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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Systemic Light Chain Amyloidosis

Version 1.2012

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Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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Updates in Version 1.2012 NCCN Multiple Myeloma Guidelines from Version 1.2011 include:

AMYL-1

- **Initial diagnostic workup:**
  - **This section has been reorganized.**
  - **Added "Mass spectometry as clinically indicated."**
  - **Added "Nerve conduction studies."**
  - **Added footnotes a and b:**
    - **Footnote a: "It is essential to confirm that patients have primary systemic amyloidosis rather than hereditary amyloidosis, senile amyloidosis or secondary amyloidosis. The amyloid deposits should be confirmed to be composed of light chains using immunohistochemistry or mass spectrometry. Immunohistochemistry for transthyretin or serum amyloid A component should be performed if kappa and lambda stains are negative."**
    - **Footnote b: "Identification of light chains in the serum or urine without confirmation of the amyloid composition in tissue is not adequate as patients with other forms of amyloidosis may have an unrelated MGUS. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002;346:1786-1791."**

AMYL-2

- **Clinical findings:**
  - **Organ involvement based on amyloidosis consensus criteria.**
  - **Added "Bortezomib[d] /melphalan/dexamethasone."**
  - **Deleted "Intermediate dose melaphalan."**
  - **Added footnotes c and e:**
    - **Footnote c: "See Organ Involvement and Response to Treatment Based on Amyloidosis Consensus Criteria (AMYL-A)."**
    - **Footnote e: "The dose of melphalan as part of stem cell transplantation can be adjusted based on factors such as age, presence/absence of cardiac involvement and number of organs involved. These risk-adapted approaches have not been evaluated in randomized studies.Skinner M, Sanchorawala V, Seldin D, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93.**
      Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant 2004;34:1025-1031.
      Perfetti V, Siena S, Palladini G, et al. Long-term results of a risk-adapted approach to melphalan conditioning in autologous peripheral blood stem cell transplantation for primary (AL) amyloidosis. Haematologica 2006;91:1635-1643."

AMYL-A

- **Added a new page: "Organ Involvement and Response to Treatment Based On Amyloidosis Consensus Criteria."**

DISCUSSION

- **The discussion section has been updated to reflect the changes in the algorithm.**

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INITIAL DIAGNOSTIC WORKUP

Clinical and amyloid-related assessment:
- Orthostatic vital signs
- History and physical

Laboratory evaluation (directed toward commonly affected organ systems):
- CBC with differential
- Prothrombin time (PT), Partial thromboplastin time (PTT), Factor X (if indicated)
- Hereditary amyloid testing (for African-American and peripheral neuropathy patients at minimum)
- Electrophoresis of serum and urine
- Immunoelectrophoresis serum and urine
- Serum free light chains
- 24 hour urinary protein and creatinine clearance
- Blood urea nitrogen, creatinine
- Brain natriuretic peptide (BNP), troponin, NT-proBNP
- Alkaline phosphatase, liver enzymes, bilirubin

Pathologic evaluation: [a,b]
- Bone marrow aspirate and biopsy with immunohistochemical staining for kappa and lambda and Congo red staining for amyloid
- Abdominal fat pad aspirate or involved organ biopsy as clinically indicated
- Mass spectrometry as clinically indicated

Special testing based on organ system involvement:
- Cardiac
  - EKG
  - Echocardiogram
  - Cardiac MRI (in certain circumstances)
  - Chest x-ray
- Liver and GI tract
  - Stool guaiacs
  - Gastric emptying scan (if gastroparesis present)
  - Ultrasound or CT scan to document craniocaudal liver span
- Peripheral Nervous System
  - EMG (if clinically significant peripheral neuropathy)
  - Nerve conduction studies
- Other
  - Endocrine testing: TSH, cortisol
  - Pulmonary testing: Pulmonary function tests

→ See Clinical Findings (AMYL-2)

[a] It is essential to confirm that patients have primary systemic amyloidosis rather than hereditary amyloidosis, senile amyloidosis or secondary amyloidosis. The amyloid deposits should be confirmed to be composed of light chains using immunohistochemistry or mass spectrometry. Immunohistochemistry for transthyretin or serum amyloid A component should be performed if kappa and lambda stains are negative.

