High responses rates with single agent Belantamab Mafodotin in relapsed systemic AL amyloidosis

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Abstract

Systemic AL amyloidosis is a rare incurable relapsing remitting plasma cell disorder. Treatment options for multiply relapsed patients especially after anti-CD38 therapy remain uncertain. Belantamab mafodotin is an antibody-drug conjugate targeting B-cell maturation antigen with approval for relapsed refractory myeloma with limited data in patients with AL amyloidosis. We report the outcomes of patients using Belantamab mafodotin monotherapy for the treatment of 11 patients (including two with advanced chronic kidney disease and one post renal transplant) with relapsed AL amyloidosis at the UK National Amyloid Centre. Eight patients (73%) are still on therapy, overall response rate (partial response or better) was 64%. Complete or very good partial response was achieved in six patients (55%). At data cut-off, all patients were alive and at a median follow up of 6.1 months (range 3.0-12.2), progression-free survival was 83% (95% CI 27-97). Apart from keratopathy (grade 1-2 - 55%; grade 3 - 18%)

requiring dose modification, no other substantial toxicity was observed (including in the patients with advanced CKD/post-transplant). Belantamab mafodotin shows promise in treatment of relapsed AL and needs further prospective trials. Efficacy is demonstrated in those with renal impairment that are traditionally excluded from trials.

Introduction

Systemic AL amyloidosis is a rare plasma cell disorder caused by extracellular deposition of misfolded immunoglobulin light chains as protein fibrils in tissues leading to vital organ damage. It is incurable and has a relapsing remitting course. With lack of approved treatments at relapse, treatments for relapsed multiple myeloma are used in AL but are challenging due to underlying organ dysfunction, most commonly cardiac and renal impairment. Most data are from the use of immunomodulatory agents and, lately, with daratumumab. However, options for patients who are relapsing after daratumumab in AL remain unclear.

Belantamab mafodotin (belamaf) is an antibody-drug conjugate linked to MMAF, targeting B-cell maturation antigen. which has been approved for relapsed refractory myeloma. In multiply pre-treated myeloma, the pivotal DREAMM-2 phase II trial reported on 96 patients after three or more prior lines of therapy showing an overall response rate (ORR) of 32% as a single agent with an intravenous dose of 2.5 mg/kg administered every three weeks.

A retrospective case series of six patients with relapsed AL amyloidosis with myeloma (1) recently reported on outcomes in a cohort of predominantly cardiac AL amyloidosis (5/6 patients) with a complete response (CR) rate of 50%. A phase 2 trial is recruiting for patients with refractory amyloidosis (NCT04617925) but excludes those with renal impairment (estimated glomerular filtration rate, eGFR <30ml/min). Renal involvement causing chronic kidney disease (CKD) is present in 70% of patients with systemic AL at diagnosis. Renal amyloidosis often progresses to end stage renal failure and requires dialysis (2). Those with end stage renal failure are almost universally excluded from clinical trials.

We report our results using Belantamab monotherapy for the treatment of patients with relapsed refractory AL amyloidosis including those with significant CKD.

Methods

This series includes all patients treated with Belamaf monotherapy at standard dose (2.5mg/kg) or dose reduction at the UK National Amyloidosis Centre between April 2021-February 2022. All patients underwent standardised assessments including measurement of

cardiac biomarkers, clonal parameters and imaging as appropriate. Organ involvement, haematological and organ response assessment was reported as the international society of amyloidosis consensus criteria (3). All patients had ophthalmology assessment in advance of treatment initiation in keeping with the licence. Adverse events were graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Results and discussion

Eleven patients were included (eight male, three female). Baseline characteristics and responses are illustrated in table 1. The median age at belamaf initiation was 65 years (range 42-74) and three (27%) patients were over 70 years. Eight patients (73%) had λ-AL-type and three (27%) κ-AL-type. At diagnosis, median involved free light-chain concentration was 534 (range 73-7181) mg/l. A median of two organs were involved at baseline (range 1-3): nine (82%) had renal involvement and four (36%) had cardiac involvement . The median eGFR at the time of fist belanatmab dose was 43 ml/min (range 7 – 120).

