bjh guideline

Guidelines on the diagnosis and management of AL amyloidosis

Methods

These guidelines have been compiled by members of the Guidelines Working Group of the UK Myeloma Forum on behalf of the British Committee for Standards in Haematology (BCSH). They are intended to set out key areas in the effective diagnosis and clinical management of AL amyloidosis.

A Medline search for literature published between January 1975 and January 2003 was performed using PubMed. A search was made for clinical trials involving AL (primary) amyloidosis and papers or reviews where AL amyloidosis was the major focus. Abstracts from relevant meetings held between 1998 and 2003 were also included. The Cochrane database was searched but did not include any relevant information. Recommendations were made based on literature review and consensus of expert opinion in consultation with representatives of other specialities and patient advocate groups. Levels of evidence and grades of recommendation are shown in Table I.

The draft guidelines were reviewed by the UK Myeloma Forum Executive, members of the BCSH and a panel of approximately 60 UK haematologists. The British Society of Blood and Marrow Transplantation also reviewed the document. The planned date for full revision of these guidelines by the Guidelines Working Group of the UK Myeloma Forum is January 2007. Interim updates will be on the UK Myeloma Forum and BCSH websites.

AL amyloidosis: the context

Systemic AL amyloidosis, formerly known as primary amyloidosis, is a protein conformation disorder associated with a clonal plasma cell dyscrasia (Falk *et al*, 1997). Multiple organ disease results from the extracellular deposition of monoclonal immunoglobulin light chain fragments in an abnormal insoluble fibrillar form. Amyloid fibrils associate *in vivo* with the normal plasma protein serum amyloid P component (SAP), and this phenomenon is the basis for the use of SAP scintigraphy for imaging and monitoring amyloid deposits (Hawkins *et al*, 1990). Accumulation of amyloid progressively disrupts the normal tissue structure and ultimately leads to organ failure, frequently including the kidneys, heart, liver and peripheral nervous system (Kyle & Gertz, 1995).

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Amyloid deposits appear to evoke little or no local reaction in the tissues and there is a poor correlation between the amount of amyloid and the degree of impairment of organ function, particularly in the kidneys. The natural history of AL amyloidosis is that it is progressive and fatal within 2 years in about 80% of patients (Kyle *et al*, 1999). However, treatments that substantially reduce the supply of monoclonal immunoglobulin light chains frequently result in the stabilization or regression of existing amyloid deposits, and are often associated with preservation or improvement in the function of organs infiltrated by amyloid (Gillmore *et al*, 1997).

Pathophysiology and relationship with other B-cell disorders

AL amyloidosis may be associated with myeloma or other B-cell malignancy, but in most cases the underlying plasma cell dyscrasia is subtle and non-proliferating, analagous to monoclonal gammopathy of undetermined significance (MGUS). The cytogenetic abnormalities that commonly occur in multiple myeloma and MGUS, such as 14q translocations and 13q deletion, have also been observed in AL amyloidosis (Harrison *et al*, 2002).

A concurrent diagnosis of myeloma or other B-cell malignancy is made at diagnosis in patients with AL amyloidosis when the diagnostic criteria for these conditions are fulfilled. Coexistent AL amyloid deposits are identified either at presentation or at some time during the course of the disease in approximately 10–15% of patients with myeloma and more rarely in Waldenström's macroglobulinaemia and other lymphoid malignancies. AL amyloid deposits that are demonstrated histologically during the course of investigations in patients with these disorders may not be clinically significant but this can only be determined following comprehensive clinical and laboratory evaluation. It is rare for AL amyloidosis to progress to overt myeloma (Rajkumar *et al*, 1998), probably because of the short survival of patients with AL amyloidosis.

AL amyloid fibrils are derived from the *N*-terminal region of monoclonal immunoglobulin light chains and consist of the whole or part of the variable (V_L) domain. Intact light chains may rarely be found, and the molecular weight therefore varies between about 8000 and 30 000 Da. All monoclonal light chains are unique and the propensity for certain ones to form amyloid fibrils is an inherent property related to their

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Table I. Levels of evidence and grades of recommendation.

Levels of evidence	
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed, non-randomized study, including phase II trials and case–control studies
IIb	Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e. studies without planned intervention, including observational studies
III	Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomized controlled trials or phase II studies which is published only in abstract form
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
Grades of recommendation	
Grade A, evidence level Ia, Ib	Recommendation based on at least one randomized controlled trial of good quality and consistency addressing specific recommendation
Grade B, evidence level IIa, IIb, III	Recommendation based on well conducted studies but no randomized controlled trials on the topic of recommendation
Grade C, evidence level IV	Evidence from expert committee reports and/or clinical experiences of respected authorities

particular structure. Monoclonal light chains that can form amyloid are able to exist in partly unfolded states, involving loss of tertiary or higher order structure. These readily aggregate with retention of β-sheet secondary structure into protofilaments and fibrils. Once the process has started, 'seeding' may also play an important facilitating role, so that amyloid deposition may progress exponentially as expansion of the amyloid template 'captures' further precursor molecules. Only a small proportion of monoclonal light chains are amyloidogenic, but it is not possible to identify these from their class or abundance.

Incidence and epidemiology

The incidence of AL amyloidosis is difficult to define precisely. The age-adjusted incidence of AL amyloidosis in the United States is estimated to be between 5·1 and 12·8 per million persons per year (Kyle *et al*, 1992), which is equivalent to approximately 600 new cases per year in the UK. AL amyloidosis is estimated to be the cause of death in 1/1500 deaths in the UK. Among 474 patients seen at the Mayo Clinic (Kyle & Gertz, 1995), 60% patients were between 50 and 70 years old at diagnosis and only 10% were less than 50 years. Similarly, among 800 UK patients with AL amyloidosis, who have been evaluated at the National Health Service (NHS) National Amyloidosis Centre (NAC), 66% were aged between 50 and 70 years old at diagnosis, and 17% were aged less than 50; 30 of these patients (4%) were aged less than 40 years, and three were aged less than 30 years (NAC database, unpublished data). The male:female ratio was equal. The relatively lower fraction of patients older than 70 years, when compared with the age incidence of myeloma and MGUS, probably reflects referral practice to tertiary centres and undiagnosed disease in the elderly.

Clinical features

The most common clinical features at diagnosis are (Kyle & Gertz, 1995): (i) nephrotic syndrome with or without renal insufficiency; (ii) congestive cardiomyopathy; (iii) sensorimotor and/or autonomic peripheral neuropathy; and (iv) hepatomegaly.

Fatigue and weight loss are extremely common presenting symptoms but the diagnosis is rarely made until symptoms referable to a particular organ appear. Although multiple organs are generally affected, dysfunction of one particular organ is usually predominant. Patients are said to have dominant renal or cardiac involvement, for example, when the relevant organ is either the only organ involved or that most severely affected. Some patients will also have the features of associated myeloma.

Renal amyloid. Nearly one-third of patients have dominant renal amyloid at diagnosis. Renal amyloidosis is mainly a glomerular lesion causing marked proteinuria, which often results in nephrotic syndrome. Evidence of mild renal dysfunction is frequently found but AL amyloidosis rarely presents as progressive renal failure. Symptoms include ankle swelling, fatigue and loss of energy. There is often peripheral oedema and there may be evidence of a pleural effusion. Occult pericardial effusion can occur. Orthostatic hypotension may be a feature of autonomic neuropathy and/or cardiac involvement but is also a feature of volume depletion, which may occur as a result of diuretic treatment.

Cardiac amyloid. About 20% of patients have dominant symptomatic cardiac amyloid at diagnosis. Abnormalities on an electrocardiogram (ECG), notably low voltages in the standard leads, may precede clinical congestive cardiac failure.

Clinical signs are mainly of right-sided heart failure (raised jugular venous pulse, right-sided third heart sound, peripheral oedema and hepatomegaly) or those associated with a low cardiac output, including orthostatic hypotension. In severe cases, atrial thrombi may be present in sinus rhythm (Dubrey *et al*, 1995); the onset of atrial fibrillation may be associated with an abrupt deterioration in cardiac performance and a high risk of thromboembolism. The cardiomyopathy in amyloidosis is restrictive in nature. Hence, the cardiac silhouette on chest X-ray is often not enlarged and the clinical differential diagnosis may include pericardial disease or tamponade.

Peripheral and autonomic neuropathy. AL polyneuropathy may give rise to a wide range of symptoms. Up to 20% of patients present with symptoms of peripheral neuropathy, most commonly parasthesiae, numbness and muscle weakness (Rajkumar *et al*, 1998). Sensory neuropathy is usually symmetrical, usually affecting the lower extremities, and may be painful; motor neuropathy is rare. Carpal tunnel syndrome is common and may predate other symptoms by over a year. There is frequently a long delay between onset of symptoms and diagnosis when neuropathy is the presenting manifestation of AL amyloidosis.

