National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Systemic Light Chain Amyloidosis

Version 2.2023 — November 28, 2022

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Systemic Light Chain Amyloidosis

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See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2023 of the NCCN Guidelines for Systemic Light Chain Amyloidosis from Version 1.2023 include:

MS-1

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

Updates in Version 1.2023 of the NCCN Guidelines for Systemic Light Chain Amyloidosis from Version 1.2022 include:

AMYL-1

- Clinical and amyloid-related assessment, 3rd bullet modified: Whole-body low-dose CT scan *or FDG PET/CT*
- Laboratory evaluation, 11th bullet modified: Coagulation studies as *clinically* indicated
- Footnote b modified: Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If FDG PET/CT or whole-body low-dose CT has been performed, then skeletal survey is not needed. *Refer to NCCN Guidelines for Multiple Myeloma for Principles of Imaging.*
- Footnote h added: Characteristic findings on cardiac MRI: global subendocardial late gadolinium enhancement (subendocardial or transmural involvement) with abnormal myocardial and blood-pool gadolinium kinetics.

AMYL-2

- Footnote modified: In those patients with very low tumor burden induction therapy may not be required. If not a candidate for HCT at initial diagnosis, reassess after ~~2 cycles of~~ initiating systemic therapy.
- Footnote n added: For IgM-related AL amyloidosis, treat underlying lymphoplasmacytic lymphoma/Waldenström macroglobulinemia as outlined in the NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. (Also on **AMYL-A 2 of 5**)

AMYL-A 1 of 5

- General Principles, 2nd bullet removed: Consider oral doxycycline as adjuvant to standard systemic therapy.
- Screening Recommendations, 2nd bullet modified: Test for hepatitis B ~~before starting carfilzomib or daratumumab~~ *as clinically indicated.*
- Bullet removed: Daratumumab may interfere with serologic testing and cause false-positive indirect Coombs test. Type and screen should be performed before using daratumumab.
- Side Effects and Lab Tests
  - 4th bullet added: Renal function should be continuously monitored while on lenalidomide to ensure appropriate dosing
  - 5th bullet added: Type and screen should be performed before using daratumumab. Daratumumab may interfere with serologic testing and cause false-positive indirect Coombs test.
- Dosing and Administration
  - 1st bullet modified: The dose of melphalan as part of HCT can be adjusted based on factors such as age, *renal function*, presence/absence of cardiac involvement, and number of organs involved.
  - 2nd bullet, 2nd sub-bullet modified: ~~Both~~ Weekly ~~and twice-weekly~~ dosing schemas of bortezomib ~~may be appropriate; weekly preferred~~ *are recommended.*

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Updates in Version 1.2023 of the NCCN Guidelines for Systemic Light Chain Amyloidosis from Version 1.2022 include:

AMYL-A 2 of 5

- Primary Therapy for Hematopoietic Cell Transplant (HCT)-Eligible Candidates and Non-Eligible Candidates
  - Table heading modified: (Note: if not a candidate for HCT at initial diagnosis, reassess after ~~2 cycles of~~ *initiating* systemic therapy *based on improvements in functional status and/or organ response*)
  - Other Recommended Regimens:
    - ◊ 4th bullet modified: Bortezomib/melphalan/dexamethasone *(if ineligible for HCT)*
  - The following regimen was moved from Other Recommended Regimens to a new section: Useful in Certain Circumstances
    - ◊ Melphalan/dexamethasone *(if ineligible for HCT)*
- Footnote a added: Consider collection of hematopoietic stem cells, if appropriate.

AMYL-A 3 of 5

- Therapy for Previously Treated Disease:
  - 3rd regimen added: Bortezomib/cyclophosphamide/dexamethasone
  - 4th regimen modified: Ixazomib~~+/-~~ + dexamethasone
- Footnote a added: Consider collection of hematopoietic stem cells, if candidate for HCT.
- Footnote e added: Recommended starting dose of lenalidomide is 10–15 mg.

AMYL-C

- Prognostic Staging System for Light Chain Amyloidosis:
  - CTnT, Value modified: ≥0.025 ~~ng/mL~~ *µ/L*(or hs-cTnT ≥40 pg/mL)
  - Prognostic Variables, 2nd row of table added: Or cnTnI, ≥0.1µ/L
  - NT-ProBNP, Value modified: ≥1,800 ~~pg/mL~~ ng/L
  - Prognostic Variables, 4th row of table added: Or BNP, ≥400 ng/L
  - FLC-diff, Value modified: ≥18 mg/dL *(180 mg/L)*
- Reference added: Muchtar E, Kumar SK, Gertz MA, et al. Staging systems use for risk stratification of systemic amyloidosis in the era of high-sensitivity troponin T assay. Blood 2019;133:763-766.

AMYL-D

- The tables on the page have been reordered.
- Reference 1 and statement added: When FLC ratio is not within the reference range, the uninvolved FLC concentration must be greater than the involved FLC concentration. Palladini G, Schonland SO, Sanchorawala, et al. Clarification on the definition of complete haematologic response in light-chain (AL) amyloidosis. Amyloid 2021 Mar;28:1-2.

