eAudit provides the opportunity to:

- identify patients with inadequate control of dyspepsia
- determine appropriate duration of PPI use for a range of clinical indications
- reflect on education provided to patients about lifestyle modification and rare but important adverse effects
- compare management to current guidelines, using the immediate feedback provided.

This eAudit is recognised for points in professional development programs and the Quality Prescribing Initiative of the Practice Incentive Program (May 2009 to April 2010).

Enrolments are open from the end of August 2009.
See www.nps.org.au/healthprofessionals

Heparins for venous thromboembolism prophylaxis – safety issues

Jocelyn S Lowinger *and* ***David J Maxwell****, NSW Therapeutic Advisory Group, Sydney*

Summary

Heparins are commonly used to prevent venous thromboembolism. Although they are effective anticoagulants, heparins have a high risk of adverse effects if used inappropriately. Safer heparin prescribing is achieved through careful patient selection by assessing the risk of venous thromboembolism. Consider the drugs' contraindications and precautions including renal function, concomitant medication use and spinal needle insertion. Comparative drug information needs to be considered when choosing the optimal heparin for an individual patient. The timing of perioperative heparin administration depends on the choice of heparin, type of surgery and type of anaesthesia. Patients should be carefully monitored during prophylaxis.

Key words: anticoagulant, dalteparin, danaparoid, enoxaparin, fondaparinux.

(Aust Prescr 2009;32:108–12)

Introduction

Heparins are effective anticoagulants and can be used to prevent venous thromboembolism in hospitalised medical and surgical patients. In Australia it has been estimated that the overall prevalence of venous thromboembolism in all hospitalised patients is 2–3 per 1000 admissions.[1] There is therefore growing Australian and international encouragement for prophylaxis, so increased numbers of inpatients will be prescribed a heparin.

'Heparin' or 'heparins' refers to the following medications available in Australia:

- unfractionated heparin
- low molecular weight heparins – dalteparin, enoxaparin
- synthetic selective inhibitor of activated factor X – fondaparinux
- heparinoid – danaparoid.

Although the benefits of using heparin in venous thromboembolism prophylaxis generally outweigh the risks, harm from low-dose heparin can be severe and the risks should not be ignored. While adverse effects are less common with low-dose heparin than with therapeutic doses of heparin, bleeding can still occur if other risk factors for bleeding are present, such as renal impairment or interaction with other drugs. Also, bleeding events can be expected to increase in frequency as the number of patients prescribed heparin for venous thromboembolism prophylaxis continues to increase. For example, a program of mandatory venous thromboembolism prophylaxis with low molecular weight heparin alone or in combination with warfarin has resulted in increased bleeding rates after hip and knee arthroplasty.[2] Incidents with anticoagulants including heparins (at all doses) continue to be commonly reported to incident reporting systems in Australia and the USA.[3,4] Clinicians must consider the patient's safety when prescribing heparin as part of a strategy for venous thromboembolism prophylaxis as discussed in publications such as 'Safe prescribing of heparins for venous thromboembolism prophylaxis: a position statement of the NSW Therapeutic Advisory Group'.[5]

Patients requiring venous thromboembolism prophylaxis

The risk of venous thromboembolism should be assessed in all adult patients before or on admission to hospital. Currently available guidelines differ regarding which patients require venous thromboembolism prophylaxis.[6–12] An Australian guideline for venous thromboembolism prophylaxis is currently under development.[13] Table 1 shows the current recommendations in the USA.[11]

Contraindications and precautions

All patients should be assessed for contraindications and the precautions needed before starting prophylaxis. Absolute contraindications to heparin include known hypersensitivity, past or present heparin-induced thrombocytopenia and active bleeding.