Autonomic neuropathy is a far more serious feature, which can give rise to postural hypotension, impotence and disturbed gastrointestinal (GI) motility and is usually associated with some degree of peripheral neuropathy. The clinical manifestations of autonomic disorders are protean and should be specifically sought through enquiry about erectile and ejaculatory failure in men, symptoms relating to poor bladder emptying, altered bowel habit, early satiety, anhidrosis or gustatory sweating, and symptoms relating to postural hypotension. The last is confirmed by demonstrating a fall in systolic blood pressure of at least 20 mmHg when a patient has been standing for 3–5 min after spending at least 5 min supine.

GI and hepatic involvement. Involvement of the GI tract may be focal or diffuse and symptoms relate to its site and extent. Macroglossia occurs in about 10% of patients and is virtually pathognomonic; it can be marked causing airway obstruction, difficulty in eating and sleep apnoea. Other features include early satiety, diarrhoea, chronic nausea, malabsorption and weight loss. GI amyloid may also present with gut perforation or frank rectal bleeding. Certain symptoms, notably early satiety and explosive post-prandial diarrhoea, often reflect disturbed GI motility due to autonomic neuropathy. Hepatomegaly is present in approximately one quarter of patients at diagnosis; in the presence of heart failure, it may not be possible to clinically differentiate amyloid infiltration from venous congestion.

Haemostatic abnormalities. Haemorrhage is a frequent manifestation of amyloidosis and can be a serious problem. It occurs at some time in about one-third of patients, and an abnormal clotting screen is present in about half (Mumford *et al*, 2000). The most common manifestation of bleeding is purpura due to vascular fragility as a result of endothelial amyloid deposits, but life-threatening bleeding is also well described and may follow liver or renal biopsy. Peri-orbital purpura ('raccoon eyes') is particularly characteristic.

Other organ systems. These include the following.

- Skin and soft-tissue thickening.
- Painful seronegative arthropathy.
- Bone involvement is demonstrated by SAP scan in approximately 30% of patients but, in contrast to myeloma, bone pain, lytic lesions or pathological fracture are not common. There are no characteristic radiological appearances. Lytic lesions and vertebral collapse may occur, but multiple lytic lesions are suggestive of myeloma. X-rays may be normal even when there is substantial amyloid involvement of bone.
- Vocal cord infiltration may produce a hoarse voice, although this is most frequently a manifestation of localized AL amyloidosis.
- Adrenal gland or thyroid infiltration occasionally results in hypoadrenalism or hypothyroidism.
- Lymphadenopathy and pulmonary infiltration can be features of systemic or localized AL amyloidosis.
- Any organ other than the brain can be involved.

Localized AL amyloidosis. AL amyloidosis can occur in a localized form that is most often identified in the upper respiratory, urogenital and GI tracts, the skin and the orbit. In such circumstances the amyloidogenic light chains are produced by a subtle focal infiltrate of clonal lymphoplasmacytoid cells in proximity to the amyloid deposits. This type of amyloid is frequently nodular in character, but can occur quite diffusely throughout a particular tissue when it is associated with a more contiguous infiltrate of clonal cells. The AL nature of localized amyloid can often be confirmed immunohistochemically or by sequencing the fibril protein but it may not be possible to characterize the associated clonal cells due to their scanty nature. Monoclonal immunoglobulin cannot be detected in the serum or urine of most patients with localized AL amyloidosis, even when using highly sensitive assays. The phenotype of hereditary systemic amyloidosis associated with certain apolipoprotein A1 variants can mimic localized laryngeal AL amyloidosis. The course of the disease is relatively benign in most patients, but severe damage to the affected organ can ultimately occur. Treatment is generally confined to local surgical intervention according to symptoms.

Diagnosis and investigation

Many patients with AL amyloidosis have multi-system involvement at diagnosis. Patients in whom the diagnosis is made at a relatively early stage have the broadest options for

treatment, and are more likely to be eligible for dose-intensive chemotherapy regimens. Diagnosis requires a high index of suspicion. AL amyloidosis should be considered in any patient who presents with nephrotic range proteinuria with or without renal insufficiency, non-dilated cardiomyopathy, peripheral neuropathy, hepatomegaly or autonomic neuropathy whether or not a paraprotein can be detected in the serum or urine. Particular vigilance should be maintained in patients with multiple myeloma or MGUS. If suspicion of the diagnosis is based on symptoms in one organ system, evidence for involvement at other sites should be sought, e.g. low voltage ECG, proteinuria or hepatomegaly, but multiple organ biopsies are potentially hazardous and are not recommended.

Diagnostic investigations

Initial investigation should confirm the diagnosis of amyloidosis on tissue biopsy and this should be followed by investigations to establish the type of amyloid present and the extent of organ involvement (Table II). It is not always easy to be certain that amyloidosis is of AL type because immunohistochemical staining for immunoglobulin light chains in amyloidosis is unreliable and the presence of a paraprotein does not *per se* confirm a diagnosis of AL amyloidosis; hereditary forms of amyloidosis are more common than previously thought and may co-exist with MGUS. This can lead to misdiagnosis (Lachmann *et al*, 2002a). In cases of doubt DNA analysis and/or amyloid fibril sequencing may be necessary. Imaging using SAP scanning may be helpful because demonstration of bone marrow involvement is strongly correlated with amyloidosis of AL type.

Histology. Amyloid deposits stain with Congo red and produce pathognomonic red-green birefringence under cross-polarized light microscopy. Biopsy of an affected organ is usually diagnostic but less invasive alternatives are possible, e.g. subcutaneous fat aspirate (Libbey *et al*, 1983). Abdominal fat aspirate and rectal and labial salivary gland biopsies yield positive results in up to 80% of cases in reported studies (Duston *et al*, 1987; Kyle & Gertz, 1995), but are non-diagnostic in up to 50% of patients in routine clinical practice. Bone marrow biopsy should also be stained with Congo red for the presence of amyloid, and involvement of the bone marrow is strongly suggestive of AL type. Evaluation of adequate specimens in experienced laboratories is necessary to maintain high diagnostic sensitivity and specificity. Both false-positive and false-negative interpretations are not uncommon.

Immunohistochemistry. Antibodies are available against most known amyloid fibril proteins but definitive results are obtained in less than 50% of patients with AL amyloid due to the presence of background normal immunoglobulin, and

Table II. Investigations required in suspected AL amyloidosis.

	Confirmation of amyloid	Determination of amyloid type	Evaluation of organ involvement	Investigation of underlying plasma cell dyscrasia	Monitoring
Pathology	Biopsy and histology of screening tissue (e.g. fat aspirate or rectal biopsy or affected organ. Congo red staining of marrow biopsy	Immunohistochemical staining of tissue biopsy with a panel of antibodies to amyloid fibril proteins	Tissue biopsy of affected organ, but once the diagnosis is known, organ biopsies merely to determine extent of amyloid involvement not recommended	Bone marrow aspirate and biopsy with light chain immunophenotyping	Follow-up tissue biopsies and bone marrow examinations are usually not helpful
Haematology/chemical pathology/immunology		Routine electrophoresis and immunofixation of serum and urine. Quantifiable serum free light (FLC) assay	Urea, electrolytes, creatinine, albumin 24-h total protein, liver function test, coagulation screen, creatinine clearance (measured or calculated)	FBC, urea and electrolytes, creatinine, calcium, albumin. Quantification of serum and urine paraprotein. Levels of normal immunoglobulins	Paraprotein level, serum FLC assay
Imaging	SAP scanning	SAP scanning (evidence of marrow involvement)	SAP scanning	Skeletal survey	SAP scanning
Other		DNA analysis, amyloid fibril sequencing	ECG; echocardiogram chest X-ray		Organ function assessments

because light chain epitopes that are recognized by antisera to kappa or lambda light chains may be lost during fibril formation and tissue fixation. In contrast, immunohistochemistry in experienced hands can confirm or exclude amyloidosis of AA type in virtually all cases.

DNA analysis. This is principally used to distinguish AL amyloidosis from hereditary forms of amyloid. Hereditary amyloidosis is an autosomal dominant disorder caused by mutations in the genes for transthyretin, fibrinogen A α-chain, lysozyme or apolipoprotein AI, but a family history is often masked due to incomplete penetrance. The clinical features may be indistinguishable from AL amyloidosis. Hereditary transthyretin and fibrinogen A α-chain amyloidosis are much more common than previously thought, and 31 of the 34 patients in whom hereditary amyloidosis was misdiagnosed as AL amyloidosis in a British series of 350 cases had amyloid of either variant transthyretin or fibrinogen A α-chain type (Lachmann *et al*, 2002a). Hereditary transthyretin amyloidosis presented with polyneuropathy and/or amyloid cardiomyopathy in each case, and there should be a low threshold for sequencing the gene for transthyretin in patients with this phenotype. Features suggestive of variant fibrinogen A α-chain amyloidosis are its almost exclusively renal presentation coupled with a distinctive appearance on renal biopsy. This type of amyloid accumulates very selectively and substantially within the glomeruli, but is characteristically absent from blood vessels and the interstitium. DNA analysis is available at the NAC, based in London.

