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REVIEW

Options for Rescue Treatment of Patients with AL Amyloidosis Exposed to Upfront Daratumumab

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Abstract

Purpose of Review This review aims to assess the therapeutic strategies available for relapsed/refractory patients with immunoglobulin light chain (AL) amyloidosis who received upfront daratumumab-based regimens.

Recent Findings The treatment landscape of AL amyloidosis has changed radically thanks to the introduction in the upfront setting of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DaraCyBorD) which improved patients' outcomes increasing the rate of hematologic and organ responses. However, many patients eventually relapse or are refractory to daratumumab and the best salvage therapy is not well defined yet. In this contest, we reviewed the available therapeutic options after daratumumab failure, and we look towards the current advances in Bcl-2 inhibitors, novel immunotherapeutic agents as chimeric antigen receptor (CAR-T) therapy and bispecific antibodies (bsAbs).

Summary Relapsed/refractory AL amyloidosis represent an unmet clinical need and novel targeted drugs require urgent prospective assessment.

Keywords AL amyloidosis · Rescue therapy · Daratumumab failure

Introduction

Systemic light chain (AL) amyloidosis is a plasma cell disorder characterized by the production and deposition of misfolded immunoglobulin light chains in multiple organs and tissues leading to organ damage [1]. Inducing a rapid and profound reduction in circulating amyloidogenic free light chain (FLC) is the early therapeutic goal in AL amyloidosis, as it can halt organ damage and eventually improves organ dysfunction prolonging survival [2]. Current treatment strategy is based on agents targeting plasma cells responsible for the secretion of the amyloidogenic light chains [3, 4]. The therapeutic armamentarium has been adapted from multiple myeloma as both diseases develop from abnormal plasma cell and occasionally coexist [5, 6]. Recently, the upfront therapy of AL amyloidosis has been changed by the introduction of daratumumab, a powerful monoclonal antibody directed against the transmembrane antigen CD38 highly expressed on plasma cells surface [7]. In 2021, daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DaraCyBorD) received accelerated approval from the Food and Drug Administration (FDA) for newly diagnosed patients with AL amyloidosis thanks to the encouraging phase III ANDROMEDA trial (NCT03201965) [8]. The introduction of daratumumab in the first-line treatment of AL amyloidosis has resulted in a major leap forward in treatment outcomes with improving patients' outcomes. Despite the high efficacy reported by the pivotal trial, patients eventually attain a suboptimal hematologic response or develop resistance to DaraCyBorD, and a subsequent line of therapy should be considered. Due to its recent approval, there is a paucity of data regarding the best rescue treatment for patients who received daratumumab in the upfront setting, and to date no approved regimen for the treatment of refractory/relapsed AL amyloidosis exist. A recent study explored the effectiveness of various treatment approaches, including autologous stem cell transplant (ASCT) and immunomodulatory agents, in a limited group of individuals who had prior exposure to DaraCyBorD. However,

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due to the small size of the patient cohort (*N*=28), drawing definitive conclusions remains still challenging [9]. Second-line treatment selection should be guided by the depth and duration of response to first-line treatment, the class of drugs previously administered and the grade of organ damage which can limit therapeutic options [3, 4]. In this review, we will discuss the management and the rescue treatment strategy available for patients with relapsed/refractory disease to DaraCyBorD. We will offer current treatment recommendations based on recent data and on the International Society of Amyloidosis (ISA) guidelines and address novel therapeutics for patients with AL amyloidosis.

Available Therapies in The Relapsed/Refractory Setting

Autologus Stem Cell Transplant (ASCT)

Autologous stem cell transplant is a highly effective treatment that can play a dual role in the management of AL amyloidosis [10–12]. It can either serve as an integral component of the initial treatment strategy or be used as a salvage therapy for carefully chosen patients in cases where the initial treatment fails to achieve a satisfactory hematologic response or when relapse occurs following first-line therapy [13]. Conditioning can be performed with full-dose (200 mg/m^2) or reduced-dose (140 mg/m^2) melphalan depending on renal function [14]. In a study conducted by Muchtar et al., the safety and outcomes of second ASCT in relapsed/refractory AL amyloidosis were evaluated in a cohort of 26 patients with relapsed/refractory AL amyloidosis. The reported rate of profound hematologic responses [at least a very good partial response (VGPR)] was 87%. Furthermore, the study observed a progression-free survival (PFS) and an overall survival (OS) of 39 and 88 months, respectively [15]. The role of second ASCT in relapsed/refractory AL amyloidosis was further evaluated by Tan et al. using the comprehensive data from the Center for International Blood and Marrow Transplant Research® (CIBMTR®) database. Notably, among the 21 evaluable patients undergoing second ASCT, the reported rate of complete hematologic response (CR) was 48% [16]. In a distinct case series comprising 31 patients with refractory AL amyloidosis, rescue ASCT induced a profound hematologic response in one-third of patients [17]. In a recent study by Zanwar et al., the effectiveness of ASCT in patients with relapsed/refractory AL amyloidosis, primarily exposed to daratumumab, was evaluated. Remarkably, 87% of patients achieved a hematologic response, with 75% reaching a CR, accompanied by a substantial progression-free survival period of 36.8 months [9].