[b] Identification of light chains in the serum or urine without confirmation of the amyloid composition in tissue is not adequate as patients with other forms of amyloidosis may have an unrelated MGUS. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002;346:1786-1791.

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CLINICAL FINDINGS	PRIMARY TREATMENT[c]
Organ involvement based on amyloidosis consensus criteria[c] →	**There are insufficient data to indicate the optimal treatment of amyloidosis and, therefore, all patients should be treated in the context of a clinical trial when possible.** **Options include:** • **Bortezomib[d] ± dexamethasone** • **Bortezomib[d] /melphalan/dexamethasone** • **Dexamethasone/alpha-interferon** • **Cyclophosphamide/thalidomide/dexamethasone** • **High-dose melphalan[e] with stem cell transplant** • **Lenalidomide/dexamethasone** • **Oral melphalan/dexamethasone** • **Thalidomide/dexamethasone** • **Best supportive care**

[c] See Organ Involvement and Response to Treatment Based on Amyloidosis Consensus Criteria (AMYL-A).

[d] Recommend herpes zoster prophylaxis for patients treated with bortezomib.

[e] The dose of melphalan as part of stem cell transplantation can be adjusted based on factors such as age, presence/absence of cardiac involvement and number of organs involved. These risk-adapted approaches have not been evaluated in randomized studies. Skinner M, Sanchorawala V, Seldin D, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93.
Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant 2004;34:1025-1031.
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ORGAN INVOLVEMENT AND RESPONSE TO TREATMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA (1 OF 2)

Organ Involvement

Kidney	**24-hr urine protein >0.5 g/day, predominantly albumin**
Heart	**Echo: mean wall thickness >12 mm, no other cardiac cause or an elevated NT-ProBNP (>332 ng/l) in the absence of renal failure or atrial fibrillation**
Liver	**Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal**
Nerve	**Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy** **Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration**
Gastrointestinal tract	**Direct biopsy verification with symptoms**
Lung	**Direct biopsy verification with symptoms** **Interstitial radiographic pattern**
Soft tissue	**Tongue enlargement, clinical** **Arthropathy** **Claudication, presumed vascular amyloid** **Skin** **Myopathy by biopsy or pseudohypertrophy** **Lymph node (may be localized)** **Carpal tunnel syndrome**

Revised Consensus Criteria for amyloidosis involvement from XII International Symposium on Amyloidosis:

Gertz M and Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion [abstract]. Amyloid 2010 17(Suppl 1):48-49. (Abstract CP-B).

Gertz M, et al., Definition of Organ Involvement and Treatment Response in Immunoglobulin Light Chain Amyloidosis (AL): A Consensus Opinion From the 10th International Symposium on Amyloid and Amyloidosis. Am J Hematol 2005 79:319-328.

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ORGAN INVOLVEMENT AND RESPONSE TO TREATMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA (1 OF 2)

Hematologic and Organ Response Toxicity

Response	Criteria
Hematologic	
Complete Response	Negative serum and urine immunofixation, normal kappa/lambda free light chain ration, normal bone marrow
Very Good Partial Response	dFLC <40 mg/dL
Partial Response	dFLC decrease ≥50%
No Response	Other
Kidney	50% decrease in24-hour urinary protein excretion in the absence of worsening of creatinine clearance by ≥25% or increase in serum creatinine of ≥0.5 g/dL
Cardiac	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by 2 New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness and/or a decrease in NT-ProBNP of ≥30% (minimum 300 ng/L) in patients with a creatinine clearance of ≥45 ml/min/1.73m^2
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm

Palladini G, et al. Validation of the criteria of response to treatment in AL amyloidosis [Abstract]. Blood 2010 116: Abstract 1364.

Gertz M and Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion [abstract]. Amyloid 2010 17(Suppl 1):48-49. (Abstract CP-B).

