Rapid Response to Single Agent Daratumumab is associated with Improved Progression-free Survival in Relapsed/Refractory AL Amyloidosis

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Abstract

Background

Daratumumab is a monoclonal antibody, which targets CD38; an antigen expressed on malignant plasma cells in AL amyloidosis thus providing a rationale for its use.

Method

Patients treated with daratumumab monotherapy (2016-2019) for relapsed / refractory systemic AL amyloidosis were identified from the database at the UK National Amyloidosis Centre.

Results

Of 50 evaluable patients, haematological responses at 3 months were: CR – 19 (38%), VGPR – 14 (28%), PR – 9 (18%) and no response - 8 (16%). Median time to response was 1 (1-6) month. Of assessable patients, cardiac, renal and hepatic responses were seen in 43.8%, 25.0% and 0% of patients whilst progression occurred in 25.0%, 12.5% and 37.5% respectively. Patients achieving a CR had longer median OS (not reached vs. 22.7 months [95% CI 17.0-28.4 months]) (p=0.036). Furthermore, patients achieving a rapid response (at 1 month) had a longer median PFS (not reached vs. 9 months [95% CI 5.8-12.2 months]) (p=0.013).

Conclusion

Daratumumab monotherapy is effective in multiply-relapsed systemic AL amyloidosis and should be considered, if available, in patients who have not received prior daratumumab therapy. Responses are achieved rapidly and overall response rate was 84%. CR predicts overall survival whilst speed of response is predictive of a longer PFS.

Keywords: daratumumab, amyloidosis, therapy.

Abbreviations

AE – adverse events

CI – confidence interval

CR – complete response

CTCAE – common terminology criteria for adverse events

CyBorD - bortezomib-cyclophosphamide-dexamethasone

dFLC – difference between involved and uninvolved free light chains

ESRF – end-stage renal failure

HR – haematological response

ITT – intention to treat

NAC – national amyloidosis centre

NR – no response

NT-proBNP - n-terminal pro hormone brain natriuretic peptide

OS – overall survival

PFS – progression free survival

PR – partial response

VGPR – very good partial response

Introduction

Patient survival in systemic AL amyloidosis is improving [1] yet most patients still relapse following initial therapy. Consequently, there is a need to develop new novel agents for use in this setting. Daratumumab is a monoclonal antibody, which targets CD38, an antigen expressed on malignant plasma cells in AL amyloidosis [2]. A number of clinical trials and case series' have examined the use of daratumumab monotherapy in systemic AL amyloidosis at relapse, documenting haematological response (HR) rates of 65-86% and rapid median time to response of 1-2.6 months [3-7]. Furthermore, the Boston group reported a HR based on the difference between involved and uninvolved light chains (dFLC) in 19/21 (90.5%) patients after a single dose of daratumumab [7].

We present the UK experience of single agent daratumumab in the setting of relapsed / refractory systemic AL amyloidosis and evaluate the impact of timing of response on survival outcomes.

Method

All patients treated with daratumumab monotherapy for relapsed / refractory systemic AL amyloidosis in the period 2016-2019 were identified from the database at the UK National Amyloidosis Centre (NAC). The diagnosis of AL amyloidosis was confirmed by Congo red staining of tissue biopsy with confirmation of subtype by immunohistochemistry with specific antibodies or mass spectrometry. Daratumumab was administered at standard doses of 16mg/kg weekly for 8 doses, fortnightly for 8 doses then monthly until disease progression. Aciclovir and co-trimoxazole were used as standard anti-microbial prophylaxis.

Haematological and organ responses were defined as per consensus guidelines [8,9]. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Overall survival (OS) was defined as the time, in months, from

commencement of daratumumab to death from any cause whilst progression-free survival (PFS) was calculated from commencement of daratumumab to haematological progression, change of treatment or death from any cause. All survival outcomes were calculated on an intention-to-treat (ITT) basis.

