bjh guideline

Guidelines on the management of AL amyloidosis

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Summary of key recommendations for treatment

- Where possible, patients should be treated in the context of clinical trials and treatment must be undertaken in selected centres experienced in treating such patients (Grade 1a).
- Treatment of AL amyloidosis is based on anti-myeloma therapy but there is no standard treatment and it has to be tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and patient's wishes (Grade 1c) with the treatment goal to achieve a very good partial response or better, if possible.
- Patients with two or more adverse risk features have a very poor prognosis in spite of treatment. Consideration may be given to a trial of treatment but some patients may not benefit from treatment and may be more appropriately managed with palliation (Grade 1b).
- Localized AL amyloidosis does occur rarely and, if problematic, can usually be treated by local resection or, in selected cases, radiotherapy (Grade 1c).
- First line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone. Proteasome inhibitor-based regimens are a preferred choice due to better response rates and outcomes in phase II studies and a bortezomib-alkylator-steroid combination is preferred where a rapid response is desirable (cardiac involvement, renal impairment, severe hypoalbuminaemia, fluid retention) (Grade 1c).
- There is greater treatment-related toxicity in patients with AL amyloidosis compared to that seen in patients with multiple myeloma and dose reductions are required (Grade 1c).
- Bortezomib is preferably given subcutaneously to reduce toxicity but may be given intravenously in patients with severe fluid overload where there is a concern about adequacy of absorption (Grade 1b).
- Thalidomide in combination with cyclophosphamide and dexamethasone is effective in the treatment of AL amyloidosis (Grade 1c).
- Thalidomide should be used with caution in patients with cardiac stage III disease and those with grade III–IV neuropathy (Grade 1c).
- In patients with grade III–IV neuropathy strong consideration must be given to avoiding neurotoxic drugs (thalidomide and bortezomib) (Grade 1c).
- There is no evidence to support using maintenance or consolidation therapies outside the context of a clinical trial (Grade 1c).
- Monitoring of response to treatment with free light chains (FLC) or M-protein should be measured after each cycle of chemotherapy during treatment and every 1–3 months thereafter (Grade 1c). The aim is to switch to an alternative regimen as soon as the current one is proving ineffectual, which may be assessed after three cycles of therapy or earlier in cardiac patients (Grade 1c).
- Difference between the involved and uninvolved light chain (dFLC) should be used to monitor haematological response as long as dFLC is >50 mg/l at diagnosis. The M-protein can be used if >5 g/l.
- There is no standard treatment at relapse. Treatment needs to be tailored to the individual patient and agents not previously used are usually preferred. However previously-used treatments may be used again if associated with a good prolonged response and if well tolerated (Grade 1c).

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- Lenalidomide at reduced dose and pomalidomide can be considered in relapsed disease (Grade 1c).
- High dose melphalan (HDM) and autologous stem cell transplantation (ASCT) (HDM-ASCT) is the preferred first line treatment for selected patients up to 65–70 years of age with estimated glomerular filtration rate (eGFR) >50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in the bone marrow at the time of transplant and lacking the contraindications mentioned in the next point (Grade 1c).
- HDM-ASCT is not generally recommended as first line therapy for patients with any of the following: Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide (NT-proBNP) >590 pmol/l and/or troponin-T > 0·06 ng/ml, severe autonomic neuropathy, significant gastrointestinal (GI) bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status (>2) (Grade 1c).
- HDM-ASCT may be a treatment for selected patients up to 65–70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy (Grade 1c).
- In patients considered as potential candidate for HDM-ASCT, consideration must be given to avoiding stem cell damaging agents (Grade 1a).
- Reduced intensity allogeneic transplantation is not generally recommended as an upfront treatment due to the high treatment-related mortality (TRM). However, selected fitter younger patients with limited organ involvement who have a matched sibling donor may be considered following relapse of their disease (Grade 1c).
- 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 1a).

Summary of key recommendations for supportive care

- Dialysis should be considered for patients with end-stage renal failure without associated severe heart failure (Grade 1c).
- Renal transplantation should be considered in selected patients who have a good performance status with little clinically significant extra-renal amyloid and if a clonal remission has been achieved (Grade 1c).
- Congestive cardiac failure should be treated predominantly with diuretics (Grade 1c).
- Younger patients with advanced cardiac amyloidosis as the predominant or only clinical feature of amyloidosis should be considered for heart transplantation, but this procedure must be followed by chemotherapy +/− ASCT (Grade 2c). In cases potentially suitable for heart transplantation, risks of chemotherapy upfront should be carefully weighted against the risk of toxicity/mortality and chemotherapy should be avoided in such cases, if possible.
- Bleeding should be managed with conventional supportive therapy (factor replacement, platelet transfusion and anti-fibrinolytic agents) (Grade 2c).
- Patients at a high risk of a venous thromboembolism should be considered for prophylactic low molecular weight heparin and patients at low risk considered for aspirin during treatment (Grade 2c).
- Patients with GI symptoms should receive nutritional supplementation. Total parenteral nutrition can be tried if GI symptoms are disabling, and the patient becomes malnourished (Grade 2c).
- Provision of appropriate information and support for patients, their families and carers is an essential component of patient management.

Methodology

This guideline has 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). The objective of this guideline is to provide healthcare professionals with clear guidance on the management and investigation of patients with AL amyloidosis. A Medline search for literature published between 1975 and January 2014 was performed using PubMed. The search included clinical trials in AL amyloidosis and papers or reviews where AL amyloidosis was the major focus. Abstracts from relevant meetings held between 1998 and 2012 were also included. The Cochrane database did not include any relevant information. Levels of evidence and grades of recommendation are based on the GRADE system (http://www.gradeworkinggroup.org/index.htm). The GRADE system is an established internationally recognized system for grading quality of evidence and providing strength of recommendations.

The draft guideline was reviewed by the UK Myeloma Forum Executive and members of the BCSH and British Society of Haematology. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists and comments incorporated where appropriate. The guidance may not be appropriate to all patients with AL amyloidosis and in all cases individual patient circumstances may dictate an alternative approach.

Principles of treatment

Therapy for AL amyloidosis is based on anti-myeloma therapy that suppresses the underlying plasma cell dyscrasia along with supportive measures to manage the amyloid-related complications. All patients with symptomatic systemic AL amyloidosis with visceral organ involvement, significant soft tissue involvement, coagulopathy or neuropathic

involvement should be considered for treatment. It is currently unclear whether patients with isolated carpal tunnel syndrome found incidentally in the absence of any clinical evidence of organ dysfunction would benefit from early treatment. However, such patients are at very high risk of systemic progression and need close long-term follow-up. AL amyloidosis can occur in a localized form that is most often identified in the upper respiratory, urogenital and gastrointestinal (GI) tracts, the skin and the orbit. 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. Selected patients may benefit from local radiotherapy.

Treatment in patients with AL amyloidosis is generally associated with much greater treatment-related toxicity than that seen in patients with myeloma (Moreau *et al*, 1998; Comenzo & Gertz, 2002; Jaccard *et al*, 2007). There is a conflict between the greater toxicity seen in AL amyloid patients and the need to produce a rapid and near complete response. In view of this toxicity, each patient has to be individually evaluated in terms of risk and treatment needs to be tailored accordingly, often using lower doses of agents than for multiple myeloma. A palliative approach may be appropriate for some patients with very poor risk disease.

Monitoring of the clonal response after each cycle of chemotherapy is important in AL amyloidosis with a view to switching to an alternative regimen as soon as the current one is proving ineffectual. However currently there is a lack of data to guide this approach although the National Amyloid Centre currently recommends this assessment after three cycles of therapy.

First line therapy

The initial aim of chemotherapy in AL amyloidosis is to achieve an adequate and durable haematological response as rapidly as possible whilst minimizing toxicity and treatment-related mortality (TRM). Given the rarity of the disease, there is a lack of randomized controlled trials and interpretation of phase II trial data is difficult due to the heterogeneity in patient selection between trials, particularly as regards inclusion of high risk patients. Myeloma-type chemotherapy has been used to treat AL amyloidosis for over 25 years (Kyle *et al*, 1997; Comenzo *et al*, 1998; Moreau *et al*, 1998; Comenzo & Gertz, 2002). A selection of the more important case series reporting chemotherapy and autologous stem cell transplantation (ASCT) are shown in Tables I and II, respectively.

