Differences and Similarities in Treatment Paradigms and Goals between AL Amyloidosis and Multiple Myeloma

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Abstract: Although there are similarities in the treatment paradigms between AL amyloidosis and multiple myeloma, there are also fundamental differences. A similarity is of course the use of anti-plasma cell drugs in both diseases; however, the most serious mistake a hemato-oncologist can make is to use the same treatment schedule in dosing and frequency in AL amyloidosis patients as in multiple myeloma patients. AL amyloidosis patients with >10% bone marrow plasma cell infiltration in particular are at risk of receiving a more intensive treatment than they can tolerate. This difference in dosing and frequency is true for many anti-clonal drugs, but it is most apparent in the use of high-dose melphalan and autologous stem cell transplantation. While in multiple myeloma in the age group of ≤70 years, more than 80% of patients are fit enough to receive this intensive treatment, this is the case in less than 20% of AL amyloidosis patients. A similarity is the alignment in the goal of treatment. Although in AL amyloidosis has long been recognized that the goal should be complete hematological remission, this has become more apparent in multiple myeloma in recent years. A common goal in the coming years will be to evaluate the role of minimal residual disease to improve survival in both diseases.

Keywords: immunoglobulin light-chain amyloidosis; multiple myeloma; drug therapy

1. Introduction

AL amyloidosis is a disease belonging to the group of plasma cell neoplasms. Other diseases in this group are monoclonal gammopathy of undetermined significance (MGUS), (smoldering) multiple myeloma (MM), plasma cell leukemia, solitary plasmacytoma of the bone, and extra-osseous plasmacytoma. These diseases all have separate definitions, as published and defined by the International Myeloma Working Group (IMWG) in 2014 [1]. MGUS and MM are the most well-known plasma cell neoplasms and also the most prevalent, while AL amyloidosis is less known and a rare disease. Importantly, and in contrast to MGUS and MM, AL amyloidosis is not defined by the percentage of infiltration of clonal plasma cells in the bone marrow. The disease is defined by a plasma cell clone of any size in the bone marrow combined with the presence of extra cellular deposits of amyloid in visceral organs and related organ dysfunction. Fibrillary amyloid deposits causes several types of organ dysfunction, which are defined per organ by international criteria [2–4]. Most patients present with two or more internal organs involved, which implies that AL amyloidosis patients are mostly fragile and more susceptible to the side effects of drugs [5].

Of all the different types of systemic amyloidosis, the AL type is the most frequent [6]. Importantly, patients can have MGUS or MM and have amyloidosis caused by another precursor protein, for example, transthyretin (TTR) [7]. Therefore, it is of the utmost importance to perform a biopsy and, if amyloid is present, to perform a correct typing of the amyloid in every patient with a plasma cell neoplasm.

Since most hematologists are familiar with MM and because treatment of AL amyloidosis is performed with the same type of drugs used in MM, there is a substantial risk
of AL amyloidosis patients being treated with myeloma-based treatment regimens that they cannot tolerate. This may result in an increased toxicity profile and in severe side effects. In the current article, we describe some of the similarities and differences between the two diseases.

2. Epidemiology

National- and hospital-based registries of AL amyloidosis estimate the incidence of AL amyloidosis at around 6–12 patients per million persons per year [8,9]. The incidence of MM is ten times higher, with an estimation of 50–60 patients per million persons per year [10]. More similar are the male-to-female ratio and the median age at diagnosis (Table 1).

Table 1. Epidemiology and plasma cell clone differences.