Amyloid fibril protein sequencing. Amyloid fibrils can be isolated from tissue biopsy samples and characterized by amino acid sequencing. This is the only uniformly definitive method for determining the amyloid fibril type, and can be performed to identify the type of amyloidosis when other methods have failed. This is the method by which the genes associated with hereditary amyloidosis have been identified, and is available at the NAC.

Evaluation of plasma cell dyscrasia. While the presence of a paraprotein does not necessarily mean that amyloidosis is of AL type, evidence of a plasma cell dyscrasia would be supportive evidence for a diagnosis of AL amyloidosis. Relevant investigations are as follows.

Serum and urinary protein electrophoresis and immunofixation. A paraprotein is detectable in the serum or urine by routine electrophoresis in approximately 50% of patients. When an intact whole monoclonal immunoglobulin is present in serum the concentration is less than 10 g/l in 30% of patients, less than 20 g/l in over 70% of patients and above 30 g/l in less than 10% (Kyle & Gertz, 1995). It is therefore essential to perform immunofixation, as the level of paraprotein in AL amyloidosis is usually very low and routine electrophoresis is often negative. However, even on immunofixation no paraprotein is detectable in serum or urine in 20% of cases.

Serum free light chain (FLC) estimation. A new immunoassay can detect and quantify FLCs in serum with remarkable specificity and sensitivity (Bradwell *et al*, 2001). The assay gives a positive result (raised level of either kappa or lambda together with an altered ratio of free kappa to free lambda light chain) in 98% of patients with systemic AL amyloidosis (Lachmann *et al*, 2003), including those in whom a monoclonal immunoglobulin cannot be demonstrated by conventional means. This assay is not specific for AL amyloidosis, and monoclonal FLC are present in about one half of patients with uncomplicated MGUS, and in virtually all patients with multiple myeloma.

Bone marrow aspirate and trephine. Bone marrow aspirate and trephine is usually reported to be normal or to show only a small increase in the percentage of plasma cells, unless the patient has overt myeloma. Immunophenotyping may help to establish clonality when only small numbers of plasma cells are present.

Differential diagnosis

The possibility of the following alternative diagnoses should be considered in all patients:

- Systemic non-AL amyloidosis including hereditary forms and AA amyloidosis. Note that patients with AA amyloidosis may not have an overt underlying inflammatory disorder, and that non-AL amyloidosis may co-exist with MGUS.
- Localized AL amyloidosis.
- Other paraprotein-associated diseases including peripheral neuropathy and immunoglobulin deposition diseases.

Evaluation of organ involvement

Once a diagnosis of AL amyloidosis has been made, investigations are required to evaluate the extent and severity of organ involvement, along with further evaluation of the underlying monoclonal plasma cell dyscrasia to exclude a diagnosis of myeloma or other lymphoid malignancy. Recommended investigations are listed in Table II.

Frequent laboratory findings on routine investigation include glomerular proteinuria (predominantly albuminuria) in 90% of patients. Hypercholesterolaemia is common in patients with nephrotic syndrome. Generalized abnormalities of liver function tests are unusual until liver amyloidosis is very advanced. The most common abnormality is isolated elevation of alkaline phosphatase. Anaemia is uncommon unless the amyloidosis is associated with myeloma, bleeding or chronic renal failure. An abnormal clotting screen is relatively common. A prolonged thrombin time is the most frequent abnormality, but this has no clinical association with a bleeding diathesis (Mumford *et al*, 2000). A prolonged

prothrombin time is the only coagulation abnormality associated with bleeding.

SAP scintigraphy. This investigation is available at the NAC, and is performed routinely in most patients who are referred for evaluation of proved or suspected amyloidosis. Radiolabelled SAP component localizes rapidly and specifically to amyloid deposits in proportion to the quantity of amyloid present. This enables the diagnosis and quantification of deposits by whole body scintigraphy, although cardiac amyloid is poorly visualized (Hawkins *et al*, 1990; Hawkins, 2002). It is useful in assessing the extent and distribution of organ involvement by amyloid, and for evaluating the effects of treatment and it is recommended that it be performed in all patients when feasible. It can also be used as supporting evidence for a diagnosis of amyloidosis when tissue biopsy is not possible.

ECG and echocardiography. Cardiac amyloid is poorly visualized by SAP scintigraphy but ECG and echocardiography provide essential information about the extent of involvement, cardiac function and prognosis. Characteristic features of cardiac amyloid on ECG include low voltages and a pattern suggestive of myocardial infarction without evidence of ischaemic damage on echocardiography. The echocardiographic features of amyloid include concentrically thickened ventricles, normal or small cavities, thickened valves and dilated atria. The ejection fraction is frequently normal, or even increased. Doppler flow studies are required to identify diastolic dysfunction, which is frequently missed in routine studies, and tissue Doppler imaging may provide further useful information. There is a poor correlation between echocardiographic and ECG findings, one or other of which may occasionally appear normal in the presence of clinically significant cardiac amyloidosis. The World Health Organisation (WHO) has described a grading system for cardiac amyloid and the New York Heart Association (NYHA) has developed a functional classification for patients with cardiac disease that can be applied to patients with cardiac amyloid (see Appendices A and B).

Chest X-ray. Chest X-ray in patients with pulmonary amyloidosis may show reticulo-nodular shadowing and there may be impaired CO diffusion on pulmonary function testing.

Nerve conduction studies. These may be required where neuropathy is the dominant presenting symptom. Nerve biopsy may be required to establish the diagnosis.

Criteria for defining organ involvement. There are no universally agreed or validated criteria for defining organ involvement. Most groups use similar but not identical criteria and only two have reported these in detail (Comenzo *et al*, 1998; Dispenzieri *et al*, 2001; see Table III).

Prognostic factors

Prognosis is variable but is generally poor if AL amyloidosis is untreated. Patients with systemic AL amyloidosis have a median survival of 1–2 years (Kyle & Gertz, 1995). Few studies have specifically addressed prognostic variables. The natural history varies with the extent and nature of organ involvement but fewer than 5% of all AL amyloidosis patients survive 10 or more years from the time of diagnosis (Kyle *et al*, 1999).

A poor prognosis is associated with:

- symptomatic or substantial echocardiographic evidence of cardiac amyloid associated with a median survival of only approximately 6 months (Kyle *et al*, 1986);
- a large whole body amyloid load on SAP scintigraphy and evidence of accumulation of amyloid on serial SAP scans (Lachmann *et al*, 2003);
- autonomic neuropathy (Rajkumar *et al*, 1998);
- liver involvement with hyperbilirubinaemia (Lovat *et al*, 1998);

Table III. Non-invasive diagnostic criteria of amyloid-related major organ involvement.*

Organ involvement	Comenzo *et al* (1998)	Dispenzieri *et al* (2001)
Heart	Mean left ventricular wall thickness on echocardiography >11 mm with no history of hypertension or valvular heart disease (or) unexplained low voltage (<0·5 mV) on ECG	Cardiac interventricular septum >12 mm and/or infiltrative cardiomyopathy and/or diastolic dysfunction determined by echocardiography
Kidney	Proteinuria >0·5 g/24 h	Proteinuria >0·5 g/24 h
Liver	Hepatomegaly with an alkaline phosphatase >200 U/l	Hepatomegaly (>4 cm below costal margin) with an alkaline phosphatase >1·5 times normal levels
Nerve	Based on clinical history, autonomic dysfunction with orthostasis, gastric atony by gastric emptying scan and abnormal sensory and/or motor findings on neurological examination	Peripheral neuropathy (other than carpal tunnel syndrome) or autonomic neuropathy

*In both these series, non-invasive diagnostic criteria were used only in patients in whom a positive diagnosis had been made by tissue biopsy.

- lack of suppression of underlying clonal disease by chemotherapy.
- associated multiple myeloma (Abraham *et al*, 2002).

A better prognosis is associated with:

- proteinuria or peripheral neuropathy (without autonomic neuropathy) as the dominant clinical feature (Kyle & Gertz, 1995);
- substantial suppression of underlying clonal disease by chemotherapy;
- regression of amyloid deposits on serial SAP scintigraphy.

A recent study characterized the repertoire of immunoglobulin light chain variable genes used by the clonal B cell in 58 AL amyloid patients and found an association between the use of certain VL germline genes and clinical presentation and outcome (Abraham *et al*, 2002).

