Daratumumab in AL amyloidosis – a small step or a giant leap?

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Abstract

Light chain amyloidosis has come far with the first ever treatment to get regulatory approval in 2021. Daratumumab based regimes achieve deep hematologic and organ responses; offering a new therapeutic backbone. Early identification, correct fibril typing, challenges of the very advanced patient and lack of therapies to remove amyloid deposits remains under study but as yet elusive. We review the progress of treatment in AL amyloidosis, the impact of daratumumab and look towards the next steps.

Introduction

Systemic AL amyloidosis is an intriguing complex multisystem disease challenging physicians from suspicion of diagnosis to management.[1] Unstable circulating monoclonal light chains originating from a plasma cell or a B cell clone cause direct tissue proteotoxicity from pre-fibrillar aggregates/oligomers which aggregate to form proteolysis resistant tissue fibrils; a duo causing rapidly progressive organ dysfunction and death. The silent start, multiple organ targets and rapid decline is a devastating combination that has defied efforts for early recognition and effective treatment. Welcome winds of change have come with novel anti-plasma cell therapies progressively improving survival in the last decade; attracting attention of researchers and industry towards this previously orphan disease culminating in 2021 with the licencing of daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (dara-VCd) for newly diagnosed patients with AL amyloidosis. [2]

The three key elements in the management of AL amyloidosis are: correct early recognition of the diagnosis, rapid control of the amyloidogenic light chains and improvement in the function of the end organs damaged by the amyloid deposits – the first and last remaining unmet medical needs.

Evolution in the treatment of AL amyloidosis

The major step changes in the treatment of AL amyloidosis (**Figure 1)** started with demonstration of the positive survival impact of high dose melphalan and autologous stem cell transplantation (HDM/SCT) in the mid 1990's making it, to-date, an important standard of care in selected patients with early disease.[3] Stringent selection criteria have reduced treatment related mortality to <5%. The key advantage of HDM/SCT is a prolonged duration of hematologic complete response (CR), event free survival and greater than a decade overall survival in patients achieving a CR. [4]

The prolonged survival using use of oral melphalan with dexamethasone was the next step change leading to its adoption as a standard of care in non-transplant eligible patients in

mid-2000's [5]. Buoyed by the success of immunomodulator agents in multiple myeloma, trials with thalidomide [6] and lenalidomide with/without additional alkylators in AL,[7] showed adequate (but rarely deep) responses with surprising and unexplained intolerance (fatigue, renal impairment and increase in cardiac biomarkers).

Bortezomib was the third and key game changer. Marked excess of misfolded toxic light chains in AL cause the plasma cells to be a log more sensitive to proteasome inhibition in AL than in multiple myeloma.[9] It was "reasonably" well tolerated and complete responses were seen in the relapsed setting[10] especially with combination of bortezomib-dexamethasone with cyclophosphamide (VCD) [11].[12] In the front-line setting, very good partial response or better is seen in over half of all patients with complete responses in quarter of the patients treated with VCD or VMdex.[13,14]

Progressive and steady improvement in survival in AL amyloidosis can well tracked to the above treatment landmarks [15-17] but challenges remain. Patients with advanced cardiac disease (NTproBNP >8500 pg/mL) continue to have high early mortality and morbidity with multiple hospital admissions; a hopeful glimmer is patients achieving CR (small proportion) having better long-term outcomes. The recognised cardiac toxicity of proteasome inhibitors leads to a concern about contribution of therapy to early deaths in AL[18] despite of lack of clear trends in case control data.[19] Crucially, the organ function improvement is slow and limited (~20% patients at 6-12 months).