The median time from AL diagnosis to first administration of Belantamab was 58 (range 12-154) months (~4.8 years) and prior lines of treatment was 3 (range 2-5). Prior therapies included immunomodulatory drugs (91%), proteasome inhibitors (100%) and anti-CD38 antibody (82%) treatment. Four patients (36%) had undergone prior melphalan-conditioned autologous stem cell transplantation.

At data cut-off, patients have received a median of 4 (range 1-10) doses of belamaf. Response rates are shown in figure 1. Eight patients (73%) are still on therapy, ORR (partial response [PR] or better) was 64%. CR/very good partial response (VGPR) was achieved in six patients (55%). Reasons for treatment discontinuation (n=1 each, 9%) were progressive disease, non-response or toxicity, respectively. At data cut-off, all patients were alive. At a median follow up of 6.1 months (range 3.0-12.2), progression-free survival was 83% (95% CI 27-97) and the median progression-free survival was not reached.

The most frequent adverse event was keratopathy which was experienced in eight (73%) patients (grade 1-2: 55%; grade 3: 18%), necessitating dose and schedule modification of the

three-weekly delivery in four (36%) patients. Ocular adverse events improved after treatment interruption (increasing drug intervals to 4-6 weekly) and topical emollient with/without topical corticosteroids. One patient required treatment cessation due to ocular toxicity preventing further dose administration despite achieving PR after just one dose (patient 8).

One patient developed transient grade 1 dyspnoea and asymptomatic liver dysfunction which is similar to the rate reported in DREAMM-2. In our cohort no patients developed cytopenia, which differed from DREAMM-2, which reported thrombocytopenia in 35% and anaemia in 24% as the most common adverse events after keratopathy. The only other series of belamaf in AL amyloidosis reported thrombocytopenia in 17% (1/6) (1). In our cohort no infusion reactions were reported nor infections observed beyond COVID (two patients mild with no hospital admissions).

The majority of the cohort required dose reduction either at initiation (patient 4, due to end stage renal failure and on haemodialysis; patient 11, post-renal transplant) or during therapy (5/11; 45%: three to 1.9mg/kg, two to 1.25mg/kg). Only one patient remained on the standard dose of 2.5mg/kg for $\geq$3 cycles. Four patients had an eGFR<30ml/min with one patient experiencing grade 1 keratopathy. Two patients (patients 4 and 11) with end stage renal failure commenced a dose of 1.25mg/kg and achieved a VGPR and CR respectively with no additional toxicity. Patient 11 was post renal transplant on tacrolumius and mycophenolate mofetil as immunosuppression – we did not see any significant toxicity with a 4 weekly dosing schedule and achieved a CR at cycle 3. Patient 3 had a 42% reduction in involved serum free light chain after two doses but then had a prolonged gap due to keratopathy and has lost the response. There were no treatment related deaths, nor hospitalisations due to belamaf; no cardiac or renal toxicities were observed in the cohort.

Belamaf demonstrates significant activity in patients with heavily pre-treated AL amyloidosis with an ORR of 64%. Given the low grade underlying clonal dyscrasia in AL, these response rate appear to compare favourably with trial and real-world data of 30% achieving responses in relapsed myeloma. Effective novel therapies in multiply relapsed refractory AL amyloidosis are welcomed as data in this setting is scant. We recently reported real-world longitudinal data

showing good outcomes and that responses do not significantly worsen with subsequent relapses in AL with 40-50% achieving at least a VGPR (4). In the current cohort, apart from keratopathy requiring dose modification and one treatment cessation, no other substantial toxicity was observed. Crucially, the common problems with AL treatment often caused by steroids, like fluid retention and fatigue were not seen with belamaf. Corneal toxicity was not unexpected; baseline and sequential ophthalmic examination may monitor corneal events. Of the current cohort, five patients would have been trial ineligible for the current prospective phase II trial (four due to renal impairment and one due to cardiac biomarkers). Two patients with severe renal impairment (stage V CKD) and one patient post-renal transplant tolerated treatment with no additional toxicity and had good responses.

Our data has inherent limitations due to its retrospective nature and small sample size however we demonstrated good efficacy and tolerability of belamaf in multiply relapsed AL including efficacy in patients with renal impairment. Belamaf shows promise in treatment of relapsed AL in the real-world setting and needs further evaluation in prospective trials including patients in patients with advanced renal and cardiac disease.