Results with the novel agents, namely bortezomib and lenalidomide-based regimens, show great promise in both newly diagnosed and relapsed/refractory AL amyloidosis (Kastritis *et al*, 2007, 2010; Sanchorawala *et al*, 2007a; Wechalekar *et al*, 2008).

Clinical benefit from chemotherapy typically does not occur for many months even following haematological response (Kyle *et al*, 1997) and patients who respond slowly often do not live long enough to derive benefit. Gradual regression of AL amyloid is often seen (Hawkins, 1994), and organ function may improve even when deposits merely stabilize rather than regress. However evidence shows that patients achieving a near complete clonal response, defined as >90% dFLC response (Pinney *et al*, 2011) or absolute dFLC concentration after chemotherapy of <40 mg/l (Comenzo *et al*, 2012) [the dFLC is defined as the difference between the involved and uninvolved free light chains (FLC), providing this is >50 mg/l prior to treatment] have significantly better outcomes than patients with poorer responses (Palladini *et al*, 2004; Sanchorawala *et al*, 2005; Dispenzieri *et al*, 2006; Pinney *et al*, 2011).

Given the disease heterogeneity and increased treatment-related toxicity seen in AL amyloidosis, there is a particular need for validated risk stratification of patients that can help guide treatment. Prognostic factors and staging systems, including the Mayo staging system, are discussed in the accompanying 'Guidelines on the diagnosis and investigation of AL amyloidosis' (Gillmore *et al*, 2014). In particular, it is important to recognize a 'high risk' group who are likely to tolerate chemotherapy very poorly, often with a need for tailoring treatment and, in some cases, with no benefit from treatment (Goodman *et al*, 2004; Skinner *et al*, 2004). It is possible to define high risk groups based on the presence one or more of the following: poor Eastern Cooperative Oncology Group performance status (ECOG PS 3 or 4), severe cardiac disease (Mayo stage III), severe salt and water retention despite aggressive diuretic therapy, severe amyloid-related autonomic neuropathy causing marked symptomatic impairment in normal activities of daily living (excluding impotence) and liver involvement by amyloid causing bilirubin >2 times upper limit of normal. A N-terminal pro-brain natriuretic peptide (NT-proBNP) >1000 pmol/l and systolic blood pressure <100 mmHg, defined a very poor risk group of stage III patients with a median survival of 3 months and with no clear benefit from chemotherapy (Wechalekar *et al*, 2013). However, such a definition has not been validated in any prospective clinical trial.

Recommendations

- **Where possible patients should be treated in the context of clinical trials and treatment must be undertaken in selected centres experienced in treating such patients (Grade 1a).**
- **Treatment of AL amyloidosis is based on anti-myeloma therapy but there is no standard treatment and it has to be tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and patient's wishes (Grade 1c) with the treatment goal to achieve a very good partial response or better if possible.**
- **Patients with two or more adverse risk features have a very poor prognosis in spite of treatment. Consideration may be given to a trial of treatment but some patients**

Table I. Selected chemotherapy studies in AL amyloidosis.

Regimen	References	Upfront treatment (%)	Clonal response (%)	OS (months)	TRM, %	Toxicity, % (≥grade 3)
MP or MPC	Kyle *et al* (1985)	All	ns	25·2	ns	
MPC	Skinner *et al* (1996)	All	ns	10·6	Nil	ns
MP or MPC	Kyle *et al* (1997)	All	28	18	ns	ns
VBMCP	Gertz *et al* (1999c)	All	31	29	ns	ns
Modified HDD	Palladini *et al* (2001)	43	35	20	9	ns
Thalidomide (standard dose)	Seldin *et al* (2003)	Nil	25	ns	ns	50
Low dose melphalan	Sanchorawala *et al* (2002)		33	5·7	ns (57% early death)	80% hospitalized (grade unclear)
HDD then dexamethsone and IFN	Dhodapkar *et al* (2004)	All	53	31	7	51
Melphalan dexamethasone	Palladini *et al* (2004)	All	67	Not reached	Nil	11
Thalidomide (low dose)	Dispenzieri *et al* (2004)	Nil	Nil	ns	Nil	ns
Intermediate dose melphalan (IDM)	Goodman *et al* (2004)	All	54	44	12	ns
Thalidomide dexamethasone	Palladini *et al* (2005)	All	48	ns	ns	65
VAD	Goodman *et al* (2005)	All	65	80	4	ns
Bortezomib ± dexamethasone	Wechalekar *et al* (2007)	All	77	22	Nil	ns
CTD	Wechalekar *et al* (2007)	40	74	Not reached	4	32
Lenalidomide ± dexamethasone	Sanchorawala *et al* (2007a)	9	67	ns	Nil	35
Lenalidomide ± dexamethasone	Dispenzieri *et al* (2007)	43	75	ns	Nil	73
Bortezomib	Kastritis *et al* (2007)	61	94	Not reached	Nil	11
Bortezomib ± dexamethasone	Kastritis *et al* (2010)	19	71	Not reached	Nil	29
CRD	Kumar *et al* (2012)	68	63	37	9	74
CRD	Kastritis *et al* (2012)	65	55	14	19	24
CRD	Palladini *et al* (2012)	Nil	62	36	Nil	57
MRD	Moreau *et al* (2010)	All	53	54% at 2 years	Nil	81
MRD	Sanchorawala *et al* (2013a)	All	44	24	13	88
Pomalidomide ± dexamethasone	Dispenzieri *et al* (2012)	Nil	48	24	3	30
CyBorD	Venner *et al* (2012)	40	81	53% at 2 years	Nil	19
CyBorD	Mikhael *et al* (2012)	58	94	–	–	12
Ixazomib	Palladini *et al* (2012)	Nil	42	–	–	42% any grade

OS, overall survival; TRM, treatment-related mortality; ns, not specified; MP, Oral melphalan and prednisone; MPC, oral melphalan, prednisone and colchicine; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide and prednisone; HDD, high dose dexamethasone; IFN, Interferon; IDM, IV intermediate dose melphalan 25 mg/m^2; VAD, vincristine, doxorubicin, dexamethasone; CTD, cyclophosphamide, thalidomide and dexamethasone; CRD, cyclophosphamide, lenalidomide (Revlimid), dexamethasone; MRD, melphalan, lenalidomide (Revlimid), dexamethasone; CyBorD, cyclophosphamide, bortezomib, dexamethasone.

may not benefit from treatment and may be more appropriately managed with palliation (Grade 1b).

- **Localized AL amyloidosis does occur rarely and, if problematic, can usually be treated by local resection or, in selected cases, radiotherapy (Grade 1c).**
- **First line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone. Proteasome inhibitor-based regimens are a preferred choice due to better response rates and outcomes in phase II studies and a bortezomib-alkylator-steroid combination is preferred where a rapid response is desirable (cardiac involvement, renal impairment, severe hypoalbuminaemia, fluid retention) (Grade 1c).**
- **There is greater treatment-related toxicity in patients with AL amyloidosis compared to that seen in patients with multiple myeloma and dose reductions are required (Grade 1c).**
- **Bortezomib is preferably given subcutaneously to reduce toxicity but may be given intravenously in patients with severe fluid overload where there is a concern about adequacy of absorption (Grade 1b).**
- **Thalidomide should be used with caution in patients with cardiac stage III disease and those with grade III–IV neuropathy (Grade 1c).**
- **Bortezomib should be used with caution in patients with grade III–IV neuropathy (Grade 1c).**

Table II. Selected studies of autologous stem cell transplantation for AL amyloidosis.

