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Review

The Evolving Landscape of Anti-Clonal Therapy in Newly Diagnosed Systemic Light-Chain (AL) Amyloidosis: Evidence and Time-Based Comparative Glimpse with Multiple Myeloma

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Abstract

Systemic light-chain (AL) amyloidosis is a rare and incurable disease, classified under the category of plasma cell neoplasms and other diseases with paraproteins in the fifth edition of the World Health Organization classification of lymphoid tumors. This entity shares some similarities with multiple myeloma (MM), remarkably a bone marrow infiltration of clonal plasma cells. Moreover, one out of five newly diagnosed AL amyloidosis (NDAL) also fulfills the current diagnostic criteria for MM. A multidisciplinary therapy approach should be established, in which hematological therapy plays a crucial role. Anti-clonal therapy is the basis of hematological therapy, besides supportive therapy and emerging anti-fibrils therapy. In recent years, advances in the anti-clonal therapy of MM have progressively transferred to carefully selected patients with systemic AL amyloidosis, significantly improving outcomes in this rapidly changing field. This review aims to critically analyze the comparative evolution and evidence-based approach of anti-clonal therapy in NDAL vs. MM since the introduction of bortezomib. Participation in clinical trials remains the first option to consider in daily clinical practice.

Keywords: systemic light-chain amyloidosis; multiple myeloma; treatment; anti-clonal therapy; immunotherapy; autologous stem cell transplant; anti-CD38 monoclonal antibodies; conjugated monoclonal antibodies; bispecific antibodies; chimeric antigen receptor T-cell therapy

1. Introduction

Immunoglobulin (Ig)-related light chain (AL) amyloidosis is a challenging and heterogeneous entity included in the 5th edition of the World Health Organization (WHO) classification of lymphoid tumors [1] into the category of “Plasma cell neoplasms and other diseases with paraproteins”, and in the family of “Diseases with monoclonal Ig deposition”.

AL amyloidosis can be local, in about 5% of patients [2], or systemic, in most cases. Systemic involvement must always be excluded in cases of local disease at the time of diagnosis. The clinical behavior of true localized AL amyloidosis is commonly benign, with a very low risk of systemic transformation. Importantly, only systemic AL amyloidosis patients require systemic treatment.

Newly diagnosed (ND) systemic AL amyloidosis (NDAL) is characterized by the presence of a clonal population of Ig secreting bone marrow plasma cells (cBMPCs), that produces a light chain (LC) as either an intact Ig or as LC-only monoclonal protein. This protein misfolds and forms insoluble amyloid fibrils that deposit in different organs, causing organ failure [3]. The spectrum of monoclonal gammopathies (MGs) includes MG of uncertain significance (MGUS), MG of clinical significance (MGCS), multiple myeloma (MM), Waldenström macroglobulinemia (WM), and other

entities [4]. The bone marrow aspirate and biopsy are crucial to characterize cBMPCs and confirm a timely and accurate diagnosis [5].

The prognostic impact of comorbidity in MM and systemic AL amyloidosis is well documented [6,7]. About 20% of patients with systemic AL amyloidosis fulfill the current diagnostic criteria for MM (AL/MM) [2], representing a peculiar form of comorbidity with negative prognostic impact. Nonetheless, AL amyloidosis may be associated with other MGs such as MGUS, MGCS, particularly MG of renal significance, WM, other types of non-Hodgkin lymphomas, and the full spectrum of MM ranging from smoldering MM (SMM) from plasma cell leukemia.

MM and systemic AL amyloidosis are both complex, incurable, and heterogeneous diseases. However, the epidemiology of these two entities [8,9] presents key differences, mainly in terms of incidence and prevalence, being considered systemic AL amyloidosis a rare disease. Consequently, the pace of research has been agile, thrilling, and dizzying in MM, while the rhythm in AL amyloidosis has been slow and challenging. Interestingly, AL/MM patients have been able to benefit from recent approved therapeutic advances in MM, showing deeper hematological (hem) and cardiac (car) responses. The response dynamics studies demonstrated that achieving an early and deep hem response was necessary in most cases to reach deep and long-lasting car response, which is the crucial endpoint in terms of overall survival (OS) [10,11]. This has been confirmed mainly in the setting of observational real-world (RW) studies. Unfortunately, patients with both diseases have usually been mutually excluded in specific clinical trials for one of the two entities.