Figure 1. Treatment responses

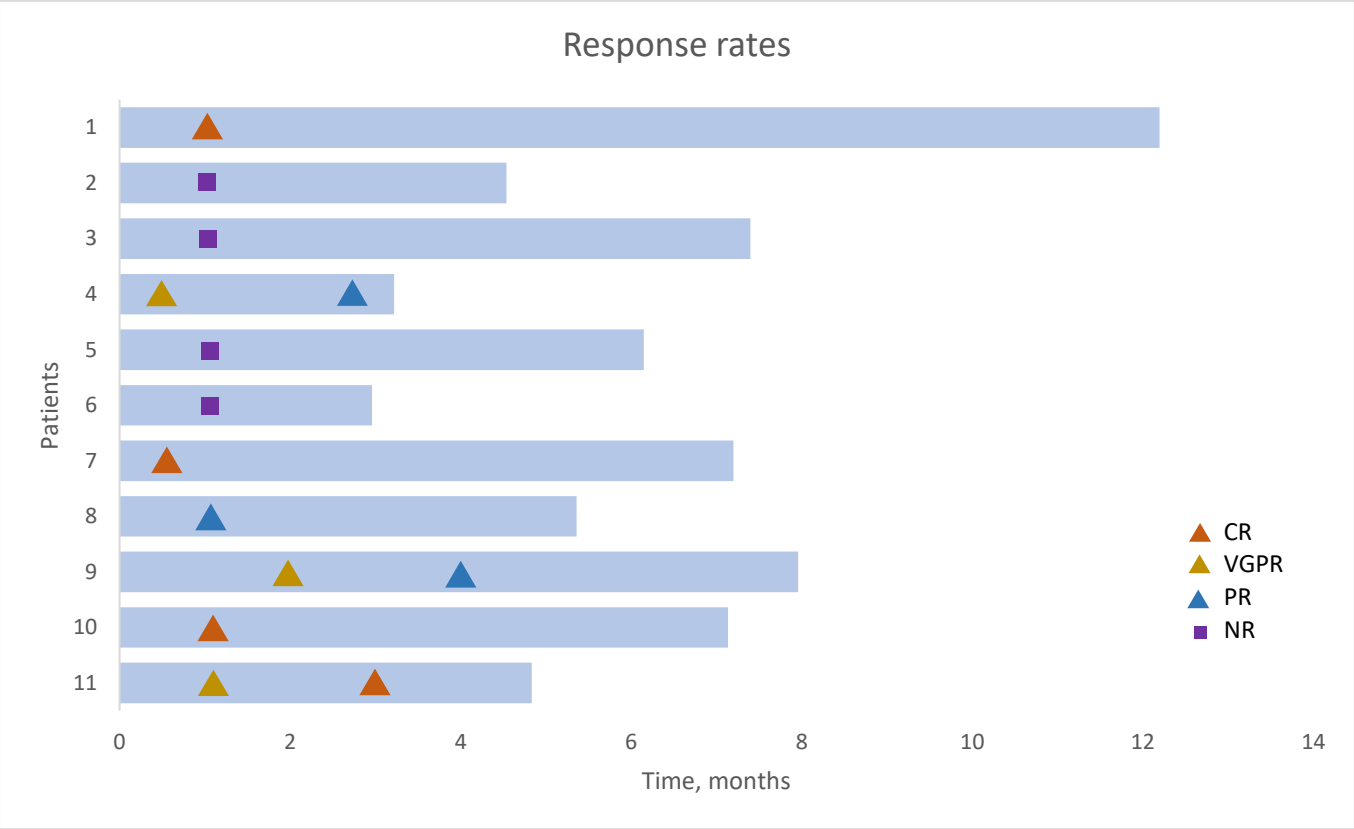
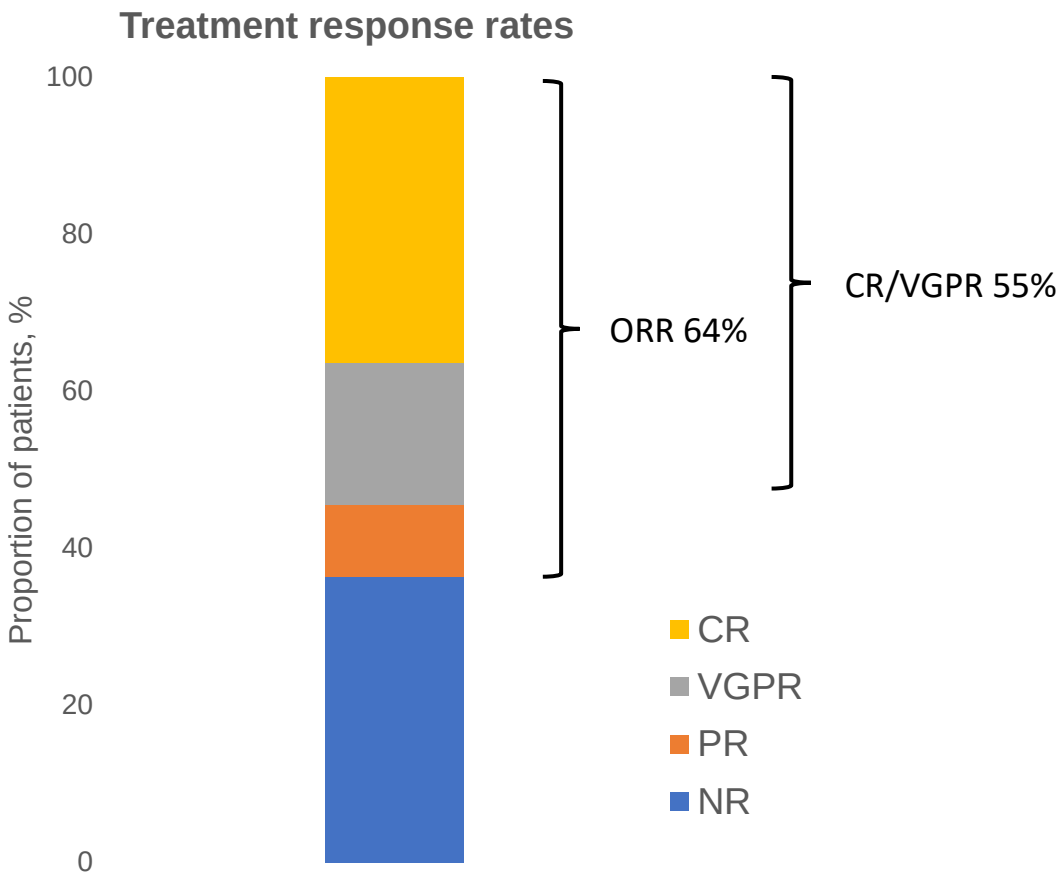