<table>
<thead>
<tr>
<th></th>
<th>AL Amyloidosis</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence per million</td>
<td>6–12</td>
<td>50–60</td>
</tr>
<tr>
<td>patients/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>68 years</td>
<td>70 years</td>
</tr>
<tr>
<td>Men/women</td>
<td>62%/38%</td>
<td>63%/37%</td>
</tr>
<tr>
<td>Median survival</td>
<td>3.8 years</td>
<td>7–10 years</td>
</tr>
<tr>
<td>Estimated diagnostic delay</td>
<td>180–441 days</td>
<td>163 days</td>
</tr>
<tr>
<td>Expression lambda</td>
<td>70%</td>
<td>40%</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(11:14) in ≈ 60% hyperdiploidy ≈ 20%</td>
<td>t(11:14) in ≈ 20% hyperdiploidy ≈ 50%</td>
</tr>
<tr>
<td>Bone marrow infiltration, median</td>
<td>7–10%</td>
<td>40%</td>
</tr>
</tbody>
</table>

In both diseases, there is a delay in diagnosis, but some reports suggest that this delay is much more prominent in AL amyloidosis, ranging from 180 to 441 days [11,12]. In addition, many patients diagnosed with AL amyloidosis need to consult numerous different physicians before receiving a correct diagnosis [13]. In MM, the estimated time from the first consultation to diagnosis is around 163 days [14]. Median survival after diagnosis can vary in both diseases and is dependent on prognostic factors (see the section on prognostic systems). In general, patients with AL amyloidosis have a shorter median survival, of less than 4 years, while in MM the median survival is currently around 7 to 10 years, also depending on age and the possibility of receiving an autologous stem cell transplant (ASCT) [5,15]. Looking in more detail at the survival curves, there is a striking difference in the shape. In AL amyloidosis, there is a very high mortality, of around 25–30%, in the first 6 months after diagnosis, but there also seem to be more long-term survivors, especially in the group of patients fit enough to receive high-dose melphalan (HDM) and ASCT. In MM, the survival curve presents a more linear shape, with a constant down slope and fewer long-term survivors [5,15,16].

3. Prognostic Systems

The prognostic systems between newly diagnosed MM and AL amyloidosis differ significantly. The prognostic system of MM is solely based on the characteristics of the plasma cell clone, while in AL amyloidosis the extent of cardiac involvement is the primary predictor of survival. In the former International Staging System (ISS), the components used in MM were serum b2 microglobulin and serum albumin, and in the revised ISS this was extended to LDH and chromosomal abnormalities of the myeloma plasma cells [17]. Three different prognostic groups can be identified, with R-ISS stage III being the largest, with a 5 year overall survival (OS) of 40%.
For AL amyloidosis, different prognostic systems are available. Currently, the mostly commonly used are the revised Mayo stage and the European modification of the original Mayo staging system [18,19].

Both systems rely on the extend of cardiac involvement as measured with serum assays for NT proBNP or BNP and Troponin I or T. These serum markers at diagnosis are closely related to survival. In the revised Mayo score of 2012 the difference between the involved and the uninvolved serum free light chain (FLC) is also a prognostic factor. In this prognostic system, four different prognostic groups are identified, and stage IV, with the highest cardiac biomarkers and a difference of FLCs (dFLC) $\geq 180$ mg/dL, measured with the Binding Site assay, has a median OS of around 6 months.

In the European staging system, the same cardiac biomarkers are used; however, stage III is subdivided into stage IIIa and stage IIIb. In addition, systolic blood pressure is incorporated as a symptom of organ failure in AL amyloidosis patients. Stage IIIb patients in particular, defined as a NT proBNP $> 8500$ pg/ml and a systolic blood pressure of $\leq 100$ mmHg, have a dismal outcome, with a median OS of 3 months [19].

The different prognostic systems clearly reflect the differences between the two diseases: MM is more dependent on the dynamics of its plasma cell clone and AL amyloidosis is more dependent on misfolding-prone FLCs and, consequently, the involvement of internal organs and their amyloid load. This is also reflected by the type of organs that are typically involved in the two diseases. MM is characterized by lytic bone lesions and sometimes the involvement of the kidney, presenting as cast nephropathy or deposition disease, and, less frequently, the peripheral nervous system. In AL amyloidosis, many more organs and systems are at risk, such as the heart, the kidneys, the peripheral nervous system, including not only sensory polyneuropathy but also autonomic neuropathy, the liver, the digestive tract, and soft tissues such as the tongue and skin purpura; there is also pulmonary and pleural involvement.

