Extended Abstract: Management and Diagnosis of Amyloid – What Is New?

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Introduction

Systemic, or immunoglobulin, light chain (AL) amyloidosis is characterized by the production of abnormal immunoglobulin light chains by a plasma cell clone. The free light chains misfold and deposit as insoluble fibrils in target organs, leading to organ dysfunction and death[1]. Currently, there are no FDA approved agents for AL amyloidosis. All available therapies, including melphalan, proteasome inhibitors, immunomodulatory imide agents (IMIDs), and recently daratumumab were translated from successful trials in multiple myeloma (MM)[2]. While more treatment regimens have become available and outcomes have improved, not all patients benefit equally, and limited options are available for patients with relapsed or refractory disease.

Advances in Management

Novel anti-plasma cell treatment and anti-amyloid fibril therapies have propelled the treatment field in a positive direction.

Anti-plasma cell therapies

Daratumumab

Daratumumab is a human IgG1 kappa antibody against CD38 approved for relapsed/refractory MM which has also demonstrated activity in AL amyloidosis[3]. A prospective phase 2 study presented during the 2017 American Society of Hematology (ASH) Annual Meeting examined use of daratumumab and dexamethasone in patients who received $\geq$1 prior therapy. Among 24 evaluable patients, overall hematologic response rate (ORR) was 63%, with 4 (17%) complete response (CR), 7 (29%) very good partial response (VGPR), and 4 partial response (PR). Responses were rapid, with all responding patients attaining a decrease in dFLC >30% after one daratumumab dose[4]. A currently-enrolling, multicenter, phase 3 trial is examining the use of daratumumab plus cyclophosphamide, bortezomib and dexamethasone (CyBorD) compared to CyBorD alone in newly diagnosed patients (NCT03201965).

Ixazomib

Ixazomib is an oral proteasome inhibitor that's particularly attractive in AL amyloidosis given the frequency of neuropathy (which may preclude use of bortezomib) and cardiomyopathy (may preclude carfilzomib) in patients. A multicenter phase 1/2 study of ixazomib +/- dexamethasone in previously treated patients with a median of 3 prior therapies has been reported. The hematologic ORR was 52% in patients treated at the maximum tolerated dose of ixazomib (4.0 mg). Organ responses were seen in 10/18 (56%) patients, with 5/11 (45%) cardiac responses and 5/11 (45%) renal responses[5]. Ongoing studies are evaluating ixazomib, cyclophosphamide and dexamethasone in newly diagnosed patients (NCT03236792), and ixazomib, daratumumab and dexamethasone in previously treated patients (NCT03283917).

Venetoclax

Venetoclax (ABT-199) is a small molecule inhibitor of BCL-2 that received FDA approval for chronic lymphocytic leukemia in 2015. It has activity as monotherapy[6] and in combination with bortezomib[7] in MM harboring t(11;14). In AL amyloidosis, t(11;14) is detected in upwards of 40-60% of patients[8,9]. Since plasma cells with t(11;14) overexpress BCL-2 relative to BCL-X_L and MCL-1[10], inhibition of BCL-2 using venetoclax appears to be a promising strategy. A currently-enrolling phase 1 study is examining the use of venetoclax and dexamethasone in relapsed or refractory AL amyloidosis patients (NCT03000660). Emerging anecdotal evidence suggests that venetoclax can be used in combination with bortezomib to effectively induce hematologic CR[11].

Bendamustine

Bendamustine is a bifunctional alkylating agent with demonstrated activity in MM[12-14]. A phase 2 multicenter trial of bendamustine and dexamethasone in patients with previously treated AL amyloidosis has reported promising data. Of 29 patients who had a median of 1.5 prior regimens, hematologic ORR was 45% (7% CR and 14% VGPR), and organ responses were also noted (of 18 patients with renal involvement, 5 had a response, and of 17 patients with cardiac involvement, 2 had a response). Median overall survival (OS) was 18.1 months and median progression free survival (PFS) was 11 months[15].

Lenalidomide and pomalidomide

The IMIDs lenalidomide and pomalidomide have both demonstrated efficacy in AL amyloidosis. Lenalidomide has been used in combination with cyclophosphamide and dexamethasone, with hematologic ORRs between 46-62% and organ ORRs 22-46% in phase 2 studies[16-19]. Similar hematologic ORRs have been reported with lenalidomide in combination with melphalan and dexamethasone[20,21]. Pomalidomide and dexamethasone has been studied in previously treated AL patients, with hematologic ORRs of 48-68%[22-24]. An ongoing trial is examining the combination of lenalidomide, elotuzumab and dexamethasone in relapsed patients (NCT03252600).