Gertz M, et al., Definition of Organ Involvement and Treatment Response in Immunoglobulin Light Chain Amyloidosis (AL): A Consensus Opinion From the 10th International Symposium on Amyloid and Amyloidosis. Am J Hematol 2005 79:319-328.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Primary systemic light chain amyloidosis is typically characterized by decreased numbers of monoclonal plasma cells in the bone marrow compared to multiple myeloma, however, the protein produced by these plasma cells has an affinity for visceral organs (such as kidney, heart, liver, and spleen), and this protein causes related end-organ dysfunction.[1] Even though patients with this disease typically have a low burden of monoclonal plasma cells their survival is often poor due to the end organ damage by the amyloid protein. The therapy of systemic light chain amyloidosis is directed to recovering the function of the target organs by targeting the abnormal plasma cell clone.

Initial Diagnostic Workup

The initial diagnostic workup includes a history and physical (H & P) examination and evaluation of orthostatic vital signs. The following biological assessments are carried out complete blood counts (CBC) with differential and platelets; and blood urea nitrogen (BUN) content, serum creatinine, coagulation studies and electrolytes. Patients with systemic light chain amyloidosis are at risk for developing acquired factor X deficiency due to binding of factor X to amyloid fibrils.[2, 3] This deficiency typically responds to treatment of the underlying amyloidosis.

Screening by serum electrophoresis alone may be inadequate, as it does not show a monoclonal spike in nearly 50% of cases. Therefore, all patients should undergo immunofixation electrophoresis of both serum and urine, which could detect a monoclonal (M-) component. The measurement of circulating serum free light chain (FLC) is a powerful diagnostic complement as the majority of patients with light chain amyloidosis will have abnormalities of the kappa or lambda chains or the kappa/lambda ratio. Additionally the FLC analysis is necessary to determine the hematologic response to therapy. Free light chains are cleared by the kidney therefore renal insufficiency increases the concentrations of FLC. In that case, the kappa/lambda ratio or the difference between involved and uninvolved free light chains should be monitored.[4]

The diagnosis of amyloidosis requires the identification of amyloid deposits in tissues either by aspiration of abdominal subcutaneous fat and/or biopsy of the organs involved and the characterization of amyloidosis as a systemic light chain type requires the demonstration of the underlying plasma cell clone. Amyloid deposits are identified by bone marrow aspiration and biopsy followed by Congo red staining. Congo red staining of the subcutaneous fat aspirate is a reliable and noninvasive test reported to identify amyloid deposits in approximately 90% of patients.[5] The monoclonal plasma cell population can be detected in bone marrow aspirates by immunohistochemical staining of kappa and lambda chains. Immunohistochemistry for transthyretin or

serum amyloid A component should be performed if kappa and lambda stains are negative. The stroma or blood vessels have been reported to be positive for amyloid in 60% of patients.[6] Identification of light chains in the serum or urine without confirmation of the amyloid composition in tissue is not adequate as patients with other forms of amyloidosis may have an unrelated MGUS.[7] Therefore it is essential to confirm that the amyloid deposits are composed of light chains by immunohistochemical methods, electron microscopy or mass spectrometry.[8, 9] The NCCN panel members recommend mass spectometry as clinically indicated.

Since the treatment is different in the various types of amyloidosis, it is essential to confirm that patients have primary systemic amyloidosis rather than hereditary amyloidosis, senile amyloidosis or secondary amyloidosis. Genetic testing especially for African-American and patients with peripheral neuropathy must be done to identify the specific mutation in the hereditary forms and avoid misdiagnosis.[7, 10]

Specialized tests based on organ involvement

A majority of the patients present with one or more organs affected by amyloidosis. The consensus criteria for organ involvement have been recently updated at the 12th International Symposium on Amyloidosis.[11]

Cardiac involvement is diagnosed by imaging techniques such as echocardiography (EKG), echocardiogram, chest x-ray, and cardiac MRI in certain circumstances.

Cardiovascular MRI has been successfully used for the diagnosis and prognosis of amyloid cardiomyopathy.[12] Cardiac biomarkers in the serum provide a quantitative assessment of cardiac dysfunction (troponin I or T) and cardiac stress (brain natriuretic peptide (BNP), and NT-proBNP), and are important predictors of outcome in amyloidosis as well as part of the cardiac response criteria.[13, 14]

Liver and gastrointestinal (GI) involvement is diagnosed by elevated serum alkaline phosphatase levels and bilirubin; performing stool guaiac tests to detect fecal occult blood; gastric emptying scan if gastroparesis is present; and ultrasound or CT scan to determine craniocaudal liver span.