Caution is required when prescribing heparin to patients with conditions that may increase the risk of bleeding (see box). In these patients, the decision to prescribe heparin should be made on an individual basis balancing the relative benefit and harm. Tests for coagulation, such as prothrombin time, are not routinely required.[5]

Renal function

Patients with moderate to severe renal dysfunction have a higher risk of bleeding with some heparins. Assessment of renal function using creatinine clearance is important before

Table 1

Recommendations for thromboembolism prophylaxis [11]*

Indications	Procedure/condition
Surgical procedures generally requiring venous thromboembolism prophylaxis	Acute spinal cord injury Major trauma Major surgery including: - general cancer or non-cancer surgery - hip and knee arthroplasty - open gynaecological surgery - open urological surgery - prolonged surgery†
Surgical procedures generally not requiring venous thromboembolism prophylaxis when no additional risk factors are present	Elective spine surgery Knee arthroscopy Isolated lower extremity injuries Laparoscopic surgery Transurethral surgery Vascular surgery
Medical conditions generally requiring venous thromboembolism prophylaxis	Congestive heart failure Severe respiratory disease Immobility plus: - cancer - previous venous thromboembolism - sepsis - acute neurological disease - inflammatory bowel disease

Mechanical methods of prophylaxis, such as stockings, are recommended in patients at high risk of bleeding.

* These recommendations are based on guidelines from the USA, pending the publication of new Australian guidelines

† Prolonged surgery may increase the risk of venous thromboembolism in patients who are over 40 or who have other risk factors

prescribing low molecular weight heparins or fondaparinux. In patients with a creatinine clearance less than 30 mL/min enoxaparin dosage should be reduced to 20 mg daily and fondaparinux is contraindicated. For danaparoid, dose reductions should be considered when creatinine clearance is under 20 mL/min. Unfractionated heparin can be prescribed without dose alteration.[5]

Interactions

Heparin should be prescribed cautiously in patients taking drugs that can increase bleeding, for example antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs) and thrombolytics. The decision to co-prescribe heparin with these drugs should be made on an individual patient basis in consultation with senior staff and taking into account patient preference. Careful clinical review and monitoring of the patient is recommended. Low-dose aspirin required for prevention or treatment of cardiovascular disease may be continued.

Examples of problems that may increase risks with heparin

Bleeding disorders, e.g. haemophilia

Concomitant use of certain medications, e.g. clopidogrel

Conditions where bleeding would be catastrophic, e.g. focal lesions, haemorrhagic stroke

Creatinine clearance <30 mL/min

High risk of uncontrolled haemorrhage, e.g. acute ulcerative gastrointestinal conditions, anaemia of unknown cause

Recent surgery on eye, brain or spinal cord

Severe thrombocytopenia (platelets <50 x 10^9/L)

Severe liver disease with coagulopathy and/or oesophageal varices

Spinal or epidural needle insertion (spinal tap or spinal anaesthesia)

Unfractionated heparin can raise potassium concentrations. This may lead to hyperkalaemia when co-prescribed with other drugs that increase potassium, for example angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, potassium sparing diuretics, potassium supplements, NSAIDs or trimethoprim. Patients receiving unfractionated heparin for more than three days who are at risk of developing hyperkalaemia should have their potassium monitored at least every four days.[14]

Spinal needle insertion

When heparins are prescribed for patients undergoing spinal needle insertion the risk of an epidural or spinal haematoma is increased. Insertion and removal of needles and catheters should occur when the anticoagulant effect is lowest, generally just before the next dose is due. If bleeding occurs during needle placement, the subsequent dose of heparin should be delayed for 24 hours and the patient should have neurological observations.[15]

Choice of heparin

Different heparins have different harm:benefit ratios, although each carries a similar bleeding risk. There are usually options available for each clinical indication, but heparins are not clinically interchangeable (unit for unit) (Table 2). When choosing a heparin consider the clinical indication, patient factors (for example renal impairment), type of surgery and anaesthesia, dosing schedule, risk of heparin-induced thrombocytopenia, reversibility and cost.[5] Unfractionated heparin is not recommended for prophylaxis in hip or knee arthroplasty or trauma patients.[11]

Timing and duration of heparin administration

Care should be taken to determine the optimal time for giving perioperative heparin.[5] The timing depends on the type and dosing schedule of the heparin chosen and the type of procedure and anaesthesia planned. There is no advantage in

Table 2

Differences between heparins when used for venous thromboembolism prophylaxis [5]

