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Review

Treatment in AL Amyloidosis: Moving towards Individualized and Clone-Directed Therapy

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Abstract: Systemic amyloid light chain (AL) amyloidosis is a rare protein deposition disease caused by a clonal B cell disorder of the bone marrow. The underlying diseases can be plasma cell disorders (monoclonal gammopathy of clinical significance, smoldering or symptomatic myeloma) or B cell non-Hodgkin's lymphoma (e.g., Waldenstrom's disease or marginal zone lymphoma) with secretory activity. It is crucial to characterize the underlying disease very precisely as the treatment of AL amyloidosis is directed against the (often small) B cell clone. Finally, the detection of cytogenetic aberrations of the plasma cell clone will likely play an important role for choosing an effective drug in the near future.

Keywords: amyloidosis; monoclonal B and plasma cells; t(11;14)

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1. Introduction

Systemic amyloid light-chain (AL-) amyloidosis is a rare monoclonal B cell disorder with poor prognosis due to the production of free light chains leading to amyloid deposition in nearly all organs [1]. Most patients succumb to advanced heart failure. The only evidence-based and recently approved therapy is cytoreduction of the underlying monoclonal aberrant plasma or B cell population to reduce or even stop the production of amyloid precursors leading to an improvement of organ functions.

In about 90% of AL patients the underlying disease is derived from clonal plasma cells (AL-PC), therefore therapeutic strategies are mostly adapted from established myeloma regimens. In about 10% the underlying clone is a B cell clone [1] and in such cases drugs established in those lymphomas are used.

2. Staging of AL Amyloidosis and Characterization of the Underlying Clone

At diagnosis of AL the first step is to assess organ involvement and to stage and quantify cardiac and renal impairment. These validated staging systems help to choose the appropriate intensity of the chemotherapy [1]. The second step is to characterize the clonal B cell disorder to choose the most efficacious treatment. Table 1 shows the current available (and future) methods to detect, characterize and quantify the clone. In the future, mass spectrometry might become available on a broader scale to quantify the monoclonal light chain in serum more specifically [2].

Table 1. Methods to detect, characterize and quantify the clone.

Method	Significance
Measurement of immunofixation in serum and urine as well as free light chains in serum	Standard non-invasive method to evaluate monoclonal gammopathy in the daily practice without sampling error

Table 1. *Cont.*

Method	Significance
Bone marrow examination	
Cytology	Number of cells, phenotype
Biopsy	Number of clonal cells (light chain restriction), phenotype
FACS	Phenotype, differentiation between clonal plasma and B cells, measurement of minimal residual disease [3,4]
iFISH	Detection of cytogenetic aberrations (gain of 1,5,15,19; deletion 13 and 17, translocations) [5,6]
Serum mass spectrometry	Qualitative detection of small amounts of amyloidogenic proteins in serum [2] Measurement of minimal residual disease [7]
MYD88 L265P, CXCR4	Clonal markers for IgM gammopathies [8]

3. Clone-Directed Treatment in AL Amyloidosis

The goal of the treatment is to avoid further organ damage, to preserve organ function, to maintain quality of life and to prolong survival of these often very sick and fragile patients. This can currently only be achieved by the eradication or reduction of the amyloidogenic clone using several approaches.

Chemotherapy against plasma cells (MGCS, smoldering myeloma, symptomatic myeloma) or against B cells (Waldenstrom's disease or other secretory active B cell NHLs such as marginal zone lymphoma) is derived from myeloma or lymphoma treatment.

Standard treatment includes alkylating chemotherapy combined with steroids (mostly dexamethasone), proteasome inhibitors and immunomodulating drugs [1]. Monoclonal antibodies are directed against several surface antigens of plasma cells (CD38, SLAM7, BCMA) or B cells (CD20) and are now also widely used in AL patients. There are few data regarding the treatment with Venetoclax targeting the anti-apoptotic bcl2-dependent pathway. Recently bispecific antibodies (BCMA, CD3) and CAR T cell therapies (BCMA, CD19) have been introduced for multiple myeloma and B cell lymphoma and might be applied also for AL amyloidosis in the near future. Targeted treatment is desirable to reduce side effects and to achieve a very rapid reduction of the clonal amyloidogenic light chains in the serum. Figure 1 shows several mechanisms, how malignant plasma or B cells can be attacked.

