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Leukemia (PH Wiernik, Section Editor)

Immunotherapy in AL Amyloidosis

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Opinion Statement

Light-chain amyloidosis is a rare disorder where a small clone of plasma cells is producing excess toxic light chains that deposit in various organs and cause dysfunction. Cardiac involvement is a major determinant of survival and rapid reduction of light chain is critical for recovery of organ function and overall survival. Immunotherapy targeting the clonal plasma cells and amyloid fibrils has emerged as a promising candidate. Daratumumab, both alone and in combinations with other anti-myeloma agents, is able to achieve deep hematologic responses and has greatly improved outcomes. Isatuximab, elotuzumab, and CAEL101 have also shown promising results and further studies are ongoing in the frontline as well as the relapsed/refractory setting. The frailty of AL patients and the relapsing/remitting nature of the disease present unique challenges, and the low toxicity of monoclonal antibodies makes them well-suited for these patients. Other immunotherapy agents including chimeric antigen receptor T cells, bispecific antibodies, and antibody-drug conjugates have altered the landscape in treatment of multiple myeloma, and are in the early phase of evaluation in patients with AL amyloidosis with results eagerly awaited.

Introduction

Light-chain amyloidosis, also known as AL amyloidosis, is characterized by a small clone of malignant plasma cells producing toxic light chains which form insoluble beta-bleated sheets of amyloid fibrils that deposit in various organs and causes damage [1]. Cardiac and renal involvements are the most common. Cardiac involvement is a major determinant of survival, with cardiac biomarkers incorporated as part of the staging system [2]. A significant proportion of patients die within 6 months of diagnosis, usually due to cardiac cause [3].

The peripheral and autonomic nervous system, liver, and spleen can also be sites of deposition and result in peripheral neuropathy, hypotension, diarrhea or constipation, and cholestasis. Given that multiple organs are often involved, AL amyloidosis often causes frailty of the patient, which can significantly impact patients' quality of life and are impediments to the therapy they can receive [4].

The mainstay of therapy is treating the clonal plasma cells to decrease light-chain production, though more recently treatments have emerged that target amyloid fibrils, the direct culprits of organ damage. Until very recently with the ANDROMEDA study [5] that resulted in the approval of subcutaneous daratumumab with cyclophosphamide, bortezomib, and dexamethasone (Dara/CyBorD), no FDA-approved therapy existed. Previously, treatment directed at the clonal plasma cells was derived from that of multiple myeloma (MM), with combinations of alkylating agents, proteasome inhibitors, and immunomodulatory agents. Treatment must be carefully tailored to each patent considering the extent of their disease, other comorbidities, and performance status.

While autologous stem cell transplant is very effective and induces deep hematologic responses, only 20% of patients with newly diagnosed disease are eligible [4]. In carefully selected patients who received autologous stem cell transplant, overall response rate was 71% with 37% of patients experiencing complete remissions; transplant-related mortality was 5%, and 5-year overall survival was 77% [6]. The majority of AL patients are not candidates for transplants and their outcome prior to Dara/CyBorD was much poorer with persistence of clonal disease and organ dysfunction.

For transplant-ineligible patients, treatment with oral melphalan and dexamethasone (MDex) had been a standard of care for many years. Different rates of response and survival have been reported due to the differences in doses and proportions of high-risk patients included, but one study of 259 patients found a hematologic response rate of 51–76% and complete response rates of 12% to 31% [7]. Recent data has suggested better outcomes for bortezomib-based combinations such as bortezomib, melphalan, and dexamethasone (BMDex) or cyclophosphamide, bortezomib, and dexamethasone (CyBorD). A phase III trial in intermediate-risk patients showed improved hematologic response (HR) rate (81% vs. 57%, CR 23% vs. 20%) in BMDex compared to MDex [8]. However, even for BMDex and CyBorD, organ responses have been suboptimal, ranging between 15 and 40%, and they lag hematologic responses by months to years [8, 9]. Translocation $t(11, 14)$ in clonal plasma cells, found in 50% of the patients with AL amyloidosis, is associated with less frequent and less deep hematologic responses with bortezomib-based therapy [10, 11].