Role of the NHS National Amyloidosis Centre (NAC)

The NAC (http://www.ucl.ac.uk/medicine/amyloidosis/nac/index.html) was commissioned directly by the Department of Health to provide a diagnosis and management advisory service for the UK national caseload of patients with amyloidosis. The clinical unit is part of the Centre for Amyloidosis and Acute Phase Proteins based in the Royal Free and University College Medical School at the Royal Free Hospital. The centre developed scintigraphic imaging (SAP scanning) of amyloid as a quantifiable diagnostic procedure and provides various specialized clinical services for patients with acquired and hereditary systemic amyloidosis, including:

- diagnosis, quantification and monitoring of amyloidosis with whole body SAP scintigraphy;
- specialized clinical chemistry service for characterization, quantification and serial monitoring of amyloid precursor proteins, including serum free monoclonal immunoglobulin light chains in patients with AL amyloidosis;
- histological review and immunohistochemistry to determine amyloid fibril type;
- dedicated echocardiography service for evaluation of cardiac amyloidosis;
- characterization and exclusion of hereditary amyloidosis and periodic fever syndromes, DNA testing and genetic counselling;
- recommendations for treatment;
- six to 12 monthly follow-up to evaluate response and requirement for further treatment;
- amyloid fibril protein sequencing and characterization in selected cases;
- providing information and support to amyloidosis patients;
- systematic evaluation of existing and new treatments.

Physicians at the NAC offer telephone advice (Tel.: +44 (0)20 7433 2815/6) and will arrange specialist laboratory investigations that are not available locally. Some investigations may be performed on peripheral blood samples following discussion.

Recommendations for diagnosis

The following recommendations are all grade B, based on level III evidence.

- maintain a high index of suspicion;
- confirm the presence of amyloid on a tissue biopsy;
- look for evidence of plasma cell dyscrasia including immunofixation and serum FLC measurements;
- consider discussion with/referral to NAC for exclusion of other forms of amyloidosis;
- perform comprehensive assessment of the extent of organ involvement by non-invasive criteria including SAP scanning when this is feasible.

Principles of treatment and assessment of response

Appropriate setting for the management of AL amyloidosis

A consultant haematologist, who is part of an approved Cancer Network in accordance with UK NHS strategy, should supervise the treatment of patients with AL amyloidosis. Effective and high-quality care requires a multi-speciality and multi-disciplinary team familiar with the range of clinical problems likely to be encountered. The following represent the core range of essential accessible expertize and services, which may be available at the treatment centre or in a neighbouring hospital. There should be clear policies and protocols for access to these services.

- Haematology/oncology nurse specialists
- Clinical pathology
- Diagnostic radiology
- Cardiology
- Neurology
- Pharmacy facilities and expertize for dispensing cytotoxic drugs
- Renal service, including rapid access to haemodialysis.
- Patients with renal amyloid should be managed jointly with a renal physician
- Accredited bone marrow/stem cell transplant centre
- Primary care liaison
- Palliative care physicians/nurses
- Physiotherapy/rehabilitation
- Administrative support for case registration, audit and clinical trials
- Social services and financial advice
- Patient support group (possibly through national organizations)

- Written information as well as guidance on access to electronic information
- Treating centres must meet standards required for level 1 care (BCSH, Clinical Haematology Task Force, 1995)

Where therapy involves autologous stem cell transplantation this must be carried out in an European Group for Blood and Marrow Transplantation accredited centre, equipped to provide level 3 care for haematological malignancies, as defined by the BCSH Clinical Haematology Task Force (1995).

Principles of treatment

No treatment is yet available that specifically targets the amyloid deposits, and therapy is therefore aimed at suppressing the underlying plasma cell dyscrasia along with supportive measures to support and possibly preserve organ function. Amyloid deposits exist in a state of dynamic turnover that varies markedly between patients, but gradual regression of AL amyloid is often seen when the supply of monoclonal light chains is suppressed (Hawkins, 1994). Furthermore, organ function may improve even when the deposits merely stabilize rather than regress. The degree by which the clonal disease needs to be suppressed to produce clinical benefit varies substantially between patients and depends on many factors, notably the turnover rate of the amyloid deposits.

Chemotherapy regimens used in AL amyloidosis are based on those that have proved to be effective in patients with multiple myeloma, although little is known about any differences in sensitivity of the clonal plasma cells between the two disorders. Clinical benefit from chemotherapy typically does not occur for many months after the underlying plasma cell dyscrasia has been adequately suppressed (Kyle *et al*, 1997). Patients who receive slow-acting chemotherapy regimens often do not live long enough to derive benefit and it is therefore important to try to suppress the clonal disease as rapidly as is reasonably possible. However, more intensive chemotherapy in patients with AL amyloidosis is associated with much greater treatment-related toxicity than that seen in patients with myeloma. This is because of multiple organ impairment, which may not be evident clinically or from the results of routine laboratory investigations prior to treatment. Selecting appropriate treatment for individual patients is therefore complicated and is compounded by the paucity of randomized controlled trials in this disorder. A summary of available data is shown in Table IV.

Monitoring treatment

The disease needs to be assessed in terms of response of:

- Plasma cell dyscrasia
  - Assessment of the clonal B-cell disease by sensitive measurements of monoclonal immunoglobulin. This is often difficult in patients with amyloid because of the generally low amount of paraprotein. The situation has improved with the introduction of the serum FLC assay, which appears to be the most effective method for monitoring the clonal disease in AL patients (see below).
  - Follow-up bone marrow examinations are frequently unhelpful or misleading due to the subtle nature of the plasma cell dyscrasias in most patients and inherent sampling error.
- Amyloid deposits
  - SAP scintigraphy.
  - Assessment of organ size clinically or by imaging techniques.
- Organ function
  - ECG/echocardiography.
  - Routine measurements of renal function, including 24-h urine protein excretion and creatinine clearance.
  - Liver function tests.
  - Assessment of other organ function as indicated.

Table IV. Outcome in previously untreated AL amyloidosis.

Regimen	Study/Ref.	No. of patients	Response (% all patients)	TRM*	Overall survival (median)	Comment
MP	Kyle *et al* (1997)	77	28	Not reported	18 months	Risk of MDS
	Gertz *et al* (1999a)	52	27	Not reported	29 months	
VAD	Lachmann *et al* (2002b)	98	54	7%	50 months	Selected patients
IDM	Lachmann *et al* (2002b)	33	46	18%	Not reached	Poor risk group
HDD	Combined data†	38	34	Not evaluable	Not reported	Three small series
PBSCT	Comenzo and Gertz (2002)	148	39% all patients 62% of evaluable	21–39%‡	60–70% at 1 year	Selected patients

MP, melphalan and prednisolone; MDS, myelodysplastic syndrome; VAD, vincristine, adriamycin, dexamethasone; IDM, intermediate dose melphalan; HDD, high-dose pulsed dexamethasone; PBSCT, peripheral blood stem plasma cell transplantation.
Response criteria have varied but generally include response of either plasma cell dyscrasia and/or organ dysfunction.
*Treatment-related mortality (TRM) is defined as death during treatment or within 100 d from completing treatment.
†Gertz *et al* (1999b), Dhodapkar *et al* (1997), Gertz *et al* (1999c), Palladini *et al* (2001). Note that the reported TRM in PBPCT studies did not include deaths during mobilization and re-infusion of peripheral blood progenitor cells.
‡21% average of four single centre studies; 39% average of two multi-centre studies.

Appendix C shows criteria for evaluation of response of amyloid-related organ dysfunction, which are based on non-invasive testing, and which are normally described as 'improved', 'stable' or 'worsened'. Multiple organ biopsies to assess amyloid deposition are of no proved value, are frequently misleading and are potentially dangerous.

Use of serum FLCs concentration in monitoring disease

Raised levels of serum FLC are detectable in most patients with AL amyloidosis, and as FLC have a circulating half-life of several hours as opposed to many weeks for intact immunoglobulins, their measurement enables response to chemotherapy to be evaluated effectively and rapidly, for example, on a monthly basis during cyclical treatments. A study of 137 patients with AL amyloidosis who were followed up at the NAC demonstrated that outcome correlated strongly with changes in concentration of circulating FLC following chemotherapy (Lachmann *et al*, 2003). Following chemotherapy, for those patients who survived 6 months, the abnormal FLC concentration fell by more than half in 86 of 137 patients. Changes in the amyloid load correlated positively with changes in FLC concentration, and survival at 5 years was 88% among patients whose FLC fell by more than half, but only 39% among patients whose FLC remained above this value ($P < 0{\cdot}0001$).

Chemotherapy and other agents

Introduction

Chemotherapy currently used in AL amyloidosis can be classified as follows.

Low dose. Single agent melphalan or cyclophosphamide (with or without prednisolone). Clinical benefit occurs in only about 20–30% of patients, and only after a median of 12 months treatment. The combination chemotherapy regimen using VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, prednisone) is not more effective.

Intermediate dose. Monthly courses of VAD (vincristine, adriamycin, dexamethasone) and similar regimes, or intravenous intermediate dose melphalan (IDM) 25 mg/m^2 with or without dexamethasone.

High dose. High-dose therapy (HDT) with intravenous melphalan (100–200 mg/m^2) and stem cell rescue.

Other approaches. Other approaches are (i) pulsed high-dose dexamethasone, and (ii) thalidomide (with or without dexamethasone) with or without other agents.