	Unfractionated heparin	Enoxaparin	Dalteparin	Danaparoid	Fondaparinux
Elimination	Liver and reticuloendothelial system	Primarily renal	Primarily renal	Renal	Renal
Dosing in renal impairment	No dosage adjustment required	Reduce dose if CrCl <30 mL/min	Unknown	Consider dose reductions if CrCl <20 mL/min	Do **not** use if CrCl <30 mL/min Use cautiously if CrCl = 30–50 mL/min
Renal function testing	Not required	At baseline	At baseline	Not required	At baseline and periodically. Discontinue in patients who develop labile renal function or severe renal impairment
Incidence of HIT	Highest incidence	Lower incidence	Lower incidence	Can be used to treat HIT	Unknown
Platelet count monitoring at baseline[17]	Yes. Repeat after 24 hours in patients administered UFH in past 100 days	Yes. Repeat after 24 hours in patients administered UFH in past 100 days	Yes. Repeat after 24 hours in patients administered UFH in past 100 days	Not required	Yes
Ongoing platelet count monitoring[17]	Every 2–4 days in postoperative and medical patients up to 14 days or until heparin is stopped (whichever is earlier)	Every week in postoperative patients up to 14 days or until heparin is stopped (whichever is earlier) Not required in medical or obstetric patients	Every week in postoperative patients up to 14 days or until heparin is stopped (whichever is earlier) Not required in medical or obstetric patients	Not required	When treatment ceased
Other monitoring[17]	Activated partial thromboplastin time testing is not required for prophylactic dosing Assess for bleeding	Assess for bleeding	Assess for bleeding	Functional anti-factor Xa (patients with renal impairment, or those weighing more than 90 kg) Assess for bleeding	Assess for bleeding
Approved indication for VTE prophylaxis	Prevention of VTE in surgical and high risk medical patients	Prevention of VTE in surgical patients and in medical patients bedridden due to acute illness	Prevention of VTE in surgical patients	Prevention of VTE in patients undergoing general or orthopaedic surgery	Prevention of VTE in high-risk orthopaedic surgery (hip fracture, knee or hip replacement) and abdominal surgery
Subcutaneous dose in VTE prophylaxis	5000 units 2–3 times daily depending on risk of VTE	20–40 mg once daily depending on risk of VTE	2500–5000 units once daily depending on risk of VTE	750 anti-factor Xa units twice daily	2.5 mg once daily Use with caution in patients who weigh <50 kg
Reversibility with protamine sulfate	Complete	Incomplete, 60% reversible	Incomplete, 60–75% reversible	Non-reversible	Non-reversible
Daily cost compared to twice-daily UFH		~1.5–2 x cost	~2 x cost	~15 x cost	~4 x cost

Refer to guidelines for the preferred heparin for each clinical indication[11]

VTE venous thromboembolism
CrCl creatinine clearance
UFH unfractionated heparin
HIT heparin-induced thrombocytopenia

starting venous thromboembolism prophylaxis preoperatively rather than postoperatively.[11] In patients undergoing neurosurgery, heparin, if indicated, should never be started preoperatively. After trauma, patients should not be started on heparin until primary haemostasis is established.[11]

Heparin should be continued while patients remain at increased risk of developing venous thromboembolism – up to 35 days postoperatively in some orthopaedic patients.[11]

Patient monitoring

While routine clotting studies are not required during prophylaxis, patients need to be assessed for bleeding. Unless they are taking danaparoid, patients will need platelet counts every few days.

Bleeding

Easy bruising and petechial haemorrhages may precede frank bleeding. Nose bleeds, haematuria or melaena may be the first sign of bleeding, so check for these signs.[5] Bleeding can often be controlled by stopping the heparin. In some patients protamine sulfate may be considered for heparin reversal, however it does not reverse the effects of danaparoid and fondaparinux (Table 2). Patients with bleeding should undergo fluid management and resuscitation as required.

Thrombocytopenia

Unfractionated heparin, and to a lesser extent low molecular weight heparins, may cause heparin-induced thrombocytopenia. A diagnosis of heparin-induced thrombocytopenia requires the presence of antibodies (heparin-dependent platelet antibodies) and one of the following events:[17]

- unexplained platelet count fall of 30–50% from baseline
- venous or arterial thrombosis
- skin lesions at heparin injection sites
- systemic anaphylactoid reactions.