These results highlight a need for novel therapies with high activity against the disease, but ones that at the same time can be safely delivered given the organ dysfunction intrinsic to the disease. Since recovery of organ function and overall survival depend upon control of the toxic light chains, the goal is to lower the light-chain burden rapidly and achieve a deep hematologic response. One potential candidate can be found in immunotherapy, which has been highly successful in multiple myeloma. The smaller size of the plasma cell clone (median bone marrow infiltrate of 10%) makes it well-suited for this disease. In this review, we aim to summarize the current data and ongoing trials for immunotherapy for AL amyloidosis in the form of monoclonal antibody, CAR-T, antibody-drug conjugate, and bispecific antibodies.

Daratumumab

Daratumumab is the first fully human monoclonal antibody targeting CD38, a transmembrane glycoprotein that is expressed in low levels on hematopoietic as well as non-hematopoietic cells, but overexpressed on the surface of plasma cell clones in MM and AL amyloidosis. CD38 has multiple roles, including mediating regulation of cell adhesion and signal transduction, and acting as a receptor and an ectoenzyme [12]. Preclinical studies have demonstrated that daratumumab can induce plasma cell death through different mechanisms, including complement-dependent cytotoxicity, antibody-dependent cell-

mediated toxicity (ADCC), antibody-dependent cellular phagocytosis, direct induction of apoptosis, and modulation of CD38 enzyme activities [13].

Daratumumab was initially approved in 2015 to treat patients with relapsed and refractory MM, and was later approved in the frontline setting as well. While showing activity as a single agent, the combination of daratumumab with other anti-myeloma agents, in particular proteasome inhibitors and immunomodulators, led to impressive responses without significant additional toxicity. The initial reports of efficacy of daratumumab in AL amyloidosis were from two heavily pretreated patients who were refractory to bortezomib, carfilzomib, and lenalidomide and progressed through an autologous stem cell transplant, but were able with daratumumab to achieve complete hematologic responses lasting more than 18 months [14]. A series of retrospective studies followed, all in the setting of relapsed/refractory amyloidosis. One study of 25 relapsed AL patients, with the majority having cardiac involvement, showed overall hematologic response rate of 96% with 36% achieving complete response (CR), and a median time to response of just 1 month [15]. Another retrospective study of 44 patients investigated the efficacy of daratumumab alone vs. in combination with mostly lenalidomide, pomalidomide, and bortezomib. In the daratumumab monotherapy group, 78% of patients achieved HR vs. 88% in the combination group. Renal response was achieved in 44% and 46%, respectively, and cardiac response in 18% and 36%, respectively [16]. The largest retrospective study reported 169 patients who were treated with daratumumab and dexamethasone, or daratumumab, bortezomib, and dexamethasone. The addition of bortezomib did not result in significantly different overall hematologic response (HR) (64% and 66%), VGPR/CR (48% and 55%), or cardiac response rates (22% and 26%) [17]. The numerous retrospective studies [18, 19] have consistently demonstrated the efficacy of daratumumab in relapsed AL amyloidosis patients, setting the stage for prospective studies (Table 1).

In addition, two phase II trials have been performed on relapsed/refractory AL amyloidosis patients. One multicenter phase II trial of 40 patients with relapsed AL amyloidosis, who had received a median of three prior lines of therapy, assessed the safety and efficacy of daratumumab monotherapy. The results showed an overall HR rate of 55%, with cardiac response in 6 of 24 patients and renal response in 8 of 26. Daratumumab was well-tolerated with no unexpected adverse events [20]. Another phase II trial of 22 patients with relapsed AL amyloidosis patients who received daratumumab monotherapy demonstrated hematological CR and VGPR in 86% of patients, with 10 of 15 patients reaching renal response and 7 of 14 patients reaching cardiac response [21].

Daratumumab has also been shown to improve responses and induce deep hematologic responses and minimal residual disease (MRD) negativity in patients, which is associated with better survival outcomes. In a small prospective study with patients who have not achieved a complete hematologic remission using standard treatment, a short course of daratumumab for consolidation improved complete response rates, reaching undetectable measurable residual disease and altering the bone marrow microenvironment [8].