The use of T-cell redirecting immunotherapy has transformed the treatment of relapsed/refractory (RR) MM (RRMM). Both chimeric antigen receptor (CAR) T cells and T-cell engagers have changed this clinical scenario, and they are being investigated in ND MM (NDMM). The prognostic relevance of achieving and maintaining measurable residual disease (MRD) negativity (MRD-) has been confirmed in both NDMM and RRMM [12,13], becoming a surrogate early endpoint of progression free survival (PFS) and OS. The growing evidence on the role of MRD in systemic AL amyloidosis seems to point in the same direction as in the case of MM [14].

The current therapeutic approach of systemic AL amyloidosis should be necessarily personalized, comprehensive, and multidisciplinary [15, 16], involving a group of specialists integrated into a specific AL clinical unit. Hematological treatment should be addressed at three levels. First, supportive therapy [17]. Second, anti-clonal therapy [18, 19]. Third, anti-fibrils therapy (currently, only available in clinical trials) [20].

Epidemiology can help to unveil clinical disparities and therefore, it could be considered the first level of heterogeneity. The incidence and prevalence of AL are much lower than those of MM, justifying slower research development.

Despite similarities between AL and MM (cBMPCs infiltration and similar anti-clonal therapy), a time-based comparative approach in [15,16] the evolution of the anti-clonal therapies is lacking. This narrative review aims to comparatively explore the evolving bortezomib-based anti-clonal therapy in NDAL vs. MM, focusing on the respective accumulated evidence and the speed with which it was obtained.

2. The Evolution over Time of Anti-Clonal Therapy in Systemic-AL Amyloidosis

The history of anti-clonal therapy in systemic AL amyloidosis mirrors what happened in MM, with some peculiarities, nuances, and a certain delay. Overall, three periods could be pointed out.

2.1. Second Half of the 20th Century, the Chemotherapy Era

The history of systemic AL amyloidosis has been recently summarized [21]. Remarkably, more than a century passed from the first clinical use of the term “amyloid” by Rudolf Virchow (1854) and the first description of a patient with primary amyloidosis, attributed to Samuel Wilks (1856), to the use of alkylating agents in the 1960s. Melphalan (M) was first used in MM [22], and later in AL amyloidosis, when the close relationship between AL and MM was pointed out [23–25].

MF was the most frequently used during the past century in both NDAL and RRAL. However, a shift to cyclophosphamide (C) occurred over the past two decades due to its immunomodulatory effect and a better safety profile in comparison with MF [26]. Since 2005, Bendamustine (B) has been an option particularly for RRAL [27].

Alkylating agents are usually administered in combination with corticosteroids, mainly prednisone (p) or dexamethasone (d).

The seemingly outdated chemo era has reached the present day. C remains in use besides daratumumab (D), bortezomib (V) and d, as a quadruplet (DVCd), being the current standard of care (soc) for NDAL patients [18,19]. On the other hand, high dose M (HDM) is still the preferred conditioning regimen for autologous stem cell transplant (ASCT) in transplant eligible (TE) AL patients [28].

2.2. First Two Decades of the 21st Century, the Era of the New Agents

Immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), the so-called new agents, have gained special prominence in the treatment of AL patients over the last two decades.

Regarding IMiDs [29], thalidomide (T) was the first-in-class drug used in this setting, followed by lenalidomide (R) and pomalidomide (P). IMiDs are mainly used in RRAL patients. These all-oral drugs should be used with caution, particularly in patients with cardiac involvement, due to their toxicity profile.

PIs [30] have been a cornerstone in the treatment of AL patients over the current century, following their success in MM. V is still the PI most frequently used, remaining involved in the present soc for NDAL. Intravenous carfilzomib and oral ixazomib are other less used PIs.

Both families of drugs can be eventually combined with each other, with alkylators, and corticosteroids, resulting in different and well-known combinations such as VCd [31].

2.3. Third Decade of the 21st Century, the Immunotherapy Era

The recognition of specific therapeutic targets in cBMPCs allowed the development of monoclonal antibodies (mAbs) [32] and Ab-drug-conjugates (ADC) [33], deeply changing the treatment paradigm of PC disorders, first in MM and then in AL.

