Primary systemic light chain amyloidosis (SLCA) is characterized by production of light chains that get converted to amyloid fibrils with an affinity for visceral organs and causing organ dysfunction. 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 amyloid fibrils. The NCCN Guidelines for SLCA provide recommendations for workup, diagnosis, and treatment of primary as well as previously treated SLCA.

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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.
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.

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The complete NCCN Guidelines for Systemic Light Chain Amyloidosis are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Systemic Light Chain Amyloidosis Panel
At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest.
NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.
Individual disclosures for the NCCN Systemic Light Chain Amyloidosis Panel members can be found on page 81. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Primary systemic light chain amyloidosis (SLCA), in contrast to multiple myeloma, is typically characterized by a 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 tract, liver, spleen, and nervous system) and cause related end-organ dysfunction. 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 patients with newly diagnosed SLCA have more than one organ involved at the time of diagnosis. According to data from the United States claims database, the incidence of amyloidosis seems to range from 9 to 14 cases per million person-years. Due to earlier diagnosis, newer therapies that provide deeper responses, and better selection of candidates 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.
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. 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. 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.

Identification of FLCs in the serum or urine without confirmation of the amyloid composition in tissue is not adequate, because patients with other forms of amyloidosis may have an unrelated monoclonal gammopathy of undetermined significance. Therefore, it is essential to confirm that the amyloid deposits are composed of light chains by immunohistochemical methods, electron microscopy, or mass spectrometry. Mass spectrometry has a higher diagnostic accuracy compared with immunohistochemistry in identifying the protein subunit and is considered the gold standard to confirm light chain amyloid (AL) subtype. 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 content, serum creatinine, creatinine clearance (calculated or measured directly), electrolytes, albumin, calcium, serum uric acid, serum lactate dehydrogenase, and beta-2 microglobulin are also
recommended by the NCCN panel. Liver function evaluation tests recommended by the panel include alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and bilirubin.

Electrocardiograms may show 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. 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 for developing acquired factor X deficiency due to binding of factor X to amyloid fibrils. This deficiency typically responds to treatment of the underlying amyloidosis. To determine if factor X is involved, prolonged thromboplastin time and activated prolonged partial thromboplastin time 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.

Because 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.

**Specialized Tests Based on Organ Involvement**

Most patients present with one or more organs affected by amyloidosis.

Cardiac involvement is diagnosed using 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. 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 gastrointestinal 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 gastrointestinal tract can be extremely helpful in establishing the presence of deposits.

An electromyogram 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.

**Organ Involvement and Response to Treatment**

The first international consensus opinion for the definition of organ involvement and response to treatment of SLCA was published in 2005. These criteria have since been updated, 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.

**Treatment of Newly Diagnosed SLCA**

All patients with newly diagnosed SLCA should be assessed for autologous HCT eligibility. 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

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| PRIMARY THERAPY FOR HEMATOPOIETIC CELL TRANSPLANT (HCT)-ELIGIBLE CANDIDATES and NON-ELIGIBLE CANDIDATES
| (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 Regimens: | Other Recommended Regimens: |
| • Daratumumab and hyaluronidase-fihj/bortezomib/cyclophosphamide/dexamethasone (category 1) | • Bortezomib 1 dexamethasone |
| • Bortezomib/cyclophosphamide/dexamethasone |
| • Bortezomib/lenalidomide/dexamethasone | • Bortezomib/belimumab/dexamethasone (if ineligible for HCT) |
| • Bortezomib/lenalidomide/cyclophosphamide/dexamethasone |
| Useful in Certain Circumstances: | |
| • Melphalan/dexamethasone (if ineligible for HCT) |

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8 Consider collection of hematopoietic stem cells, if appropriate.
9 See General Considerations for Systemic Therapy for SLCA (AML-Y-A 1 of 5).
10 For IgM-related AL amyloidosis, treat underlying lymphoplasmacytic lymphoma/Waldenström macrophage/Lymphoma as outlined in the NCCN Guidelines for Waldenström Macroglobulinemia/lymphoplasacytic lymphoma.