4. Plasma Cell Characteristics

The diagnosis of AL amyloidosis requires the presence of a monoclonal gammopathy. This most frequently consists of a relatively small clone that would be considered a MGUS if it were not for the presence of the amyloidosis. The median bone marrow plasma cell infiltration in AL amyloidosis is 7–10% but the range is large [18]. In MM, by definition, the plasma cell infiltration is $\geq 10\%$, but the median infiltration at diagnosis is around 40% [20].

As mentioned earlier, the size of the plasma cell clone is not defined in AL amyloidosis and therefore it is not common to diagnose patients with $>10\%$ bone marrow infiltration, which is seen in almost 30% of patients [21]. Very rare is the combined diagnosis of symptomatic MM with lytic bone lesions and organ dysfunction due to amyloidosis. In a study of 1255 newly diagnosed AL amyloidosis patients, a total of 100 (8%) simultaneously presented with symptomatic MM with at least one clinical CRAB (hypercalcemia, renal disease, anemia, bone disease) criterion. These patients had worse clinical outcomes compared to the AL amyloidosis patients without concurrent MM [22].

However, the opposite can also occur, in the sense that amyloid deposits are detected in newly diagnosed MM patients. This is not an infrequent finding when actively sought in bone marrow and/or fat pad biopsies, but the reported frequency differs considerably, between 1 and 40% [23–25]. However, without clear visceral organ involvement, this finding should not impact treatment decisions, since progression to systemic amyloidosis is rare (2.7%) [26]. Furthermore, patients with AL amyloidosis can progress to MM and patients with a former diagnosis of MM can later develop organ dysfunction due to amyloid deposits [27,28]. This clearly indicates that both diseases are on the same spectrum and overlap does exist. Treatment decisions after careful examination of the patient’s condition have to be made on the most prominent feature that threatens the patient the most [29].

In general, the plasma cell clone in AL amyloidosis has a lower proliferation index compared to the plasma cell clone in MM [30]. Furthermore, in gene expression profiling, amyloidosis plasma cells have a different profile compared to myeloma plasma cells [31]. A
more easily detectable difference is the expression and secretion of the light chain between plasma cell clones. In AL amyloidosis, around 70% of plasma cells express lambda, while this is the case in 40% of MM patients [5]. This difference is probably due to biophysical and structural differences between lambda and kappa light chains, associated with a greater propensity to aggregate as amyloids for lambda light chains [32].

The differences in cytogenetic abnormalities (CA) between the clones is also striking. In AL amyloidosis, t(11;14)(q13;q32) is the most common translocation detected with FISH analysis, and can be found in almost 60% of patients. This is approximately three times as often as that detected in MM patients [33,34]. This translocation is strongly associated with the lack of an intact immunoglobulin in AL amyloidosis, and may therefore contribute to this phenomenon, which is frequently seen in AL amyloidosis [35]. By contrast, in MM, hyperdiploidy is seen in around half of patients, while this is the case in only 20% of AL amyloidosis patients [36]. The standard high-risk CA as defined in MM are very rare in AL amyloidosis. Both the IgH translocations t(4:14) and t(14:16) are detected in only 2–3% of newly diagnosed AL amyloidosis patients and 17p deletion rarely occurs [35,37]. The gain of 1q is seen in 20–25% of patients and, as in MM, seems to be a negative prognostic factor for survival [38].

There is a debate over the prognostic value of the CA in AL amyloidosis. The t(11:14) in particular seems to be negatively associated with survival but other studies indicated this was related to the type of treatment [39,40]. The poor outcome in t(11:14) may be overcome by treatment with high-dose chemotherapy and ASCT [40]. Most of these studies are performed as single-center analyses, which may skew the results. In the large international Andromeda study, the addition of daratumumab to a bortezomib-based regimen demonstrated a favorable outcome in all CA groups, including t(11;14) [41]. Currently, there is no general treatment advice provided in international guidelines specific for a certain CA and type of treatment, as is sometimes the case in MM for high-risk CA [42]. In the near future, this may change if prospective trials show favorable effects of the use of a BCL-2 inhibitor specifically in t(11;14)-positive patients. MM patients seems to be very sensitive to venetoclax treatment when a t(11:14) is present and some publications, including a prospective phase I trial with the combination of daratumumab and venetoclax, suggest that this may also be the case in AL amyloidosis [43–46].