Intermediate and high-dose chemotherapy are thought to be clinically beneficial in more than 50% of patients, but have not been compared in randomized trials either with each other, or with low-dose chemotherapy, or with no treatment.

Standard and intermediate dose therapy

Colchicine. Colchicine is effective in the treatment of AA amyloidosis complicating familial Mediterranean fever by suppressing the underlying inflammatory disease, but has no role in AL amyloidosis. In a randomized controlled trial Kyle *et al* (1997) studied 220 patients who were treated with either colchicine alone, melphalan and prednisolone (MP), or MP and colchicine. Median survival was 8·5, 18 and 17 months respectively ($P < 0{\cdot}001$).

Recommendation

- There is no role for colchicine in the management of AL amyloidosis (grade A recommendation; level Ib evidence).

Melphalan and prednisolone. Histological regression of amyloid has been documented on repeat liver biopsy after therapy with MP (Gertz & Kyle, 1986). It is the only chemotherapy regimen that has been evaluated in randomized controlled clinical trials. Several studies using slightly different regimens of MP have confirmed the efficacy of this treatment over no therapy or colchicine alone. The first of these trials was a placebo-controlled, double blind study of 55 patients with AL amyloidosis (Kyle & Greipp, 1978), which showed benefit in terms of organ function for those patients receiving MP. A randomized trial confirmed that MP was superior to colchicine alone in terms of response and survival (Kyle *et al*, 1997). Response, assessed by organ function and paraprotein levels, was seen in 28% of patients on MP and only 3% of those on colchicine. Survival in patients receiving MP was 18 months compared with 8·5 months for colchicine alone. It has also been shown that the addition of colchicine to MP did not confer any extra benefit over MP alone (Skinner *et al*, 1996; Kyle *et al*, 1997). In a later study, comparing MP with VBMCP, the median survival of patient's randomized to MP was 25 months (Gertz *et al*, 1999a).

Patients who respond to MP survive significantly longer than non-responders (89 months vs. 14 months) (Kyle *et al*, 1997). The median time to response in this study was 12 months. Patients must therefore live long enough to receive several cycles of chemotherapy before any survival benefit is seen. Patients with symptomatic cardiac amyloid rarely benefit from treatment with standard MP but encouraging results have recently been reported with continuous oral melphalan in patients with cardiac amyloidosis who were unfit for more aggressive therapy (Sanchorawala *et al*, 2002). The adverse effects of melphalan include myelotoxicity, and in patients who survive longer than 3·5 years, there is a 20% risk of myelodysplasia often leading to secondary leukaemia (Gertz & Kyle, 1990).

Recommendations

- Melphalan with or without prednisolone may be considered as initial treatment of choice for patients in whom intermediate or HDT is not considered appropriate (grade A recommendation; level Ib evidence).
- Treatment should be continued when feasible until the clonal disease has been substantially suppressed, i.e. by at least 50–75%, or until plateau, and should be monitored where possible by the serum FLC assay (grade C recommendation; level IV evidence).
- The evidence of benefit from steroids in standard doses has not been evaluated in AL amyloidosis. In myeloma the evidence of benefit from steroids in standard doses is controversial. It may therefore be reasonable not to include prednisolone, particularly in patients at risk of steroid-related side effects (grade C recommendation; level IV evidence).

Combination chemotherapy. The VBMCP regimen has been evaluated in a prospective, randomized study of 101 patients who were randomized to receive either this therapy or MP. No improvement in haematological or organ function, response rate or survival was found among patients receiving this form of combination chemotherapy. The overall response rate in both groups in this study was 30%, suggesting that either earlier diagnosis or improvements in supportive therapy have lately led to better survival following treatment with MP (Gertz *et al*, 1999a). There are no reported studies of other alkylator-based combination regimens.

Recommendations

- There is no role for the use of VBMCP in the management of AL amyloidosis (grade A recommendation; level Ib evidence).
- There is no evidence to support the use of other alkylator-based combination regimens such as ABCM (adriamycin, bleomycin, cyclophosphamide, mitomycin-C) or VMCP (vincristine, melphalan, cyclophosphamide, prednisone)-VBAP (vincristine, carmustine, adriamycin, prednisone).

Interferon-α2b. No benefit from treatment with interferon (IFN)-α2b was identified in a phase II trial (Gertz & Kyle, 1993) in 15 patients with AL amyloidosis who had shown no response to conventional chemotherapy. There are no data on IFN in newly diagnosed patients, or its role as maintenance therapy following response to other regimens (except pulsed dexamethasone).

Recommendation

- There is no role for the use of IFN-α2b in the management of AL amyloidosis (grade B recommendation; level IIa evidence).

VAD. The VAD infusional regimen is an established induction therapy in myeloma. It is associated with a high response rate of 60–80%, a complete response rate of 10–25% and a rapid reduction in tumour burden (Samson *et al*, 1989; Alexanian *et al*, 1990). It therefore has theoretical advantages in treating AL amyloidosis where a rapid response is desirable. In addition, it does not deplete stem cell reserve, keeping open the option for subsequent peripheral blood stem cell transplantation (PBSCT). Potential problems with the use of VAD in AL amyloidosis are the cardiotoxicity of adriamycin, and, probably more importantly in practice, exacerbation of peripheral and autonomic neuropathy by vincristine. High-dose dexamethasone can cause severe fluid retention causing problems in patients with renal or cardiac amyloidosis, and can lead to bone fractures and vertebral collapse in those with bone involvement. Adriamycin has not been reported to exacerbate amyloid cardiomyopathy, but caution is recommended.

There have been anecdotal reports of good responses to VAD in AL amyloidosis (Wardley *et al*, 1998; Sezer *et al*, 1999), although the regimen has not been assessed in a randomized, controlled trial. The most substantial experience of this approach has been obtained in 98 patients with AL amyloidosis who were evaluated and followed up at the NAC. These patients received a median of four cycles of standard dose VAD or CVAMP (cyclophosphamide, vincristine, adriamycin, methyl-prednisolone) as first-line therapy. Their median age was 55·5 years (range 29–77 years), 36% had echocardiographic features of cardiac involvement and 10% were dialysis dependent. Patients with symptomatic heart failure, autonomic neuropathy or severe peripheral neuropathy were excluded. The treatment-related mortality, as defined by death during chemotherapy or within 100 d of completing treatment, was 7%. The underlying clonal plasma cell dyscrasia responded in 53 patients (representing 63% of 84 evaluable patients), as defined by a fall in the amyloidogenic class of serum FLC concentration by more than 50%. In more than 50% of these responders, SAP scintigraphy demonstrated subsequent regression of amyloid deposits. The function of organs predominantly affected by amyloid improved in half of all patients. There was subsequent progression of the plasma cell dyscrasia in 11 of the 53 responding patients after a median of 20 months (range 7–54 months), associated in six cases with reaccumulation of amyloid. After a median follow-up of 21 months the projected median overall survival was 50 months.

In myeloma oral idarubicin and dexamethasone (Z-Dex) is used as an alternative to VAD; there are no data on the use of Z-Dex in AL amyloid.

Recommendations

- VAD should be considered as first-line therapy in patients under the age of 70 years who do not have symptomatic cardiac failure, autonomic neuropathy or peripheral neuropathy (grade B recommendation; level III evidence).
- careful monitoring is required because of increased risk of toxicity in these patients (grade C recommendation; level IV evidence).

High-dose pulsed dexamethasone (HDD). Dexamethasone alone in myeloma has similar efficacy to VAD in terms of initial response (Kumar *et al*, 2002) and avoids the potential toxicity of vincristine and adriamycin. When used alone, pulsed high-dose dexamethasone, as used in the VAD regimen, was shown to induce a response in three of 25 (12%) previously treated patients with AL amyloid (Gertz *et al*, 1999b) and three of 19 (16%) untreated patients (Gertz *et al*, 1999c). Dhodapkar *et al* (1997) observed a response rate of 67% (six of nine patients) in patients treated with high-dose dexamethasone followed by IFN maintenance (3–6 million units three times/week). Because of preliminary experience of toxicity with three pulses per cycle, Palladini *et al* (2001) treated 23 patients (13 previously treated and 10 untreated) with a single 4-d pulse of dexamethasone every 21 d; 35% of all patients responded, with very little toxicity.

From these three series the overall response with HDD in untreated patients is approximately 34% when compared with over 50% with VAD (Table IV). The higher response rate reported by Dhodapkar *et al* (1997) may have been due to addition of IFN, although IFN alone has not shown to be effective. There are no data on durability of response.

Recommendation

- HDD may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those who are refractory to chemotherapy (grade B recommendation; level IIa evidence).