Two other key findings intensified the need to find novel combinations: 1. significant survival benefit of achieving a very deep light chain response over and above "CR" (difference in the involved and uninvolved light chains (dFLC) <10 mg/L [13] or involved FLC (iFLC) <20 mg/L)[20] [21] and minimal residual disease (MRD) assessment showing MRD negativity leads to organ responses in over ~75% cases.[22,23] 2. Demonstration that a rapid response breaks the fibrillogenesis-proteotoxicity chain stopping/slowing organ failure translating into better outcomes – it is now is clear that deep response at 1 month is a crucial marker (where daratumumab has a major role) .[23]

Daratumumab in AL amyloidosis

Daratumumab is a high affinity human IgGκ1 monoclonal antibody binding to CD38, an antigen ubiquitously expressed all plasma cells, causing cell death by multiple pathways. Daratumumab containing triplet and quadruplet combinations in myeloma can lead to deep MRD negative responses with improved PFS and OS.

Daratumumab in relapsed AL amyloidosis

Single agent daratumumab was reported to be effective in relapsed AL amyloidosis in two cases [24] followed by a large retrospective study of 25 patients showing rapid hematologic responses (CR – 36% and VGPR 24%).[25] Over twelve studies have been published using daratumumab in a total of 569 patients with relapsed AL amyloidosis (two prospective phase II studies and rest retrospective) [26-37]showing a combined overall hematologic response rate of 83% (Figure 2). Two prospective phase 2 trials in relapsed AL amyloidosis confirmed these findings of high VGPR or better in 48-86% with a median time response of 1-4 weeks,[34,38] translating to improved organ function with renal and cardiac responses in over half of all the patients treated. However, the complete responses are only seen in ~1/3rd patients (variable proportion in individual studies reflecting impact of prior therapies and patient selection). Long term follow-up of patients from BU[36] showed that those continuing on daratumumab for > 12 cycles had significantly longer major organ deterioration progression free survival (MOD-PFS) (30 vs.13 months; p = .0018) and overall survival (not reached vs. 15 months; p < .0001). NTproBNP > 8500 pg/mL, presence of 1q21 gain and shorter duration of therapy (</= 12 cycles) were strong negative predictive factors for outcomes with daratumumab therapy in AL amyloidosis.[36] In a study by the German group, cardiac responses were seen in 22% with daratumumab-dexamethasone and 26% with additional bortezomib (DVD). [32] Nephrotic range proteinuria was associated with poorer EFS and OS [32] but not in the recently updated series from our group in BU[36] - potential urinary loss of daratumumab in nephrotic patients compromising responses needs further clarification as the pharmacokinetic data from the

ANDROMEDA (broadly similar PKs in AL amyloidosis and myeloma) did not model patients with nephrotic vs. non-nephrotic. [39]

Daratumumab in front-line treatment of AL amyloidosis

ANDROMEDA was the pivotal phase III trial comparing dara-VCd (up to 24 cycles) with VCd alone (6 cycles) in 388 patients with newly diagnosed systemic AL amyloidosis [2] (excluding very advanced disease) with a primary end point of hematologic complete response and secondary end points of organ responses and MOD-PFS. December 2021 update,[39] at a median follow-up of 25.8 months, reports hematologic CR and VGPR were significantly superior for the dara-VCd arm compared to VCd alone (59.5% vs 19.2% and 79.0% vs 50.3% respectively) with significantly better MOD-PFS in the daratumumab group. The hematologic responses in the dara-VCd arm were rapid compared to VCd arm (median time to first response 16 days vs. 24 days, respectively). At 18 months, cardiac and renal responses were also higher in dara-VCd arm (53% and 58% respectively) compared to VCd arm (24% and 26% respectively). A total of 79 deaths have occurred (dara-VCd (34 patients,17%) compared to VCd (45 patients, 24%)) but survival data is still not mature.

The European Myeloma Network (EMN) reported early results of a phase II study in stage IIIb cardiac AL amyloidosis in 17 patients (planned recruitment – 40 patients) with overall response rate of 71% (3 patients (18%) achieving CR, 6 (35%) VGPR, and 3 (18%) a PR) and overall survival of 70%/53% at 6 mos./12 mos. respectively. [40]

Ongoing trials include combinations of daratumumab with Ixazomib (newly diagnosed; NCT03283917), with pomalidomide (relapsed; NCT04895917) and a study of DVD in advanced cardiac AL (newly diagnosed; NCT04474938).