From a frontline setting, ANDROMEDA was a phase III trial evaluating Dara/CyBorD vs. CyBorD in patients with newly diagnosed AL amyloidosis. Subcutaneous daratumumab was given weekly for the first 8 doses, every 2 weeks for the next 8 doses, followed by monthly for up to 2 years, whereas

Table 1. Studies evaluating immunotherapy in AL amyloidosis

Therapy regimens	Number of patients	Setting	Hematologic response	Complete response	Organ response	Median PFS/OS (months)
Daratumumab monotherapy [15]	25	RRAL	96%	36%	-	-/-
Daratumumab monotherapy [16]	22	RRAL	78%	14%	Cardiac 18% Renal 44%	At 10 months: 100%/100%
Daratumumab combination therapy* [16]	22	RRAL	88%	19%	Cardiac 36% Renal 46%	At 10 months: 83%/89%
Daratumumab/dexamethasone [17]	106	RRAL	64%	8%	Cardiac 22% Renal 24%	11.8/25.6
Daratumumab/bortezomib/dexamethasone [17]	62	RRAL	66%	11%	Cardiac 26% Renal 31%	At 16 months: 19.1/NR
Daratumumab monotherapy [20]	40	RRAL	55%	8%	Cardiac 25% Renal 31%	At 26 months: 24.8/NR
Daratumumab monotherapy [21]	22	RRAL	86%	41%	Cardiac 50% Renal 67%	At 20 months: 28/NR
Daratumumab-CyBorD [5]	195	NDAL	92%	53%	Cardiac 42% Renal 54%	-/-
Isatuximab monotherapy [25]	35	RRAL	77%	3%	-	At 1 year: 85%/97%
NEOD001 [30]	69	RRAL	-	-	Cardiac 53% Renal 63%	-/-
CAEL-101 [35]	27	RRAL	-	-	67%	-/-

CyBorD, cyclophosphamide, bortezomib, and dexamethasone
*Daratumumab, pomalidomide, and dexamethasone (DPD, 36%); daratumumab, lenalidomide and dexamethasone (DRD, 32%); and daratumumab, bortezomib, and dexamethasone (DVD, 18%) were the most commonly used daratumumab combination therapies

CyBorD was given weekly for six 4-week cycles. The safety run-in study included 28 patients, where 27 of the patients achieved a hematologic response (96%) with a CR in 82% of the patients [5]. The preliminary results of the 388 patients indicate that the addition of daratumumab to chemotherapy results in significantly higher hematologic (92% vs. 77%), cardiac (42% vs. 22%), and renal (54% vs. 27%) response rates.

Of importance was that the median time to first hematologic response and deep response was 9 days and 19 days, respectively. The rapidity of hematologic response is very relevant as a rapid reduction in the light chain is critical to preserving organ function and hence survival. In addition, this study uses a subcutaneous formulation of daratumumab, which was well-tolerated and associated with low rates of infusion-related reactions, few injection site reactions, and reduced administration times compared with intravenous daratumumab. The small administration volume is particularly advantageous given that volume overload is frequently a concern due to cardiac involvement frequently seen in AL amyloidosis. The caveat with daratumumab is the higher rate of infection, with underlying immunodeficiency associated with plasma cell disorders augmented by natural killer cells depletion (also expressing CD38) [22].

The robust hematologic and organ responses, both of which are strong predictors of overall survival in this disease, established the role of daratumumab in frontline therapy and opens the landscape for further trials of daratumumab in combination with different anti-myeloma agents. On January 15, 2021, FDA granted accelerated approval to daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone for the treatment of newly diagnosed adult patients with AL amyloidosis.