The emergence of antiCD38 mAbs represented a revolution in the treatment of AL, being D the first antiCD38 used [34]. The addition of D to VCd in the phase 3 Andromeda trial [35] was the basis for the first FDA approved regimen for NDAL in 2021. Subsequently, other antiCD38 mAbs were developed. Isatuximab (Isa) as monotherapy has demonstrated similar results than D in the RRAL setting [36].

Elotuzumab (Elo) is a mAb targeting the signaling lymphocytic activation molecule family member F7 (SLAMF7). It has been mainly used in RRAL, in combination with IMiDs [37].

B-cell maturation antigen (BCMA) is a glycoprotein expressed on cBMPCs which has become a key therapeutic target for MM and AL. Several BCMA-targeting approaches have been developed [38,39]. First, belantamab mafodotin (belamab) is a BCMA-directed IgG1 conjugated to monomethyl auristatin F, a microtubule-disrupting agent. Curiously, the first report on the use of belamab as single agent in AL was also in 2021, involving six RR AL/MM patients [40]. Second, T-cell redirecting bispecific Abs (BsAbs). Several BCMA-CD3 BsAbs have been used in RRAL, mainly teclistamab [41] and elranatamab [42], whereas ABBV-383 (etentamig) [43], linvoseltamab, and others, are under development. Third, chimeric antigen receptor (CAR) T-cells [44]. Several anti-BCMA CAR-T cells have been used in AL: NXC201 (HBI0101) [45,46], idecabtagene vicleucel (Ide-cel, BB2121) [47], ciltacabtagene autoleucel (Cilta-cel) [48,49], and cesnicabtagene autoleucel (ARI0002h) [50]. Fourth, emerging anti-BCMA therapeutic approaches. Trispecific Abs (TsAbs) may potentially overcome acquired resistance to BsAbs. JNJ-5322 is a TsAb dually targeting BCMA and G protein-coupled receptor class C group 5 member D (GPRC5D), showing a 100% overall response rate (ORR) in a recent phase 1 study (NCT05652335) for RRMM patients [51].

3. The Evolving Landscape of Bortezomib-Based Therapies in NDAL vs. NDMM

New drugs for MM and AL are usually first tested in the RR setting and then in ND patients. V has demonstrated a crucial role in both entities since its accelerated approval by FDA in 2003 for its use in RRMM, based on the phase II SUMMIT trial [52]. Five years passed before its approval for NDMM in 2008.

From the beginning, V was commonly used in combination with d (Vd), due to a well demonstrated synergism. Step by step, different Vd-based combinations that were used in NDMM were also tested in NDAL, except for those associated with an unacceptable toxicity profile, particularly in terms of cardiotoxicity, such as Adriamycin (A) in VAd. Progressively, different alkylating agents were associated with the Vd backbone, mainly M, C, and B, as well as IMiDs (T, R, P), and mAbs (D, Isa, Elo), in diverse triplets or quadruplets.

AL is a rare entity and therefore the evidence in the evolving landscape of the treatment in NDAL patients comes mainly from case reports and small single-center series of real-world retrospective studies. To avoid potential bias in the comparison between the respective evolution of NDMM and NDAL anti-clonal therapy, only chronologically ordered, V-based, phase II and III clinical trials for both clinical scenarios were analyzed in Table 1, after an intensive English PubMed search including the following terms: “multiple myeloma, systemic AL amyloidosis, clinical trials, induction, therapy, treatment, bortezomib, and newly diagnosed”.

Table 1. Comparative evolution of bortezomib-based phase II/III trials in newly diagnosed multiple myeloma vs. newly diagnosed light-chain (AL) amyloidosis.

Anti-clonal therapy	NDMM				NDAL			
	Year/ Authors	Study	n	Name	Year/ Author	Study	n	Name
Vd	2005 Jagannath S et al. [53]	Phase II	32	-	2014 Huang X et al. [60]	Phase III Vdx2 & ASCT/ASCT	28/28	NCT01998503
	2006 Harousseau JL et al. [54]	Phase II	48	-	2015 Santhorawa la V et al. [61]	Phase II	25	NCT01083316
	2007 Rosñol L et al. [55]	Phase II	40	-	2019 Minnema MC et al. [62]	Phase II	50	HOVON 104 NTR3220
	2010 Harousseau JL et al. [56]	Phase III Vd/vAd	121/1 21	IFM 2005-01	2020 Landau H et al. [63]	Phase II	19	NCT01383759
	2015 Girnus SK et al. [57]	Phase II	50	NCT0109092 1	-			
	2015 Niesvizky R et al. [58]	Phase III Vd/VTd/VMp	168/1 67/16 7	UPFRONT NCT0050741 6	-			