Heparin-induced thrombocytopenia usually occurs 4–10 days (sometimes weeks) after starting heparin (earlier in patients exposed to heparin in the previous three months). Management requires cessation of heparin and alternative anticoagulation (danaparoid or lepirudin). Low molecular weight heparins should not be used in patients who have a history of heparin-induced thrombocytopenia with unfractionated heparin.

A milder, reversible thrombocytopenia may also develop. In these cases antibodies are not present. If the platelet count remains greater than 100 x 10^9/L, heparin may be continued.[17]

Platelet counts should be measured intermittently in patients prescribed unfractionated heparin or low molecular weight heparins, and at baseline in patients prescribed fondaparinux, but are not required in patients prescribed danaparoid.[17] Recommendations for platelet count monitoring vary depending on the type of patient and the choice of heparin (Table 2).[16,17]

Future directions

The forthcoming Australian guidelines will clarify the indications for thromboembolism prophylaxis[13], however practice may soon have to change. Dabigatran and rivaroxaban have recently been approved for use in Australia. As these anticoagulants can be given orally, they may supersede heparins in some indications.

Conclusion

Heparin is an effective but high-risk drug that can cause bleeding even in low doses. Safer heparin prescribing can be achieved through careful patient selection taking into consideration the clinical indication for venous thromboembolism prophylaxis, contraindications and precautions. Heparin choice should be matched to the individual patient's requirements. Patients should be monitored for bleeding while heparin administration is continued.

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Conflict of interest: none declared

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Dutasteride

Avodart (GlaxoSmithKline)

500 microgram capsules

Approved indication: benign prostatic hyperplasia

Australian Medicines Handbook section 13.2.2

Although surgery is the definitive treatment for benign prostatic hyperplasia, some patients can be managed with drugs (see 'Drug treatment of benign prostatic hypertrophy', Aust Prescr 1995;18:30–2). The drug treatments include finasteride which inhibits the conversion of testosterone to dihydrotestosterone. This androgen is thought to be responsible for stimulating the growth of the prostate.

Like finasteride, dutasteride is a 5-alpha reductase inhibitor. Finasteride mainly inhibits the type II enzyme found in the prostate, while dutasteride also inhibits the type I enzyme found in the liver and skin. After two weeks of treatment with dutasteride there is a reduction of up to 90% in the concentration of dihydrotestosterone.

The bioavailability of the drug varies from 40% to 94% and it is extensively metabolised. Although cytochrome P450 3A4 is involved in the metabolism, few specific studies of interactions have been carried out in patients. There is a potential for interactions with other drugs metabolised by this enzyme. Most of the metabolites are excreted in the faeces. The half-life of the drug is up to five weeks so it remains in the body for several months after treatment stops. The onset of the full treatment effect is also slow.

In placebo-controlled clinical trials the efficacy of dutasteride has been evaluated using symptom scores in 4325 men. At the start of the studies the average score was 17/35. After two years of treatment this score was significantly reduced by 4.5 points. Dutasteride significantly reduced the volume of the prostate gland. It also significantly improved the urinary flow rate and reduced the risk of acute urinary retention.[1] These effects continued during a two-year open-label extension of the trials.[2]

Dutasteride has adverse effects on sexual function. Patients may develop a decreased libido, ejaculation disorders or impotence. Serum testosterone may increase, but prostate specific antigen concentrations will be reduced by dutasteride.

As dutasteride may affect the development of a male fetus the capsules should not be handled by pregnant women.

Like finasteride (see 'The price of urine', Aust Prescr 1995;18:26–7), the effect of dutasteride is modest. A placebo can improve a patient's symptom score by 2.3 points and the statistically significant change in urinary flow rate is only 1.3 mL/second greater than placebo.[1] Drug treatment should therefore only be used if self-management strategies do not work.

T manufacturer provided only the product information

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Eculizumab

Sorilis (Alexion)

30 mL vials containing 10 mg/mL

Approved indication: paroxysmal nocturnal haemoglobinuria

Australian Medicines Handbook Appendix A

Paroxysmal nocturnal haemoglobinuria is a rare cause of haemolytic anaemia. Patients have stem cells with a somatic mutation which results in red blood cells being unable to anchor a complement inhibitory protein to their cell membrane. The absence of this protein makes the affected red blood cells vulnerable to complement-induced haemolysis. This haemolysis results in haemoglobinuria and anaemia. Patients are also prone to thrombosis, and thromboembolism is a common cause of death.