5. IgM AL Amyloidosis

An important difference between MM and AL amyloidosis is that the malignant cells in AL amyloidosis can also originate from a lymphoplasmacytic (LPL) clone instead of a plasma cell clone. This disease is called IgM amyloidosis and it is important to recognize this entity because of the treatment differences. IgM-associated AL amyloidosis is less frequent than non-IgM AL amyloidosis and comprises around 5–7% of all AL amyloidosis patients [47,48]. Of all the patients with IgM AL amyloidosis, about half can be diagnosed with a ≥10% LPL clone upon bone marrow examination [49]. The typical MYD88 L265P mutation was detected in this case series in 84% of patients with an LPL morphology and chemokine receptor CXCR4 WHIM mutations in 29%.

The clinical picture of IgM-associated AL amyloidosis differs somewhat from non-IgM AL amyloidosis. There is more soft tissue (40% versus 20%), and peripheral nerve involvement (32% versus 15%). By contrast, cardiac involvement seems to be less frequent (56% versus 73%) [47,48]. These differences are probably due to differences in light chain variable region gene usage. Peripheral nerve involvement could be related to more frequent light chain, LV2-14 usage, less frequent cardiac involvement and less usage of LV1-44 in IgM amyloidosis [50].

In the treatment of IgM AL amyloidosis, the use of an anti-CD20 antibody is typically incorporated in non-transplant-based regimens. In general, in AL amyloidosis, the quality of response is crucial and the goal should be to achieve a very good partial response (VGPR) or better, which implies a more aggressive treatment than is most commonly used in indolent lymphomas such as LPL. Non-transplant regimens are based on standard B
cell lymphoma regimes, such as dexamethasone-rituximab-cyclophosphamide (DRC) or rituximab-bendamustin (RB), but there is a clear lack of data and, therefore, of guidelines. In a recent European collaborative study, the use of 22 different front line regimes was reported [48]. An analysis of treatment with RB in 122, mostly relapsed, IgM amyloidosis patients from two large European amyloidosis centers was reported in 2018 [51]. The hematologic response obtained was 58% with a complete response (CR) in one patient (2%) and a very good partial response (VGPR) in seven (19%), and response was strongly associated with survival. One prospective phase II trial recently reported using the same drug combination but no separate mention of the IgM phenotype [52]. The patients received a median of four cycles (range, 2–12 cycles), with 57% of patients achieving a partial response (PR) or better (11% CR, 18% VGPR). Furthermore, bortezomib in combination with rituximab and dexamethasone was investigated in a prospective trial with 10 IgM AL amyloidosis patients. The depth of responses was not extensively described, but 50% of the patients demonstrated a PR or better. The side-effects were mostly of a neurological character: hypotension and peripheral neuropathy [53].

Because of the frequent presence of the MYD88 L256P mutation, ibrutinib or other Bruton Tyrosine Kinase (BTK) inhibitors would also be an option for the treatment of IgM AL amyloidosis patients. So far, eight patients have been reported in research, with disappointing results [54]. Only two hematological responses were observed and the most frequent adverse events were peripheral edema and polyneuropathy. Two patients developed atrial fibrillation and one patient with preexisting atrial fibrillation experienced a transient ischemic attack. First-generation BTK inhibitors as single agents do not generally lead to CR or many VGPR remissions, which are necessary for AL amyloidosis patients, and newer BTK inhibitors or combinations may be more promising. At the time of writing, the patient with relapsed and refractory IgM amyloidosis described in a recent case report still responded well to ibrutinib treatment after reaching a VGPR [55].