Study references	Number of patients	Haematological response (%)	OS	TRM, %
Comenzo *et al* (1998)	25	62% CR	68% at 24 months	ns
Moreau *et al* (1998)	21	30%	57·5% 4-year survival	43
Mollee *et al* (2004)	20	56%	60 months	35
Skinner *et al* (2004)	356	40% CR	55 months	13
Gertz *et al* (2005a)	171	68%	>6 years for responders	ns
Cohen *et al* (1987)*	45	79%	76% at 18 months	4·4
Schonland *et al* (2005)	41	50% CR	89% at 2 years	7
Seldin *et al* (2006) (age > 65 years)	65	32% CR	48 months	10·3
Perfetti *et al* (2006)	22	55% (36% CR)	68 months	14
Goodman *et al* (2006)	91	66%	63 months	23
Sanchorawala *et al* (2007b)†	80	40% CR	57 months (>10 years if in CR)	8
Jaccard *et al* (2007)	50	66%	22 months	24
Gertz *et al* (2010)	434	76% (39% CR)	Not reached if CR; 107 months if PR; 32 months if no response	11
Cibeira *et al* (2011)	421	34% CR*	6·3 years	14

OS, overall survival; TRM, treatment-related mortality; CR, complete response; PR, partial response; ASCT, autologous stem cell transplantation; ns, not specified.

*Risk-adapted melphalan with adjuvant thalidomide dexamethasone.

†Double autograft trial: 22 patients not in CR after first ASCT received a second ASCT.

- **There is no evidence to support using maintenance or consolidation therapies outside the context of a clinical trial (Grade 1c).**

Treatment at relapse

There is no randomized trial data to guide treatment at relapse. Patients with a good duration of response who tolerate initial treatment well may be retreated with the same initial regimen. Patients with a poor response are best treated with an alternative agent combination using agents to which the patient has not been exposed, palliation or in a clinical trial tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and the patient's wishes. Lenalidomide and pomalidomide can be considered in relapsed disease although data on durability of response are limited. Toxicity with lenalidomide is a significant issue and it is recommended to start at a dose of 15 mg daily [with further dose reduction based on glomerular filtration rate (GFR) in renal failure] in AL amyloidosis patients.

High dose melphalan (HDM) and autologous stem cell transplantation (ASCT) (HDM-ASCT) may be a treatment for selected patients up to 65–70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy.

Recommendations

- **There is no standard treatment at relapse. Treatment needs to be tailored to the individual patient and agents not previously used are usually preferred. However previously used treatments may be used again if associated with a good response and if well tolerated (Grade 1c).**
- **Lenalidomide at reduced dose and pomalidomide can be considered in relapsed disease (Grade 1c).**
- **HDM-ASCT may be a treatment for selected patients up to 65–70 years of age with relapsed/refractory disease (Grade 1c).**

Monitoring treatment

Monitoring of the clonal response after each cycle of chemotherapy is important during treatment in AL amyloidosis, with a view to switching to an alternative regimen as soon as the current one is proving ineffectual.

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

Plasma cell dyscrasia

Measurement of serum FLC is the most effective method for monitoring the clonal disease in the majority of AL patients (Palladini *et al*, 2012). Serum FLC should be measured after each cycle of chemotherapy during treatment and every 1–3 months thereafter. The use of dFLC, the difference between the involved (amyloidogenic) and uninvolved light chain concentration, has recently been recommended for disease monitoring (Dispenzieri *et al*, 2008; Kumar *et al*, 2010) and is applicable with renal impairment (Pinney *et al*, 2011). A difference between the involved and uninvolved FLC of 50 mg/l at diagnosis has been defined as being necessary for using changes in dFLC as a disease marker (Palladini *et al*,

2012) and this includes about 85% of newly diagnosed AL amyloid patients. It is important to note that 10–15% of AL patients have only minimally abnormal FLC (dFLC < 50 mg/l) and for these patients FLC cannot be used for accurate monitoring. The current serum FLC assay is well established and recognized to have some variability. Newer emerging assays for FLC analysis have not been validated and studies are needed to look at comparability and sensitivity.

Monitoring the intact paraprotein is often difficult in patients with amyloidosis because of a low concentration at baseline in the majority of patients. A measurable M-protein, which has been defined as >5 g/l (Palladini *et al*, 2012), is useful for monitoring the haematological response for those 15% of patients with minimally abnormal FLC. One to two percent of patients with AL amyloidosis lack a measurable serum or urine marker to monitor response.

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. The value of assessing minimal residual disease using high sensitivity flow cytometry after chemotherapy is the subject of ongoing studies and may have a role in the 1–2% of patients who have no measurable serum/urine marker for monitoring.

Amyloid deposits (recommended every 6–12 months)

- Serum amyloid P component (SAP) scintigraphy.
- Assessment of organ size clinically or by imaging techniques.

Organ function (recommended every 3–6 months)

- Electrocardiography (ECG)/echocardiography/NT-proBNP/cardiac magnetic resonance imaging.
- Routine measurements of renal function, including creatinine clearance and 24-h urine protein excretion and/or urine protein-creatinine ratio.
- Liver function tests.
- Assessment of other organ function as indicated.

Recommendations

- **Monitoring of response to treatment with FLC or M-protein should be measured after each cycle of chemotherapy during treatment and every 1–3 months thereafter (Grade 1c). The aim is to switch to an alternative regimen as soon as the current one is proving ineffectual, which may be assessed after three cycles of therapy or earlier if appropriate (Grade 1c).**
- **Difference between the involved and uninvolved light chain (dFLC) should be used to monitor haematological response as long as dFLC is >50 mg/l at diagnosis. The M-protein can be used if >5 g/l.**

Definition of response

The definitions of haematological and organ responses has recently been published as a consensus guideline (Comenzo *et al*, 2012) and a large international series has validated some of the response measurements (Palladini *et al*, 2012). The assessment of response in AL amyloid is more complicated than in multiple myeloma as it requires assessment of the haematological/plasma cell clone, assessment of the organ responses and assessment of clinical outcomes including quality of life, progression-free survival (PFS) and overall survival (OS). Although the greater the haematological response, the greater is the likelihood of organ responses, there is often discrepancy between the haematological response and organ response in a significant number of patients, with some patients showing no organ response despite a significant haematological response and others showing organ responses with less than optimal haematological responses.

Haematological response is defined as follows (Comenzo *et al*, 2012): Partial response (PR), a 50% reduction in dFLC; very good PR (VGPR), a reduction in the dFLC to <40 mg/l; complete response (CR), normal FLC levels with a normal kappa/lambda ratio and negative serum and urine immunofixation. For the 15% of patients with AL and normal FLC or dFLC <40 mg/l at baseline, standard criteria for response used in myeloma are available if the M-protein is >5 g/l. A bone marrow examination may be required as part of a clinical trial but the consensus opinion does not support this outside of a trial in order to define a CR (Comenzo *et al*, 2012).

Progression from CR is defined as any detectable monoclonal protein or abnormal FLC ratio (involved light chain must double). Progression from PR is defined as a 50% increase in serum M protein to >5·0 g/l or 50% increase in urine M protein to >200 mg/d (a visible peak must be present) or FLC increase of 50% to >100 mg/l.

Organ responses

Table III shows the updated consensus criteria for evaluation of response of amyloid-related organ dysfunction, which are based on non-invasive testing (Comenzo *et al*, 2012). Multiple organ biopsies to assess amyloid deposition are of no proven value, are frequently misleading and are potentially dangerous.

Details of treatments

Melphalan and steroids

Melphalan and prednisolone (MP) was shown to be beneficial in the 1990s (Bradstock *et al*, 1978; Schwartz *et al*, 1979; Kyle *et al*, 1982, 1997; Benson, 1986; Skinner *et al*, 1996), providing palliation even in patients with advanced cardiac

Table III. Updated consensus criteria for organ response and progression in AL amyloidosis (Gertz *et al*, 2005b; Gertz & Merlini, 2010).

Organ	Response	Progression
Heart	NT-proBNP response (>30% and >35 pmol/l decrease in patients with baseline NT-proBNP ≥ 77 pmol/l) ***OR*** NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP progression (>30% and >35 pmol/l increase)* ***OR*** cTn progression (≥33% increase) ***OR*** Ejection fraction progression (≥10% increase)
Kidney	50% decrease (at least 0·5 g/d) of 24-h urine protein (pre-treatment urine protein must be >0·5 g/d) Creatinine and creatinine clearance must not worsen by 25% over baseline	50% increase (at least 1 g/d) of 24-h urine protein to >1 g/d ***OR*** 25% worsening of serum creatinine or creatinine clearance
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm	50% increase of alkaline phosphatase above the lowest value
Peripheral nervous system	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity

NT-proBNP, N-terminal pro-brain natriuretic peptide; cTN, cardiac troponin; NYHA, New York Heart Association classification (Appendix I). Adapted from: Gertz *et al* (2005b). Copyright © 2005 Wiley-Liss, Inc., A Wiley Company, and Gertz and Merlini (2010), with permission from Informa UK Ltd.

*Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

failure (Sanchorawala *et al*, 2002) but haematological responses are slow, taking a median of 9–12 months (Kyle *et al*, 1997). In the era of novel agents leading to rapid clonal responses, MP is considered to be a sub-optimal treatment in AL. The infusional VAD regimen (vincristine, adriamycin, dexamethasone) in AL amyloidosis produced combined CR and PR rates of 65% and a median survival of 80 months among 229 patients with AL amyloidosis (Sezer *et al*, 1999; Gono *et al*, 2004) but is no longer recommended given the novel agent data, the cardiotoxicity associated with anthracyclines and the problems of infusional chemotherapy.

Pulsed high-dose dexamethasone has been investigated in three series, with an overall response rate in untreated patients of approximately 34% and, subsequently, dexamethasone has been the preferred steroid in combination studies although high doses are associated with significant toxicity (Gertz *et al*, 1999a,b; Palladini *et al*, 2001; Dhodapkar *et al*, 2004).

Palladini *et al* (2004) treated 46 patients with advanced AL amyloidosis with oral melphalan and high dose dexamethasone (Mel-dex) and achieved haematological combined CR and PR rates of 67% within a median of 4·5 months. The same group recently reported an impressive 4·9-year median duration of clonal remission among 9/15 patients who achieved haematological CR with Mel-dex (Palladini *et al*, 2007).

However, two recent studies with Mel-dex using the identical regimen used by Palladini have shown median survivals of <1·5 years, reflecting that these studies had more patients with advanced cardiac disease (Lebovic *et al*, 2008; Dietrich *et al*, 2010). Mel-dex was compared with HDM-ASCT in a randomized trial of AL amyloidosis patients conducted in France (Jaccard *et al*, 2007). Median survival among the 50 patients in the Mel-dex group was 56 months and the regimen was well tolerated with improved outcomes compared to the transplant arm although this study was criticized for poor patient selection in the transplant arm, reflected in a high TRM (Jaccard *et al*, 2007). The Italian group has recently reported good long term outcomes with oral Mel-dex (Palladini *et al*, 2014). Use of full dose dexamethasone was associated with better responses and outcomes. Haematological response rates were 76%, with 31% complete remissions in the full-dose group, and 51% (12% CR) in patients receiving the attenuated schedule. Median survival was 7·4 years in the full-dose group and 20 months in the attenuated-dose group (Palladini *et al*, 2014) However, this may well be due to poorer risk patients being selected for lower dose dexamethasone. At present, there is limited data on once weekly *versus* pulsed 4 d dexamethasone with Mel-Dex regimen but a small study suggest non-inferiority of weekly dexamethasone although overall response rates in this study were much lower (Sanchorawala *et al*, 2010). Mel-dex is generally well tolerated among patients with AL amyloidosis and is often a regimen of choice in patients with neuropathic disease and in elderly patients.

The variable absorption of melphalan from the GI tract led Schey *et al* (1998) to investigate the use of intravenous melphalan (25 mg/m^2) and oral dexamethasone (IDMD) in patients with untreated multiple myeloma, with high response rates being obtained. At the National Amyloidosis Centre (NAC), 144 patients with advanced disease were treated with IDMD (Goodman *et al*, 2004). Haematological response rates and median OS were 54% and 40 months, respectively. However, TRM was high, at 12%, with IDMD, probably reflecting the high proportion of patients with advanced disease and poor performance status at commencement of chemotherapy.

Mollee *et al* (2012) used a similar approach but with a dose of IV melphalan of 20 mg/m^2 in patients not suitable for HDM-ASCT and found this dose was too toxic, with early deaths and excessive myelotoxicity. Dietrich *et al* (2010) used a dose of IV melphalan of 16 mg/m^2 together with dexamethasone and had less haematological toxicity, suggesting this may be a preferable dose, but the responses were poor. Melphalan is stem cell toxic and stem cell harvesting is recommended for any patient who may be a potential candidate for later HDM and PBSCT although, practically, this may not be possible and the efficacy of HDM-based therapy in patients with relapsed or refractory disease has not been studied.

Recommendations

- **Mel-dex is effective in the treatment of AL amyloidosis (Grade 1c).**
- **IV melphalan with or without dexamethasone has efficacy in AL amyloidosis but has significant toxicity (Grade 1c).**

Bortezomib

A phase I/II dose-escalation study of bortezomib that specifically excluded the use of corticosteroids and excluded patients with advanced heart failure looked at two different bortezomib schedules either as a conventional biweekly or a weekly regimen, producing haematological responses in approximately 69% of patients with 37·5% CR using 1·6 mg/m^2 once-weekly dosing and a rapid median time to response of 2·1 months (Reece *et al*, 2009).

Several studies have shown rates of haematological response in excess of 80% with bortezomib in patients with relapsed or refractory disease. Haematological responses were remarkably rapid in some patients, although one-third developed grade 3 toxicity or needed to discontinue bortezomib treatment (Kastritis *et al*, 2007; Wechalekar *et al*, 2008). A collaborative European study from 33 centres of 94 patients (81% of whom had received prior therapy) showed a haematological response rate of 71%, a CR rate of 25% and a cardiac response in 29% (Kastritis *et al*, 2010). More recently, the combination of bortezomib-dexamethasone was given to 26 patients; 18 received this as first-line therapy with an overall response rate of 54%, with 31% CR and a median time to response of 7·5 weeks (Lamm *et al*, 2011).

The combination of cyclophosphamide-bortezomib-dexamethasone has recently been reported by two groups. The NAC (Venner *et al*, 2012) used the following regimen: bortezomib 1·0 mg/m^2 IV on days 1, 4, 8 and 11 (increased to 1·3 mg/m^2 if well tolerated); cyclophosphamide 350 mg/m^2 orally on days 1, 8 and 15; and dexamethasone 20 mg orally on days 1, 4, 8 and 11 (increased to 20 mg for 2 d if well tolerated). Forty-three patients (74% had cardiac involvement, 46% Stage III) were treated and showed an overall haematological response rate of 81·4% (41·9% CR, 51·4% VGPR or better), an estimated 2-year PFS of 66·5% for patients treated at presentation and 41·4% for relapsed patients and an estimated 2-year OS of 97·7%.

The combination of cyclophosphamide-bortezomib-dexamethasone was also reported by the Mayo Clinic (Mikhael *et al*, 2012) who treated 17 patients (10 naive and seven previously treated) with a regimen consisting of bortezomib 1·5 mg/m^2 days 1, 8 and 15, cyclophosphamide 300 mg/m^2 orally days 1, 8, 15 and 22 and dexamethasone 40 mg days 1, 8, 15 and 22. Ten (58%) had symptomatic cardiac involvement, 14 (82%) with two or more organs involved and responses occurred in 16 (94%) with 71% achieving a CR and 24% a PR with a time to response of 2 months.

Lower neurotoxicity is seen with subcutaneous bortezomib compared to IV bortezomib with equal clinical efficacy in multiple myeloma (Arnulf *et al*, 2012). Less toxicity is seen with the weekly bortezomib regimen and/or dose reduction from the standard 1·3–1 mg/m^2. In a small series from the NAC, bortezomib was used subcutaneously in 11 patients and appeared to be well tolerated with grade II neuropathy in two patients (Gibbs *et al*, 2012).

Bortezomib regimens appear an attractive option, particularly in view of the rapidity of responses, and may be the drug of choice for patients with cardiac disease although further phase II/III studies are awaited. Starting with lower doses and/or a weekly schedule may allow better tolerance in many patients.