VAd	2009 Jakubowiak AJ et al. [64]	Phase II	40	-	-			
	2010 Palumbo A et al. [65]	Phase II	102	-	-			
	2012 Sonneveld P et al. [66]	Phase III VAd/vAd	413/4 14	HOVON-65/ GMMG-HD4	-			
VMp/VMd	2008 San Miguel JF et al. [67]	Phase III VMp/Mp	344/3 38	VISTA NCT00111319	2020 Kastritis E et al. [72]	Phase III VMd/Md	53/56	EMN-03 NCT01277016
	2010 Mateos MV et al. [68]	Phase III VMp/VTp	130/1 30	GEM05 NCT00443235	-			
	2010 Palumbo A et al. [69]	Phase III VMp/VMpT	257/2 54	GIMEMA- MM-03-05 NCT01063179	-			
	2016 Mateos MV et al. [70]	Phase II VMp/Rd seq vs alt	118/1 15	GEM2010 NCT01237249	-			
	2025 Mateos MV et al. [71]	Phase III VMp-Rd/KRd/ DKRd	154/1 54/15 3	GEM- 2017FIT NCT03742297	-			
VCd	2009 Reeder CB et al. [73]	Phase II	33	-	2022 Shen K-n et al. [80]	NR VCd/VCddo x	55/56	NCT03401372
	2010 Bensingher WI et al. [74]	Phase II VCd /VTd seq	44	-	-			
	2012 Kumar S et al. [75]	Phase II VCd/VCd mod /VRd/VRCd	33/17 /42/4 8	EVOLUTIO N NCT00507442	-			
	2015 Mai EK et al. [76]	Phase III VCd/VAd	251/2 51	MM5- GMMG	-			
	2016 Moreau P et al. [77]	Phase III VCd/VTd	170/1 70	IFM 2013-14 NCT01564537	-			
	2017	Phase II	414	DSMM XI	-			

	Einsele H et al. [78]			NCT00833560				
	2019 Tanaka et al. [79]	Phase II	38	-	-			
BVp	2013 Berdeja J et al. [82]	Phase II	43	-	-			
	2015 Mateos MV et al. [83]	Phase II	60	NCT01376401	-			
VTd	2010 Cavo M et al. [84]	Phase III VTd/Td	241/239	NCT01134484	-			
	2012 Rosiñol L et al. [85]	Phase III VTd/Td/QT+V	56/56/57	NCT00461747	-			
	2015 Ludwig H et al. [86]	Phase II VTd/VTCd	49/49	NCT00531453	-			
VRd	2017 Durie BGM et al. [87]	Phase III VRd/Rd	235/225	SWOG S0777 NCT00644228	-			
	2019 Rosiñol L et al. [88]	Phase III	458	GEM2012 NCT01916252	-			
	2020 Kumar S et al. [89]	Phase III VRd/KRd	542/545	ENDURANCE NCT01863550	-			
	2024 Ailawadhi S et al. [90]	Phase III VRd/DRd	459	SWOG S2209 NCT05561387	-			
PVd	2023 Saj F et al. [91]	Phase II	34	POMACE	-			
EloVRd	2017 Laubach J et al. [92]	Phase II	41	NCT02375555	-			
	2021 Usmani SZ et al. [93]	Phase II EloVRd/VRd	48/52	SWOG-1211 NCT01668719	-			
	2024 Mai EK et al. [94]	Phase III EloVRd/VRd	279/280	GMMG-HD6	-			