ABBR-1

- New section added: Abbreviations

INITIAL DIAGNOSTIC WORKUP[a]

Clinical and amyloid-related assessment

- History and physical (H&P)
- Orthostatic vital signs
- Whole-body low-dose CT scan[b] or FDG PET/CT
- ECG

Laboratory evaluation (directed toward commonly affected organ systems)

- CBC, differential, platelet count
- Peripheral blood smear
- Prothrombin time (PT), partial thromboplastin time (PTT), and Factor X (if indicated)
- Serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin
- Creatinine clearance (calculated or measured directly)
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- NT-proBNP,[c] troponin T (TnT)
- Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin
- Coagulation studies as clinically indicated

Pathologic evaluation[d,e]

- Unilateral bone marrow aspirate + biopsy[f]
- Plasma cell fluorescence in situ hybridization (FISH) on bone marrow
- Abdominal fat pad sampling[g] and/or involved organ biopsy as clinically indicated
- Amyloid tissue subtyping with mass spectrometry

Special testing based on organ system involvement

- Cardiac
  - Echocardiogram with strain assessment to examine longitudinal strain
  - Cardiac MRI (in certain circumstances)[h]
- Liver and GI tract
  - Gastric emptying scan (if gastroparesis present)
  - Abdominal ultrasound or abdominal CT scan to document craniocaudal liver span as clinically indicated
- Peripheral nervous system
  - Electromyography (EMG) (if clinically significant peripheral neuropathy)/nerve conduction studies
- Other
  - Endocrine testing: Thyroid-stimulating hormone (TSH), cortisol
  - Pulmonary testing: Pulmonary function tests
  - Chest CT without contrast as indicated

→ See Clinical Findings (AMYL-2)

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If FDG PET/CT or whole-body low-dose CT has been performed, then skeletal survey is not needed. Refer to NCCN Guidelines for Multiple Myeloma for Principles of Imaging.
[c] If NT-proBNP is not available, BNP can be performed. If troponin T is not available, then troponin I is acceptable.
[d] It is essential to confirm that patients have primary systemic light chain amyloidosis (SLCA) rather than hereditary amyloidosis, wild-type transthyretin-related (ATTR) cardiac 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. 99mTc-pyrophosphate scan can help distinguish cardiac involvement with SLCA from ATTR.
[e] 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 monoclonal gammopathy of undetermined significance (MGUS). Lachmann HJ, et al. N Engl J Med 2002;346:1786-1791.
[f] Congo red staining for amyloid. Congo stain does not differentiate between types of amyloid.
[g] Alternate sites could include rectal or minor salivary gland biopsy.
[h] Characteristic findings on cardiac MRI: global subendocardial late gadolinium enhancement (subendocardial or transmural involvement) with abnormal myocardial and blood-pool gadolinium kinetics.

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CLINICAL FINDINGS	TREATMENT OF NEWLY DIAGNOSED DISEASE[a,i,j]	RELAPSED/REFRACTORY DISEASE[i]
Organ involvement based on amyloidosis consensus criteria[i] → Evaluate for hematopoietic cell transplant (HCT) candidacy[k,l]	Clinical trial or Therapy for newly diagnosed disease[m,n] (see AMYL-A) and Best supportive care See NCCN Guidelines for Palliative Care See NCCN Guidelines for Survivorship	Therapy for relapsed/refractory disease (See AMYL-A) and Best supportive care See NCCN Guidelines for Palliative Care

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[i] See Definition of Organ Involvement and Response to Treatment Based on Amyloidosis Consensus Criteria (AMYL-B).
[j] See Definition of Organ and Hematologic Response and Progression Criteria (AMYL-C).
[k] In those patients with very low tumor burden induction therapy may not be required. If not a candidate for HCT at initial diagnosis, reassess after initiating systemic therapy.
[l] Patients eligible for HCT can elect to collect stem cells and delay transplant to a later line of therapy.
[m] Organ transplant, as clinically indicated.
[n] For IgM-related AL amyloidosis, treat underlying lymphoplasmacytic lymphoma/Waldenström macroglobulinemia as outlined in the NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.

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GENERAL CONSIDERATIONS FOR SYSTEMIC THERAPY FOR SLCA

General Principles
- Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.

Screening Recommendations
- Screen for HIV and hepatitis C, as clinically indicated.
- Test for hepatitis B as clinically indicated.

Prophylaxis Recommendations
- Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.

Side Effects and Lab Tests
- Regimens containing bortezomib are associated with a higher risk of treatment-related peripheral and autonomic neuropathy, especially in those with disease-related baseline neuropathy. Close monitoring or alternative therapies should be considered in some patients.
- Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
- Patients with cardiac amyloid should be carefully monitored while on lenalidomide therapy.
- Renal function should be continuously monitored while on lenalidomide to ensure appropriate dosing.
- Type and screen should be performed before using daratumumab. Daratumumab may interfere with serologic testing and cause a false-positive indirect Coombs test.

Dosing and Administration
- The dose of melphalan as part of HCT can be adjusted based on factors such as age, renal function, presence/absence of cardiac involvement, and number of organs involved. These risk-adapted approaches have not been evaluated in randomized studies.
- Proteasome inhibitors:
  - Subcutaneous bortezomib is the preferred method of administration.
  - Weekly dosing schemas of bortezomib are recommended.
  - Carfilzomib may be used once or twice weekly and at different doses.

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References

PRIMARY THERAPY FOR HEMATOPOIETIC CELL TRANSPLANT (HCT)-ELIGIBLE CANDIDATES[a] AND NON-ELIGIBLE CANDIDATES[b,c] (Order of regimens is alphabetical and does not indicate preference.) (Note: If not a candidate for HCT at initial diagnosis, reassess after initiating systemic therapy based on improvements in functional status and/or organ response.)
Preferred Regimen: • Daratumumab and hyaluronidase-fihj/bortezomib/cyclophosphamide/dexamethasone (category 1)
Other Recommended Regimens: • Bortezomib ± dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/melphalan/dexamethasone (if ineligible for HCT)
Useful in Certain Circumstances: • Melphalan/dexamethasone (if ineligible for HCT)

[a] Consider collection of hematopoetic stem cells, if appropriate.
[b] See General Considerations for Systemic Therapy for SLCA (AMYL-A 1 of 5).
[c] For IgM-related AL amyloidosis, treat underlying lymphoplasmacytic lymphoma/Waldenström macroglobulinemia as outlined in the NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.

