Use of Ixazomib, Lenalidomide and Dexamethasone in patients with relapsed AL amyloidosis

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Abstract word count: 200

Main text word count: 2333

Tables: XXx

Figures: XXX

Acknowledgements

We would like to thank all the clinical and nursing staff at the National Amyloidosis Centre and the treating hematologists who helped with the clinical care of the patients' involved in this study. We also would like to thank the International Myeloma Society (IMS) for support to present this study at the International Myeloma Workshop 2019.

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Abstract

With improving outcomes in AL amyloidosis, all patients eventually relapse leading to increasing need to study novel agents in this setting. We report outcomes of 40 patients with relapsed AL amyloidosis treated with Ixazomib-lenalidomide-dexamethasone (IRd). Hematological responses were assessed in 38/40 patients at 3 months: complete response (CR) - 8 (21.1%), very good partial response (VGPR) - 8 (21.1%), partial response (PR) - 7 (18.4%). Six patients subsequently improved response. Best responses were: CR - 10 (26.3%), VGPR - 8 (21.1%), PR - 7 (18.4%), NR - 13 (34.2%). Cardiac and renal organ responses were documented in 6.3% and 13.3% respectively. Median PFS was 17.0 months (95% CI 7.3-20.7 months), improving to 28.8 months (95% CI 20.6-37.0 months) in those achieving CR/VGPR. Median OS was 29.1 months (95% CI 24 -33 months). Serious adverse events were seen in 14 (35.0%) patients inclusive of 15 admissions due to: infection (6/15, 40.0%), fluid overload (5/15, 33.3%), cardiac arrhythmia (2/15, 13.3%), renal dysfunction (1/15, 6.6%) and anaemia (1/15, 6.6%). In summary, this data confirms IRd is efficacious and has a manageable toxicity profile in relapsed AL amyloidosis with deep responses in 47% patients. The PFS is excellent and IRd merits further prospective study.

Introduction

AL amyloidosis is a systemic disorder characterised by extracellular deposition of misfolding monoclonal light chains, produced by a small plasma cell clone, resulting in progressive organ dysfunction (1). The outlook for AL amyloidosis has transformed over the last 40 years with 4-year overall survival (OS) doubling from 21% (1977-1986) to 42% (2003-2006) (2); directly coinciding with the remarkable development of novel plasma cell targeting therapies (3) and improved patient selection for autologous stem cell transplantation (ASCT) (4).

Suppressing production of monoclonal light chains to attain a deep hematological response, without incurring additional organ toxicity over and above that caused by amyloid deposition, remains the keystone of treatment (5). Bortezomib-based regimens are routinely used for upfront treatment with good hematological responses in 60% (6) due to enhanced susceptibility of plasma cells in AL amyloidosis to proteasome inhibitor led killing (7). All patients eventually relapse after chemotherapy leading to increasing need to study novel agents at relapse. Lenalidomide-dexamethasone is commonly utilized (8) either alone or in combination with cyclophosphamide (9) or melphalan (10) leading to hematological response rates of 60% and 58% respectively. Tolerance limits lenalidomide dose and, hence, response.

Ixazomib is an oral proteasome inhibitor (PI), which has been assessed in a phase 1/2 study in relapsed/refractory AL amyloidosis demonstrating a 52% hematological response (11). Trials assessing the role of single agent ixazomib in AL amyloidosis in the relapsed refractory setting (NCT01659658), maintenance (NCT03618537) and in combination with daratumumab (NCT03283917) and cyclophosphamide (NCT03236792) are currently recruiting/have completed recruitment. The combination of ixazomib-lenalidomide-dexamethasone (IRd) is established in multiple myeloma (MM) and demonstrates significantly longer PFS than lenalidomide-dexamethasone alone (12). We report the real-world use of IRd in patients with relapsed systemic AL amyloidosis.