Lenalidomide has been associated with worsening NT-proBNP[25] and renal dysfunction[26]. Additionally, fluid retention and significant fatigue may occur[27]. Pomalidomide may be better tolerated than lenalidomide, and consideration should be given to using both of these agents at lower doses than is typical for MM.

Anti-amyloid fibril therapies

Multiple anti-amyloid fibril therapies have been developed with the goal of inducing early organ response, especially in cardiac amyloidosis which is a key determinant of outcomes[28].

NEOD001

NEOD001 is a monoclonal antibody that was originally developed against AA amyloidosis but which also showed some efficacy in animal models of AL amyloidosis[29]. Based on the immature conclusion that the conformational neoepitopes formed during fibrillogenesis are identical in AA and AL amyloidosis, a phase 1 trial was launched. In this study of 27 AL patients who had received prior therapy, NEOD001 was well-tolerated and promising organ responses were noted[30]. Unfortunately, further confirmation of activity did not materialize. Both the phase 2b PRONTO study (comparing NEOD001 to placebo in patients with prior hematologic response and cardiac dysfunction) and the phase 3 VITAL study (comparing NEOD001 to placebo in newly diagnosed patients receiving a proteasome inhibitor-containing chemotherapy) failed to show benefit for NEOD001, and development of this agent has been discontinued[31].

CAEL-101

CAEL-101, formerly 11-1F4, is an IgG1 antibody targeted against human kappa amyloid fibrils which has undergone extensive preclinical in vitro and in vivo testing[32,33]. Confirmation of its specificity for amyloid was demonstrated when I-124 labeled 11-1F4 was visualized in amyloid-laden organs on PET/CT imaging in human subjects[34]. This antibody has entered clinical testing, and final analysis of the phase 1 trial results was presented at ASH 2017. Overall, 63% (5 of 8) of evaluable patients demonstrated organ response after one infusion of 11-1F4 in phase 1a, and 61% (11 of 18) of evaluable patients showed organ response in phase 1b. The median time to response was 2 weeks after the start of treatment, with a tendency for faster responses at higher dosages. Organ response was independent of light chain type[35]. A randomized phase 3 trial will open in early 2019.

CPHPC + Anti-SAP antibody

Amyloid fibrils contain serum amyloid P component (SAP), a normal plasma protein. CPHPC is a small molecule which depletes the circulating SAP in plasma. It is given in conjunction with an IgG1 anti-SAP antibody that targets SAP deposits in tissues. In a phase 1 study of 15 patients with different types of systemic amyloidosis, CPHPC + anti-SAP antibody demonstrated ability to clear amyloid from the liver and kidney[36]. An ongoing phase 2 trial is investigating the use of this therapy in patients with cardiac amyloidosis (NCT03044353).

Doxycycline

The antibiotic doxycycline has been shown to interfere with amyloid fibril formation[37]. A retrospective analysis compared 30 patients who received doxycycline in addition to standard chemotherapy to 73 age and disease-matched controls who only received chemotherapy. Comparing the doxycycline group to the control group, responses were uniformly superior in the former — hematologic ORR was 93% versus 59%, cardiac response 60% versus 18%, and survival at 12 months 82% versus 53%[38]. An upcoming prospective study will examine the effects of adding doxycycline to standard chemotherapy in newly diagnosed patients (NCT02207556). Another will compare doxycycline + bortezomib-based therapy to other antibiotics + bortezomib-based therapy in newly diagnosed patients with cardiac involvement (NCT03474458).

EGCG

Epigallocatechin-3-galiate (EGCG), a compound found in green tea, has been reported to disrupt amyloid fibril formation[39]. A randomized trial (TAME-AL) comparing use of EGCG at several dosages to placebo in patients with cardiac AL amyloidosis did not find a benefit to the use of EGCG on left ventricular mass[40].

Diagnosis and response assessment

The most important factor in the diagnosis of AL amyloidosis is to think of the diagnosis. Patient experience surveys routinely show that the average time from onset of symptoms to diagnosis is 1-2 years, and 32% of patients visit $\geq$5 physicians before they are diagnosed[41,42]. Given this, there is interest in screening people with monoclonal gammopathy of undetermined significance (MGUS) for AL amyloidosis by measuring biomarkers of organ dysfunction such as NT-proBNP, albuminuria, and alkaline phosphatase[43].

After a diagnosis of amyloidosis on biopsy, amyloid typing by immunohistochemistry or mass spectrometry to confirm AL-type is essential[44], with the latter being the gold standard given its high specificity and sensitivity[45]. Assessment of hematologic response should include measurement of the dFLC. Organ responses should also be assessed, with measurement of NT-proBNP for cardiac