Intermediate dose melphalan (IDM). The variable absorption of melphalan from the GI tract led Schey *et al* (1998) to investigate the use of intravenous IDM (25 mg/m^2) and oral dexamethasone in patients with untreated multiple myeloma. Their results showed that this treatment could be delivered safely on an outpatient basis in patients up to the age of 78 years; 82% of patients achieved an objective response and 30% a complete haematological and clinical remission. The median overall survival of the study group was 37 months. This regimen has been used as first-line therapy in 33 patients with AL amyloidosis who have been evaluated and followed up at the NAC. These patients were selected for IDM on the basis that they were not fit enough to receive VAD, either due to age, poor performance status, severe amyloid cardiomyopathy or neuropathy. Their median age was 64 years (range 47–77 years), 51% had echocardiographic features of cardiac involvement and 15% were dialysis dependent. Treatment-related mortality, as defined by death during chemotherapy or within 100 d of completing treatment, was 18%, but at a median follow-up of 8 months, 20 of 33 (61%) patients were alive. The underlying clonal plasma cell dyscrasia responded completely or partially in 46% of all patients (55% of evaluable patients) and in more than 70% of patients in whom SAP scintigraphy demonstrated subsequent regression of existing amyloid deposits. Complete clonal disease responses occurred in some patients after as few as two courses of treatment. It is too early to assess survival data as median follow-up is currently only 8 months but as the response rate appears similar to that seen with VAD and toxicity is acceptable, IDM should be considered in patients not suitable for VAD. Clonal disease responses have also been observed at the NAC among patients who have either been refractory to VAD, or who had relapsed following response to VAD. It may be prudent to harvest stem cells from patients in whom IDM is considered, who might subsequently benefit from PBSCT, as the IDM regimen may deplete stem cell reserves.

Recommendation

- Intermediate dose melphalan may be considered in patients who are fit for intravenous therapy, but in whom VAD is contraindicated or has produced an inadequate response (grade C recommendation; level III evidence).
- Stem cell harvesting prior to treatment with IDM should be considered in patients who might subsequently benefit from PBSCT as the IDM regimen may deplete stem cell reserves (grade C recommendation; level IV evidence).

Thalidomide. Thalidomide is an effective therapy for multiple myeloma, although its mechanism of action is unclear (Cavenagh & Oakervee, 2003). Response rates of over 30% in relapsed and refractory disease are observed and when dexamethasone is added the rate of response is over 60%. Commonly observed side effects are somnolence, constipation and peripheral neuropathy. There is a clear increase in the risk of venous thrombo-embolism in patients receiving thalidomide in combination with chemotherapy, but the risk is significantly lower in patients receiving thalidomide alone or

with dexamethasone (Cavenagh & Oakervee, 2003). Arterial thromboses may also occur.

A preliminary analysis of a phase I/II trial in 12 patients with AL amyloidosis has been reported (Seldin *et al*, 2001). All but one patient had been previously treated. Patients with peripheral neuropathy were excluded because of the frequency of this side effect with thalidomide. Thalidomide was started at 200 mg daily and the dose escalated to the maximum-tolerated dose (MTD). The median MTD was 500 mg, although some patients later reduced the dose because of cumulative side effects. All patients suffered expected side effects and several had more unusual toxicity including dyspnoea and/or exacerbation of congestive cardiac failure. Four patients stopped treatment early because of side effects. Five of 11 patients had a haematological response, but all were <50% improvement based on bone marrow plasmacytosis, monoclonal protein measurement, κ:λ ratio or proteinuria.

Thalidomide therefore appears to have some activity in AL amyloidosis but further information regarding efficacy and toxicity is required. There are no data at present on the use of thalidomide in combination with dexamethasone.

Recommendations

- Thalidomide may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those who are refractory to chemotherapy (grade C recommendation; level IV evidence).
- where possible, patients should be treated in the context of clinical trials (grade C recommendation; level IV evidence).

HDT and autologous stem cell transplantation

The use of high-dose melphalan therapy and PBSCT in patients with AL amyloidosis was first reported in 1996, and a series of 25 patients was reported shortly afterwards (Comenzo *et al*, 1998). Since then encouraging results have been reported in several series of patients in various centres (Moreau *et al*, 1998; Gillmore *et al*, 1999; Gertz *et al*, 2000; Sanchorawala *et al*, 2001). HDT and PBSCT can result in reversal of the clinical manifestations of AL amyloidosis in up to approximately 60% of patients who survive the procedure. This is associated with regression of AL deposits on SAP scanning, reduction or elimination of the causative clonal plasma cell disorder and improved performance status and quality of life for patients. However, the efficacy of PBSCT in AL amyloidosis has not been investigated in any controlled comparative study, and procedure-related mortality has been consistently and substantially higher among patients with amyloid than those with multiple myeloma. The 100-d mortality in two experienced single-centre US studies has been around 14% (Gertz *et al*, 2000; Sanchorawala *et al*, 2001) and was 39% in two multi-centre European studies (Moreau *et al*, 1998; Gillmore *et al*, 1999). This reflects compromised function of multiple organ systems by amyloid, and, therefore, refinement of patient selection and improvement of peri-transplantation clinical management are priorities.

The transplant-related mortality (TRM) of PBSCT is associated with the number of organ systems involved with amyloid, based on clinical evaluation of the kidneys, heart, liver and GI system, and peripheral/autonomic nervous system. Of 43 patients transplanted in two single-centre studies (Comenzo *et al*, 1998; Gertz *et al*, 2000), patients with ≤2 organ systems involved had significantly superior 100 d survival (81%, 25 of 31) compared with those who had >2 organ systems involved (33%, four of 12; $P < 0{\cdot}01$, Fisher's exact test). Similar conclusions have been reported in multi-centre studies (Moreau *et al*, 1998; Gillmore *et al*, 1999). The causes of death included cardiac arrhythmias, intractable hypotension, multi-organ failure and GI bleeding. Patients with poor renal function and those who are already dialysis dependent fare very badly (Comenzo & Gertz, 2002). In addition, patients with dominant or symptomatic cardiac amyloid have a very high TRM (Saba *et al*, 1999).

There is also a significant risk, including death, associated with stem cell mobilization in patients with AL amyloidosis, even when granulocyte colony stimulating factor (G-CSF) is used alone (Comenzo & Gertz, 2002). Complications have included sudden onset of pulmonary oedema, and/or an unexplained syndrome of progressive hypoxia and hypotension, which may occur in patients without cardiac amyloid. It is therefore recommended that patients receive twice daily dosing of G-CSF; collections may need to be interrupted because of worsening hypoxia or oedema. Measures that can reduce morbidity and mortality during the PBSCT procedure itself include avoidance of substantial prehydration, administering the melphalan in two divided doses, using a dose of >5 × 106 $CD34^+$ cells/kg, and avoiding G-CSF support (Comenzo & Gertz, 2002).

The high TRM associated with PBSCT is a major concern. Moreover, although outcome is apparently better than that reported for standard dose treatment, this might substantially reflect patient selection. Dispenzieri *et al* (2001) examined data from patients with AL amyloid treated at the Mayo Clinic from 1983 to 1997 and identified 229 patients who would now have been eligible for PBSCT based on age less than 70 years and well preserved cardiac, renal and hepatic function. At a median follow-up of 52 months their median survival was 42 months and 5- and 10-year survival rates were 36% and 15% respectively.

The role of PBSCT therefore remains unclear, and because of its special problems in AL amyloidosis, it is recommended that such patients be treated in units with expertise of this particular disease. It seems reasonable to restrict PBSCT to younger patients with one or two involved organs, who have not had previous amyloid-related GI bleeding, and who do not have severe cardiomyopathy, advanced renal failure or are dialysis dependent.

Data from non-randomized studies at the NAC (Lachmann *et al*, 2003) have suggested that patients who achieve a 50% or

greater fall in FLC concentration after treatment with VAD or IDM have a similar survival to patients achieving the same response after HDT. It may therefore be appropriate to offer patients VAD or IDM treatment initially and reserve HDT, with its high associated TRM, for those patients who do not respond adequately to initial therapy.

Recommendations

- High-dose therapy and PBSCT is not recommended in patients with any of the following:
- symptomatic cardiac amyloid;
- symptomatic autonomic neuropathy;
- history of GI bleeding due to amyloid;
- dialysis-dependent renal failure;
- age over 70 years;
- more then two organ systems involved.
- Peripheral blood stem cell transplantation may be considered in other selected patients, including:
- good-risk patients (no cardiac involvement, one to two organs involved and glomerular filtration rate >50 ml/min);
- patients treated with VAD or other initial therapy who have not responded;
- patients with early relapse of plasma cell dyscrasia after VAD or other treatment.
- Transplantation should be performed according to an agreed protocol in centres with particular expertize/interest caution is required during mobilization and harvesting of stem cells prior to transplantation and this should also be performed according to an agreed protocol in centres with particular expertize/interest.

Allogeneic bone marrow transplantation (BMT). The first successful allogeneic BMT for AL amyloidosis was reported by Gillmore *et al* (1998) and was associated with complete clinical recovery at 3 years post-BMT. This supports the hypothesis that, as in myeloma, a small proportion of patients may defive significant clinical benefit from the procedure but at present it remains experimental, and is likely to be associated with extremely high TRM. There are currently no data on the use of reduced-intensity conditioning in AL amyloid.