By contrast, ASCT does seem to be highly effective for the treatment of IgM AL amyloidosis. ASCT is mostly performed after high-dose melphalan (HDM) instead of BCNU/carmustine, etoposide, ara-C and melphalan (BEAM) myeloablative therapy and perhaps underutilized. In the European collaborative study, only 1.8% of patients received an ASCT [48]. In a retrospective analysis of 38 patients, in whom half received some kind of induction therapy before ASCT, the overall response rate was 92%, with 76% VGPR [56]. Of the 38 patients, 32 received HDM and 6 received BEAM conditioning chemotherapy, and the 100 day mortality rate was 5%. The median progression-free survival (PFS) and overall survival (OS) were 48 and 106 months, respectively, and organ response was seen in >50% of patients.

6. Treatment: General Principles and Goals

There are many similarities in the treatment of both plasma cell neoplasms, but also many differences. In AL amyloidosis, the diagnosis unequivocally implies treatment, since allowing toxic FLC to persist will increased the amyloid load in the body and thereby increases organ damage. In MM, patients without end organ damage or myeloma defining events are classified as asymptomatic MM without the need for immediate treatment. With the exception of lytic lesions, treatment can restore many symptoms in MM, such as hypercalcemia and anemia, in a short timeframe, while in AL amyloidosis, there is much less and much slower reversibility of symptoms. This is because the amyloid deposits themselves cannot be treated or removed by anti-plasma cell-directed treatment. Amyloid clearance has to be performed by the macrophages in the body itself and this occurs at a very slow pace. However, cardiac function can be restored more quickly, since the prefibrillar species of the light chain amyloid fibril formation pathway, such as misfolded monomers and oligomers, are already toxic to cardiac myocytes, and rapid lowering of the FLCs is therefore important in cardiac disease [57]. This concept has been incorporated into the new organ response criteria, in which the biomarker NT proBNP and the New
York Heart Association (NYHA) classification have replaced the former echocardiography criterion [3].

The goal of treatment in AL amyloidosis is a CR with negative immunofixation of both serum and urine and a normalization of the FLC ratio, when applicable [58]. Many years ago, a clear relation between depth of response and survival was noted and the achievement of CR or VGPR was recommended as the general goal of treatment [3,59]. Furthermore, in MM, achieving a VGPR or better on first-line treatment is associated with a more favorable outcome and survival, but this correlation is more diffuse due to the superior organ function and condition of MM patients in general.

Another difference between the diseases is the definitions of the response categories. In AL amyloidosis, the term dFLC was introduced, which means the difference between involved and uninvolved FLC, in order to produce a more precise and prognostic response category system [1,4,60]. New data are emerging on the prognostic value of minimal residual disease testing on bone marrow aspiration, which are discussed in another article of this issue [18,61].

In MM treatment, there can be long treatment-free intervals between therapies. When biochemical progression is noted but no end organ damage is seen, MM patients can still enjoy some months or even years of watchful waiting before a new line of treatment is started. This is not the case if a hematological relapse is noted in AL amyloidosis patients. Patients with cardiac disease in particular need to start anti-plasma cell-directed therapy promptly, while patients after ASCT and prolonged organ responses can perhaps tolerate the rise of the toxic FLC a little better [62,63].

Risk-adapted treatment is preferred in AL amyloidosis, since most patients are fragile and do not tolerate commonly used dosing regimens. Three risk categories are defined, with low-risk patients transplant-eligible patients in the minority (≤20%). High-risk patients are defined by Mayo stage IIIb and/or having New York Heart Association class III or IV heart disease. Other factors to consider are age, performance status, glomerular filtration rate (GFR), and systolic blood pressure [64]. Frequent assessments of hematological response during treatment are needed and, since the goal is to achieve a CR or VGPR, early adjustments to the treatment regime must be considered if this is not reached [65].

7. Intensive Therapy with High-Dose Melphalan and Autologous SCT

Most patients with MM under the age of 70 years can tolerate intensive treatment with ASCT, which is performed in 80% of patients in this group. By contrast, in AL amyloidosis, less than 20% of patients can tolerate this type of treatment. A careful selection of patients is needed to avoid treatment-related mortality (TRM) of this procedure in AL amyloidosis. Indeed, in more recent publications, TRM has substantially decreased to a similar risk to that seen in MM patients [66].