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THERAPY FOR PREVIOUSLY TREATED DISEASE[a,b]
Consider repeating initial therapy, especially if relapse-free for several years • **Bortezomib ± dexamethasone** • **Bortezomib/cyclophosphamide/dexamethasone** • **Bortezomib/melphalan/dexamethasone** • **Daratumumab[d]** • **Ixazomib + dexamethasone** • **Ixazomib/lenalidomide/dexamethasone[e]** • **Lenalidomide/cyclophosphamide/dexamethasone[e]** • **Lenalidomide/dexamethasone[e]** • **High-dose melphalan with HCT** • **Melphalan/dexamethasone** • **Pomalidomide/dexamethasone**
Useful in Certain Circumstances • **Bendamustine/dexamethasone** • **Carfilzomib for non-cardiac amyloidosis ± dexamethasone** • **Venetoclax t(11;14) ± dexamethasone**

[a] Consider collection of hematopoetic stem cells, if appropriate.
[b] See General Considerations for Systemic Therapy for SLCA (AMYL-A 1 of 5).
[d] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[e] Recommended starting dose of lenalidomide is 10–15 mg.

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References

SYSTEMIC LIGHT CHAIN AMYLOIDOSIS THERAPY
REFERENCES FOR TREATMENT OPTIONS

- **Bendamustine/dexamethasone**
  - Lentzsch S, Lagos GG, Comenzo RL, et al. Bendamustine with dexamethasone in relapsed/refractory systemic light-chain amyloidosis: Results of a phase II study. J Clin Oncol 2020;38:1455-1462.
- **Bortezomib/cyclophosphamide/dexamethasone**
  - Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood 2012;119:4387-4390.
  - Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012;119:4391-4394.
- **Bortezomib ± dexamethasone**
  - Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood 2011;118:865-873.
  - Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol 2010;28:1031-1037.
  - Singh V, Saad A, Palmer J, et al. Response to bortezomib based induction therapy in newly diagnosed light chain (AL) amyloidosis [abstract]. Blood 2009;114: Abstract 1867.
  - Lamm W, Willenbacher W, Lang A, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. Ann Hematol 2011;90:201-206.
  - Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood 2009;114:1489-1497.
- **Bortezomib/lenalidomide/dexamethasone**
  - Kastritis E, Dialoupi I, Gavriatopoulou M, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. Blood Adv 2019;3:3002-3009.
- **Bortezomib/melphalan/dexamethasone**
  - Gasparetto C, Sanchorawala V, Snyder RM, et al. Use of melphalan (M)/dexamethasone (D)/bortezomib in AL amyloidosis [abstract]. J Clin Oncol 2010;28:Abstract 8024.
- **Carfilzomib/dexamethasone**
  - Manwani R, Mahmood S, Sachchithanantham S, et al. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with peripheral and autonomic neuropathy. Br J Haematol 2019;187:638-641.
- **Daratumumab**
  - Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017;130:900-902.
- **Daratumumab and hyaluronidase-fihj/bortezomib/cyclophosphamide/dexamethasone**
  - Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood 2020;136:71-80.

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SYSTEMIC LIGHT CHAIN AMYLOIDOSIS THERAPY
REFERENCES FOR TREATMENT OPTIONS

- **High-dose melphalan with HCT**
  - 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.
  - D'Souza A, Dispenzieri A, Wirk B, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: A center for international blood and marrow transplant research study. J Clin Oncol 2015;33:3741-3749.
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- **Ixazomib + dexamethasone**
  - Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood 2017;130:597-605.
- **Ixazomib/lenalidomide/dexamethasone**
  - Cohen OC, Sharpley F, Gilmore JD, et al. Use of ixazomib, lenalidomide and dexamethasone in patients with relapsed amyloid light-chain amyloidosis. Br J Haematol 2020;189:643-649.
- **Lenalidomide/cyclophosphamide/dexamethasone**
  - Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood 2012;119:4860-4867.
  - Palladini G, Russo P, Milani P, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. Haematologica 2013;98:433-436.
- **Lenalidomide/dexamethasone**
  - Sanchorawala V, Wright D, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007;109:492-496.
  - Dispenzieri A, Lacy M, Zeldenrust S, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109:465-470.
  - Dispenzieri A, Lacy M, Zeldenrust S, et al. Long term follow-up of patients with immunoglobulin light chain amyloidosis treated with lenalidomide and dexamethasone [abstract] Blood 2008;112: Abstract 1737.
- **Oral melphalan/dexamethasone**
  - Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007;110:787-788.
  - Jaccard A, Leblond V, Royer B, et al. Autologous stem cell transplantation (ASCT) versus oral melphalan and high-dose dexamethasone in patients with AL (primary) amyloidosis: long term follow-up of the French multicentric randomized trial [abstract]. Blood 2010;116: Abstract 1344.
- **Pomalidomide/dexamethasone**
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  - Sanchorawala V, Shelton A, Lo S, et al. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: Results of a phase 1 and 2 trial. Blood 2016;128:1059-1062.
- **Venetoclax/dexamethasone**
  - Premkumar VJ, Lentzsch, Pan S, et al. Venetoclax induces deep hematologic remissions in t(11;14) relapsed/refractory AL amyloidosis. Blood Cancer J 2021;11:10.

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DEFINITION OF ORGAN INVOLVEMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA[1]

Organ Involvement

Kidney	**24-h urine protein >0.5 g/d, 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).

[1] Adapted with permission from John Wiley and Sons, Inc. Gertz M, Comenzo R, Fermand JP, 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, Tours, France,18-22 April 2004. Am J Hematol 2005;79:319-328. Copyright (2005).

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PROGNOSTIC STAGING SYSTEM FOR LIGHT CHAIN AMYLOIDOSIS

Prognostic Variables	Value	Assigned Prognostic Variable Score
cTnT	≥0.025 µ/L(or hs-cTnT ≥40 pg/mL)	1
Or cTnI	≥0.1 µ/L	
NT-ProBNP	≥1,800 ng/L	1
Or BNP	≥400 ng/L	
FLC-diff	≥18 mg/dL (180 mg/L)	1

REVISED STAGING SYSTEM BASED ON THE ABOVE THREE PROGNOSTIC SCORES

Total Prognostic Score	Stage
0	Stage I
1	Stage II
2	Stage III
3	Stage IV

References:
[1] Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012;30:989-995.
[2] Muchtar E, Kumar SK, Gertz MA, et al. Staging systems use for risk stratification of systemic amyloidosis in the era of high-sensitivity troponin T assay. Blood 2019;133:763-766.