Overview of treatment recommendations

The objective of chemotherapy in AL amyloidosis is to suppress production of amyloidogenic monoclonal immunoglobulin light chains as quickly and safely as possible, but the relative efficacies of different chemotherapy regimens have not been determined. Recent experience at the NAC suggests that treatment strategies in individual patients are presently best guided by their early effect on quantifiable measurements of circulating free immunoglobulin light chains (Bradwell *et al*, 2001; Lachmann *et al*, 2003). Although these patients were selected and had not been randomized to receive particular therapies, it is notable that neither the magnitude nor durability of the clonal disease responses differed significantly among patients who were treated with VAD, monthly intravenous IDM or stem cell transplantation.

Recommendations

- Present recommendations for choice of therapy are as follows:
- Where possible, patients should be treated in the context of clinical trials.
- Patients who are fit enough should receive VAD as initial therapy.
- IDM should be considered in patients who are fit for intravenous therapy, but in whom VAD is contraindicated or has produced an inadequate response. PBSC harvest should be considered before proceeding with IDM.
- If not fit for VAD or IDM, the treatment options are as follows, but the evidence base is very small and there have been no comparative, randomized, controlled trials. No firm recommendation can therefore be made, and treatment choice will depend on individual factors.
- MP: well-tolerated but slow response;
- HDD: rapid response but no data on durability;
- Thalidomide: more data needed;
- Novel therapies;
- Palliative care.
- High-dose therapy and PBSCT may be considered in selected patients (see above).
- Supportive care is important in all patients.

General supportive care and organ transplantation

Organ function in amyloid is extremely brittle and renal or cardiac failure is easily precipitated even in individuals with apparently normal organ function by factors such as intravascular fluid depletion or intercurrent infection.

Nephrotic syndrome and renal failure

Nephrotic syndrome or renal failure are commonly present at diagnosis in patients with AL amyloidosis. The oedema of nephrotic syndrome generally requires treatment with loop diuretics. These may need to be in high doses and resistant cases may require addition of thiazide and/or potassium-sparing diuretics. Salt and, in some cases, fluid restriction may be advised. Hypertension should be treated aggressively. Angiotensin converting enzyme inhibitors are the antihypertensive agents of first choice for their anti-proteinuric effect but should

be initiated with appropriate monitoring of renal function. Treatment of hypercholesterolaemia should be considered. There is a theoretical risk of renal vein thrombosis in patients with AL amyloidosis and nephrotic syndrome but in practice this is rarely seen (NAC, unpublished data). In view of the bleeding tendency that is sometimes present in AL amyloidosis, prophylactic anticoagulation is not recommended. End-stage renal failure can be successfully treated with dialysis and improves survival, particularly for patients without associated cardiac involvement (Martinez-Vea *et al*, 1990; Gertz *et al*, 1992).

Renal transplantation

Transplantation has rarely been used, because of concerns about prognosis due to extra-renal amyloid and possible recurrence of amyloid in transplanted kidneys. There are a few case reports and small series reported in the literature of renal transplantation in AL amyloidosis but there is insufficient evidence to make firm recommendations (Hartmann *et al*, 1992). There are descriptions of patients with long-term survival but a suggestion of relatively high early mortality due to infection. This mode of treatment needs to be considered on an individual case basis, but seems reasonable in patients whose underlying clonal plasma cell disease has remitted following chemotherapy.

Recommendations

- Patients with end-stage renal failure should be considered for dialysis (grade C recommendation; level IV evidence).
- Renal transplantation may be considered in selected patients on a case-by-case basis (grade C recommendation; level IV evidence).

Congestive cardiac failure

The presence or absence of cardiac amyloidosis is the most important factor affecting survival. Sudden death is common and is usually not presaged by evidence of arrhythmias. The mainstay of treatment for congestive heart failure is diuretics and increasing doses are required as progression of the cardiomyopathy occurs. The addition of spironolactone to loop diuretic therapy is very effective in some cases. Cardiac amyloidosis is a restrictive cardiomyopathy, and an adequate cardiac output depends crucially on maintaining relatively high filling pressures. It has not been established whether angiotensin-converting enzyme inhibitors are beneficial, and low cardiac output or orthostatic hypotension may limit their use. Calcium-channel blockers and beta-blockers are contraindicated in cardiac amyloidosis (Gertz *et al*, 1985). Digoxin may cause toxicity at therapeutic levels (Rubinow *et al*, 1981) but is not necessarily contraindicated in the management of patients with cardiac amyloidosis and supraventricular tachyarrhythmias.

Cardiac transplantation

Where AL amyloidosis is limited to the heart, death usually occurs suddenly or as a result of progressive heart failure. Cardiac transplantation has been performed in a small number of these patients (Hosenpud *et al*, 1991; Dubrey *et al*, 2001), although the procedure remains controversial because of the scarcity of donor hearts, the high TRM (due to extra-cardiac amyloid) and the likelihood of amyloid deposition in the graft. Chemotherapy used in association with cardiac and other organ transplantation is required to prevent recurrence of amyloid or its progression in other organ systems.

Recommendations

- Congestive cardiac failure should be treated predominantly with diuretics, and angiotensin-converting enzyme inhibitors should be used with caution (grade C recommendation; level IV evidence).
- Calcium-channel blockers and beta-blockers are best avoided in cardiac amyloidosis (grade C recommendation; level IV evidence).
- Cardiac amyloidosis is a relative contraindication to the use of digoxin (grade C recommendation; level IV evidence).
- In patients where cardiac manifestations are the predominant or only signs/symptoms of cardiac amyloidosis, patients should be considered for heart transplantation but this procedure should be followed by chemotherapy treatment to prevent re-accumulation of amyloid in the transplanted heart (grade C recommendation; level IV evidence).

Orthostatic hypotension

Orthostatic hypotension is frequently a feature of autonomic neuropathy, and it may be exacerbated by cardiac amyloidosis and hypoproteinaemia. Adrenal amyloid deposits are common, but adrenal insufficiency is rare and can be excluded by the short Synacthen test. Many patients with apparently severe supine and orthostatic hypotension remain asymptomatic and do not require treatment.

Measures should be made to minimize hypovolaemia; support stockings may also be helpful. Fludrocortisone 100–200 μg/d can be helpful in some patients, but may cause or exacerbate fluid retention. The most effective agent available is midodrine (ProAmatine), starting at a dose of 2·5 mg t.d.s., gradually increasing up to 15 mg t.d.s. Midodrine forms an active metabolite, desglymidodrine, which is an alpha-1 agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure. Its chief adverse effect is supine hypertension, and other pressor agents must be co-administered with caution.

Recommendations

- Orthostatic hypotension may respond to use of support stockings coupled with modest doses of fludrocortisone (grade C recommendation; level IX evidence).
- Midodrine is the most effective drug for orthostatic hypotension in patients with amyloidosis, but can cause supine hypertension (grade C recommendation; level IX evidence).

Bleeding

The most common cause of bleeding problems in AL amyloidosis is a generalized vasculopathy due to amyloid deposition in blood vessels throughout the body. This occurs to some extent in all patients. Loss of elasticity in amyloid laden tissues may also contribute to bleeding following trauma, surgery and biopsy procedures.

Factor X deficiency is well recognized in AL amyloidosis but is uncommon and there are anecdotal reports of other factor deficiencies. Other conditions including hypofibrinogenaemia, disseminated intravascular coagulation and increased fibrinolysis may contribute to a bleeding tendency (reviewed in Mumford *et al*, 2000). It has been proposed that clotting factors bind to amyloid and there are anecdotal reports of improvements in haemostasis after removal of heavily infiltrated spleens (Greipp *et al*, 1979). However, in a recent systematic study of 337 patients, Mumford *et al* (2002) found subtle coagulation defects in 51% of cases but no correlation with whole body amyloid load measured by SAP scanning.

Recommendations

- All recommendations are level IV, grade C.
- There are no evidence-based recommendations for the management of bleeding in patients with amyloidosis.
- Conventional supportive therapy should be considered. This may include factor replacement where coagulation assays indicate a need and platelet transfusion when the platelet count suggests that thrombocytopenia might be making a contribution to the bleeding. In addition, anti-fibrinolytic agents and local measures to secure haemostasis may be employed.
- A conservative approach to surgery is recommended, and biopsies should not routinely be used to document the extent of organ involvement after the initial diagnosis has been made. Liver biopsies are best avoided, or made via the trans-jugular route.
- There are anecdotal reports of resolution of clotting abnormalities following treatment with chemotherapy and splenectomy but these are not substantive enough to form the basis of a clear recommendation.

Most abnormalities in coagulation were explained by either impaired fibrin polymerization or reduction in factor X activity. There are also reports of reversal of coagulopathy following cytotoxic chemotherapy (Camoriano *et al*, 1987).