Immunomodulatory Drugs (IMiDs)

Immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide have been considered the backbone rescue treatment in patients with relapsed/refractory AL amyloidosis [18]. Besides their immunomodulatory and antiangiogenic effects, they retain direct anti-plasma cell properties modulating gene expression and promoting apoptosis [19–21]. Immunomodulatory drugs demonstrated to be effective in patients previously exposed to the proteosome inhibitor bortezomib. Lenalidomide, a second-generation IMiDs, has been largely used in relapsed/refractory patients with AL amyloidosis at the maximum tolerated dosage of 15 mg [22, 23]. Given its potential nephrotoxicity, it should be used with great caution in patients with renal involvement, especially with severe proteinuria [24]. The efficacy of lenalidomide in combination with dexamethasone (LDex) in the relapsed/refractory setting has been explored in phase II studies as well as in different retrospective series [23, 25–28]. The reported overall hematologic response rate (ORR) to LDex raged from 31% to 61% with a low rate of profound hematologic response. At least a very good partial response (≥VGPR) was observed in less than 30% of cases (Table 1). In a retrospective study by Cohen et al., the addition of the proteasome inhibitor ixazomib to LDex (IxaLDex) in relapsed/refractory AL amyloidosis provided a high rate of overall hematologic response (64%), with 45% of patients achieving at least a deep hematologic response [CR 25%, VGPR 20%] [29]. Of note, all patients reported in the latter study were previously exposed to bortezomib. Despite the reported studies were on patients who received different lines of therapies, none of them was previously exposed to daratumumab.

Pomalidomide, a third generation immunomodulatory agent, combined with dexamethasone demonstrated to be effective in relapsed/refractory AL amyloidosis patients regardless previous exposure to lenalidomide [30–32]. The role of pomalidomide in the relapsed/refractory setting has been explored by phase II clinical trials and in retrospective series [30–33]. The reported overall hematologic response rate raged from 44% to 68%, with one third of patients attaining a profound hematologic response. In our series of patients treated with pomalidomide and dexamethasone, 3 subjects had previously received daratumumab combinations. In the whole cohort of heavily pre-treated patients, the overall hematologic response was 44% and, in the subset of previously daratumumab expose, 2/3 patients obtained a partial hematologic response to therapy [33]. The use of pomalidomide as a salvage therapy after DaraCyBorD failure has not been explored. Currently, two phase II studies are evaluating