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DEFINITION OF ORGAN AND HEMATOLOGIC RESPONSE AND PROGRESSION CRITERIA

Hematologic Response and Progression Criteria[1]

Response Category	Criteria
Complete	Normalization of the FLC levels and ratio,[2] negative serum and urine immunofixation
Very good partial	Reduction in the dFLC to <40 mg/L
Partial	A greater than 50% reduction in the dFLC
No response	Less than a PR
Progression	From CR, any detectable monoclonal protein or abnormal FLC ratio (light chain must double) From PR, 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/d (a visible peak must be present) Serum-FLC increase of 50% to >100 mg/L

Abbreviations: CR, complete response; dFLC, difference between involved FLC and uninvolved FLC; FLC, free light chain; PR, partial response.

Organ Response and Progression Criteria

Organ	Response	Progression
Heart[1]	NT-proBNP response (>30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥650 ng/L) or NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP progression (>30% and >300 ng/L increase)[a] or cTnT progression (≥33% increase) or Ejection fraction progression (≥10% decrease)
Kidney[3]	≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of renal progression	≥25% decrease in eGFR
Liver[1]	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[2]	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity

Abbreviations: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; cTnT, cardiac troponin; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

[a] Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

[1] Reproduced with permission from Springer Nature: Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 2012;26:2317-2325. Copyright (2012).

[2] When FLC ratio is not within the reference range, the uninvolved FLC concentration must be greater than the involved FLC concentration. Palladini G, Schonland SO, Sanchorawala, et al. Clarification on the definition of complete haematologic response in light-chain (AL) amyloidosis. Amyloid 2021;28:1-2.

[3] Adapted with permission from the American Society of Hematology: Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 2014;124:2325-2332.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ABBREVIATIONS

AL	light chain amyloidosis
ATTR	amyloid transthyretin
BNP	brain natriuretic peptide
BUN	blood urea nitrogen
CBC	complete blood count
CR	complete response
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
dFLC	difference between involved FLC and uninvolved FLC
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDG	fluorodeoxyglucose
FLC	free light chain
FLC-diff	free light chain difference
GI	gastrointestinal
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
hs-cTnT	high sensitivity cardiac troponin T
IgM	immunoglobulin M
LDH	lactate dehydrogenase
M protein	monoclonal protein
MRI	magnetic resonance imaging
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PET	positron emission tomography
PR	partial response
SLCA	systemic light chain amyloidosis
99mTc	Technetium-99m

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Systemic Light Chain Amyloidosis

Discussion

This discussion corresponds to the NCCN Guidelines for Systemic Light Chain Amyloidosis (Last updated: November 28, 2022)

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NCCN Guidelines Version 2.2023
Systemic Light Chain Amyloidosis

Overview

Primary systemic light chain amyloidosis (SLCA) in contrast to multiple myeloma is typically characterized by low burden of monoclonal plasma cells in the bone marrow. The abnormal plasma cells produce light chains that get converted to amyloid fibrils that have an affinity for visceral organs (such as the kidney, heart, gastrointestinal [GI] tract, liver, spleen, and nervous system) and cause related end-organ dysfunction.[1]

The therapy for SLCA is directed to recovering the function of the affected organs by targeting the abnormal plasma cell clone and slowing deposition of harmful amyloid fibrils. Around 69% of newly diagnosed patients have more than one organ involved at the time of diagnosis. According to data from the U.S. claims database, the incidence of amyloidosis seems to range from 9 to 14 cases per million person-years.[2] Due to earlier diagnosis, newer therapies that provide deeper responses, and better selection of candidate patients for autologous hematopoietic cell transplant (HCT) consolidation, the early mortality rates (including transplant-related mortality) of patients with SLCA have decreased and survival has improved.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for SLCA, an electronic search of the PubMed database was performed to obtain key literature in SLCA, using the following search terms: Systemic Light Chain Amyloidosis and Amyloidosis. The PubMed database was chosen as it is the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[3]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The results of the PubMed search were examined for their potential relevance. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Initial Diagnostic Workup

The workup of patients with suspected amyloidosis is geared towards demonstration of the amyloid protein in tissue, identification of the protein of origin, and in the setting of light chain amyloidosis demonstration of the monoclonal plasma cell disorder. Subsequent workup is geared towards identifying the organs involved and the severity of organ involvement and assessment of the feasibility and safety of different treatment approaches.

Clinical and Amyloid-Related Assessment

The initial diagnostic workup includes a detailed history and physical (H&P) examination, evaluation of orthostatic vital signs, and careful evaluation for the pathognomonic signs of amyloidosis.

Laboratory Evaluation

The laboratory evaluation begins with complete blood counts (CBCs) with differential including platelet counts.

Screening by serum and urine protein electrophoresis (SPEP and UPEP) alone may not be adequate, as it does not show a monoclonal spike in

nearly 50% of cases. Therefore, serum immunofixation electrophoresis (SIPE) and 24-hour urine immunofixation electrophoresis (UIPE) is essential and along with serum free light chain (FLC) ratio analysis. The measurement of circulating serum FLC is a diagnostic necessity, as the majority of patients with light chain amyloidosis will have immunoglobulin abnormalities of the kappa or lambda chains or the kappa/lambda ratio.[4] The workup should also include urinalysis with quantification of proteinuria by 24-hour urine collection and measurement of creatinine clearance. FLCs 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 FLCs should be monitored.[4] In the setting of a monoclonal process, imaging with whole-body low-dose CT scan or FDG PET/CT can detect osteolytic bone lesions. A skeletal survey is acceptable in certain circumstances (ie, limited access to health care resources), but it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If FDG PET/CT or whole-body low-dose CT has been performed, then a skeletal survey is not needed.