In addition to cardiac staging, other eligibility criteria for ASCT are performance status 0 to 2, NYHA class I or II, a left ejection fraction of ≥45–50%, the absence of severe orthostatic hypotension (i.e., systolic blood pressure ≥90 mm Hg), and GFR > 40 ml/min. Induction therapy before stem cell mobilization can be given, especially to patients who have ≥10% bone marrow plasma cell infiltration. In contrast to MM patients, stem cell mobilization and leukapheresis can be associated with unexpected morbidity in AL amyloidosis. A syndrome of hypoxia and hypotension has been described both during mobilization with granulocyte colony stimulating factor (G-CSF) and during the leukapheresis procedure itself, probably as a result of a capillary leak syndrome triggered by G-CSF. Therefore, the use of reduced doses of G-CSF (10 µg/kg per day for 4–5 days) is recommended. In low-burden disease (i.e., plasma cells <10%) the use of cyclophosphamide in mobilization schemes does not seem to be necessary.

Conditioning regimens are similar and based on high-dose melphalan (HDM). The usual melphalan dose is 200 mg/m², since lower-dose melphalan is associated with decreased hematological response and PFS; therefore, other non-transplant treatment options may be more suitable [67].
8. Treatment of ASCT-Ineligible Patients

The majority of patients with AL amyloidosis are treated with non-ASCT based treatment due to organ impairment and general frailty, which makes them ineligible for intensive treatment. For these patients, there are several treatment options. Whenever possible, a bortezomib-based regimen is preferred as a first-line treatment due to its excellent results. The use of bortezomib features a more extended toxicity profile in AL amyloidosis than in MM patients. Dizziness, hypotension, heart failure, and increased peripheral sensory neuropathy in particular are more often witnessed in AL amyloidosis patients compared to MM patients [68]. Because of this different toxicity profile and tolerability, bortezomib is dosed once a week (Table 2). In the HOVON 104 trial, bortezomib was dosed twice weekly, combined with dexamethasone, and 30% of patients could not proceed to HDM and ASCT, mostly due treatment-related toxicity [66].

Table 2. Dosing and schedules of anti-plasma cell therapies in AL amyloidosis and MM.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Multiple Myeloma</th>
<th>AL Amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>bortezomib</td>
<td>1.3 mg/m² day 1,4,8,11/21 days</td>
<td>1.3 mg/m² day 1,8,15,21/28 days</td>
</tr>
<tr>
<td>ixazomib</td>
<td>4 mg day 1,8,15/28 days</td>
<td>4 mg day 1,8,15/28 days</td>
</tr>
<tr>
<td>carfilzomib</td>
<td>Maximal 20/56 day 1,2,8,9,15/16/28 days</td>
<td>drug not preferred</td>
</tr>
<tr>
<td>melphalan</td>
<td>Diverse dosing, po and iv</td>
<td>Similar dosing po and iv</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>500 mg/m², iv, per week</td>
<td>300 mg/m², max 500 mg, p.o, per week</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>40 mg per week</td>
<td>10–20 mg per week</td>
</tr>
<tr>
<td>thalidomide</td>
<td>200 mg daily</td>
<td>50–100 mg daily</td>
</tr>
<tr>
<td>lenalidomide</td>
<td>25 mg 1–21/28 days</td>
<td>15 mg 1–21/28 days</td>
</tr>
<tr>
<td>pomalidomide</td>
<td>4 mg 1–21/28 days</td>
<td>4 mg 1–21/28 days</td>
</tr>
<tr>
<td>daratumumab</td>
<td>1800 mg sc or 16 mg/kg iv</td>
<td>1800 mg sc or 16 mg/kg iv</td>
</tr>
<tr>
<td>isatuximab</td>
<td>10–20 mg/kg iv</td>
<td>20 mg/kg iv</td>
</tr>
</tbody>
</table>

po = per oral, sc = subcutaneous, iv = intravenous.