Results

Fifty three patients were included in the study. Baseline characteristics are reported in Table I. Median time from diagnosis of AL amyloidosis to commencement of daratumumab was 32 months (range 3-115 months). Haematological responses were assessable in 50 patients (2 low baseline dFLC [<20mg/L] and 1 death prior to response assessment). Haematological responses at 3 months were: complete response (CR) – 19 (38%), very good partial response (VGPR) – 14 (28%), partial response (PR) – 9 (18%) and no response (NR) - 8 (16%) (Figure 1A). Five patients with Mayo IIIb biomarkers were included within the study in whom responses were: CR – 2 (40%), VGPR – 2 (40%) and NR – 1 (20%). The majority of patients (36/53, 67.9%) received lenalidomide-based therapy immediately prior to daratumumab monotherapy. There was no significant difference between patients who received lenalidomide-based therapy immediately prior to daratumumab when compared to other agents (p=0.50). Haematological response by Mayo stage is documented in Table II.

Median time to response was 1 month (1-6 months). Of 26 patients who responded at 1 month, 19/26 (73.1%) achieved a CR/VGPR compared to 12/15 (80%) who responded at 2-3 months. Beyond 3 months, only 2 patients went on to achieve a haematological response whilst a further 2 improved their response (1 VGPR to CR and 1 NR to PR). 17 (34%) achieved a dFLC <10 mg/L (Figure 1A). However, since initial haematological response assessment occurred at 1 month, we are unable to comment on the speed of response and its impact on outcome prior to the 1 month time point.

Organ responses were evaluated 6 months post-initiation of daratumumab therapy. Of 39 patients with cardiac involvement, 16 were evaluable at 6 months (8 missing data as patients yet to return to NAC for reassessment, 6 not reached 6 months, 5 baseline N-terminal pro hormone brain natriuretic peptide [NT-proBNP] <650ng/L and 4 NT-proBNP not assessable due to end-stage renal failure [ESRF]). Of these patients, 7/16 (43.8%) had a cardiac response, 4/16 (25.0%) progressed and 5/16 (31.3%) were non-responders. Of cardiac responders, 5/7 (71.4%) had demonstrated a HR at 1 month and 6/7 (85.7%) achieved a CR. In patients with Mayo IIIb disease, 2/5 (40%) lived beyond 6 months but neither was assessable for organ response (1 did not attend for re-assessment, 1 on dialysis). Whilst NT-proBNP was not assessable for cardiac response due to dialysis in this patient, his echocardiogram improved (2-dimensional global longitudinal strain improvement from -8.7% to -11.4%). He continues in CR on daratumumab 18 months from commencement of therapy.

Thirty patients had renal involvement of which just 8 were assessable for organ response at 6 months (9 not reached 6 months, 5 ESRF at baseline, 4 missing data and 4 baseline urinary protein <0.5g/24h). Two patients (25.0%) had a renal response, 1/8 (12.5%) progressed and 5/8 (62.5%) were non-responders. Finally, 14 patients had liver involvement inclusive of 8 evaluable for organ response at 6 months (1 not reached 6 months and 5 missing data). There were no patients who achieved a hepatic response. Of the remainder, 3/8 (37.5%) progressed and 5/8 (62.5%) were non-responders. The haematological responses in patients achieving any organ response were: CR – 7 (77.8%) and PR – 2 (22.2%). Of these patients, 7/9 (77.8%) achieved a haematological response at 1 month in comparison to 26/50 (52%) within the entire cohort. Within patients evaluable for a renal response, haematological response were evaluable in 5/6 (83.3%) non-responders (CR – 1 [20.0%], VGPR – 1 [20.0%], PR – 2 [50.0%] and NR – 1 [20.0%]).

Patients were followed up for a median of 9 months (2-35 months) from the start of daratumumab therapy. During the period of follow up, 35 (66.0%) patients continue on daratumumab, 10 (18.9%) patients died, 4 (7.5%) patients stopped treatment and 4 (7.5%) patients moved to next line therapy (addition of pomalidomide to daratumumab in 3 cases and addition of lenalidomide in the 4th case). Of the 10 patients who died, 5 died of progressive amyloidosis whilst 5 died whilst in a haematological response. Three of the four patients who had an immunomodulatory agent added improved their depth of HR. One patient stopped due to concerns regarding ongoing daratumumab maintenance in the setting of cardiac transplantation and the remainder due to inadequacy of HR as opposed to toxicity. Of the 10 patients who died, 1, 4 and 4 were in CR, PR and no response (1 died prior to response assessment), respectively. Two patients stopped treatment with daratumumab following progression and were palliated prior to death. Median PFS was 19.9 months (95% CI 8.2-31.8 months) whilst median OS was not reached. Patients achieving a CR had a significantly longer median OS (not reached) compared to those in a lesser haematological response (median 22.7 months [95% CI 17.0-28.4 months]) (p=0.036) (Figure 2). Furthermore, patients achieving a rapid response (at 1 month) had a significantly longer median PFS (not reached) than those responding at a later time point (9 months [95% CI 5.8-12.2 months]) (p=0.013).