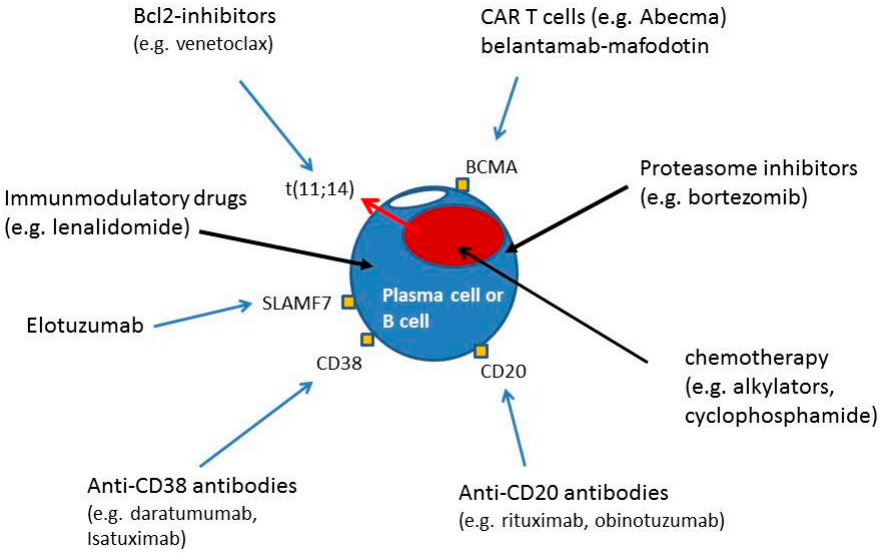

Figure 1. Mechanisms of drugs to attack the clonal cells in AL amyloidosis.

4. Alkylators

Melphalan and cyclophosphamide (plus corticosteroids) are used as part of combinations with newer agents. Melphalan plus dexamethasone (MDex) have been a standard for transplant ineligible patients [9] and was later on combined with bortezomib (BMDex) in a Phase III trial with high response rates [10]. Gain of 1q21 was identified as negative prognostic marker for AL patients treated with MDex [11]. In multivariate concordance analyses the adverse prognosis carried by gain of 1q21 was an independent prognostic factor (overall survival; OS: $p = 0.003$, average hazard ratio (AHR) 3.64, hematologic event-free survival; hemEFS: $p = 0.008$, AHR 2.35), along with the well-established Mayo cardiac staging. Patients with t(11;14) had a longer median OS with 38.2 months versus 17.5 months, though no statistical significance was reached.

The most intense regimen is high-dose chemotherapy with autologous stem cell transplantation (ASCT); the standard conditioning is still melphalan 200 mg/m^2 [12]. The use of induction therapy and maintenance is depending on the burden of the plasma cell clone trying to reduce the risk of early progression [13,14].

The prognostic value of cytogenetic aberrations was investigated in 123 AL patients who received high-dose melphalan with ASCT [15]. In multivariate analysis, t(11;14) was confirmed as a favorable prognostic factor regarding hemEFS along with lower values for the difference between involved and uninvolved free light chains. Conversely, deletion13q14, gain of 1q21 and hyperdiploidy had no significant prognostic impact.

The International Society of Amyloidosis (ISA) together with European Hematologic Association (EHA) has currently published their guidelines for high-dose chemotherapy and ASCT [16]. The transplant-related mortality has significantly decreased in the last 20 years in experienced centers, but the selection of eligible patients remains crucial. The rate of complete remission varies between 30–50% and long-term survival can be achieved. A cure of the underlying disease might be possible in a small number of CR patients [17]. Therefore, HDM with ASCT is a very effective treatment for AL amyloidosis in selected patients. A direct comparison with new and clone-directed treatments within randomized clinical trials is desirable, but extremely difficult as patients have denied this in several studies in the past [18]. The best treatment could therefore be a combination of both strategies as it will be likely the case in multiple myeloma, at least for patients not reaching MRD negativity.

Bendamustine-based regimens are mostly used for AL patients with underlying B cell malignancies [19], but can also be used in PC-AL [20].

5. Proteasome Inhibitors (PIs)

Clonal plasma cells in AL amyloidosis are dependent on proteasome integrity. Targeting the proteasome is highly effective in AL amyloidosis. Bortezomib-containing regimens are considered as the primary therapy for AL amyloidosis in most centers, in Europe and US.

Bortezomib–cyclophosphamide–dexamethasone (CyBorD) or bortezomib–Dexamethasone are commonly used today [18]. However, bortezomib cannot be used in AL patients with peripheral polyneuropathy and may be less effective in patients with a translocation t(11;14) [6,21,22]. In multivariable Cox regression models incorporating established hematologic and clinical risk factors, t(11;14) was an independent adverse prognostic marker for hemEFS (HR, 2.94; 95% CI, 1.37 to 6.25; P 0.006) and OS (HR, 3.13; 95% CI, 1.16 to 8.33; P 0.03).