GI tract symptoms

When GI symptoms occur, it may be difficult to distinguish motility problems due to autonomic failure from symptoms due to intestinal mucosal deposition of amyloid. Severe diarrhoea may respond to octreotide. Patients with severe malabsorption or pseudo-obstruction may require long-term parenteral nutrition. In advanced intestinal amyloid, nausea is frequently a prominent symptom. Cisapride and metoclopramide may be ineffective (Gertz, 1999).

Experimental approaches to treatment

Improved understanding of the mechanisms underlying amyloid fibrillogenesis has identified novel therapeutic possibilities including investigation of small molecules, peptides and glycosaminoglycan analogues that bind to and stabilize fibril precursors, or interfere with refolding and/or aggregation into the cross-β core structure common to amyloid fibrils. Immunotherapy is also being explored. A potential therapeutic approach that may be applicable to all types of amyloidosis, and which is already being tested in patients, is inhibition of the binding of SAP to amyloid fibrils, which contributes significantly to amyloidogenesis (Pepys *et al*, 2002).

Future directions

Priorities for future research include development of the therapeutic approaches described above. There is also clearly a need for controlled, comparative trials of intermediate and HDT with long-term follow-up.

Recommendation

- Where possible patients receiving new therapies should be treated in the context of clinical trials (grade C recommendation; level IV evidence).

Multiple myeloma and AL amyloidosis

In patients with myeloma in whom there are features suggestive of AL amyloidosis, attempts should be made not only to confirm the presence of both pathologies, but also to

evaluate the contribution of each process to symptoms and organ dysfunction. The extent of organ involvement by amyloid may influence the choice of chemotherapy for myeloma. This is particularly important for those patients in whom HDT is being considered, as the toxicity of this procedure in patients with significant amyloid organ involvement is substantially greater than that seen in patients receiving the same treatment for myeloma alone. However, AL amyloid deposits can be clinically insignificant in some patients with myeloma, in whom their mere presence does not affect the choice of treatment significantly and such patients can be treated conventionally.

Recommendation

- Where myeloma and AL amyloidosis co-exist, choice of treatment for myeloma should take into account the extent of organ involvement with amyloid and the potential toxicities of individual treatments (grade C recommendation; level IV evidence).

Patient information and support

As for patients with myeloma, provision of patient information and support is an essential component of patient care to assist patients in making informed choices on treatment options, as well as understanding the importance of compliance with treatment regimens which, at times, can be very demanding. The International Myeloma Foundation (UK) [IMF (UK)] produces patient information on AL amyloidosis as does several other organizations.

It is important for patients and their families to understand that, although treatment is not curative, it will in most cases relieve symptoms and prolong life; the positive aspects of treatment need to be stressed. Patients with AL amyloidosis should be aware of support networks in the community where these exist. The specialist team should be able to provide patients and their families with information on local support networks.

The specialist team also needs to have information available for the patient and family on State benefits, e.g. Disability Living Allowance and Attendance Allowance. AL amyloidosis may result in long-term disability and preclude many patients returning to work. Conventional chemotherapy regimens and HDT also make employment impractical for periods of several months. Patients commonly need advice on socio-economic problems, which result from the condition and its treatment.

Recommendations

- The diagnosis needs to be communicated honestly to the patient with the minimum of delay. The information should be communicated in a quiet area with privacy, ideally in the company of a close relative and with the presence of a specialist nurse.
- Patients and their partners/carers should be given time to ask appropriate questions once they have been given the diagnosis; this may be best be done after an interval of a few hours or days.
- At the end of a consultation, it is recommended that patients and their family/carers are given written material which provides information on the condition. It should also guide patients and their family/carers on access to information services. IMF (UK) and the Leukaemia Research Fund produce useful, patient-orientated booklets on the condition and its treatment (see below). Written information is also available from the NAC.
- Patients need to be informed of the names of the key members of the specialist team or teams who are in charge of their care, and importantly, who is responsible for coordinating their care. Clear information on access to advice/support from the team should also be made available.
- The management plan needs to be communicated simply to the patient and his/her carer and should be clearly written in the case record so that the information is readily accessible to other members of the multi-disciplinary specialist team.
- Patients and their families should be cautioned about the amount of unregulated information accessible on the internet; they should be given recommendations to access appropriate sites, such as http://www.amyloidosis.org. An appropriately trained person, normally a specialist nurse, should be available to discuss/inform patients on information materials including guidance for using the internet as an information source.
- Patients should be given the opportunity of receiving more than one medical opinion.

Useful information sources

The IMF (UK) is a UK-based patient support group of the IMF. The main office is in Edinburgh with a help and advice line for patients, 0800 980 3332. It produces useful written material on myeloma and related plasma cell disorders including AL amyloidosis and runs a series of patient and family seminars during the year in the UK and Ireland. Information can also be obtained from the website (http://www.myeloma.org.uk).

The Leukaemia Research Fund supports research in myeloma and also provides patient information booklets regarding AL amyloidosis. Further information can be obtained by telephone 020 7405 0101 or from the website (http://www.lrf.org.uk).

Appendix A

WHO staging system for cardiac amyloid

1 No symptomatic or occult cardiac amyloid by biopsy or non-invasive testing.
2 Asymptomatic cardiac involvement by biopsy or non-invasive testing, e.g. wall thickness >1·1 cm in the absence of prior hypertension or valvular disease, unexplained low voltage ECG.
3 Compensated symptomatic cardiac involvement.
4 Uncompensated cardiomyopathy.

Appendix B

NYHA classification: a functional and therapeutic classification for prescription of physical activity for cardiac patients

Class I: patients with no limitation of activities, suffering no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity, comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity, comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Appendix C

Criteria for therapeutic response/outcome assessment (criteria used at Memorial Sloan Kettering Hospital) (Comenzo et al, 1998)

Amyloid-related organ response will be evaluated on the basis of the accepted criteria described below. Based on the criteria below, amyloid-related organ involvement should be scored as improved, stable or worsened at 6 months/1 year after initiation of therapy and annually thereafter.

An improvement of one or more affected organ(s) is defined by:

Kidneys. A 50% reduction in 24-h urine protein excretion in the absence of progressive renal insufficiency.

Heart. A ≥2 mm reduction in the mean left ventricular thickness (average of posterior wall and septal thickness) by echocardiogram, or a decrease by two points in NYHA classification (e.g. from 3 to 1).

Liver. A ≥50% decrease of an initially elevated alkaline phosphatase level with reduction in the size of the liver by at least 2 cm [determined by ultrasound or computed tomography (CT) scan].

Neuropathy. Clinical improvement supported by clinical history, neurological examination, orthostatic vital signs, resolution of severe constipation or reduction of diarrhoea to less than 50% of previous movements per day, and electromyography (EMG) studies if indicated.

Worsening of one or more affected organ(s) is defined by:

Kidneys. Doubling of urinary protein loss if <3 g/24 h at baseline, or 50% increase in urinary protein loss if ≥3 g/24 h, or reduction of creatinine clearance by ≥50%, or increase in serum creatinine of ≥176·8 μmol/l.

Heart. Evidence of echocardiographic progression with an increase in cardiac wall thickness by ≥2 mm or a decrease in ejection fraction by ≥20%.

Liver. ≥50% increase in the alkaline phosphatase level or doubling of serum bilirubin or liver enzymes (aspartate transaminase, alanine transaminase) due to amyloid, or increase in the size of the liver by at least 3 cm (determined by physical examination, ultrasound, or CT).

Neuropathy. Clinical worsening supported by history, worsening orthostatic vital signs and symptoms, and EMG studies if indicated.

Stable disease. It is defined when none of the criteria for improvement or for worsening disease are met.

Response of the clonal plasma cell disease

Evaluation of the clonal plasma cell disease is based on standard electrophoretic and immunofixation tests of blood and urine for a monoclonal protein (M protein), and bone marrow biopsy stained for isotypic plasma cells. The difference between the serum and/or urine M protein pre- and post-treatment will be calculated. This may be in the form of an M spike or quantifiable immunoglobulin or light chain measurements. The percentage reduction in clonal plasma cell disease will usually be assessed by subtracting the post-chemotherapy value from the baseline value, dividing by the baseline value, and multiplying by 100%. A reduction of ≥50% in this measurement will be considered a 'response'. A >90% reduction of the M protein with its persistence by immunofixation will be considered a 'very good response'. A 'complete response' to therapy requires the M protein to be undetectable by immunofixation of serum and/or urine and normalization of the bone marrow biopsy.

Monoclonal immunoglobulins are often difficult to detect or are unquantifiable in many patients with AL amyloidosis using traditional methods. The limitations and inaccuracies of using electrophoresis, etc., are therefore self-evident, and use of fully quantifiable serum FLC measurements are strongly encouraged (Lachmann *et al*, 2003).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society of Haematology, the UK Myeloma Forum nor the publishers accept any legal responsibility for the content of these guidelines.

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