Pathologic Evaluation

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. Characterization of amyloidosis as a systemic light chain type requires the demonstration of the underlying plasma cell clone. Therefore, identification of FLCs in the serum or urine must be followed by confirmation of amyloid in the tissue by pathologic evaluation.

Congo red staining of the subcutaneous fat aspirate is a reliable and noninvasive test reported to identify amyloid deposits in approximately 85% of patients.[5,6] Amyloid deposits can be identified by bone marrow aspiration and biopsy followed by Congo red staining. The monoclonal plasma cell population can be detected in bone marrow aspirates by immunohistochemical staining of kappa and lambda chains. Immunohistochemistry for transthyretin or the 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.[7]

Identification of FLCs 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 monoclonal gammopathy of undetermined significance (MGUS).[8] Therefore, it is essential to confirm that the amyloid deposits are composed of light chains by immunohistochemical methods, electron microscopy, or mass spectrometry.[9-11] Mass spectroscopy has a higher diagnostic accuracy compared to immunohistochemistry in identifying the protein subunit and is considered the gold standard to confirm light chain amyloid (AL) subtype.[12]

If fat pad aspirate and bone marrow biopsy are negative and amyloidosis is still suspected, then the affected organs (eg, kidney, liver, heart) should be evaluated.

Tests to assess renal function such as serum blood urea nitrogen (BUN) content, serum creatinine, creatinine clearance (calculated or measured directly), electrolytes, albumin, calcium, serum uric acid, serum lactate dehydrogenase (LDH), and beta-2 microglobulin are also recommended by the NCCN panel. Liver function evaluation tests recommended by the panel include alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin.

Electrocardiogram may demonstrate low voltages and rhythm abnormalities. Cardiac biomarkers in the serum provide a quantitative assessment of cardiac dysfunction (troponin I or T), and cardiac stress brain natriuretic peptide (BNP) or N-terminal prohormone of brain

natriuretic peptide (NT-proBNP) are important predictors of outcome in amyloidosis as well as part of the cardiac response criteria.[13,14] The NCCN panel recommends assessing BNP if NT-proBNP assessment is not available. If troponin T is not available, then troponin I is acceptable.

The panel also recommends performing coagulation studies as clinically indicated. Patients with SLCA are at risk of developing acquired factor X deficiency due to binding of factor X to amyloid fibrils.[15,16] This deficiency typically responds to treatment of the underlying amyloidosis. To determine if factor X is involved, prolonged thromboplastin time (PT) and activated prolonged partial thromboplastin time (PTT) tests may be performed. 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. 99mTc-pyrophosphate scan can help distinguish cardiac involvement with AL from amyloid transthyretin (ATTR).

Since the treatment is different in the various types of amyloidosis, it is essential to confirm that patients have light chain amyloidosis (AL) rather than hereditary amyloidosis, senile amyloidosis, or secondary amyloidosis. Genetic testing, especially for African American patients and patients with peripheral neuropathy, must be done to identify the specific mutation in the hereditary forms and avoid misdiagnosis.[17,18]

Specialized Tests Based on Organ Involvement
The majority of patients present with one or more organs affected by amyloidosis.

Cardiac involvement is diagnosed by imaging techniques such as echocardiogram with strain assessment to examine longitudinal strain and cardiovascular MRI in certain circumstances. Cardiovascular MRI has been successfully used for the diagnosis and prognosis of amyloid cardiomyopathy.[19] Characteristic findings on cardiac MRI include global subendocardial late gadolinium enhancement (subendocardial or transmural involvement) with abnormal myocardial and blood-pool gadolinium kinetics.

Liver and GI involvement may be confirmed by performing a gastric emptying scan if gastroparesis is present; and abdominal ultrasound or CT scan as clinically indicated to determine craniocaudal liver span. Endoscopy with random biopsies of suspected affected portions to confirm AL involvement of the GI tract can be extremely helpful in establishing the presence of deposits.

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 and cortisol levels) and pulmonary function tests may be performed if involvement of the endocrine system or lungs is suspected. Chest CT without contrast may be performed if clinically indicated.

Staging

While multiple prognostic models have been proposed for patients with amyloidosis, the NCCN panel recommends use of a staging system that incorporates NT-proBNP ≥1800 ng/L (or BNP ≥400 ng/L), cTnT ≥0.025 µ/L (or cardiac troponin I [cTnI] ≥ 0.1 µ/L), and the difference between involved and uninvolved serum free light chains (dFLC) ≥18 mg/dL as risk factors.[20,21]

Patients with no risk factors are classified as stage I, those with one elevated risk factor as stage II, those with two elevated risk factors as stage III, and those with three elevated risk factors as stage IV. For patients classified as having stage I, II, III, or IV disease, the median

overall survival (OS) from diagnosis is 94, 40, 14, and 6 months, respectively.[20]

Organ Involvement and Response to Treatment

The first international consensus opinion for the definition of organ involvement and response to treatment for SLCA was published in 2005.[22] These criteria have since been updated,[23,24] and the tables with definitions for hematologic and organ involvement and criteria for response to treatment are included in the NCCN Guidelines algorithms. It is important to note that the definition of complete response (CR) has been updated to highlight that beyond the need for having negative amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) in immunofixation electrophoresis of both serum and urine, either an FLC ratio within the reference range or the uninvolved FLC concentration greater than involved FLC concentration with or without an abnormal FLC ratio is acceptable.[25]

Treatment of Newly Diagnosed SLCA

All patients with newly diagnosed SLCA should be assessed for autologous HCT eligibility.[26,27] Those with low tumor burden can proceed to receive HCT immediately. Those who are not eligible for HCT due to high tumor burden may receive systemic therapy first, and their eligibility for transplant may be assessed after initiating systemic therapy based on improvements in functional status and/or organ response. The NCCN panel members recommend that treatment of SLCA 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.