Recommendations

- **Bortezomib is preferably given subcutaneously to reduce toxicity but may be given intravenously in patients with severe fluid overload where there is a concern about adequacy of absorption (Grade 1c).**
- **Bortezomib is preferably used in a weekly schedule in combination with other agents such as dexamethasone, alkylators and/or immunomodulatory drugs (IMiDs) (Grade 1c).**
- **Patients with advanced stage III cardiac disease should commence on a lower dose of bortezomib with consideration for inpatient continuous cardiac monitoring initially and a view to dose escalation if tolerated (Grade 1c).**
- **In patients with grade III–IV neuropathy, strong consideration must be given to avoiding bortezomib (Grade 1c).**

Thalidomide

Thalidomide is synergistic in multiple myeloma when combined with either cyclophosphamide, melphalan or other agents. In a small phase II study of thalidomide in AL amyloidosis, haematological responses were reported in 48% of

patients (19% complete haematological responses) but treatment-related toxicity was frequent (Dispenzieri *et al*, 2003), although this study used high dose thalidomide (up to 400 mg/d) whilst a subsequent study, also from the Mayo clinic, showed that lower doses of thalidomide were associated with low response rates (Dispenzieri *et al*, 2004). Palladini *et al* (2009) prospectively treated 22 patients with advanced cardiac amyloidosis with oral melphalan, thalidomide and reduced intensity dexamethasone (MTD) with six early deaths, eight haematological responses and four durable improvements in cardiac dysfunction.

The cyclophosphamide, thalidomide and dexamethasone (CTDa) regimen has been investigated retrospectively in 139 newly diagnosed patients with AL amyloidosis, with a clonal response in 67%, organ response in 42%, grade 3/4 toxicity in 21% of patients, TRM of 3% and rapid responses seen in all responding patients achieving clonal responses by the end of cycle 3 of chemotherapy (Wechalekar *et al*, 2007).

The safety and efficacy of CTD has recently been prospectively compared with Mel-dex in a feasibility study by the UK Amyloidosis Treatment Trial (UKATT) (Gillmore *et al*, 2010a). Among 24 randomized patients, the toxicity and haematological response rates were comparable between the two regimens although CTD was associated with more rapid haematological responses than Mel-dex (Gillmore *et al*, 2010a). In a recent analysis of 250 patients in a prospective observational study of AL amyloidosis at the NAC, grade 3 or greater toxicity occurred in approximately 60% of patients treated with CTD (Lane *et al*, 2010).

The use of thalidomide and dexamethasone has also been investigated in the relapsed setting in 31 patients, with 15 (48%) achieving a haematological response, 6 (19%) complete remissions and 8 (26%) organ responses. Treatment-related toxicity was frequent (65%) with only 11 (35%) managing the 400 mg/d dose and with symptomatic bradycardia being a common (26%) adverse reaction (Palladini *et al*, 2005).

These studies show efficacy for thalidomide but toxicity is an issue and, if used, it is advisable to start at a dose of 50 mg daily and increase slowly if tolerated. Thalidomide has been used in the UK as front line therapy over the last decade but a substantial proportion of patients may experience toxicities. There is no comparison between thalidomide and other immunomodulatory agents in front line setting. Lenalidomide and pomalidomide are not available for routine front line use in the UK at the time of writing. Unusual toxicities of thalidomide are seen in AL amyloidosis compared to myeloma patients and include fluid retention, worsening of congestive heart failure, increase in markers of cardiac damage and cardiac arrhythmias and it has to be used with special caution, if at all, in patients with stage III disease. As well as its efficacy and rapid onset of action, CTD has the advantage of being stem cell sparing and may be useful for patients who may be future candidates for HDM and ASCT.

Recommendations

- **Thalidomide in combination with cyclophosphamide and dexamethasone is effective in the treatment of AL amyloidosis (Grade 1c).**
- **Thalidomide should be used with caution in patients with cardiac stage III disease and those with grade III–IV neuropathy (Grade 1c).**

Lenalidomide

Lenalidomide is a potent immunomodulatory agent that has become a standard treatment in multiple myeloma. Two phase II studies of lenalidomide with and without dexamethasone in AL amyloidosis showed response rates of 41% (Sanchorawala *et al*, 2007b) and 67% (Dispenzieri *et al*, 2007), with a median response duration and OS of 19·2 and 31 months respectively in the Mayo study (Dispenzieri *et al*, 2007). Significant toxicities were seen in these two studies, particularly cytopenias, fatigue, cramp and rashes, with 86% of patients experiencing grade 3 or higher adverse effects in the Mayo study and hence a recommendation was made to start patients at a dose of 15 mg daily rather than the 25 mg daily dose as used in multiple myeloma (Dispenzieri *et al*, 2007). Lenalidomide and dexamethasone showed significant activity in the relapsed setting with 41% of relapsed patients, all of whom had failed at least two lines of therapy, showing a haematological response but, again, toxicity is an issue with 50% developing grade 3/4 adverse events even starting at a dose of 15 mg (Palladini *et al*, 2014).

Several studies have combined lenalidomide with an alkylating agent, either melphalan or cyclophosphamide, and dexamethasone. Moreau *et al* (2010) carried out a phase I/II dose escalation study of lenalidomide, melphalan and dexamethasone in newly diagnosed patients, with 15 mg/d of lenalidomide achieving a complete haematological response in 42% and an the estimated 2-year OS and event-free survival (EFS) of 80·8% and 53·8%, respectively. More recently, two more studies using melphalan-dexamethasone-lenalidomide showed much lower response rates due to significant toxicity, leading to dose reductions in 88% cases in one study (Sanchorawala *et al*, 2013a) and a high proportion of cardiac deaths in the other (Dinner *et al*, 2013a). Kumar *et al* (2012) treated 35 patients (24 untreated, 43% Stage III disease) with lenalidomide, cyclophosphamide and dexamethasone using the following regimen: 4-week cycles of lenalidomide given at 15 mg orally (PO) days 1–21; cyclophosphamide 300 mg/m^2 PO given days 1, 8 and 15; and dexamethasone 40 mg PO given days 1, 8, 15 and 22**.** The overall haematological response was 60% (40% with VGPR), with organ responses in 29% of patients, and the PFS and the OS were 28·3 and 37·8 months, respectively. A grade 3 or higher toxicity occurred in 26 patients (74%) including ≥grade 3 haematological toxicity in 16 patients (46%) and ≥grade 3 non-haematological toxicity in 25 patients (71%). Kastritis *et al* (2012) also explored a similar regimen in a phase I/II study,

but used dexamethasone 20 mg on days 1–4 (80 mg per cycle), oral cyclophosphamide 300 mg/d on days 1–10 and lenalidomide 15 mg/d on days 1–21 every 28 d in the phase II study, and treated 37 patients overall in phase I and II, 65% previously untreated, with 55% of patients achieving a haematological response with a median time to progression of 10 months. The commonest non-haematological toxicities in these studies include fatigue, oedema, rashes, non-neutropenic infections and GI symptoms.

It is clear that lenalidomide has significant activity in AL amyloidosis but has to be used at a dose of 15 mg daily initially. The role of combination of lenalidomide with alkylators is promising but risks greater toxicity and as yet the benefit of this approach over just lenalidomide-dexamethasone remains to be proven. Lenalidomide-based regimens are likely to be first line regimens of choice in patients with AL with neuropathic disease although there are no randomized data.

Pomalidomide

Pomalidomide is an immunomodulatory drug with activity in multiple myeloma including in patients refractory to bortezomib and lenalidomide. In a phase II study, Dispenzieri *et al* (2012) treated 33 patients with relapsed AL amyloidosis with pomalidomide and dexamethasone and showed a 48% haematological response rate with a median overall and PFS of 28 and 14 months, respectively. The main grade 3–4 toxicities seen were neutropenia and fatigue.