Table 1 Studies on IMIDs on relapsed/refractory AL amyloidosis

Variables	Lenalidomide							Pomalidomide			
	Sanchorawala et al. 2006 [23]	Dispenzieri et al. 2007 [22]	Palladini et al. 2012 [26]	Mahmood et al. 2014 [28]	Kastritis et al. 2018 [25]	Cohen et al. 2020 [29]	Basset et al. 2021 [27]	Dispenzieri et al. 2012 [30]	Sanchorawala et al. 2016 [31]	Palladini et al. 2017 [32]	Milani et al. 2020 [33] *
Type of study	Phase II	Phase II	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Phase II	Phase I/II	Phase II	Retrospective
Regimen used	LDex	L or LDex	LDex	LDex	LDex	IxaLDex	LDex	PDex	PDex	PDex	PDex
Number of patients	34	23	24	84	55	40	260	33	27	28	153
Age, years, median (range)	65 (44 – 84)	62 (44 – 88)	59 (42 – 72)	64 (45 – 79)	63 (42 – 82)	66 (42 – 80)	60 (34 – 79)	66 (52 – 82)	68 (44 – 79)	64 (41 – 80)	64 (55 – 71)
Cardiac involvement, n(%)	13 (38)	14 (64)	16 (67)	42 (50)	40 (72)	26 (65)	182 (70)	27 (82)	18 (67)	22 (79)	93 (61)
Renal involvement, n (%)	n.a.	16 (73)	18 (75)	52 (62)	41 (75)	28 (70)	144 (55)	12 (36)	14 (52)	11 (39)	92 (60)
Previous lines of treatment, median (range)	1 (0 – 5)	1 (0 – 3)	3 (2 – 5)	2 (1 - 6)	1 (1 – 4)	2 (1 – 4)	2 (1- 6)	2 (1 -8)	2 (1 – 6)	2 (1 – 7)	3 (2- 7)
ASCT, n (%)	19 (56)	6 (27)	7 (29)	13 (15)	7 (13)	10 (25)	87 (33)	16 (48)	n.a.	n.a.	37 (24)
Bortezomib, n (%)	n.a.	n.a.	24 (100)	58 (69)	40 (73)	40 (100)	177 (68)	n.a.	n.a.	27 (96)	143 (93)
Lenalidomide, n (%)	n.a.	-	-	-	2 (4)	12 (30)	-	n.a.	n.a.	7 (25)	124 (81)
Hematologic response %	16 (67)	9 (41)	41%	51 (61)	28 (51)	26 (65)	62 (31)	16 (48)	12 (44)	19 (68)	67 (44)
CR, n (%)	7 (29)	n.a.	-	17 (20)	3 (5.5)	10 (25)	11 (5)	1 (3)	8 (30)	1 (4)	5 (3)
VGPR, n (%)	-	n.a.	-	6 (8)	11 (20)	8 (20)	29 (15)	5 (15)	1 (4)	7 (25)	35 (23)

Legend: *ASCT* Autologus stem cell transplant, *CR* Complete response, *L* lenalidomide, *LDex* Lenalidomide and dexamethasone, *PDex* Pomalidomide and dexamethasone, *VGPR* Very good partial response

*Three patients included in the study were daratumumab-exposed.

the efficacy of pomalidomide in combination with daratumumab (DaraPDex) in patients with AL amyloidosis previously exposed to at least one line of therapy including daratumumab (NCT04895917, NCT04270175) [34]. Of note, the NCT04270175 study is focused solely on patients daratumumab exposed and in preliminary results, 8 out of 9 patients enrolled attained a hematologic response with 6 patients achieving a deep response (2 CR, 4 VGPR) as recently reported at the last America Society of Hematology meeting (2023) [34].

Venetoclax

Venetoclax, a potent inhibitor of the anti-apoptotic protein B cell lymphoma 2 (Bcl-2), has proven to be highly effective as anti-plasma cell agent especially in the presence of the t(11;14) translocation [35, 36]. Different clinical trials exploring the safety and efficacy of venetoclax in relapsed/refractory AL amyloidosis - including daratumumab-exposed patients - as single agent (NCT05451771) or in combination with other anti-plasma cell such as daratumumab (NCT05486481) or ixazomib (NCT04847453) are ongoing. Recently published retrospective case series reported high rates of hematologic response in relapsed/refractory AL amyloidosis receiving venetoclax-based therapies (Table 2) [37–41]. In a multicentric retrospective study by Lebel et al., venetoclax granted profound (ORR 88%; ≥VGPR 70%) and prolonged hematologic responses. Of note, most of patients included in the latter study were refractory or attained an insufficient response to daratumumab. No safety concerns were reported even in patients with advanced heart involvement (Mayo cardiac stage ≥3a) [40]. Similarly, Orland et al. described a case series of 21 daratumumab-refractory patients harboring the t(11;14) translocation and treated with venetoclax-based combinations. Patients included in the study achieved a rapid hematologic response and 88% of them achieved at least a VGPR (ORR 95%) [39]. The efficacy of venetoclax in daratumumab-exposed patients with AL amyloidosis, especially in the ones harboring the t(11;14), has been also reported in a study by Premkumar et al. [ORR 75% in t(11;14) patients vs 67% in non-t(11;14) patients; ≥VGPR 69% in t(11;14) patients vs 50% in non-t(11;14) patients] [37].