All current strategies include systemic therapy to destroy the plasma cells responsible for the synthesis of immunoglobulin light chains. Several active regimens are available for the treatment of SLCA. Most are 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 were updated at the 12th International Symposium on Amyloidosis.[23]

The preferred primary treatment for patients with SLCA is in a clinical trial, and participation in clinical trials should be encouraged.

Primary Therapy for SLCA

Preferred Regimen for Primary Treatment of SLCA
Daratumumab and Hyaluronidase in Combination with Bortezomib/Cyclophosphamide/Dexamethasone

Data supporting the use of this regimen come from a phase 3 trial (ANDROMEDA) in which patients (n = 388) with newly diagnosed amyloidosis were randomized to receive six cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) with or without subcutaneous daratumumab (daratumumab and hyaluronidase).[28,29]

Those receiving subcutaneous daratumumab as part of their regimen received single-agent daratumumab monthly as maintenance therapy for up to 2 years. After a median follow-up of 11.4 months, the addition of daratumumab to CyBorD resulted in higher rates of hematologic CR (53% vs. 18%), cardiac response (42% vs. 22%), and renal response (53% vs. 24%). The addition of daratumumab also delayed major organ deterioration, hematologic progression, and death (hazard ratio [HR], 0.58; 95% CI, 0.36–0.93).[29] The most common grade 3 or 4 adverse events in the daratumumab arm compared with the control arm were lymphopenia (13.0% vs. 10.1%), pneumonia (7.8% vs. 4.3%), cardiac failure (6.2% vs. 4.8%), and diarrhea (5.7% vs. 3.7%).[29] The U.S. Food and Drug Administration (FDA) has approved this regimen for patients with SLCA.

The NCCN panel has included daratumumab and hyaluronidase in combination with CyBorD as a category 1, preferred as primary therapy option for patients with SLCA.

Other Recommended Regimens for Primary Treatment of SLCA

Bortezomib/Cyclophosphamide/Dexamethasone

The CyBorD regimen was reported to have high hematologic response rates and CR in two independent studies.[30,31] In one study, 17 patients (including 10 who did not receive any prior therapy) treated with CyBorD achieved a hematologic response of 94% and a CR rate of 71%.[30] The median duration of response was 22 months. Organ response was observed in 50% of the patients with renal involvement. Three patients originally ineligible for autologous HCT became eligible after treatment with CyBorD.[30] In another study, 43 patients (including 20 who did not receive any prior therapy) were treated with biweekly administration of CyBorD.[31] The hematologic response rate was 81.4% with a CR rate of 41.9%. A small retrospective study of patients newly diagnosed with systemic amyloidosis and multiple myeloma treated with the CyBorD regimen containing subcutaneous bortezomib reported a high response rate and minimal toxicity.[32] A survey of European centers using CyBorD in newly diagnosed patients reported a response rate of 60%.[33]

Bortezomib with or without Dexamethasone

Clinical studies have reported bortezomib with or without dexamethasone to be active as primary treatment as well as for relapsed amyloidosis.[34-37]

In a study comparing two doses of bortezomib, it was seen that bortezomib is well tolerated at doses up to 1.6 mg/m^2 on a once-weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule.[38] Although once-weekly and twice-weekly bortezomib were seen to be generally well tolerated, those on the once-weekly bortezomib regimen had lower neurotoxicity.[38] After 51.8 months of median follow-up, the median OS for all patients was 62.7 months,[39] suggesting that achievement of organ response has a positive impact on OS.

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% of patients (47% CR was in previously untreated patients).[34] In another study, 26 patients (18 who did not receive any prior therapy) were treated with the combination of bortezomib/dexamethasone. The overall response rate was 54%, with a 31% CR rate.[36]

The combination of bortezomib and dexamethasone was studied as consolidation therapy in patients after HCT to see whether depth of response can be improved. At 24 months, greater than 60% had a partial response (PR), 40% had a CR, and organ responses were seen in 70% of patients.[40] The OS at 12 months was 88% and 82% at 24 months.[40]

Bortezomib/Melphalan/Dexamethasone (if ineligible for HCT)

Combining weekly bortezomib with melphalan in a small series of patients has yielded hematologic response rates of 94%.[41] Bortezomib in combination with melphalan and dexamethasone was evaluated in a small phase II trial, and resulted in a best-response rate of over 80% and a CR rate of 42%.[42]

Data supporting the use of this regimen are from a phase III trial of transplant-ineligible patients (n = 109) with SLCA who were randomly assigned to receive primary therapy with bortezomib/melphalan/dexamethasone versus melphalan/dexamethasone.[43] Hematologic response at 3 months was 79% vs. 52%; very good partial response [VGPR] plus CR rate (64% vs. 39%) and superior OS (median OS not reached vs. 34 months; HR, 0.50; 95% CI, 0.27–0.90). The rates of peripheral neuropathy were lower with subcutaneous bortezomib compared with intravenous bortezomib.[43]

The NCCN panel has included bortezomib/melphalan/dexamethasone as an option under “other recommended regimens” for those not eligible for HCT.

Bortezomib/Lenalidomide/Dexamethasone
Bortezomib/lenalidomide/dexamethasone is widely used in newly diagnosed patients with multiple myeloma and has been associated with high response rates in newly diagnosed patients with systemic amyloidosis.[44] A study compared bortezomib/lenalidomide/dexamethasone to CyBorD and found that bortezomib/lenalidomide/dexamethasone induced rapid and deeper responses compared to CyBorD. However, there was a risk of increased toxicities with this regimen including rash, infections, constipation, and peripheral neuropathy.

Useful in Certain Circumstances for Primary Treatment of SLCA
Oral Melphalan/Dexamethasone (if ineligible for HCT)
Hematologic response rates of up to 76% have been reported with oral melphalan/dexamethasone in transplant ineligible patients.[45] The NCCN panel has included oral melphalan/dexamethasone as an option for patients with SLCA who are not candidates for HCT.