Blocking the action of complement on the abnormal cells could reduce haemolysis. Eculizumab achieves this by binding to complement protein C5.

Eculizumab is a humanised monoclonal mouse antibody (IgG). After infusion over 35 minutes, eculizumab rapidly reduces complement activity. This infusion is given weekly for five weeks and then repeated every two weeks. The half-life of eculizumab is approximately 11 days and maintaining the serum concentration above 35 microgram/mL suppresses haemolysis.

A preliminary study treated 11 patients for 12 weeks. Concentrations of lactate dehydrogenase, a marker of haemolysis, fell after the first dose of eculizumab. Haemolytic activity was completely blocked in patients whose serum concentration remained above 35 microgram/mL.[1] These patients continued in a 52-week extension study and nine showed complete blockade of haemolysis throughout. This reduction in haemolysis raised the proportion of affected cells, as a proportion of the total number of red cells, from 37% at baseline to 58% at 64 weeks.[2]

To investigate the effect of eculizumab on transfusion requirements 87 patients were randomised in a double-blind controlled trial. After 26 weeks haemoglobin concentrations had stabilised in 49% of the patients given eculizumab and 51% had not required a blood transfusion. The haemoglobin did not stabilise in the placebo group and they all needed transfusions. The mean number of units of packed cells used was three in the eculizumab group and 11 in the placebo group. Patients given eculizumab had an improved quality of life.[3]

An open-label study, with less stringent inclusion criteria, then treated 97 patients for 52 weeks. Haemolytic activity was suppressed in 89 patients throughout the study. The survival of the affected cells increased their proportion in the red cell population from 39% to 55%. Transfusions reduced from an annual mean of 12 units of packed cells to six units. There were 49 patients who did not need a transfusion while being treated with eculizumab.[4]

During this study the most frequent adverse effects were headache, upper respiratory tract symptoms, nausea and fever. These symptoms tended to be less frequent during the second six months of treatment.[4] Infections are common, but usually mild, however eculizumab increases susceptibility to meningococcal infections because of its effect on the complement system. Patients should therefore be given a meningococcal vaccine before starting treatment.

Patients can develop antibodies to eculizumab, but so far these have not reduced the effect of the drug. There is still a potential for infusion reactions.

An analysis of the thromboembolism rate in the studies found that it fell from 7.37 events/100 patient years to 1.07 events/100 patient years with treatment.[5] While the reduction is significant, there is not yet enough evidence to change the management of patients being treated with anticoagulants. The effect of eculizumab on survival is currently unknown.

Bone marrow transplantation can cure the condition, but donors are scarce and the procedure has significant risks. Eculizumab can reduce haemolysis, but the outcome of long-term treatment is uncertain. As treatment increases the proportion of affected cells in the circulation, people may have a high risk of serious haemolysis when they stop the drug. While eculizumab will reduce the need for treatments such as transfusion, these savings will not offset the high cost of the drug.

X manufacturer did not respond to request for data

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Tocilizumab

Actemra (Roche)

4 mL, 10 mL and 20 mL vials containing 20 mg/mL

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2

Patients with moderate to severe rheumatoid arthritis, which does not respond to disease-modifying antirheumatic drugs, can be treated with biological therapies such as the inhibitors of tumour necrosis factor alpha (see 'Tumour necrosis factor alpha inhibitors for the treatment of adult rheumatoid arthritis', Aust Prescr 2004;27:43–6). One of the actions of tumour necrosis factor is regulating the production of pro-inflammatory molecules such as the interleukins. High concentrations of interleukin-6 have been associated with inflammatory disorders including rheumatoid arthritis. The inflammatory action may be blocked by antibodies against interleukin-6 receptors, such as tocilizumab.

Tocilizumab is a humanised monoclonal antibody (IgG) produced in Chinese hamster ovary cells by genetic engineering. It binds to the interleukin-6 receptors throughout the body leading to rapid reductions in erythrocyte sedimentation rate and concentrations of C-reactive protein.