Ixazomib was given in a randomized Phase III trial in relapsed AL patients but the primary endpoints of the study (hematologic response rate and 2-year vital organ deterioration or mortality rate) have unfortunately not been met. The drug is a therapeutic option for proteasome-naïve patients with symptomatic polyneuropathy [23]. Carfilzomib is effective but not yet widely used due to potential cardiac toxicity [24].

6. Immunomodulatory Agents (IMiDs)

The first IMiD thalidomide is not broadly used in AL amyloidosis in standard dosage because of higher rates of polyneuropathy [25]. Lenalidomide is also less well tolerated in AL compared to myeloma patients, the recommended dosage is 15 mg [26]. The main side effects are fluid retention, increase of NT-ProBNP and marked hypotension [27]. However, it is quite effective if used as upfront or relapse treatment in combination with dexamethasone or with alkylating agents [28] or with the monoclonal antibody daratumumab (DRD) [29]. Gain of 1q21 had an adverse impact on treatment results [27,29]. In DRD treated AL patients calculated median hemEFS and OS were 17.4 and 29.1 months, respectively. On univariable analysis, hemEFS was adversely influenced by dFLC > 180 mg/L (HR 2.71, $p = 0.027$) and gain 1q21 (HR 9.8, $p = 0.003$). Translocation t(11;14) did not affect outcome. Exploratory multivariable analysis of the two univariably significant factors in combination with albumin-to-creatinine ratio (ACR) > 220 mg/mmol confirmed gain 1q21 as highly significant (HR 8.9, $p = 0.005$).

Pomalidomide is increasingly used in AL patients and might be the best tolerated IMID in AL patients with some hematologic toxicities. It is an effective relapse treatment in doublet or triplet combination therapies [30].

7. Monoclonal Antibodies

Currently combination treatments with daratumumab, isatuximab and elotuzumab or antibody-conjugates such as belantamab-mafodotin are approved to treat multiple myeloma [31] and are also used for treatment in AL patients [29,32].

The ANDROMEDA trial included 388 patients with newly diagnosed AL. Patients have been randomized to receive either CyBorD or CyBorD + daratumumab 1800 mg s.c. [28]. After a median follow-up of 11.4 months the CR rate in the study arm was significantly higher than in the standard arm (53.3% vs. 18.1%). Furthermore, at 6 months cardiac and renal responses occurred more frequently in the daratumumab arm (41.5% vs. 22.2% and 53% vs. 23.9%) [33]. Recently, Daratumumab in combination with CyBorD was approved in the US and Europe for newly diagnosed patients with AL amyloidosis.

Data on daratumumab treatment in Rel/Ref-AL have been recently reviewed [34]. This treatment is very effective in daratumumab-naïve AL patients and generally well tolerated. However, the efficacy is reduced in patients with nephrotic range albuminuria [32] and gain of 1q21 [29].

AL patients with an underlying B cell malignancy can be treated with combinations of anti-CD20 monoclonal antibodies in combination with chemotherapy [35].

Table 2 shows the targets and ongoing clinical trials for AL patients.

Table 2. Lists of recruiting clinical trials using monoclonal antibodies in AL.

Identifier	Target	Drug Combinations	Type	Institution
NCT04895917	CD38	Dara + pomalidomide	Second line	Amyloidosis Center Pavia, Italy
NCT04474938	CD38	Dara-bortezomib–dexamethason	Upfront, Mayo Stage 4	University Beijing, China
NCT04131309	CD38	Dara-bortezomib–dexamethason	Upfront, Mayo Stage IIIb	Multicenter Europe
NCT03283917	CD38	Dara-ixazomib–dexamethason	Upfront and relapsed/refractory	MD Anderson, Houston, USA
NCT04270175	CD38	Dara-pomalidomide–dexamethason	relapsed/refractory	Multicenter USA
NCT04754945	CD38	Isatuximab	High-risk	Multicenter USA
NCT04617925	BCMA	Belantamab–mafodotin	Phase II, pre-treated	Multicenter Europe
none	SLAMF7	Elotuzumab		
none	CD20	Rituximab		

8. Bispecific Antibodies and CAR-T-Cells

Bispecific antibodies and CAR-T cells are intensively studied in B cell lymphoma and multiple myeloma [31] and might also be investigated in AL patients in the near future. Given their highly specific mechanism of action against individual cell types with respective marker profiles such as CD19, BCMA or CD38, these novel immune-therapeutic approaches might be ideal to eradicate the underlying clonal cell population. However, side effects such as cytokine release syndrome or neurotoxicities might limit their use in certain subsets of patient with renal, neurologic or cardiac involvement.