Recommendations

- **Lenalidomide (at reduced dose) and pomalidomide can be considered in relapsed disease (Grade 1c).**
- **Lenalidomide is one of the preferred treatment regimens for patients with AL amyloidosis with significant peripheral neuropathy (Grade 1c).**
- **At present, there are no data on comparative efficacy of lenalidomide, pomalidomide or thalidomide.**

Transplantation

Autologous stem cell transplantation

The use of HDM-ASCT following induction therapy in patients with AL amyloidosis was first reported in the 1990s and was followed by encouraging results in selected patients (Comenzo *et al*, 1998; Moreau *et al*, 1998; Gillmore *et al*, 1999; Gertz *et al*, 2000; Dispenzieri *et al*, 2001; Sanchorawala *et al*, 2001; Seldin *et al*, 2004). The procedure-related mortality has been consistently and substantially higher among patients with amyloidosis than those with multiple myeloma (Gertz *et al*, 2000; Sanchorawala *et al*, 2001). The reported causes of death include cardiac arrhythmias, intractable hypotension, multi-organ failure and GI bleeding. Patients with poor renal function, especially if dialysis-dependent, and patients with dominant or symptomatic cardiac amyloid have a very high TRM (Saba *et al*, 1999; Comenzo & Gertz, 2002). However selected patients with cardiac involvement may undergo HDM-ASCT, as shown by the Mayo series of 187 selected patients with cardiac involvement (Madan *et al*, 2012). Although half of the patients received reduced-dose melphalan (100–160 mg/m^2), the TRM was 16% with haematological responses and cardiac responses in 66% and 41% of patients respectively, with a median OS of 66 months from diagnosis. In multivariate analysis of baseline factors, only reduced-dose melphalan predicted shorter OS (Madan *et al*, 2012). Similarly, it is feasible to perform HDM-ASCT in selected patients with renal failure with reduced doses of melphalan but the overall benefit of such an approach is not clear.

Patient selection bias with improvements in patient selection make evaluation of HDM-ASCT difficult and improved supportive care may also be a factor for improved outcome post-ASCT, with those transplanted most recently doing better (Vesole *et al*, 2006). A case control study compared the OS of 63 patients undergoing HDM-ASCT with matched controls not undergoing transplant with the groups matched for age, gender, time to presentation, left ventricular function, serum creatinine, interventricular septal thickness, nerve involvement and 24-h proteinuria. One-, 2- and 4-year OS rates for the transplant *versus* non-transplant groups were 89% vs. 71%, 81% vs. 55% and 77% vs. 41% respectively, showing significantly better OS for the patients undergoing HDM-ASCT (Dispenzieri *et al*, 2001). Mel-dex was compared with HDM-ASCT in a randomized trial of AL amyloidosis patients conducted in France (Jaccard *et al*, 2007). The median survival was 56 months for the 50 patients in the Mel-dex group and 22 months in the HDM-ASCT group with a TRM of 24% (Jaccard *et al*, 2007). A major criticism of this trial was that the only exclusion criterion was an ECOG PS of $\geq$3, so only 37/50 patients received their planned treatment in the HDM-ASCT arm and 10 patients received a reduced dose of 140 mg/m^2 of melphalan. A meta-analysis including the one randomized control trial, two other control studies, and nine single arm studies also did not find a survival benefit with HDM-ASCT although the authors commented that the quality of evidence was low (Mhaskar *et al*, 2009).

The major problem for ASCT in patients with AL amyloidosis is a high TRM, which is a criticism of all these studies. It is apparent that the high TRM reflected poor patient selection and a failure to properly risk-categorize patients and the published meta-analysis was also criticized for its methodology (Mehta *et al*, 2010). Recent studies have reported a reduced TRM following HDM-ASCT, which has continued to fall with better patient selection to 13% in a UK series (Goodman *et al*, 2006) and as low as 4–7% in two series from North America (Cohen *et al*, 2007). Cibeira *et al*

(2011) looked at 421 patients treated with HDM-ASCT at a single referral centre and showed an overall TRM of 11·4% (5·6% in the last 5 years), a CR rate of 34% and a median EFS and OS of 2·6 and 6·3 years, respectively. In the Mayo series of 434 transplants, the TRM was 11% with a haematological response achievable in 76%, CR in 39% and organ responses in 47% of patients. Median OS was not reached for patients achieving a haematological CR and was 107 and 32 months respectively, for those with a PR and no haematological response, with haematological response being the strongest predictor of organ response rates in the Mayo series (Gertz *et al*, 2010). In the United States, the Southwest Oncology group (SWOG) designed a trial using two sequential cycles of modified high-dose melphalan at 100 mg/m^2 and ASCT (mHDM/SCT) in AL amyloidosis (light-chain amyloidosis, AL), AL with myeloma (ALM) and host-based high-risk myeloma (hM) patients. Ninety-three eligible patients were enrolled at 17 centres in the United States (59 with AL, nine with ALM and 25 with hM). The median OS for patients with AL and ALM was 68 and 47 months respectively, and has not been reached for patients with hM. The median PFS for patients with AL and ALM was 38 and 16 months respectively, and has not been reached for patients with hM. The TRM was 12% (11/93) and was observed only in patients with AL after SCT (Sanchorawala *et al*, 2013b).

The TRM of HDM-ASCT is associated with the number of organ systems involved with amyloid. Several studies have shown that patients with ≤2 organ systems involved had significantly superior 100-d survival compared with those who had >2 organ systems involved (Moreau *et al*, 1998; Gillmore *et al*, 1999) but these studies were conducted in the era before routine use of cardiac biomarkers and may not be accurate or reproducible. The Mayo group has used cardiac biomarkers for identifying patients at high risk of TRM with a view to developing selection guidelines to determine the eligibility for SCT of patients with light-chain amyloidosis.

The group from the Mayo clinic reviewed two cohorts of patients undergoing ASCT between 1996 and 2009 (n = 410) and between 2009 and 2011 (n = 89) (Gertz *et al*, 2013). One hundred-day TRM was 10·5% (43/410) in the earlier group and 1·1% (1/89) in the later group. In the earlier group, 25% patients with NT-proBNP > 590 pmol/l and serum troponin T > 0·06 ng/ml died by 10·3 and 3·7 months, respectively. In the latter group, the only death was in a patient with NT-proBNP > 590 pmol/l. They suggest that patients with serum troponin T > 0·06 ng/ml or NT-proBNP > 590 pmol/l (not on dialysis) should not be considered candidates for ASCT because of high early mortality.

Reduction of the melphalan conditioning dose is associated with loss of efficacy (Comenzo & Gertz, 2002; Gertz *et al*, 2004; Cibeira *et al*, 2011), which questions the rationale for using lower doses in patients with significant renal or cardiac disease. HDM-ASCT should probably only be considered as first line therapy in low risk patients who are likely to tolerate full-dose melphalan (200 mg/m^2) conditioning. There is extremely limited data on tandem transplantation and it is not recommended outside a clinical study. A small study using bortezomib-melphalan conditioning for ASCT reported high response rates (Sanchorawala *et al*, 2011) but the data are too preliminary to recommend use outside clinical trials. Similarly, there are interesting data using bortezomib or thalidomide as consolidation post-ASCT for patients who do not achieve a CR. Although thalidomide consolidation post-ASCT can improve response, this is at the expense of significant toxicity (Cohen *et al*, 2007). Bortezomib, in an adjuvant setting, is better tolerated and leads to an increase in the CR rate to over 70% with median PFS not reached at 5 years and an OS of over 8 years (Landau *et al*, 2013).

The question of whether induction therapy is needed before HDM-ASCT has only been explored in a single randomized trial in 100 patients who were randomized to two cycles of MP before HDM-ASCT or proceeded straight to HDM-ASCT (Sanchorawala *et al*, 2004). No advantage in OS or haematological or clinical response was observed for the MP group (Sanchorawala *et al*, 2004). Two ongoing trials are looking at the value of bortezomib induction prior to ASCT.

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. Cyclophosphamide-primed stem cell harvest is not recommended in AL amyloidosis. Measures that may reduce morbidity and mortality during the ASCT procedure itself include avoidance of substantial prehydration, administration of the melphalan in two divided doses, using a dose of >5 × 10^6 CD34$^+$ cells/kg, and possibly avoiding G-CSF support, although this is controversial (Comenzo & Gertz, 2002).

HDM-ASCT appear to be associated with the best PFS and OS but, because of the associated complications that are unique to AL amyloidosis, it is recommended that such patients be treated in units with expertise in this particular disease. Currently it seems reasonable to consider HDM-ASCT for the approximately 20% of patients who are young, who have not had previous amyloid-related GI bleeding or clinically significant autonomic disease, have a good performance status, who do not have advanced renal failure or recurrent symptomatic amyloid related pleural effusions, a troponin T < 0·06 ng/ml or a NT-proBNP < 590 pmol/l. Future refinement of patient selection and improvement of peri-transplant supportive clinical management remain priorities.