Belantamab Mafodotin

Belantamab mafodotin is a first-in-class monoclonal antibody directed against the B-cell maturation antigen (BCMA) expressed on plasma cell surface [42]. In 2020, the FDA granted accelerated approval to belantamab mafodotin for relapsed/refractory multiple myeloma. However, this drug has been recently withdrawn from the US and European market for the treatment of relapsed/refractory multiple myeloma patients based on the results of the DREAMM-3 trial (NCT04162210), in which the primary endpoint was not met. The role of belantamab in relapsed/refractory AL amyloidosis was investigated, but published data are scanty and limited to small series. Interim analysis of the phase II EMN27 clinical trial (NCT04617925), demonstrated an overall hematologic response rate of 60% with a low rate of deep response (VPGR 36%). A total of 18 (72%) patients were previously exposed to daratumumab and amongst them the hematologic ORR was 50%. Of note 20% of patients suspended treatment due to ocular toxicities [43]. A retrospective study by Khwaja et al. investigated the efficacy of belatamab mafodotin in a cohort of 11 relapsed/refractory AL patients, of them 6 patients achieved at least a VGPR.

Table 2 Studies on venetoclax on relapsed/refractory AL amyloidosis

Variables	Premkumar et al. 2021 [37]	Sidiqi et al. 2021 [35]	Orland et al. 2023 [39]	Lebel et al. 2023 [40]	Roussel et al. 2023 [41]
Type of study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Number of patients	43	12	21	26	51
Age, years, median (range)	63 (42 – 82)	64 (52 – 76)	65 (48 – 80)	64 (50 – 86)	62 (54 – 70)
Cardiac involvement, n(%)	40 (72)	(50)	15 (71)	20 (77)	36 (70)
Renal involvement, n (%)	41 (75)	(75)	11 (52)	22 (85)	29 (57)
Previous lines of treatment, median (range)	3 (1 -10)	2 (1 – 4)	2 (1 – 5)	3 (1 -7)	2 (1 – 56)
t(11;14), n (%)	31 (72)	11 (92)	21 (100)	22 (88)	3 (6)
Daratumumab-exposed, n (%)	25 (58)	4 (33)	21 (100)	22 (85)	37 (72)
Hematologic response %	24 (63)	7 (88)	20 (95)	23 (88)	46 (90)
CR, n (%)	13 (34)	4 (50)	11 (53)	9 (35)	31 (61)
VGPR, n (%)	11 (29)	3 (38)	7 (33)	9 (35)	7 (14)

Legend: *CR* Complete response, *VGPR* Very good partial response

Treatment was well tolerated except in one patients who interrupted treatment due to keratopathy [44].

Bispecific Antibodies

Bispecific antibodies (bsAbs) are novel immunotherapeutic agents binding simultaneously a plasma cell antigen [e.g., BCMA, G protein-coupled receptor family C group 5 member D (GPRC5D), Fc receptor homolog 5 (FcRH5)] along with CD3 on T-cells inducing a selective cytotoxic T-cell response against plasma cells [45]. Common toxicities associated to bsAbs are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenia, hypogammaglobulinemia, and infections [45, 46]. In the last few years, bsAbs have changed the treatment landscape of relapsed/refractory multiple myeloma providing encouraging outcomes. Teclistamab, a T-cell redirecting BCMA bsAbs (BCMA x CD3), has been the first bsAbs receiving the regulatory approval for the treatment of relapsed/refractory multiple myeloma [47]. In contrast, bsAbs safety and efficacy in the context of relapsed/refractory AL amyloidosis is not well established and published data are limited to small case series [48–50]. Chakraborty et al. reported the results of teclistamab as a rescue treatment in a series of 6 relapsed/refractory AL patients previously exposed to daratumumab [49]. All patients achieved a profound hematologic response and median time to response was less than one month from treatment initiation. Teclistamab was well tolerated in all patients and most reported toxicities were infections [49]. Similarly, in a study conducted in 17 relapsed/refractory AL amyloidosis, teclistamab provided high rate of rapid and deep hematologic responses (CR 41%, VGPR 47%) despite the presence of heavily pretreated patients. Indeed, all but one patient were previously exposed to daratumumab, bortezomib and lenalidomide. Teclistamab demonstrated a good safety profile: severe infections were reported in 35% of patients and solely a grade 3 ICANS was observed [50].