EAMY-L-A
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Continued References

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therapy based on improvements in functional status and/or organ response. The NCCN panel recommends 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.22

The preferred primary treatment of 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 III trial (ANDROMEDA) in which patients (n=388) with newly diagnosed amyloidosis were randomized to receive 6 cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) with or without subcutaneous daratumumab (daratumumab and hyaluronidase).27,28 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).28 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%).28 The US 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 2 independent studies.29,30
In one study, 17 patients (including 10 who did not receive any prior therapy) treated with CyBorD experienced a hematologic response of 94% and a CR rate of 71%. 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. In another study, 43 patients (including 20 who did not receive any prior therapy) were treated with biweekly administration of CyBorD. 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. A survey of European centers using CyBorD in newly diagnosed patients reported a response rate of 60%.

**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.

Bortezomib was seen to be generally well tolerated, those on the once-weekly bortezomib regimen had lower neurotoxicity. After 51.8 months of median follow-up, the median OS for all patients was 62.7 months, suggesting that achievement of organ response has a positive impact on OS. Data from 3 international centers from 94 patients (18 previously untreated) treated with bortezomib reported a 71% (67 of 93 patients) overall response rate with CR in 25% of patients (47% CR was in previously untreated patients). In another study, 26 patients (18 of whom did not receive any prior therapy) were treated with the combination of bortezomib and dexamethasone. The overall response rate was 54%, with a 31% CR rate. 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, more than 60% had a partial response (PR), 40% had a CR, and organ responses were seen in 70% of patients. The OS at 12 months was 88%, and it was 82% at 24 months.
It resulted in a best-response rate of over 80% and a CR rate of 42%. Data supporting the use of this regimen are from a phase III trial of transplant-ineligible patients with SLCA who were randomly assigned to receive primary therapy with bortezomib/melphalan/dexamethasone versus melphalan/dexamethasone. Hematologic response at 3 months was 79% versus 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.

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 systemic amyloidosis. A study compared bortezomib/lenalidomide/dexamethasone to CyBorD and found that bortezomib/lenalidomide/dexamethasone induced rapid and deeper responses compared with CyBorD. However, there was a risk of increased toxicities with this regimen including rash, infections, constipation, and peripheral neuropathy.

**Systemic Light Chain Amyloidosis Therapy**

**References for Treatment Options**

- **High-dose melphalan with HCT**

- **Bortezomib + dexamethasone**

  - Ixazomib/lenalidomide/dexamethasone
  - Lenalidomide/cyclophosphamide/dexamethasone
  - Lenalidomide/dexamethasone

- **Bortezomib, VD, and RD**

- **Oral melphalan/dexamethasone**

- **Bortezomib With or Without Dexamethasone**

  - Studied in the relapsed setting only, a small study of patients with relapsed or progressive amyloidosis on prior therapies showed hematologic response in 94% of patients.
including CR in 44% (n=7)\(^5\) 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) experienced a CR and 65% (n=13) experienced a PR.\(^3\) In another multicenter phase I/II dose-escalation study of bortezomib, hematologic responses were seen in 50% of patients (15 of 30 evaluable pretreated patients) with a CR rate of 20% (n=6).\(^4\)

### Bortezomib/Cyclophosphamide/Dexamethasone

Studies of CyBorD in patients with SLCA have included those with newly diagnosed and relapsed/refractory disease.\(^2\)\(^9\)\(^3\)\(^0\)\(^3\)\(^2\)

The NCCN panel notes that regimens containing bortezomib are associated with a higher risk of treatment-related peripheral and autonomic neuropathy, especially in patients 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.\(^4\)\(^2\) The 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.\(^4\) 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 1,800 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%).\(^4\)\(^7\)–\(^4\)\(^9\) The toxicity profile is similar to that seen in patients with multiple myeloma; however, infection is more common in patients with SLCA.\(^5\)\(^0\)

### 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 after 1 to 2 prior lines of therapy.\(^5\)\(^1\) 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 for 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/lenanidomide/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 who had CR/VGPR, the PFS was further improved to 28.8 months. Serious adverse events included infection (40%), fluid overload (33.3%), cardiac arrhythmia (13.3%), renal dysfunction (6.6%), and anemia (6.6%).