Toxicity of Daratumumab in AL amyloidosis

Overall, in AL amyloidosis, apart from infections, the toxicity of daratumumab appears to be limited with only rare grade 3 or 4 infusion or administration related reactions. In the ANDROMEDA, serious adverse events occurred in 43% vs. 34% in dara-VCd vs. VCd groups

with slightly higher incidence of grade 3 or 4 infections (16.6% vs. 10.1%, respectively) but led to treatment discontinuation in only ~4% patients in either group. Lymphopenia, neutropenia and respiratory infections were the commonest grade ≥ 3 AE's.[2] Heart failure was reported in 6.2% of daratumumab group vs. 4.8% in the control group. In relapsed AL amyloidosis, infections occurred in ~ 60% patients with about third being ≥ grade 3.[30] In the BU study, atrial fibrillation and heart failure were reported in 18% and 14%, respectively.[34] In stage IIIb patients with AL amyloidosis, there were 6 deaths, 65% patients had a SAE and 9 (53%) cardiac SAE.[40] All SAE's/deaths were considered unrelated to daratumumab.

Limitations

Data on daratumumab in AL is rapidly accumulating but many limitations remain. Until the EMN study shows impact of daratumumab in stage IIIb cardiac AL amyloidosis, data remains unclear. The impact as well as safety of dara-VCd in advanced cardiac AL amyloidosis is early stages of a study in China. Dara-VCd, whilst moving the care of patients with AL amyloidosis significantly forward, still involves the components (bortezomib, dexamethasone) that cause significant clinical problems. A lack of dramatic reduction in early mortality in ANDROMEDA, despite the remarkable rapidity of hematologic response, raises a crucial question: have we reached the limits of what can be achieved by simply reducing the precursor without addressing the actual deposits? Lastly, with dara-VCd, 40% patients did not achieve a CR. Strategies for improving responses in these patients as well those relapsing after dara-VCd remain unclear.

The impact of maintenance daratumumab in AL amyloidosis is not clear since ANDROMEDA had no maintenance randomization but data from BU show daratumumab for >12 cycles lead to better MOD-PFS and OS. UK data have previously demonstrated that patients treated with VCD alone without maintenance reaching a CR had not reached median time to next treatment at 4 years. Data on benefit, safety and cost effectiveness (a key requirement in many health care systems), of ongoing maintenance are crucially needed.

Other considerations in treatment of AL amyloidosis

The impact of the underlying clonal disease needs greater focus. Patients with greater plasma cell burden >20% [42] and/or presenting with high FLC (>400 mg/L) have high risk of early relapse and substantially worse outcomes.[42] Patients with t(11;14) translocation (40% of patients) have poorer responses and worse outcomes with bortezomib based therapies [44]; an adverse prognostic factor potentially overcome by dara-VCD as seen in subgroup analysis of ANDROMEDA. Importantly, deep responses can be reached in ~70% of this group with venetoclax with low toxicity.[45] Shifting focus towards using clonal parameters using the opportunity of targeted therapy and patient selection for escalation/de-escalation of therapy in high/low clonal burden patients, respectively, is needed. The exciting data from active immunotherapy (chimeric antigen receptor T cells and bi-specific antibodies) in relapsed myeloma, where responses are seen in hours/days [45], could be truly transformational for AL amyloidosis with even the prospect of "cure" due to the MGUS like nature of the clone in majority. [47]

Lastly, the two critical and ultimate therapeutic goals are: rapid improvement in organ function and impact of therapies on quality of life. Quality of life studies remain small and data limited. CAEL101 (an anti-fibril antibody) showed encouraging renal and cardiac responses in a phase 1 trial;[48] phase III studies are ongoing (NCT04512235 and NCT04504825). With a survival benefit in post-hoc analysis of the VITAL trial, prospective re-appraisal of birtamimab is in progress (NCT04973137).[48] The tools to assess impact of therapies which remove amyloid fibrils is still a missing ingredient due to lack of clarity on the utility of the current response criteria in this setting. Evaluation of new tools like pan-amyloid imaging agents AT01[50] or Florbetaben/Florbetapir;[51] target engagement demonstration using FDG-PET or macrophage specific markers;[51] re-evaluation of role of cardiac biomarkers (NT-proBNP/troponin) and developing amyloidosis specific PROMS (patient reported outcome measures) is imperative. Wider appreciation that therapies for other organs that severely impact quality of life/survival (advanced renal dysfunction, severe autonomic neuropathy,