An electromyogram (EMG) or nerve conduction testing can be performed if the patient has significant peripheral neuropathy to confirm peripheral nervous system involvement.

Endocrine tests [thyroid stimulating hormone (TSH) and cortisol levels] and pulmonary function tests may be performed if involvement of the endocrine system or lungs is suspected.

Primary Treatment of Systemic Light Chain Amyloidosis

All current strategies include systemic therapy to destroy the plasma cells responsible for the synthesis of immunoglobulin light chain. Several active regimens are now available for the treatment of systemic light chain amyloidosis. Most are those derived from the treatment of multiple myeloma. The goals of therapy include eliminating the misfolded amyloid light chains as promptly as possible, minimizing treatment toxicity, and supporting the function of the damaged organs. The consensus criteria for hematologic and organ response have been recently updated at the 12th International Symposium on Amyloidosis.[11]

The NCCN panel members recommend that treatment of systemic light chain amyloidosis should be in the context of a clinical trial when possible because data are insufficient to identify optimal treatment of the underlying plasma cell disorder.

High-dose melphalan followed by stem cell transplant (SCT) is one of the therapeutic options listed by the NCCN panel. However, patients

have to be carefully selected as this treatment modality is associated with significant treatment-related mortality.[15-17] The extent of organ involvement is considered as predictor of outcome.[18] In eligible patients, high-dose chemotherapy along with stem cell support has been associated with higher response rates and improved overall survival (OS) than standard chemotherapy.[18] The best outcomes following SCT have been reported in patients who achieve complete response (CR) to high-dose primary chemotherapy[19] including improvement of organ-related disease.[20] There are a number of groups that have evaluated dose-adjustment of the high dose melphalan during a transplant based on factors such as age, number of organs involved and presence or absence of cardiac involvement.[20-22] The reported toxicity of reduced-dose of melphalan is substantially less than high dose.[21] However it should be noted that higher doses of melphalan are associated with a higher CR rate, and improved OS and event-free survival (EFS).[23]

Melphalan and dexamethasone has also been used in the management of systemic light chain amyloidosis. Promising results have been shown in patients with primary amyloidosis who are ineligible for SCT treated with combination of melphalan and high-dose dexamethasone. A small study reported hematologic response in 67% (n = 31) and complete remission in 33% (n = 15) treated with melphalan and high dose dexamethasone in a median of 4.5 months.[24] Improvement in organ function was seen in 48% (n = 22). The updated results reported that CR induced by melphalan and high dose dexamethasone was maintained in 70% of the patients for up to 3 years, survival at a median follow-up of 5 years was about 50%.[25]

The French Myeloma Collaborative Group compared melphalan/dexamethasone to high dose melphalan followed by SCT in a randomized trial and found no significant differences for hematologic or organ responses.[26] In a recent update, with a longer follow-up, the authors found that survival or remission duration were not statistically different between melphalan/dexamethasone versus high dose melphalan followed by SCT even after eliminating treatment related mortality in from SCT arm.[27]

Other treatment options include dexamethasone and alpha-interferon. In a multicenter, cooperative group trial (n = 93), complete hematologic response was seen in 24% and improvement of organ dysfunction in 45% of the evaluable patients; overall median survival was 31 months; and 2-year survival rate was 60%.[28]

Thalidomide in combination with dexamethasone was studied in a small group of patients.[29] Only 11 patients out of the 31 enrolled tolerated 400 mg/day of thalidomide for a median of 5.7 months; 20 patients experienced toxicity of grade 3 or more.[29] This combination although active is associated with substantial toxicity.