9. Pathway-Inhibition

The characteristic cytogenetic aberration of the clonal plasma cells in AL amyloidosis is the translocation t(11;14), which can be detected in about 50% of AL patients [36]. Venetoclax is a drug targeting the anti-apoptotic bcl2-dependent pathway and is very effective in plasma cells harboring t(11;14). Venetoclax is active and approved in several diseases such as CLL [37] and AML [38]. Several studies are ongoing in multiple myeloma where venetoclax is used in combination with other anti-myeloma drugs [39] but currently stopped due to increased mortality in the venetoclax arm.

Venetoclax has recently been evaluated in AL. The first report came from the Mayo clinic [40] and afterwards an international group collected 43 pretreated (median 3 regimen) patients to analyze the efficacy and side effects of venetoclax in AL [41]. A total of 31 out of 42 patients carried the t(11;14) The hematologic response rate ($\geq$VGPR) was higher in patients with the translocation (81% vs. 40%). There are currently no open clinical trials using bcl2 inhibitors in AL.

In opposite to Waldenstrom's disease it has been shown in a small case series that ibrutinib as monotherapy is not well tolerated in AL patients [42] and is not leading to a deep remission.

Table 3 shows the advantages and disadvantages of the different treatment approaches.

Table 3. Pro's and con's of main treatments.

Drug	Pro	Con
High-dose melphalan and ASCT	High rate of hematologic remission and organ response Long-term efficacy, probably cure in some patients	Only available for selected patients Increased treatment-related mortality and morbidity Risk of secondary malignancies
Proteasome-inhibitors	Fast reduction of the tumor burden Subcutaneous application	Risk of polyneuropathy Reduced efficacy in patients with t(11;14)
IMID's	Effective in combination therapies Oral application	Reduced efficacy in patients with gain 1q21 Cardiac and renal side effects
CD38 antibodies	High rate of CR/VGPR and organ responses in combination with chemotherapy Approved therapy in many countries Few side effects	No long term data available
Bcl-2 inhibitors	High efficacy in patients with t(11;14)	No long term data available

10. Anti-Amyloid Treatment

Many AL patients are diagnosed in an advanced stage of organ damage which leads to rapid organ failure and/or shortened survival. Most of these patients do not benefit from reduction of amyloidogenic light chains as the amyloid organ damage is not reversible anymore. Therefore, it would be desirable to include anti-amyloid drugs which not only inhibit amyloid formation or deposition during or after the clone directed treatment, but actively remove amyloid deposits. There have been a few approaches with several drugs in the past, but these have not been successful yet. However, two anti-amyloid antibodies are currently investigated in prospective clinical trials (Table 4).

Table 4. Summary of drugs for anti-amyloid treatment.

Drug (and Reference)	Mechanism of Action	Current Status
Epigallocatechinegallat (EGCG), green tea substance [43]	Inhibition of amyloid formation and/or degradation	Clinical trial not successful. Compound cannot be applied in high dosages due to liver toxicity. Poor intestinal resorption.
Doxycycline [44]	Inhibition of fibril formation	One clinical trial ongoing (NCT03474458), no effect in one randomized clinical trial [45]
Miridesap + dezamizumab [46]	SAP depletion in plasma + SAP removal from the tissue	Phase III trial was closed due to toxicity issues
Birtamimab [47]	Immunoglobulin G1 kappa monoclonal antibody, binds to light chain aggregates	Two clinical trials closed due to missing efficacy in interim analysis; one ongoing prospective Phase III trial in patients with cardiac stage Mayo IV
CAEL-101 [48]	Chimeric immunoglobulin G1 kappa monoclonal antibody binds to a cryptic epitope at light chain proteins that adopt a non-native structure	Two ongoing prospective Phase III trials in patients with cardiac AL patients, ongoing (NCT02245867)

11. Summary

Patients with systemic AL amyloidosis represent a very fragile population. Goal of therapy is a rapid and deep reduction of the toxic light chain in the blood using a feasible approach. The intensity of the therapy is relying on highly validated risk adaption using cardiac and renal biomarkers. In a next step the underlying disorder is characterized as plasma or B cell clone and respective effective regimen are chosen. In PC-AL it is highly recommended to use iFISH for the detection of cytogenetic aberrations. Recent publications from different centers suggest that t(11;14) can be used to select the most effective therapies. Translocation t(11;14) favors melphalan treatment (either conventional or as high-dose) and venetoclax in opposite to bortezomib. Gain of 1q21 might be a poor prognostic factor irrespective the given therapy. Finally, new immunotherapies in combination with established drugs will further enhance anti-clonal efficacy leading to an improvement of overall survival in the majority of the patients. For patients in advanced stages of the disease anti-amyloid strategies are investigated in prospective clinical trials.

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