**Lenalidomide/Dexamethasone**

Lenalidomide/dexamethasone has also been studied in patients with relapsed/refractory disease. A phase II trial of newly diagnosed patients ($n=23$) and patients with relapsed SLCA treated patients with lenalidomide 25 mg. Dexamethasone was added if no hematologic response was seen. In this trial, patients who received lenalidomide/dexamethasone had a hematologic response rate of 75%. 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). 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.

**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%. Lenalidomide/cyclophosphamide/dexamethasone is one of the therapeutic options listed in the NCCN Guidelines for SLCA. This treatment modality is associated with significant...
treatment-related mortality; therefore, careful evaluation of patients who are potential candidates is key. The extent of organ involvement is considered a predictor of outcome.

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

A number of groups have evaluated dose adjustment of high-dose melphalan during transplant based on factors such as age, number of organs involved, and presence or absence of cardiac involvement. 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 in which 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. Over the past decade, transplant-related mortality rates have decreased from 40% to about 7%; therefore, careful evaluation of patients who are potential candidates is key. The extent of organ involvement is considered a predictor of outcome.

A long-term single-center study of outcomes for patients who underwent treatment with high-dose melphalan followed by HCT reported survival of up to 20 years in 28.6% of patients. Although survival was strongly dependent on experience of a hematologic CR, those who did not experience CR and/or who had relapse after CR also had a survival benefit with HCT.

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. 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%.

<table>
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<tr>
<td>Heart1</td>
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<td>Kidney3</td>
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<td>Peripheral nervous system2</td>
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Abbreviations: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; cTNT, cardiac troponin T; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

1 Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.
2 When FLC ratio is not within the reference range, the uninvolved FLC concentration must be greater than the involved FLC concentration.
between melphalan and dexamethasone versus high-dose melphalan followed by HCT even after eliminating treatment-related mortality from the HCT arm.79

Pomalidomide/Dexamethasone

The safety and efficacy of pomalidomide and dexamethasone were studied in a prospective phase II study.80 Patients with previously treated SLCA (n = 33) were enrolled in the trial and on 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 1 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 II trial evaluated this regimen in patients with persistent or progressive SLCA after at least 1 prior therapy.81 Responses (PR or better) were seen in 57% of patients. Seven 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.81

Carfilzomib for Non-cardiac Amyloidosis With or Without Dexamethasone

Data from a phase I/II study of carfilzomib with patients with relapsed/refractory SLCA showed the maximum tolerated dose to be 36 mg/m² twice weekly (after initial 20 mg/m² dosing).82 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.83 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 patients without t(11;14) (n = 11), 12-month PFS and OS were 45% and 82%, respectively. Also, 81% (22 of 27) of patients with t(11;14) experienced at least a PR and 78% (21 of 27) experienced a VGPR/CR.83

Treatments Targeting Amyloid Fibrils

Although 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,84 a recent randomized controlled study in China failed to demonstrate a benefit of doxycycline with standard-of-care therapy.86 A trial of doxycycline versus standard supportive therapy in patients with newly diagnosed cardiac AL amyloidosis who are undergoing bortezomib-based therapy is underway (ClinicalTrials.gov identifier: NCT03474458), and the panel at present cannot recommend the use of amyloid-targeting agents outside the setting of clinical trials.87

Summary

The treatment of patients with SLCA has been challenging and has evolved over the years. The clinical manifestations are diverse and diagnosing SLCA 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.

References


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Systemic Light Chain Amyloidosis, Version 2.2023
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