After many single-arm prospective studies and retrospective database analyses, the benefit of bortezomib was recently demonstrated in a randomized phase III trial comparing the combination of melphalan-dexamethasone (MD) to MD plus bortezomib (BMD) in patients with Mayo stage I-IIIa disease [69]. In this trial, the addition of bortezomib improved the hematological response rate from 52 to 79% and showed an overall survival benefit, with a median OS in MD arm of 34 months, which was not reached in the BMD arm. Grade 3 and 4 toxicities did occur more frequently in the BMD group, which mainly consisted of cytopenias, peripheral neuropathy, and cardiac failure.

Previously, the combination of cyclophosphamide-bortezomib-dexamethasone (Cy-BorD) had also been shown to be effective in AL amyloidosis, although not in a randomized trial [70]. Even though no head-to-head comparisons of BMD and CyBorD have been performed, response rates appear to be comparable in the first-line setting. In a prospective observational study of 230 ASCT-ineligible patients treated with CyBorD, the hematological response rate was 60%, although the 20 Mayo stage IIIb patients included in this study demonstrated disappointing lower response rates and poor outcomes [70]. Another large prospective observational study of 915 AL amyloidosis patients, 94.9% of whom were treated with CyBorD as first-line therapy, demonstrated a hematological response rate of 65%, with 49% CR/VGPR and a median OS of 72 months [71]. Importantly, in the CyBorD regimen, both bortezomib and cyclophosphamide are dosed differently compared to MM treatment schedules. Cyclophosphamide is preferably given orally and at a lower dose, with a maximum of 500 mg per week. Furthermore, dexamethasone dosing can be very troublesome in AL amyloidosis patients, especially those with nephrotic syndrome and...
heart failure. The maximum tolerated dose seems to be 20 mg per week, but patients can also be treated with 10 mg per week. Therefore, the regimen called VCD in MM patients is very different from the CyBorD regimen applied to AL amyloidosis patients, although the same drugs are used.

Recently, the addition of the monoclonal antibody daratumumab to CyBorD was demonstrated to further improve hematological responses in a randomized phase III Andromeda trial for patients with newly diagnosed AL amyloidosis Mayo stage I-IIIA [41]. In this trial of 388 patients, the CR rate was 53.3% versus 18.1% for the dara-CyBorD and the CyBorD arm respectively. This also translated into improved hematological progression-and major organ deterioration-free survival as well as improved organ responses. As in MM, daratumumab is very well tolerated by AL amyloidosis patients in the subcutaneous setting and does not seem to feature a different toxicity profile. Therefore, it can be dosed similarly to its dosage for MM patients.

Patients who cannot tolerate bortezomib, mostly due to disease-related sensory and autonomic neuropathy, are candidates for treatment with melphalan-dexamethasone or, alternatively, lenalidomide-dexamethasone. Again, lenalidomide dosing is lower than in MM patients because the dose of 25 mg daily is not tolerated [72]. In a prospective study, grade 3–4 toxicities consisted of neutropenia (45%), thrombocytopenia (27%), rash (18%), and fatigue (18%). Therefore, the recommended starting dose of lenalidomide is 15 mg.

Mayo stage IIIb patients are very difficult to treat and demonstrate a short median survival of 6 months. Most guidelines advise treatment with single drugs at lower doses and to increase these if they are tolerated [42]. Currently, a prospective trial EMN22 is investigating the use of single-agent daratumumab in this group (NCT04131309).

9. Conclusions

A range of therapeutics can be used to suppress the plasma cell clone and improve the outcome of patients with both plasma cell neoplasms AL amyloidosis and MM. Compared to those with MM, AL amyloidosis patients require an even more balanced approach to their treatment due to the multi-organ involvement of this disease. This also requires a highly specialized, multidisciplinary, and experienced team to provide every patient with the best treatment possible and limit unnecessary toxicity. In this regard, the establishment of expert treatment centers is very important. In the future, the development of effective anti-amyloid therapeutics added to a backbone of anti-plasma cell drugs may even improve the outcome of AL amyloidosis patients.

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