Isatuximab

Isatuximab is another IgG1 monoclonal antibody, which binds to a unique epitope on CD38, targeting a different amino acid sequence compared to daratumumab [23]. In preclinical models, it demonstrates potent proapoptotic activity, and was able to induce plasma cell death through mechanisms such as CDC, ADCC, ADCP, and inhibiting CD38 enzymatic activity. In the phase III IKEMA trial, patients with relapsed/refractory MM were randomized to isatuximab in combination with carfilzomib and dexamethasone, and to carfilzomib and dexamethasone alone [24]. The PFS for patients receiving isatuximab in combination with carfilzomib and dexamethasone was not reached, compared to 20.27 months in the carfilzomib and dexamethasone alone arm. Based on this result, isatuximab in combination with carfilzomib and dexamethasone is FDA-approved for this setting. A multicenter phase II study of isatuximab for patients with previously treated AL amyloidosis showed that for the 35 patients receiving at least 1 dose of isatuximab, hematologic complete response, very good partial response (PR), and PR were observed in 3%, 54%, and 20% of patients, respectively [25]. One-year-estimated OS is 97%, and 1-year-estimated PFS is 85%. So far, isatuximab has demonstrated a good safety profile similar to other CD38 monoclonal antibodies. The most common grade ≥ 3 treatment-related adverse events (AEs) were lymphopenia in three patients (9%), lung infection in two patients (6%), and an infusion-

related reaction in one patient (3%). A trial evaluating isatuximab in the frontline setting for high-risk AL amyloidosis has recently been initiated (NCT04754945).

Elotuzumab

Elotuzumab is a humanized IgG1κ monoclonal antibody targeting the signaling lymphocytic activation molecule family member F7 (SLAMF7), a glycoprotein that is moderately expressed by normal plasma cells and by cytolytic lymphocyte subsets such as natural killer (NK) cells, NKT cells, or CD8+ T cells, and highly expressed on MM plasma cells [26]. Similar to daratumumab, elotuzumab has multiple mechanisms of actions, but appears to predominantly act through ADCC. However, in contrast to daratumumab, elotuzumab has limited efficacy as a single agent in preclinical and clinical studies, but needs to be combined with other agents such as lenalidomide or bortezomib to reach its maximal effect. Elotuzumab in combination with lenalidomide and pomalidomide has shown efficacy in relapsed and refractory MM [27], and has been investigated in AL amyloidosis as well. A case report has been published of a woman with RRMM and concurrent AL amyloidosis who received four prior lines of therapy along with two autologous stem cell transplants, and was able to subsequently achieve and maintain a complete hematological response after treatment with elotuzumab, lenalidomide, and dexamethasone [28]. A phase II trial evaluating elotuzumab, lenalidomide, and dexamethasone with or without cyclophosphamide followed by EloRD maintenance in relapsed AL amyloidosis is currently underway (NCT03252600).

NEOD001

NEOD001 is a humanized form of murine monoclonal antibody 2A4 that binds an epitope derived from a cleavage site of serum amyloid protein A containing a -Glu-Asp- amino acid pairing [29]. This antibody also binds amyloid fibrils composed of immunoglobulin light chains with high affinity, and is thought to neutralize circulating LC aggregates and clear insoluble deposits. In a phase I/II study of 69 patients who had received at least one line of treatment for AL amyloidosis, organ responses were observed in 53% of cardiac-evaluable patients and 63% of renal-evaluable patients [30]. Treatment was also found to be safe and well-tolerated. A phase IIb placebo-controlled trial RAIN was initiated to evaluate treatment of renal function in previously treated patients who achieved a hematological response. PRONTO, a phase IIb placebo-controlled study, evaluated patients with previously treated AL amyloidosis with persistent cardiac dysfunction [31]. VITAL, a phase III trial, enrolled patients with newly diagnosed disease and cardiac involvement where patients were randomized to NEOD001 or placebo combined with a bortezomib-based regimen. The PRONTO and VOTAL trials were discontinued due to a futility analysis [32]. The RAIN trial closed at that time as well. In the VITAL trial, subsequent analysis showed that Mayo stage IV patients may have had a survival benefit. Stage IV patients receiving NEOD001 had a median

overall survival that was not reached compared to 8.3 months for placebo. Despite initial promising results, development of NEOD001 was terminated although information regarding its use in a new study has been forwarded (http://www.globenewswire.com/en/news-release/2021/02/01/2167691/24041/en/Prothena-Announces-Confirmatory-Phase-3-AFFIRM-AL-Study-of-Birtamimab-in-Mayo-Stage-IV-Patients-with-AL-Amyloidosis-under-SPA-Agreement-with-FDA.html).