				NCT0249592 2				
DVd	2023 Nagarajan C et al. [95]	Phase II	27	AMN006 NCT0369574 4	2024 Shen K-n et al. [96]	Phase II	40	NCT04474938
DVMp	2018 Mateos MV et al. [97]	Phase III DVMp/VMp	350/3 56	ALCYONE NCT0219547 9	-			
DVCd	2019 Yimer et al. [98]	Phase II	86	LYRA NCT0295181 9	2021 Kastritis E et al. [35]	Phase III DVCd/VCd	195/19 3	ANDROME DA NCT03201965
	2023 Beksac M et al. [99]	Phase II	29	EMN19 NCT0416656 5	2023 Rosenzweig M et al. [101]	Phase II DVCd	75	AQUARIUS NCT05250973
	2024 Mollee P et al. [100]	Phase II DVCd/VCd	64/57	AMaRC 03- 16 ACTRN1261 7000202369	2024 Hagen P et al. [102]	Phase III DVCd/DVC d-ASCT	143/14 3	SWOG S2213 NCT06022939
DVTd	2020 Roussel M et al. [103]	Phase III DVTd/VTd	543/5 42	CASSIOPEIA NCT0254138 3	-			
DVRd	2023 Voorhees PM et al. [104]	Phase II DVRd/VRd	104/1 03	GRIFFIN NCT0287474 2	-			
	2024 Sonneveld P et al. [105]	Phase III DVRd/VRd	355/3 54	PERSEUS NCT0371060 3	-			
	2025 Usmani SZ et al. [106]	Phase III DVRd/VRd	197/1 98	CEPHEUS NCT0365206 4	-			
DCVRd	2023 Kaiser MT et al. [107]	Phase II	107	OPTIMUM (MUKnine) NCT0318817 2	-			
IsaVRd	2022 Goldschmidt H et al. [108]	Phase III IsaVRd/VRd	331/3 29	GMMG-HD7 NCT0361773 1	-			
	2024 Facon T et al. [109]	Phase III IsaVRd/VRd	265/1 81	IMROZ NCT0331966 7	-			

	2024 Leleu X et al. [110]	Phase III IsaVRd/IsaRd	135/1 35	BENEFIT NCT0475187 7	-			
	2025 Askeland FB et al. [111]	Phase II IsaVRd	51	REST NCT0493984 4	-			

A: pegylated liposomal doxorubicin (adriamycin), alt: alternating, B: bendamustine, C: cyclophosphamide, D: daratumumab, d: dexamethasone, dox: doxycycline, Elo: elotuzumab, Isa: istuximab, K: carfilzomib, M: melphalan, mod: modified, NR: not reported, P: pomalidomide, p: prednisone, QT: chemotherapy, R: lenalidomide, seq: sequential, T: thalidomide, V: bortezomib, v: vincristine.

Several phase II and two phase III trials [53–58] assessed Vd in NDMM (2005-2015) whereas in the NDAL setting, a small observational study [59] including 18 consecutive AL patients (11 NDAL and 7 RRAL) treated with Vd pointed out an excellent 94% ORR. Shortly after a phase III tested direct ASCT vs. two cycles of Vd as induction followed by ASCT [60], showing a better outcome for patients treated with Vd induction. The corresponding phase II studies for NDAL [61–63] presented an evident delay (2015-2020) with respect to those for NDMM.

VAd was utilized as induction in NDMM mainly during the first decade of the current century [64–66], but this triplet was not applied to NDAL due to the A-associated cardiotoxicity risk.

Until the advent of D, the soc for NDAL patients was a combination of Vd and an alkylating agent, M (VMd or VMp) or C (VCd). Again, a huge difference in the time frame and the associated supporting evidence was obvious between both clinical scenarios. Regarding VMp, several phase II and III trials (2008-2025) demonstrated excellent outcomes in TI NDMM [67–71]. Remarkably, 682 patients were recruited in the phase III VISTA trial (2008) over less than two years [67]. In contrast, only one relatively recent (2020) phase III trial established VMd as soc in NDAL [72]. This study included 109 patients, and the recruitment took place over five years.

The clinical impact of VCd was also extensively analyzed in phase II and III trials (2009-2019) for NDMM patients [73–79] whereas most studies investigating the role of this triplet in NDAL patients were retrospective. Only one recent trial [80] demonstrated a lack of clinical benefit when doxycycline was added to VCd compared with VCd alone in cardiac NDAL patients. The most relevant retrospective study using VCd in NDAL enrolled 230 patients during more than six years [81].

Frontline BVp was explored in NDMM [82,83], but no trials were identified on the use of this triplet in NDAL patients.