Therapy for Previously Treated SLCA

There are no clinical trial data to determine the appropriate regimens for previously treated SLCA. The treatment would depend on prior therapy received, patient preferences, and toxicity profile. The NCCN panel recommends considering repeating the initial therapy, especially if the patient has no relapse of disease for several years.

Bortezomib with or without Dexamethasone
As mentioned in the primary therapy section, studies have shown that bortezomib with or without dexamethasone has activity in both untreated as well as relapsed amyloidosis.[34,35,46]

In the relapsed setting only, a small study of patients (n = 18) with relapsed or progressive amyloidosis on prior therapies showed hematologic response in 94% (n = 14) including CR in 44% (n = 7)[46] when treated with bortezomib/dexamethasone. The National Amyloidosis Center in Britain conducted a study of patients (n = 20) with relapsed or refractory SLCA treated with bortezomib, and reported a hematologic response in 80% (n = 16), of which 15% (n = 3) achieved a CR and 65% (n =13) achieved a PR.[35] In another multicenter phase I/II dose-escalation study of bortezomib, hematologic responses were seen in 15% of patients (15 out of 30 evaluable pretreated patients) with a CR rate of 20% (n = 6).[47]

Bortezomib/Cyclophosphamide/Dexamethasone
Studies of CyBorD in patients with SLCA have included newly diagnosed and relapsed/refractory patients.[30,31,33]

The NCCN panel notes that patients on regimens containing bortezomib are associated with a higher risk of treatment-related peripheral and autonomic neuropathy, especially in those with disease-related baseline neuropathy. Therefore, close monitoring, judicious dosing, or alternative therapies should be considered in some patients.

Bortezomib/Melphalan/Dexamethasone
A multicenter, randomized, controlled, open-label clinical trial assessed the efficacy of bortezomib/melphalan/dexamethasone compared with melphalan/dexamethasone in previously untreated patients (n = 109) with SLCA who were not candidates for HCT.[43] Hematologic response rate at 3 months was higher in the bortezomib arm (79% vs. 52%; $P = .002$). Also, higher overall response rates (64% vs. 39%; HR, 2.47; 95% CI, 1.30–4.71) and improved OS with a 2-fold decrease in mortality rate (HR, 0.50; 95% CI, 0.27–0.90) were reported in the bortezomib-containing arm.[43] Grade 3

and 4 adverse events including cytopenia, peripheral neuropathy, and heart failure were more common in the bortezomib arm.

Daratumumab
Daratumumab may be administered subcutaneously (daratumumab 1800 mg with hyaluronidase 30,000 units) or intravenously (daratumumab 16 mg/kg). Subcutaneous administration has fewer infusion-related reactions and a faster administration time. Single-agent daratumumab has been associated with high rates of overall hematologic response (66.6%–90%).[48-50] The toxicity profile is similar to that seen in patients with multiple myeloma; however, the rates of infection are more common in patients with SLCA.[51]

Ixazomib/Dexamethasone
A phase III trial (TOURMALINE-AL1) studied patients (n = 168) with relapsed or refractory SLCA randomized to either ixazomib/dexamethasone or to physician's choice of a non-proteasome inhibitor-containing regimen following 1 to 2 prior lines of therapy.[52] Hematologic response rate was the same, and occurred in 53% of patients treated with ixazomib/dexamethasone and in 51% with physician's choice (*P* = .76). The CR rate was 26% with ixazomib versus 18% (*P* = .22). Median time to vital organ deterioration or mortality was longer with ixazomib at 34.8 versus 26.1 months (HR, 0.53; 95% CI, 0.32–0.87; *P* = .01). Importantly, median treatment duration of patients treated with ixazomib was longer at 11.7 versus 5.0 months. Adverse events included diarrhea (34% vs. 30%), rash (33% vs. 20%), cardiac arrhythmias (26% vs. 15%), and nausea (24% vs. 14%).

Ixazomib/Lenalidomide/Dexamethasone
A phase I/II trial evaluated the outcomes of patients (n = 40) with relapsed SLCA treated with ixazomib/lenalidomide/dexamethasone. Hematologic responses were seen at 3 months in 57.9% of patients. Median progression-free survival (PFS) was 17 months in the overall study patients. In those achieving CR/VGPR, the PFS was further improved to 28.8 months. Serious adverse events were infection (40%), fluid overload (33.3%), cardiac arrhythmia (13.3%), renal dysfunction (6.6%), and anemia (6.6%).[53]

Lenalidomide/Cyclophosphamide/Dexamethasone
In previously treated patients with relapsed SLCA, treatment with lenalidomide/cyclophosphamide/dexamethasone has been shown to produce a response rate of 62%.[54-56]

Lenalidomide/Dexamethasone
Lenalidomide/dexamethasone has also been studied in patients with relapsed/refractory disease.

A phase 2 trial of newly diagnosed patients (n = 23) and patients with relapsed SLCA treated patients with lenalidomide 25 mg and dexamethasone was added if no hematologic response was seen. In this trial, patients who received lenalidomide/dexamethasone had a hematologic response rate of 75%.[57]

The results of another phase 2 trial (n = 34 and 91% of patients had prior therapy) demonstrated that the reduced dose of lenalidomide at 15 mg per day had acceptable toxicity and good hematologic responses.[58] Of the 24 evaluable patients, reduced dose of lenalidomide along with dexamethasone showed an overall hematologic response rate of 67% (29% CR and 38% PR).[58]

In a more recent study, patients (n = 84) previously treated with thalidomide and/or bortezomib were treated with lenalidomide and dexamethasone. The overall hematologic response rate was 61%, including a 20% CR rate. The 2-year OS and PFS rates were reported as 84% and 73%, respectively.[59]

High-Dose Melphalan Followed by HCT

High-dose melphalan followed by HCT is one of the therapeutic options listed in the NCCN Guidelines for SLCA. This treatment modality is associated with significant treatment-related mortality;[60-66] therefore, careful evaluation of patients who are potential candidates is key. The extent of organ involvement is considered a predictor of outcome.[63,64,67]