Recommendations

- **HDM-ASCT can be considered without prior induction chemotherapy in patients with low level bone marrow plasma cell infiltration.**
- **HDM-ASCT is the preferred first line treatment for selected patients up to 65–70 years of age with estimated glomerular filtration rate (eGFR) >50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in the bone marrow at the time of transplant and lacking the contraindications mentioned in the next point (Grade 1c).**
- **HDM-ASCT is not recommended as first line therapy for patients with any of the following: cardiac amyloidosis with NT-proBNP > 590 pmol/l and/or troponin-T > 0·06 ng/ml, severe autonomic neuropathy, significant GI bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid related pleural effusions, poor ECOG PS (>2) (Grade 1c).**
- **HDM-ASCT may be a treatment for selected patients up to 65–70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy (Grade 1c).**
- **Both stem cell harvesting and HDM-ASCT should be performed according to agreed protocols only in selected centres with particular expertise (Grade 1c).**
- **In patients considered as potential candidates for HDM-ASCT, consideration must be given to avoiding stem cell damaging agents (Grade 1a).**
- **Patients not achieving a VGPR or CR after HDM-ASCT could be considered for further adjuvant chemotherapy with bortezomib or IMiDs to improve response (Grade 1b) and the results of ongoing trials addressing bortezomib in induction and maintainence or consolidation are awaited.**

Allogeneic bone marrow transplantation (BMT)

The first successful allogeneic BMT for AL amyloidosis was reported by Gillmore *et al* (1998). The European Group for Blood and Marrow Transplantation registry retrospectively reported on 19 patients with AL amyloidosis who underwent allogeneic (allo, $n = 15$) or syngeneic (syn, $n = 4$) haematopoietic stem cell transplantation (SCT) between 1991 and 2003 (for allo-SCT, full-intensity conditioning $n = 7$, reduced-intensity conditioning $n = 8$; Schonland *et al*, 2006). Overall transplant-related mortality (TRM) was 40%. Seven patients achieved long-term survival and a sustained CR and this was associated with chronic graft-*versus*-host disease in five out of seven patients (Schonland *et al*, 2006). Donor lymphocyte infusions have also been used successfully in a few patients with AL amyloidosis (Schonland *et al*, 2009). This approach still remains largely unexplored and is not recommended outside of clinical trials.

- **Reduced intensity allogeneic transplantation is not generally recommended as an upfront treatment due to the high TRM. However, selected, fitter younger patients with limited organ involvement who have a matched sibling donor may be considered following relapse of their disease (Grade 1c).**

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 overload or intercurrent infection. Care should be taken to maintain the circulating volume and avoid intravascular volume depletion. Fluid overload should be managed with salt and fluid restriction. Diuretics are often necessary. Salt-poor human albumin infusions can be helpful in refractory cases and during chemotherapy. Patients with amyloidosis have multisystem involvement and patients must be treated in a centre with appropriate multidisciplinary care with availability of haematology, cardiology, nephrology, gastroenterology and neurology services that have an interest and expertise in amyloidosis. Due to rarity of the disease, care is best provided in limited centres, which can develop expertise in managing these complex fragile patients.

Recommendation

- **Patients with amyloidosis should be mostly treated in designated centres that have on-site availability of multidisciplinary care with interest and experience in managing patients with amyloidosis.**

Nephrotic syndrome and renal impairment

Significant renal impairment and/or nephrotic syndrome are present at diagnosis in approximately 70% of patients with AL amyloidosis. The oedema of nephrotic syndrome generally requires treatment with loop diuretics. High doses may be required and resistant cases may require addition of a thiazide and/or potassium-sparing diuretics. Salt and, in many cases, fluid restriction may be advisable. In patients who have difficulty maintaining their intravascular volume, infusions of salt-poor human albumin can be very helpful.

Hypertension is relatively unusual but should be treated aggressively. Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers 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. End-stage renal failure can be treated by dialysis and

this improves survival, particularly for patients without associated cardiac involvement (Martinez-Vea *et al*, 1990; Gertz *et al*, 1992; Pinney *et al*, 2011). Survival is reduced in comparison to age-matched non-diabetic patients and there is no evidence that peritoneal or haemodialysis has a better outcome.

Recommendation

- **Dialysis should be considered for patients with end-stage renal failure without associated severe heart failure (Grade 1c).**

Renal transplantation

Transplantation has rarely been used, due to concerns about prognosis due to extra-renal amyloid and possible recurrence of amyloid in transplanted kidneys (Hartmann *et al*, 1992). However, among selected patients whose underlying clonal plasma cell disease has remitted following chemotherapy and who have a good performance status without significant extra-renal amyloidosis, outcomes with renal transplantation are comparable to other causes of end-stage renal disease (Sattianayagam *et al*, 2010; Pinney *et al*, 2011).

Recommendation

- **Renal transplantation should be considered in selected patients who have a good performance status with little clinically significant extra-renal amyloid if a clonal remission has been achieved (Grade 1c).**

Congestive cardiac failure

Cardiac involvement occurs in 30–50% of patients with AL amyloidosis, usually with clinically significant amyloid deposition in other organ systems, and is a major cause of morbidity with a very poor prognosis (Falk, 2005). Impaired left ventricular systolic function, right ventricular dysfunction on echocardiography and a poor performance status are especially poor prognostic factors and regrettably, such patients rarely survive long enough to benefit from chemotherapy. 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 may improve symptoms in some cases. Cardiac amyloidosis causes 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 they are often poorly tolerated due to low cardiac output, orthostatic hypotension or autonomic neuropathy. Calcium-channel blockers are contraindicated in cardiac amyloidosis (Gertz *et al*, 1985). Beta blockers should be used with caution and may exacerbate heart failure in some patients. Cardiac arrhythmias are common and 24-h monitoring should be considered. 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. Amiodarone is also widely used as an antiarrhythmic but good data on efficacy are lacking. Prevention of sudden death due to cardiac amyloidosis is difficult and a recent study suggested that the majority of patients with severe cardiac amyloidosis fail to benefit from implantable cardioverter-defibrillators, as electromechanical dissociation rather than arrhythmia appears to be the cause of death (Kristen *et al*, 2008). More recent studies have suggested that appropriate shocks are delivered by an implantable cardioverter defibrillator (ICD), however, this has not translated into a survival benefit (Lin *et al*, 2013; Varr *et al*, 2014). This needs further study and ICD therapy should be considered in occasional patients who may benefit.

Recommendations

- **Consider 24-h ECG monitor (Holter) following diagnosis (Grade 1c).**
- **Congestive cardiac failure should be treated predominantly with diuretics (Grade 1c).**
- **Selected patients with cardiac amyloidosis may benefit from appropriate device therapy (Grade 1c).**

Cardiac transplantation

In younger patients with advanced irreversible cardiac failure due to AL amyloidosis and without significant extra-cardiac amyloid, cardiac transplantation offers a possibility of long term survival. Cardiac transplantation has been performed in a small number of such patients (Hosenpud *et al*, 1991; Dubrey *et al*, 2001, 2004) although the procedure remains controversial due to the scarcity of donor hearts, the high transplant-related mortalilty (due to subclinical extra-cardiac amyloid) and the likelihood of subsequent amyloid deposition in the graft. Cardiac transplantation in AL amyloidosis should be followed by chemotherapy or HDM-ACST to prevent recurrence of cardiac amyloid or its accumulation within other organ systems (Gillmore *et al*, 2006; Sattianayagam *et al*, 2010).

Recommendation

- **Younger patients with advanced cardiac amyloidosis as the predominant or only clinical feature of amyloidosis should be considered for heart transplantation, but this procedure must be followed by chemotherapy +/− ASCT (Grade 2c). In cases that are potentially suitable for heart transplantation, risks of chemotherapy**

upfront should be carefully weighted against risk of toxicity/mortality and chemotherapy should be avoided in such cases if possible.