CAEL-101

CAEL-101, formerly known as 11-1F4, is a humanized monoclonal antibody reacting specifically with light-chain fibrils, irrespective of their kappa or lambda isotype, but not soluble precursor proteins. It leads to removal of amyloid aggregates by triggering Fcy-receptor mediated proteolysis and promoting phagocytic clearance. In vivo, CAEL-101 accelerated the removal of amyloidomas made of human LC fibrils [33]. A phase Ia/b study enrolled patients with relapsed or refractory AL amyloidosis found early and sustained organ response in five of the six patients who completed follow-up [34]. One year follow-up showed that 67% of renal and/or cardiac-evaluable patients demonstrated organ responses [35]. The organ responses were seen independent of free light-chain type with median time to response of 3 weeks after treatment. It is also the first study to demonstrate improvement in global longitudinal strain, a sign of cardiac remodeling, in 9 of 19 patients. The combination of CAEL-101 with CyBorD was evaluated in a phase II trial, where two of the seven patients had early organ responses [36]. There are currently two phase III studies that have recently started enrolling patients with Mayo cardiac stage IIIa and IIIb disease with the primary endpoint of overall survival.

The potential of using radiolabeled CAEL-101 as a companion diagnostic tool to image real-time targeting of human amyloidosis has also been explored. In particular, PET imaging has been shown to successful visualize cardiac-derived amyloid fibrils [37].

Anti-SAP

Another target for monoclonal antibodies is human serum amyloid P component (SAP) from the plasma, ubiquitous in all human amyloid deposits due to its high affinity but reversible binding to amyloid fibrils irrespective of type [38]. A small-molecule drug, miridesap, has been shown to rapidly deplete circulating SAP in the plasma but leaves SAP in amyloid deposits. The residual SAP then serves as a target for SAP antibodies that can trigger complete removal of the SAP. Dezamizumab is a fully humanized monoclonal SAP antibody [39]. A phase I study assessed 15 patients with different types of amyloidosis, including 8 with AL amyloidosis patients. Patients underwent dual therapy with miridesap first and dezamizumab once the SAP concentration dropped below 2 mg/l. There was significant decrease in liver stiffness in six of eight patients who had hepatic involvement, with four of the eight patients showing a significant reduction in hepatic amyloid load by I-SAP scintigraphy [40]. The phase 1b part of the trial extended the study by eight additional patients [41]. Of the three patients with cardiac involvement of AL amyloidosis, one of the

patients had a 17% reduction in left ventricular mass as assessed by cardiac MRI after treatment. Amyloid clearance from the liver was faster and more extensive than from other organs, which may be attributed to the sinusoidal hepatic capillary endothelium allowing easy access of antibodies and complements to where the amyloid deposits are located. Even though the early studied showed clinical activity and good safety profile, the dual therapy is no longer in development due to a change in risk/benefit profile.

Future directions

CAR-T

Chimeric antigen receptor T cells (CAR-T) have changed the treatment landscape for B-cell neoplasms, proving efficacy both in the frontline and relapsed/refractory setting, and has been an evolving strategy for the treatment of MM [42]. CAR-T therapy engineers T cells to target selected antigens that are present on the surface of malignant cells. The CAR is a recombinant receptor, composed of an extracellular antigen binding domain, a hinge, a transmembraine domain, an intracellular signaling region, and in second- and third-generation CAR, a costimulary domain to enhance CAR-T survival and proliferation [43].

B-cell maturation antigen (BCMA) is a transmembraine glycoprotein expressed on the surface of late memory B cells and plasma cells, with amplification of expression upon differentiation [44, 45]. It is not present on non-hemopoietic cells, or hemopoietic stem cells and naïve B cells. The specificity of BCMA for plasma cells makes it a target for CAR-T, and multiple candidates have been tested in phase I trials. The first-in-human trial in 24 heavily treated RRMM patients were enrolled, 16 of them received the highest dose level. The lowest doses showed minimal anti-MM activity, but patients at the highest dose level had an overall response rate (ORR) of 81%, with 63% of patients achieving a very good partial response (VGPR) or better. The median event-free survival in this heavily pretreated population was 31 weeks [46]. Subsequently, other CAR-T-cell products, such as LCAR-B38M, CART-BCMA, bb2121, bb21217, and JCARH125 have shown heterogenous phase I results that are overall impressive in achieving deep responses.