Regarding combinations of V with IMiDs, several trials were identified for NDMM patients with the following triplets: VTd [84–86], VRd [87–90], and PVd [91]. However, no trials with these triplets were tested in NDAL patients.

As expected, all the previously commented anti-clonal combinations were challenged with the progressive introduction of different mAbs directed against specific therapeutic targets such as anti-SLAMF7 (Elo), anti-CD38 (D, Isa) and anti-BCMA (Belamaf). Overall, VRd has been the most widely used regimen to combine with the new mAbs in NDMM. This way, EloVRd revealed excellent results in NDMM [92–94], but trials are lacking in NDAL.

Following thrilling clinical development schedules, first D and then Isa-based anti-clonal therapies have highlighted the key role of targeted anti-CD38 therapy in NDMM and NDAL. D was the first anti-CD38 used in association with the full range of previous V-based regimens in NDMM. Interestingly, two phase II trials on the use of DVd in MM [95] and in AL [96] were published almost simultaneously. The DVMp regimen was successfully applied to transplant ineligible (TI) NDMM [97], but no trials were developed for NDAL. Remarkably, DVCd was also tested earlier in NDMM [98] than in NDAL [35], and other recent trials have confirmed good outcomes in both settings [99–102]. Regarding D-based combinations with IMiDs, DVTd [103], and mainly DVRd [104–107], which

is the current soc, have been extensively employed in NDMM, but no trials with these combinations have been tested in NDAL, probably due to the toxicity profile of IMiDs.

Alternatively, Isa-based combinations, mostly IsaVRd [108–111], have also been developed in NDMM with excellent results, but no completed trials are still available for NDAL.

Early assessment of new immunotherapy approaches in NDAL are being evaluated in ongoing clinical trials, but they are beyond the scope of this review, as well as anti-clonal therapy in the RRAL setting.

3. Discussion

The global landscape of V-based phase II/III trials focused on NDMM and NDAL over the last two decades is summarized in Table 2.

58 trials (27 of them were phase III) were included in the analysis, and only 10 of them (17.2%) were performed in the setting of NDAL.

23 (85.2%) out of 27 phase III trials were performed in NDMM, and only 4 in NDAL [35,60,72,102], associated with Vd, VMd, and DVCd.

16 combinations, including doublets, triplets, and quads, were compared in both scenarios. There was at least one NDAL study to compare in 5 (31.2%) of these regimens (Vd, VMp, VCd, DVd, and DVCd), highlighting the real evolution of anti-clonal therapy in NDAL in which V and D appear as the crucial drugs, along with an increasingly cautious use of corticosteroids.

Regarding the long-lasting debate about the use of alkylators in both scenarios, HDM conditioning with ASCT remains in use for TE NDMM and NDAL patients. On the other hand, C is the preferred alkylator for induction in NDAL (DVCd).

Figure 1 shows graphically the important delay in phase II and III trials between NDMM and NDAL regarding four common V-based regimens.

Table 2. Summary of bortezomib-based phase II/III trials on newly diagnosed multiple myeloma vs. systemic light-chain (AL) amyloidosis.

Regimen	n (MM /AL)	Period MM	Period AL
Vd	6/4	2005-2015	2014-2020
VAd	3/0	2009-2012	-
VMp/VMd	5/1	2008-2025	2020
VCd	7/1	2009-2019	2022
BVp	2/0	2013-2015	-
VTd	3/0	2010-2015	-
VRd	4/0	2017-2024	-
PVd	1/0	2023	-
EloVRd	3/0	2017-2024	-
DVd	1/1	2023	2024
DVMp	1/0	2018	-
DVCd	3/3	2019-2024	2021-2024
DVTd	1/0	2020	-
DVRd	3/0	2023-2025	-
DCVRd	1/0	2023	-
IsaVRd	4/0	2022-2025	-
Total	48/10	2005-2025	2014-2024

A: pegylated liposomal doxorubicin (adriamycin), alt: alternating, B: bendamustine, C: cyclophosphamide, D: daratumumab, d: dexamethasone, dox: doxycycline, Elo: elotuzumab, Isa: istuximab, K: carfilzomib, M: melphalan, mod: modified, NR: not reported, P: pomalidomide, p: prednisone, QT: chemotherapy, R: lenalidomide, seq: sequential, T: thalidomide, V: bortezomib, v: vincristine.