Thalidomide has also been combined with cyclophosphamide, and dexamethasone. Wechalekar et al studied the use of oral regimen of cyclophosphamide, thalidomide, and dexamethasone (CTD) in phase II study involving 75 patients with advanced systemic light chain amyloidosis, including 44 patients with clonal relapse after prior therapy.[30] Elderly patients (> 70 years), those with heart failures, and those with significant fluid overload received a risk attenuated CTD regimen (CTDa). The study reported overall hematologic response in 74% (48 out of 65 evaluable patients treated with either CTD or CTDa), including complete responses in 21% (n = 14) and partial responses in 53% (n = 34). About 8% (n = 6) discontinued treatment due to toxicities within 8 weeks of initiating therapy. Grade 2 toxicities were reported in 52% (n = 39) of patients and treatment related mortality was 4% (n = 3).[30] Among patients with complete and partial hematologic response,

the three year estimated OS based on the data was 100% and 82% respectively.

Phase II studies have shown lenalidomide in combination with dexamethasone is active in the treatment of patients with systemic light chain amyloidosis, including those with relapsed/refractory disease.[31-33] Common adverse effects reported in patients on the study included rash, cytopenia, and fatigue. The incidence of dermatologic adverse effects with combination of lenalidomide and dexamethasone was found to be higher in patients with amyloidosis compared to those with myeloma.[34] In addition, progressive azotemia has been reported in patients with amyloidosis, warranting careful monitoring of patients on this regimen.[35]

Bortezomib is rapidly active in systemic light chain amyloidosis with high rates of hematologic and organ responses. Clinical studies have reported bortezomib with or without dexamethasone to be active in untreated and relapsed amyloidosis.[36-40] The National Amyloidosis Center in Britain reported on 20 relapsed or refractory patients treated with bortezomib.[37] A hematologic response was seen in 80% (n = 16) of patients, 15% (n = 3) achieved CR and 65 % (n =13) achieved a partial response.[37] In a multicenter phase I/II dose-escalation study of bortezomib, hematologic responses were seen in 15 % (15 out of 30 evaluable pretreated patients) with CR rate of 20% (n = 6).[41] The median time to response was 1.2 months. Although once-weekly and twice-weekly bortezomib was seen to be generally well tolerated in the study, the once-weekly bortezomib regimen was associated with lower neurotoxicity. [41]

Efficacy of bortezomib in association with dexamethasone was also evaluated in small study of 18 patients included those who had relapsed or progressed on prior therapies. Out of 16 evaluable patients, hematologic response was seen in 94% (n = 14) including complete response in 44% (n = 7).[36] A phase II clinical trial studied the bortezomib and dexamethasone adjuvant therapy in 21 patients not achieving a CR post-SCT. At 1 year post-SCT out of 12 evaluable patients, there was an overall response rate of 92% (n= 11), 67% (n = 8) achieved a CR and 50% (n = 6) had organ responses.[42] Data from three international centers from 94 patients (18 previously untreated) treated with bortezomib reported a 71% (67 out of 93 patients) overall response rate with CR in 25% (47% CR was in previously untreated patients).[38]

Combining weekly bortezomib with melphalan in small series of patients yielded hematologic response rates of 94%.[43] Bortezomib in combination with melphalan and dexamethasone was evaluated in a small phase II trial and results with a best-response rate of over 80% and a CR rate of 42%.[44] These encouraging preliminary results and the fact that bortezomib in combination oral melphalan and prednisone has improved survival in patients with myeloma had led to an ongoing phase III trial is comparing bortezomib in combination with melphalan and dexamethasone to melphalan and dexamethasone as frontline therapy in patients with systemic amyloidosis.

Based on the evidence discussed above, the current NCCN guidelines list the following as therapeutic considerations for management of patients with systemic light chain amyloidosis (all category 2A recommendation): high-dose melphalan followed by SCT; oral melphalan and dexamethasone; dexamethasone in combination with alpha-interferon, thalidomide plus dexamethasone, lenalidomide and dexamethasone, bortezomib with or without dexamethasone; bortezomib weekly with melphalan plus dexamethasone; and cyclophosphamide/thalidomide/dexamethasone.

The treatment options are listed alphabetically in the NCCN guidelines and do not indicate or imply preference. As the optimal therapy for systemic light chain amyloidosis still remains unknown, the NCCN panel members strongly encourage treatment in the context of a clinical trial when possible.

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