Given that the burden of clonal plasma cells in the BM is typically less in AL amyloidosis compared to MM, AL could be particularly suitable for immunotherapy, with elimination of a small malignant clone. While one study found the expression of BCMA to be low in AL [47], this was challenged by a plethora of other studies. Thirty-four bone marrow biopsies of AL found the median BCMA expression to be 80% with the median staining intensity of 2 [48]. Membrane-bound BCMA is also shed as a soluble form, sBCMA, due to γ-secretase mediated cleavage (GSI, LY-411575)[49]. Among 20 patients with AL amyloidosis, sBCMA is detected in the plasma of all of the patients and correlated with disease activity, free light-chain levels, and plasma cell tumor burden [50].

CS-1, a cell surface receptor belonging to the SLAM family, also called SLAM7 and CD319, is present on plasma cells as well as NK cells [26]. In a prospective study evaluating bone marrow biopsies of 20 patients, 10 with AL and 10 with MM, CS1 was found on the plasma cells of all AL patients and therefore could be a promising target [47]. In CS1+ tumor-bearing mice, CS1 CAR-T cells induced significant tumor regression. Clinical trials using CS1 CAR-T construct are being

planned. Simultaneously, CAR-T cells are being developed to target a number of other plasma cell antigens including CD38, CD138, CD56, and CD19 [51]. Given that the novel therapies in AL amyloidosis have their basis in MM, it is likely that some of these treatments will be tested in AL amyloidosis. There are currently no clinical trials investigating CAR-T cell therapies in AL amyloidosis but experts are optimistic about initiating them in the near future.

Antibody-drug conjugate

Another agent using BCMA as a target is belantamab mafodotin. It is an anti-BCMA antibody conjugated with MMAF, a microtubule inhibitor, via a noncleavable linker [52]. Binding to BCMA internalizes the antibody-drug conjugate, releasing the cytotoxic load and leading to cell death. Belantamab mafodotin has shown efficacy in RRMM, with a phase II trial of 196 patients achieving an overall response of 30% [53]. No use has been reported so far in AL amyloidosis but a phase II trial is planned.

Bispecific antibodies

Bispecific antibodies are antibodies that can simultaneously bind two separate and unique antigens. Bispecfic T-cell engagers (BiTEs) are bispecific antibodies that bind an epitope on the tumor and a T-cell antigen, mostly CD3 [54, 55]. BiTEs that target BCMA and CD3, as well as CD38 and C3, have been developed with the former showing promising overall response rate of 83% in 12 patients with RRMM [56]. There is ongoing research focusing on development of bispecific antibodies that can target macrophage/neutrophil cell surface markers in addition to AL amyloid to enhance amyloid elimination [57].

Conclusion

AL amyloidosis represents an area of significant unmet need as the majority of patients are not eligible for stem cell transplant and the course is relapsing/remitting similar to that of MM, requiring the use of novel agents. Timely diagnosis and treatments with quick onset as well as a good safety profile are critical to preventing and minimizing organ damage in frail AL patients and thereby extending survival. Monoclonal antibodies show great promise, with daratumumab especially inducing rapid and deep responses to a level that has not been seen heretofore. The path to novel therapies is not without setbacks, as exemplified by NEOD001 and anti-SAP therapy. Immunotherapy targeting both the precursor plasma cells and amyloid fibrils, and development of antibody-based therapy against a multitude of plasma cell markers, shows great potential in altering the landscape for future therapies.

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Compliance With Ethical Standards

Conflict of Interest

Yifei Zhang declares that he has no conflict of interest. Raymond L. Comenzo has a patent issued (WO2016187546A1) for anti-cd38 antibodies for treatment of light-chain amyloidosis and other cd38-positive hematological malignancies

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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