Chimeric Antigen Receptor T-cell Therapy (CAR-T)

Chimeric antigen receptor T-cell (CAR-T) therapy is based on adoptive transfer of engineered CAR-T cells targeted to epitope of plasma cells [51]. BCMA-targeted CAR-T cell therapy was the first approved by FDA for the treatment of relapsed/refractory multiple myeloma and yielded unprecedented results in heavily pre-treated patients in terms of deep and sustained hematologic responses [52]. Given safety concerns, related to the occurrence of severe infections, CRS or ICANS in patients with a cardiac or renal dysfunction, CAR-T cell therapy have been scarcely investigated in patients with AL amyloidosis. However, case series suggested that CAR-T cell can be a feasible treatment for relapsed/refractory AL amyloidosis. The first case of BCMA-targeted CAR-T cell in AL amyloidosis was reported in 2021 by Oliver-Caldes et al., in which one patient with relapsed/refractory multiple myeloma and renal AL amyloidosis attained a minimal residual disease (MRD) negativity and a renal response after CAR-T cell therapy [53]. Soon after, the Mayo clinic group reported two patients with relapsed/refractory multiple myeloma and concurrent AL amyloidosis with renal and/or cardiac involvement who were successfully treated with BCMA-targeted CAR-T cell therapy achieving a minimal residual disease (MRD) negativity [54]. In both case reports, patients were previously exposed to daratumumab, proteasome inhibitors and IMiDs. Moreover, no safety concerns were reported, however prophylactic strategies to avoid CRS were adopted. Currently, a phase I clinical trial (NCT04720313) is exploring the safety and efficacy of the anti-BCMA CAR-T HBI0101 in patients with relapsed/refractory AL amyloidosis and preliminary data regarding the first 9 enrolled patients have been recently presented. All patients included in the NCT04720313 study were heavily pretreated, 7 out of 9 had a cardiac involvement with 4 patients with severe heart involvement (≥3a Mayo cardiac stage). The CAR-T HBI0101 provided profound hematologic response: 5 out 9 patients achieved a MRD negativity and 3 achieved a VPGR, without any treatment-related deaths [55].

Conclusions

Establishing the optimal treatment sequencing after daratumumab failure is one of the greatest challenges in the management of relapsed/refractory AL amyloidosis. Outcomes in daratumumab-exposed patients have been recently investigated in a case series of 33 patients by Theodorakakou et al. Rescue strategies adopted in this study were various and raged from venetoclax to re-treatment with daratumumab-based regimens. The reported hematologic ORR was 55%, with 14 (42%) patients attaining at least a VGPR. Of note, patients rechallenged with daratumumab containing therapies retain a lower hematologic response rate compared to the other subjects (ORR 22% vs 68%; ≥VGPR 22% vs 50%) corroborating that switching drug class is preferable to increase the response rate [56]. Similarly, Zanwar et al. examined the outcomes associated with different treatment strategies in a cohort of 28 patients with AL amyloidosis who received upfront DaraCyBorD. Consistent with prior findings, rechallenging patients with daratumumab-based therapies was associated with an inferior progression free survival compared to both venetoclax or ASCT, which emerged as the optimal therapeutic approaches in this setting [9]. Advances in treatment of multiple myeloma are offering new powerful therapeutic options. The Bcl-2 inhibitor venetoclax is a promising agent for the treatment of daratumumab-exposed

relapsed/refractory AL amyloidosis, especially for patients harboring the t(11;14) in which it provided an overall hematologic response rate ranging from 75% - 88% with a good safety profile. Given its efficacy and limited toxicities, it could represent the treatment of choice in relapsed/refractory AL amyloidosis with t(11;14). The role of IMiDs-based regimens in daratumumab-exposed patients is not well clarified, however both pomalidomide and lenalidomide demonstrated a limited efficacy in the relapsed/refractory setting. Nevertheless, preliminary results of the NCT04270175 study suggest that pomalidomide in combination with daratumumab could be an effective salvage regimen for patients previously treated with daratumumab-based regimens. Novel BCMA-directed therapies, particularly bsAbs and CAR-T cell, provided exciting results with manageable safety profile in daratumumab-exposed patients and could represent the next wave for the treatment of relapsed/refractory AL amyloidosis. However, efficacy data, although promising, are still immature and needed to be confirmed in larger cohorts of patients. In conclusion, future comparative studies are needed to define the optimal treatment strategies that should be carefully tailored based on disease and patients' characteristics.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest Giovanni Palladini has received research funding from Gate bioscience and The Binding Site; has received compensation for lectures from Alexion, Argobio, Janssen, Protego, The Binding Site, Pfizer, Prothena, Sebia, and Siemens; and has received compensations for participation on advisory boards from Alexion, Argobio, Janssen, and Protego. Paolo Milani has received compensations for lectures from Pfizer and Janssen; and has received compensation for participation on advisory boards from Janssen and Siemens. Claudia Bellofiore has received travel funding from Janssen, Sanofi and Amgen.

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