Daratumumab monotherapy was generally well tolerated amongst the study population and there were no therapy-related deaths or ≥ grade III infusion related reactions. No patients discontinued daratumumab due to toxicity. One patient stopped treatment due to clinical concern regarding the effects of ongoing maintenance in the context of a cardiac transplant. During the period of follow up, 6 (11.3%) patients were admitted to hospital (2 fluid overload, 2 falls [1 secondary to postural hypotension, 1 unexplained], 1 non-cardiac chest pain and 1 anaemia requiring blood transfusion in a patient with end-stage renal

failure). Excluding the admissions listed, there was no grade III adverse events (AE). The commonest grade I-II AEs were infusion reaction 7/53 (13.2%), thrombocytopenia 6/53 (11.3%), fatigue 6/53 (11.3%), infection 5/53 (9.4%), anaemia 5/53 (9.4%) and fluid overload 4/53 (7.5%). The nature of the infections listed were: tonsillitis, upper respiratory tract infection, lower respiratory tract infection (x2) and a urinary tract infection. A full list of toxicities are documented in Table III.

Discussion

Daratumumab monotherapy is effective in relapsed systemic AL amyloidosis with an overall HR rate of 84% in this study, which is consistent with previous literature [3-7]. Importantly, the majority of patients included in this study had already been treated with both bortezomib (92.5%) and lenalidomide (83.0%) therapy – both common agents used in the upfront setting. These response rates appear to be superior to those achieved with alternate novel agents in the relapse setting such as ixazomib (53% [10]), pomalidomide (46-61% [11]) and carfilzomib (63% [12]). Furthermore, the toxicity profile is manageable with grade III AEs seen in just 11.3%, which compares favourably with alternative agents [ixazomib: 59% [10], carfilzomib: 71% [12]]. On pomalidomide therapy, discontinuation rates of 66-93% [11] are reported, whilst in this study, no patient discontinued due to documented toxicity.

Whilst rapid response to daratumumab monotherapy has been demonstrated [3-7], we show that time to reaching response is prognostic and confers a PFS advantage. A longer period of follow up is required to determine if a rapid response also confers an OS advantage. Only 2 patients responded beyond 3 months suggesting that late responses rarely occur and, in this setting, a change in therapy should be considered early. The Mayo group have published outcomes of 22 patients treated with daratumumab combination therapy (most bortezomib, pomalidomide or lenalidomide) demonstrating an 88% overall response rate [3]. Furthermore, if the results of the run-in cohort of the ANDROMEDA trial of upfront

daratumumab with bortezomib-cyclophosphamide-dexamethasone (CyBorD) vs. CyBorD alone (NCT03201965) are confirmed, this regimen may be practise-changing in incorporating daratumumab into frontline therapy. A second trial is underway examining the use of daratumumab in combination with ixazomib and dexamethasone (NCT03283917). Whilst these combination regimens certainly hold promise, the significantly greater toxicity of any chemotherapy regimen in patients with AL amyloidosis compared to patients with multiple myeloma makes daratumumab monotherapy an appealing option in this patient cohort.

Our group have previously demonstrated that rapid haematological responses (CR or VGPR at day 30) improves overall survival in patients with Mayo IIIb cardiac AL amyloidosis [13]. A high proportion of organ responders achieve a prior haematological response in patients treated with daratumumab [14]. Furthermore, patients achieving early organ response (within one year of normalisation of serum free light chains) have superior overall survival [15]. In our cohort, patients achieving an organ response achieved haematological responses within 1 month in 78.8% of cases in comparison to 52% for the cohort overall suggesting that a rapid response may impact subsequent organ response but further assessment using greater patient numbers is required for validation. Notably, the renal response rate was poor (25% of evaluable patients). This has also been reported by the German amyloid group in patients with nephrotic-range proteinuria [17]. The reason for this remains unclear but may reflect a poor haematological response in this patient cohort with just 1/6 (16.7%) patients who failed to achieve a renal response achieving a CR.