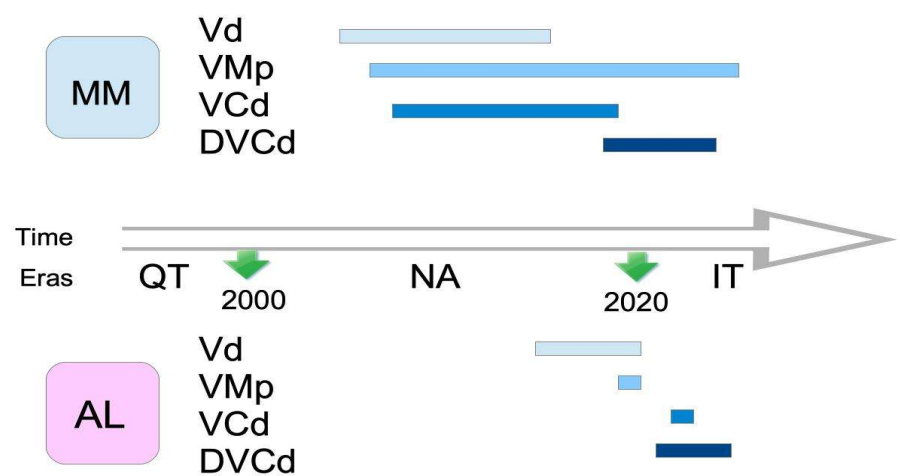


Figure 1. Comparative delay in key bortezomib-based phase II and III trials in newly diagnosed multiple myeloma vs. newly diagnosed systemic light-chain (AL)-amyloidosis. C: cyclophosphamide, D: daratumumab, d: dexamethasone, IT: immunotherapy era, M: melphalan, NA: new agents' era. QT: chemotherapy era, V: bortezomib.

5. Conclusions

The implementation of V-based phase II and III trials in NDAL shows a significant delay when compared with NDMM over the last two decades. Moreover, the number of trials, particularly phase III trials, is significantly lower in the NDAL setting. This is mainly attributed to differences in the epidemiological background of both entities, underlining the difficulty of performing clinical trials in the context of very rare diseases. Despite this, large collaborative research platforms led by referral centers increasingly allow studies to be carried out.

At the present time, two quads (DVRd and DVCd), only changing one drug, are the soc for NDMM and NDAL, respectively. Remarkably, since its introduction two decades ago, V remains a cornerstone in the induction of both entities. On the other hand, anti-CD38 mAbs have also demonstrated a crucial role in the induction therapy of these two scenarios, also in the event of the coexistence of both diseases (AL/MM).

Hopefully, the research background for the introduction of new therapeutic advances in NDAL will be shortened in the coming years and will resemble what happens in NDMM, a model of highly efficient dynamic research.

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Abbreviations

The following abbreviations are used in this manuscript:

ADC	Antibody-drug-conjugates
AL	Light-chain amyloidosis
AL/MM	Light-chain amyloidosis and multiple myeloma
ASCT	Autologous stem cell transplant
B	Bendamustine
BCMA	B-cell maturation antigen
BsAbs	Bispecific antibodies
C	Cyclophosphamide
CAR	Chimeric antigen receptor
cBMPCs	Clonal bone marrow plasma cells
d	Dexamethasone
D	Daratumumab
Elo	Elotuzumab
HDM	High dose melphalan
Ig	Immunoglobulin
IMiDs	Immunomodulatory drugs
Isa	Isatuximab
LC	Light chain
M	Melphalan
mAbs	Monoclonal antibodies
MGs	Monoclonal gammopathies
MGCS	Monoclonal gammopathy of clinical significance
MGUS	Monoclonal gammopathy of uncertain significance
MM	Multiple Myeloma
MRD	Measurable residual disease
ND	Newly diagnosed
NDAL	Newly diagnosed systemic AL amyloidosis
NDMM	Newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
p	Prednisone
P	Pomalidomide
PIs	Proteasome inhibitors
R	Lenalidomide
RR	Relapsed/refractory
SMM	Smoldering multiple myeloma
T	Thalidomide
TE	Transplant eligible
TI	Transplant ineligible
TsAbs	Trispecific antibodies
V	Bortezomib
WM	Waldenström macroglobulinemia

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