gastrointestinal symptoms, and the ubiquitous fatigue) is needed. Time is approaching for reappraisal of the role of SCT in AL amyloidosis with unprecedented hematologic responses rated with incorporation of dara-VCd in the AL treatment paradigm.

Conclusions

AL amyloidosis has entered a new and exciting phase. Whilst questions and challenges for the very advanced patients remain, treatment with daratumumab based regimes clearly offer the chance to reach deep responses in remaining 70-80% patients with less advanced disease, translating into organ responses and improved quality of life; and, likely, better overall survival. This is a welcome broad brush across the board. Early identification remains elusive as ever and efforts need be redoubled. The increasing identification of ATTR amyloidosis in older patients with overlapping presence of MGUS makes correct typing of the pathologic amyloid fibrils truly critical. We must embark on the subtler steps – refinement of therapies based on biomarkers/clonal characteristics/genetics, addressing the question of organ improvement, issue of ongoing maintenance, capturing cost and quality impacts of therapy, incorporating therapies that remove amyloid fibrils accelerating organ improvement and using the upcoming wave of active immunotherapy towards “cure” approach.

Is daratumumab a small step or giant leap? We say a welcome giant leap without a doubt. But remember, it is only the first leap and we have a way to go.

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Figure legends:

Figure 1: The changing landscape in AL amyloidosis. The number of available therapies has improved overall survival in the last two decades from median of ~1 year to more than 5 years mirrored by a significant decline in the mortality of all stages except those with very advanced cardiac disease.

Figure 2: Overall and complete hematologic response to daratumumab based therapies in newly diagnosed and relapsed refractory systemic AL amyloidosis

Table 1: Selected studies of daratumumab in relapsed/refractory patients with AL amyloidosis

Study	**N**	**Prospective (P)/ Retrospective (R)**	**Response**	**Complete response (CR) (or ≥VGPR)**	**Overall Survival (OS)/Event free (EFS) or Progression free survival (PFS)**
Abeykoon et at (2019)[26]	44	R	88%	17%	OS – NA EFS - 15m
Chung A et al (2020)[27]	72	R	77%	40%	At 2 yrs: OS 86%; TTNT not reached 62%
Van de Wyngaert Z et al (2020)[37]	15	R	86%	43%	OS-87% at 8 months
Milani P et al (2020)[32]	72	R	82%	15%	NA
Kimmich CR et al (2020)[29]	106	R	64%	≥VGPR 48%	OS – 25m EFS 11 m
Lecumberri R et al (2020)[30]	38	R	72%	28%	At 12 m: OS 59% EFS 52%
Sanchorawala V et al (2020)[34]	22	P	90%	41%	PSF-20m
Roussel M et al (2020)[33]	40	P	55%	15%	At 2 yrs OS 74%
Cohen OC et al (2020)[28]	50	R	84%	38%	OS – NR PFS – NR
Lee H et al (2021)[31]	10	R	90%	20%	NA
Shragai T et al (2021)[35]	49	RR	81%	≥VGPR 64%	OS- NR PFS – 28 m
Szalat RE et al (2022)[36]	107	RR	93%	44%	OS – NR MOD-PFS 36m

Figure 1:

Therapeutic landscape improving survival and decreasing mortality

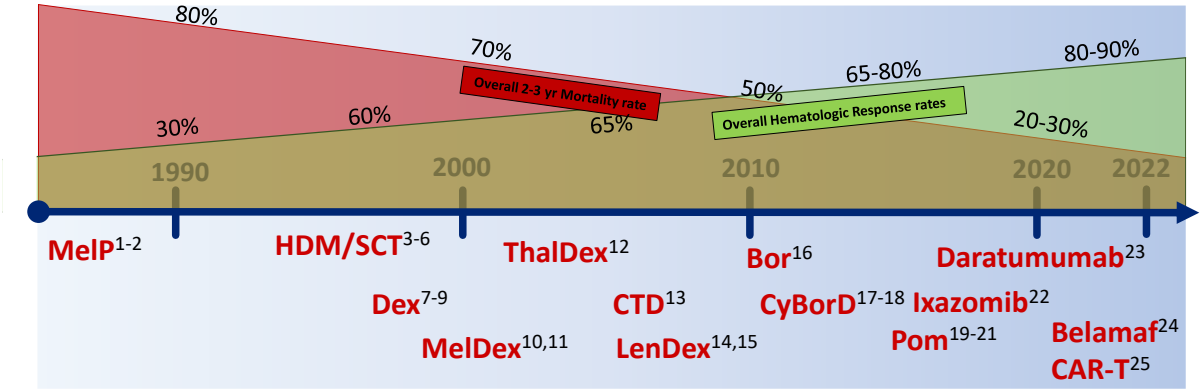

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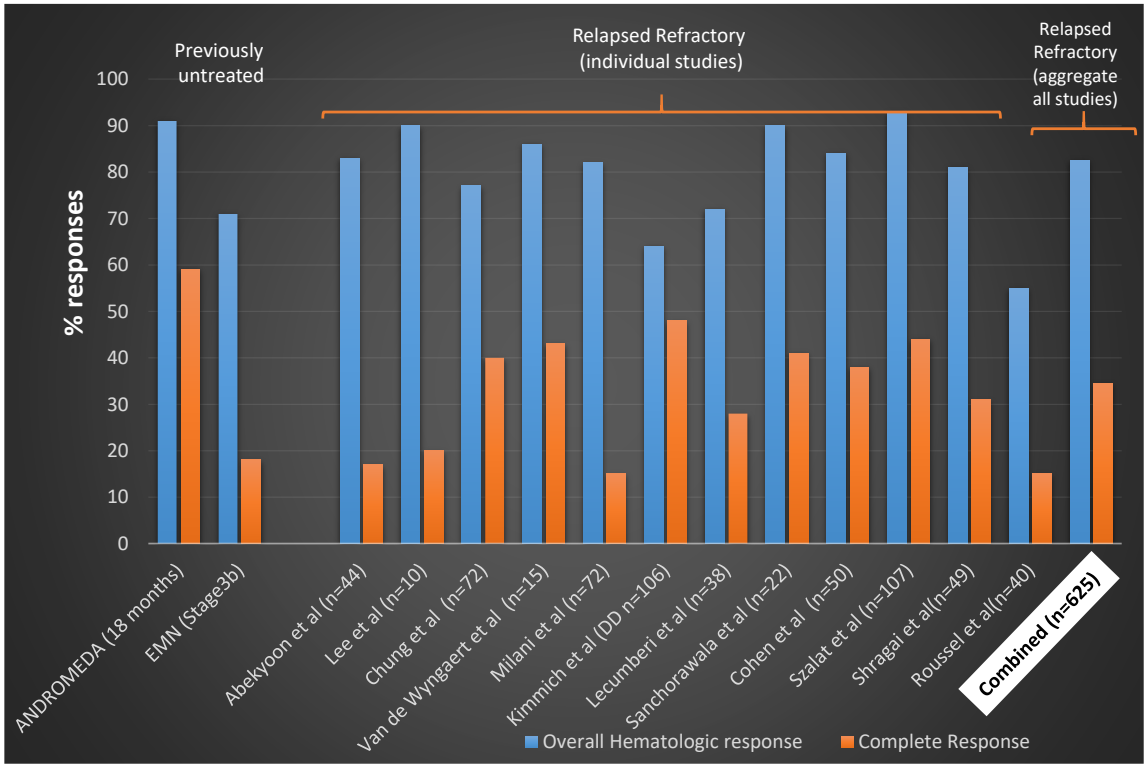
Figure 2:



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