In summary, daratumumab monotherapy is a safe effective therapy in patients with multiply-relapsed systemic AL amyloidosis. Responses are rapid, seen in 84% of patients and long lasting, especially in patients who respond by one month. Furthermore, 43.8% of assessable patients with cardiac involvement demonstrated an organ response making daratumumab an attractive option in this subgroup. In the era of daratumumab combination

241 therapies, there remains a role for daratumumab monotherapy in patients with relapsed
242 systemic AL amyloidosis.

243 **Author Contributions**

244 OCC and AW conceived the study, analysed data and wrote the manuscript. MB and IB
245 collected data. MB, IB, SR, SL, JDG, HL, SS, SM, CW, CK, NR, RP KY, SC, RS, SW and
246 PH contributed to the manuscript and provided critical input. All authors reviewed the final
247 version of the manuscript.

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252 **Disclosure Statement**

253 No conflicts of interest to declare

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Table I: Baseline Patient Characteristics at Time of Daratumumab Initiation

	N(%)/Median(range)
Age, median (range)	68 (42-85)
Male, N (%)	34 (64.2)
Disease Isotype	
IgG	31 (58.5)
Light Chain Only	14 (26.4)
IgA	5 (9.4)
IgM	2 (3.8)
IgD	1 (1.9)
Light chain isotype Lambda	36 (67.9)
dFLC, median (range) (mg/L)	78.9 (0.3-4897)
Bone marrow plasma cell (%)	16 (3-85)
Mayo Stage at Presentation	
1	11 (20.8)
2	19 (35.8)
3A	18 (34.0)
3B	5 (9.4)
Organ Involvement	
Cardiac	39 (73.6)
Renal	30 (56.6)
Liver	14 (26.4)
Soft Tissue	15 (28.3)
Peripheral Nerve	6 (11.3)
Autonomic Nerve	5 (9.4)
Gastrointestinal	4 (7.5)
Baseline Organ Function	
Median eGFR ml/min per 1.73m^2	51.5 (<15 – >90)
Proteinuria, g per 24h,	2.5 (0.1-16.8)
NT-proBNP, ng/L, median (range)	1962.5 (90-46412)
ALP, IU/L, median (range)	85 (17-516)
Albumin, g/L, median (range)	39 (22-48)
Prior Lines of Therapy	
Median (range)	3 (1-4)
Bortezomib	49 (92.5)
Lenalidomide	44 (83.0)
ASCT	13 (24.5)

Abbreviations: dFLC: difference between involved and uninvolved free light chains; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro hormone brain natriuretic peptide; ALP: alkaline phosphatase; ASCT: autologous stem cell transplantation.

Table II: Haematological Response by Mayo Stage

	CR	VGPR	PR	NR	Total
Mayo I	3	1	3	3	10 (20%)
Mayo II	7	6	3	2	18 (36%)
Mayo IIIa	7	5	3	2	17 (34%)
Mayo IIIb	2	2	0	1	5 (10%)
Total	19 (38%)	14 (28%)	9 (18%)	8 (16%)	50 (100%)

Abbreviations: CR: complete response; VGPR: very good partial response; PR: partial response; NR: no response.

Table III: Adverse Events

Adverse event	Any grade, n (%)	Grade 3-4, n (%)
Infusion Reaction	7 (13.2)	0
Fatigue	6 (11.3)	0
Thrombocytopenia	6 (11.3)	0
Infection	5 (9.4)	0
Anaemia	5 (9.4)	1 (1.9)
Fluid Overload	4 (7.5)	2 (3.8)
Diarrhoea	3 (5.7)	0
Fall	2 (3.8)	2 (3.8)
Nausea	2 (3.8)	0
Insomnia	2 (3.8)	0
Hypertension	1 (1.9)	0
Blurred vision	1 (1.9)	0

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Figure Legends

Table I: Baseline Patient Characteristics at Time of Daratumumab Initiation

Table II: Haematological Response by Mayo Stage

Table III: Adverse Events

Figure 1:

A) Haematological Response by both international consensus criteria and dFLC response [16].
B) Percentage Change in dFLC at 3 months

Figure 2

A: Progression-free and overall survival from commencement of daratumumab monotherapy
B: Overall survival of patients achieving a complete response vs. patients achieving a very good partial response vs. patients achieving a lesser response (partial response or worse).