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. Patients should be advised to slowly change from a supine to an upright posture, to avoid exertion after large meals and in cases of micturiton syncope, males should be advised to pass urine seated. Support stockings may be helpful. Measures to minimize hypovolaemia should be undertaken, including reducing diuretics. Fludrocortisone 100–200 μg/d can be helpful in some patients, but may cause or exacerbate fluid retention. Fludorcortisone should be avoided in patients with significant cardiac amyloidosis and is contraindicated in patients who are on regular diuretics. One of the more effective available agents is midodrine (ProAmatine), starting at a dose of 2·5 mg t.d.s. and gradually increasing 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 in selected cases (Grade 1c).**
- **Midodrine is the most effective drug for orthostatic hypotension in patients with amyloidosis, but can cause supine hypertension (Grade 1c).**

Bleeding/Thrombosis

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 (FX) 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 (Mumford *et al*, 2000). It has been proposed that clotting factors bind to amyloid fibrils and there are anecdotal reports of improvements in haemostasis after removal of heavily infiltrated spleens (Greipp *et al*, 1979), although a more recent study did not support this theory and attributed most abnormalities in coagulation to either impaired fibrin polymerization or a reduction in FX activity (Mumford *et al*, 2000). There are also reports of reversal of coagulopathy following cytotoxic chemotherapy (Camoriano *et al*, 1987). FX concentrate is available and anecdotal evidence suggests it is effective although it has a markedly shortened half-life and may need repeated dosing every 24 h (compared to every few days in other cases of FX deficiency). Use of recombinant factor VIIa may be considered in patients lacking a clearly identifiable coagulation defect.

There is a theoretical risk of renal vein thrombosis in patients with AL amyloidosis and nephrotic syndrome but in practice this is rarely seen (A.D. Wechalekar and J.D. Gillmore, unpublished data). Patients with nephrotic syndrome with a serum albumin <25 g/l are at a much higher risk of thrombotic events. Thalidomide, lenalidomide and other IMIDs all significantly increase the risk of venous thromboembolism (VTE) to >10% in multiple myeloma (Larocca *et al*, 2012). Based on the data for myeloma patients (Larocca *et al*, 2012), AL amyloid patients with risk factors for VTE (advanced age, a history of VTE, an indwelling central venous catheter, diabetes, cardiac disease, immobilization and recent surgery) or those with nephrotic range proteinuria receiving one of these drugs should be considered for prophylactic anticoagulation with low molecular weight heparin or warfarin. For patients without risk factors for a VTE receiving one of these drugs, aspirin or prophylactic doses of low molecular heparin should be considered. Given that amyloid patients may also have a bleeding tendency and multiple comorbidities, a decision around anticoagulation can only be made on an individual patient basis.

Recommendations

- **Bleeding should be managed with conventional supportive therapy (factor replacement, platelet transfusion and anti-fibrinolytic agents). FX concentrate can be used, when available, in cases with proven FX deficiency (Grade 2c).**
- **Patients at a high risk of a VTE should be considered for prophylactic low molecular weight heparin and patients at low risk considered for aspirin during treatment (Grade 2c).**

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. Gastrointestinal dysmotility usually presents with delayed transit and a mixture of loss of appetite, gastro-oesophageal reflux, dysphagia, nausea, vomiting due to gastroparesis, constipation or even chronic intestinal pseudo-obstruction (Petre *et al*, 2008). Diarrhoea can be due to bacterial overgrowth and a lactose breath test or empirical antibiotics should be considered. Patients with severe malabsorption or pseudo-obstruction may require long-term total parenteral nutrition (TPN). In advanced intestinal amyloid, nausea is frequently a prominent symptom. Anti-emetics should be used to control nausea and vomiting (Hayman *et al*, 2001; Poullos & Stollman, 2003). Patients with GI symptoms should receive nutritional supplementation. TPN can be tried if symptoms are disabling and the patient becomes malnourished. However, TPN has risks in this fragile patient group, including risk of infections and fluid overload. Patients with advanced disease should be carefully counselled about risk and quality of life issues including palliative care options.

Recommendation

- **Patients with GI symptoms should receive nutritional supplementation. In highly selected cases, TPN can be tried after appropriate counselling if GI symptoms are disabling, and the patient becomes malnourished (Grade 2c).**

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-ß core structure common to amyloid fibrils. A potential therapeutic approach that may be applicable to all types of amyloidosis, and which has already being tested in patients, is inhibition of the binding of SAP to amyloid fibrils, which contributes significantly to amyloidogenesis (Pepys *et al*, 2002; Gillmore *et al*, 2010b). Immunotherapy is also being explored, including a combination of SAP depletion and immunotherapy using anti-SAP antibodies (Bodin *et al*, 2010). A phase I trial using this approach with GSK2398852 co-administered with GSK2315698 is ongoing. Another phase I trial using the anti-fibril antibody, NEOD001, is ongoing and preliminary results suggest that this is well tolerated with a suggestion of reduction in NT-proBNP in some of the treated patients. Priorities for future research include development of the therapeutic approaches described above. Other important areas of research include improving our understanding of how certain light chain variable regions lead to tissue tropism, particularly the identification of pathogenic mutations in the light chain variable region using genomics. There is clearly a need for controlled, comparative trials of intermediate and high dose therapy with long term follow-up.

Symptomatic multiple myeloma and amyloidosis

In patients with symptomatic 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. However, incidental clinically insignificant AL amyloid deposits are common in myeloma and do not affect treatment outcomes and prognosis and the finding of such deposits should not be used as a reason to change from using conventional treatments. Otherwise, patients with significant amyloid deposition should be treated along the lines of amyloidosis and the extent of organ involvement by amyloid may influence the choice of chemotherapy for myeloma. The survival of patients with AL amyloidosis with concurrent myeloma is inferior to those without myeloma (Dinner *et al*, 2013b). A large study from the Mayo group (Kourelis *et al*, 2013) recently reported that the median survival of patients with AL amyloidosis without myeloma and <10% bone marrow plasma cells was 46 months. For patients with AL amyloidosis with >10% bone marrow plasma cells but no myeloma-related organ toxicity (by the CRAB criteria; hyperCalcaemia, Renal insufficiency, Anaemia, Bone lesions) survival was 16·2 months and for patients with AL with symptomatic myeloma, survival was only 10 months. This is particularly important in planning therapy in patients with AL amyloidosis, especially those patients for whom high dose therapy is being considered, and the risks are similar to other patients with AL dependant on organ involvement.

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 1a).**

Patient information and support

Provision of appropriate information and support for patients, their families and carers is an essential component of patient management. Information and support helps patients to make informed choices about their treatment and care options, as well as understanding the importance of compliance with treatment regimens which, at times, can be very demanding. Where possible, patients should be encouraged to attend the NAC for assessment and follow-up, as described in the companion guideline (Gillmore *et al*, 2014).

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, where these exist, in the community. The specialist team should be able to provide patients and their families with information on local support networks. Myeloma UK has a patient information pack on AL amyloidosis as well as information on their website.

The specialist team also needs to have information available for the patient and family regarding 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 high dose therapy may also make employment impractical for periods lasting 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 that provides information on the condition. It should also guide patients and their family/carers on access to information services. Written information is also available from the NAC. The Myeloma UK website** (www.myeloma.org.uk) **also has useful, patient-orientated information on the condition and its treatment (see below).**
- **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 multidisciplinary 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 the UK amyloidosis information website (http://www.amyloidosis.org.uk/), the Myeloma UK site http://www.myeloma.org.uk and the American site 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 informed about any available clinical trials.**
- **Patients should be given the opportunity of receiving more than one medical opinion.**

Useful information sources

Myeloma UK, based in Edinburgh, operates a help and advice line for patients, 0800 980 3332. It has useful information on myeloma and related plasma cell disorders, including AL amyloidosis, on its website and runs a series of patient and family seminars during the year in the UK and Eire.

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.

Author contributions

ADW and GP designed study, conducted research, wrote paper. JGD, HL, PNH, JB, JC, SH and MK conducted research and wrote paper. All authors were involved in formulation and approval of final guidelines. All authors approved the final version of the manuscript.

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Appendix I

New York Heart Association (NYHA) Classification: A functional and therapeutic classification for prescription of physical activity for cardiac patients.

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

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

Class III: patients with marked limitation of activity; they are 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.