Tocilizumab has to be diluted and given by infusion over one hour. The infusion is repeated every four weeks. Although clearance is concentration dependent, the pharmacokinetics of tocilizumab may be nonlinear at low concentrations. At steady state the half-life of the drug is 8–14 days, but this is prolonged at higher concentrations. The activity of cytochrome P450 1A2, 2C9, 2C19 and 3A4 may increase with tocilizumab, potentially affecting the metabolism of other drugs.

After development in Japan, a phase II trial was carried out in Europe. It randomised 359 patients who had experienced an inadequate response to methotrexate. They were given tocilizumab 2 mg, 4 mg or 8 mg/kg, with or without methotrexate, or methotrexate alone, for 16 weeks. Using the criteria of the American College of Rheumatology, a 20% improvement occurred in 41% of the patients taking methotrexate, 31–63% of those taking tocilizumab and 63–74% of those taking both drugs.[1]

Phase III studies then used doses of 4 mg or 8 mg/kg. In one randomised study 418 patients received these doses and 204 had placebo infusions. Although the patients had had an inadequate response, they all continued their weekly doses of methotrexate for the 24 weeks of the trial. The response to the combined treatment was significantly greater than to methotrexate alone. A 20% improvement was achieved by 59% of the patients taking tocilizumab 8 mg/kg, 48% of those taking 4 mg/kg, but only 26% of the control group.[2]

Another trial included patients whose rheumatoid arthritis had persisted despite treatment with disease-modifying antirheumatic drugs. A group of 805 patients were randomised to add tocilizumab 8 mg/kg while 415 added a placebo. The patients were treated every four weeks for 24 weeks. A 20% improvement was obtained by 61% of the tocilizumab group and 25% of the placebo group. Concentrations of C-reactive protein fell to normal within two weeks of starting tocilizumab.[3]

The SAMURAI study in Japan compared the radiological effects of tocilizumab monotherapy to those of disease-modifying antirheumatic drugs. A total of 265 patients were treated for 52 weeks. There was no progression of joint damage in 56% of the patients given tocilizumab compared with 39% of the others.[4]

Tocilizumab has also been studied in patients whose rheumatoid arthritis had not responded to tumour necrosis factor inhibitors. These drugs were stopped, and the 499 patients were given methotrexate for at least 12 weeks before being randomised to also have infusions of tocilizumab (4 mg or 8 mg/kg) or placebo every four weeks. After 24 weeks, there had been a 20% improvement in 50% of the patients given 8 mg/kg, 30% of those given 4 mg/kg, but only 10% of those who took methotrexate and placebo. This response was not influenced by whichever tumour necrosis factor inhibitors had been used previously.[5]

As tocilizumab affects the immune system, patients are at risk of infections. There may be a decline in the neutrophil count (and platelets) so the full blood cell count should be monitored. Serious infections, such as pneumonia and cellulitis, are more common with the higher doses of tocilizumab. Patients should be tested for latent tuberculosis before starting treatment.

There is an increased risk of cancer in patients with rheumatoid arthritis and this could be elevated by tocilizumab. In the SAMURAI study three cancers were found in the tocilizumab group with none in the group given disease-modifying antirheumatic drugs.[4]

As tocilizumab is an immunoglobulin some patients will have infusion reactions, including anaphylaxis. Approximately 6% of the patients given 8 mg/kg had infusion reactions.

Gastrointestinal disorders are common. Although they are mainly mouth ulceration and gastritis, a few patients have suffered perforation of the gut, mainly as a complication of diverticulitis.

Particularly when given with methotrexate, tocilizumab can alter liver function. Regular monitoring of liver function is required and the dose should be adjusted according to the results. It is uncertain if treatment increases overall cardiovascular risk, but tocilizumab can cause a rise in lipids and blood pressure.

Tocilizumab appears to work best in combination with other drugs. It is therefore approved for use with methotrexate or non-biological disease-modifying antirheumatic drugs when previous therapy has been unsatisfactory or not tolerated.

Monotherapy can be used if the patient has moderate to severe disease and cannot take methotrexate. The long-term safety of monthly infusions is unknown, but studies are continuing.

T T T manufacturer provided clinical evaluation

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* 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 Medicines Agency (www.emea.europa.eu).

Answers to self-test questions

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

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