Figure 1. Treatment response rates



Complete response, CR; Very good partial response, VGPR; No response, NR, Overall response rate, ORR

Table 1. Baseline characteristics and responses

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age, gender	60F	72M	42F	65F	64M	74M	63M	73M	66M	68M	58M
iFLC at diagnosis, mg/l	2368	97	1069	73	499	7181	2330	1940	534	495	235
Organ involvement											
Cardiac	✓	x	✓	x	✓	x	✓	x	x	x	x
Renal	x	✓	✓	✓	x	✓	✓	x	✓	✓	✓
Liver	x	✓	x	✓	x	x	x	x	x	✓	x
Soft tissue	✓	✓	x	x	✓	x	x	✓	✓	x	x
Prior lines of therapy	4	2	3	4	3	3	4	4	3	5	3
Prior therapy											
Immunomodulatory	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓
Proteasome inhibitor	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anti-CD38	✓	✓	✓	✓	✓	x	✓	✓	x	✓	✓
Melphalan ASCT	x	x	x	x	x	x	✓	✓	✓	✓	x
iFLC at Belantamab initiation, mg/l	267	31	194	172	57	341	109	453	89	133	45
Cycles delivered	10	4	6	4	4	4	8	1	5	6	4
Dose reduction	✓	✓	x	✓	✓	x	✓	x	✓	x	✓
Toxicity											
Keratopathy, grade	1	1	2	-	3	-	2	3	2	1	-
Dyspnoea, grade	-	1	-	-	-	-	-	-	-	-	-
Liver dysfunction, grade	-	1	-	-	-	-	-	-	-	-	-
Haematological response	CR 21d	FLC: CR PP: NR	NR	VGPR 13d	NR	NR	CR 15 d	PR .	VGPR .	CR 21 d	CR

Time to best response, days Response duration, months	10 m	ORR:NR		1m			5 m	4 m	2 m		

iFLC= involved free light-chain

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