In eligible patients, high-dose chemotherapy along with HCT has been associated with higher response rates and improved OS than standard chemotherapy.[67] The best outcomes following HCT have been reported in patients who achieve a CR to high-dose primary chemotherapy,[68] including improvement of organ-related disease.[69] The most significant indicator of treatment benefit is the depth of the response to therapy measured by the lowest level of serum FLCs post-transplantation.[70]

There are a number of groups that have evaluated dose adjustment of high-dose melphalan during a transplant based on factors such as age, number of organs involved, and presence or absence of cardiac involvement.[69,71,72] The reported toxicity of reduced-dose melphalan is substantially less than that of high-dose melphalan.[71] Older studies indicated that higher doses of melphalan were associated with a higher CR rate, and improved OS and event-free survival, but these publications occurred during an era where patients received transplant as primary therapy, and those receiving lower doses of melphalan typically had more advanced AL, and thus were destined for inferior outcomes.[73] Over the past decade, transplant-related mortality rates have decreased from 40% to about 7%.[74-76]

A long-term single-center study of the outcomes of patients who underwent treatment with high-dose melphalan followed by HCT reported survival of up to 20 years in 28.6% of patients.[75] While the survival was strongly dependent on achievement of a hematologic CR, those who do not achieve a CR and/or who relapsed after CR also had a survival benefit with HCT.[58]

Melphalan/Dexamethasone

The melphalan/dexamethasone regimen has also been used in the management of SLCA. It has shown promising results in patients with primary amyloidosis who are ineligible for HCT. A small study reported hematologic response in 67% (n = 31) and complete remission in 33% (n = 15) of patients treated with melphalan and high-dose dexamethasone in a median of 4.5 months.[77] Improvement in organ function was seen in 48% (n = 22) of patients. The updated results reported that the CR induced by melphalan and high-dose dexamethasone was maintained in 70% of patients for up to 3 years, and survival at a median follow-up of 5 years was about 50%.[78]

The French Myeloma Collaborative Group compared melphalan and dexamethasone to high-dose melphalan followed by HCT in a randomized trial and found no significant differences for hematologic or organ responses.[79] With a longer follow-up, the authors found that neither survival nor remission duration were statistically different between melphalan and dexamethasone versus high-dose melphalan followed by HCT even after eliminating treatment-related mortality from the HCT arm.[80]

Pomalidomide/Dexamethasone

The safety and efficacy of pomalidomide and dexamethasone were studied in a prospective phase II study.[81] Patients with previously treated SLCA (n = 33) were enrolled in the trial and upon treatment with pomalidomide and dexamethasone, confirmed response was reported in 48% (n = 16) with a median time to response of 1.9 months. The median OS rate was 28 months and PFS rate was 14 months; the OS and PFS rates at one year were 76% and 59%, respectively.

Useful in Certain Circumstances for Previously Treated SLCA

Bendamustine/Dexamethasone

Bendamustine/dexamethasone is for patients who have received multiple prior regimens. A multicenter phase 2 trial evaluated this regimen in patients with persistent or progressive SLCA after at least one prior therapy.[82] Responses (PR or better) were seen in 57% of patients. Seven out of 24 patients with organ involvement had overall organ response. The median PFS and OS were 11.3 months and 18.2 months, respectively. OS was better among those with a hematologic response. The most common adverse events were myelosuppression, fatigue, nausea, and vomiting.[82]

Carfilzomib for Non-cardiac Amyloidosis with or without Dexamethasone

Data from a phase 1/2 study of carfilzomib with patients with relapsed/refractory SLCA showed the maximum tolerated dose to be 36 mg/m^2 twice weekly (after initial 20 mg/m^2 dosing).[83]

Patients in this trial had a hematologic response rate of 63%. Grade 3 or 4 adverse events occurred in 71% of patients with multiple cardiac events, including hypotension, hypertension, decreased ejection fraction, and symptomatic ventricular tachycardia. Eleven patients had worsening of NT-proBNP on carfilzomib, with 5 of those patients developing progressive cardiac dysfunction. Therefore, the NCCN panel has listed carfilzomib as an option for treatment of relapsed/refractory SLCA in select patients with no cardiac involvement.

Venetoclax t(11;14) with or without Dexamethasone

A multicenter, international, retrospective cohort study reported on outcomes of patients (n = 43) with relapsed/refractory SLCA treated with venetoclax-containing regimens.[84] The overall PFS and OS at 12 months were 78% and 93%, respectively. However, in patients (n = 30) harboring t(11;14), median PFS and OS were not reached and 12-month PFS and OS were 90% and 97%, respectively. In comparison, among non-t(11;14) patients (n = 11), 12-month PFS and OS were 45% and 82% respectively. Also, 81% (22 out of 27) of patients with t(11;14) achieved at least a PR and 78% (21 out of 27) achieved a VGPR/CR.[84]

Treatments Targeting Amyloid Fibrils

While prior small studies demonstrated a potential role doxycycline may have in reducing early mortality in cardiac patients when used prophylactically in combination with plasma cell-directed therapy,[85,86] a recent randomized controlled study in China failed to demonstrate a benefit of doxycycline with standard-of-care therapy.[87] A trial of doxycycline versus standard supportive therapy in newly diagnosed cardiac AL amyloidosis patients undergoing bortezomib-based therapy is underway (NCT03474458), and the panel at present cannot recommend the use of amyloid-targeting agents outside the setting of clinical trials.[88]

Summary

The treatment of patients with SLCA has been challenging and has evolved over the years. The clinical manifestations are diverse and diagnosing it accurately and at an early stage are key to improved outcomes. The therapeutic options have expanded significantly and newer therapies are helpful in inducing rapid and deep responses that in turn translate into high rates of organ response. Patients should be treated within clinical trials whenever possible.

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