Method

All patients with AL amyloidosis treated with IRd chemotherapy between XXX -XXX were identified from the database at the UK National Amyloidosis Centre (NAC). In all cases, a diagnosis of amyloidosis was confirmed by Congo red staining of a tissue biopsy with demonstration of characteristic birefringence under cross-polarized light. The amyloid subtype was confirmed by immunohistochemistry with specific antibodies, or by mass spectrometry (13). All patients had a detailed baseline assessment including serum free light chains (sFLC), serum protein electrophoresis, imaging and organ assessment including cardiac biomarkers.

Hematological and organ response was assessed using uniform criteria devised by the Roundtable on Clinical Research in Immunoglobulin Light-chain Amyloidosis (AL) (14). Responses were assessed at 3 months and best response achieved whilst on therapy. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Ixazomib was given at a dose of 4mg orally weekly on days 1, 8 and 15 of a 28-day cycle. Lenalidomide was started at a standard dose of 15mg (Days 1-21) whilst dexamethasone was 40mg weekly.

Statistical analysis was performed using SPSS version 25. Approval for analysis and publication was obtained from the institutional review board at the University College London, and written consent was obtained from all patients in accordance with the Declaration of Helsinki. The primary outcomes were hematological responses and OS. Overall survival was defined as time in months from commencement of IRd therapy to death from any cause whilst PFS was a secondary outcome, calculated from commencement of IRd to hematological progression or death from any cause. All survival outcomes are reported on an intention-to-treat (ITT) basis.

Results

Forty two patients were identified - 2 patients were excluded (1 declined follow up and 1 commenced treatment prior to review). Forty patients were included and baseline characteristics are detailed in Table 1. Median time from diagnosis to IRd was 21 months (5-132 months). The median

number of cycles was 7 (range 1-36). Two patients received one treatment cycle (1 death, 1 grade 3 maculopapular rash).

Hematological responses were assessed in 38/40 patients; 1 death prior to any response assessment and 1 missing data were excluded from response analysis (but included in survival analysis). At 3 months, responses were: complete response (CR) - 8 (21.1%), very good partial response (VGPR) - 8 (21.1%), partial response (PR) - 7 (18.4%) and no response - 15 (39.5%). Six patients subsequently improved their response. Best responses were: CR - 10 (26.3%), VGPR - 8 (21.1%), PR - 7 (18.4%) and NR - 13 (34.2%) (See Figure 1). Median time to any and best response were both 2 months (range 1-9 months). Seventeen out of eighteen (94.1%) patients who achieved VGPR or better reached this response within 2 months. None of the 12 patients who had received lenalidomide previously achieved a CR at 3 months, 58.3% ultimately achieved ≥PR. Three out of the four (75%) patients who were refractory to prior lenalidomide did not respond to IRd.

Overall median PFS was 17.0 months (95% CI 7.3-20.7 months). The median PFS for patients achieving CR/VGPR was 28.8 months (95% CI 20.6-37.0 months) and for ≤PR was 10.1 months (95% CI 6.0-13.6 months). Median OS for the cohort was 29.1 months (95% CI 24.4-33.8 months), for patients achieving CR/VGPR - 35.3 months (95% CI 32.0-38.6 moths) and ≤PR - 25.2 months (95% CI 19.1-31.4 months) (Log rank p=0.103 for the latter two groups) (See Figure 2). There was no significant difference in PFS (p=0.185) compared with lenalidomide-naïve patients.

Organ responses were assessed at 6 months. The utility of NT-proBNP for assessment of cardiac response whilst on lenalidomide remains unclear; and the cardiac responses here need to be interpreted with this caveat and caution as they may be marked under reported due to the paradoxical increase of NT-proBNP during lenalidomide treatment. Of the twenty-six patients (65.0%) with cardiac involvement, 7 were not assessable for response (4 missing data and 3 NT-proBNP <650ng/L). Of the remaining 19 patients, there was only one cardiac responder (5.3%) in the entire cohort. The patient who achieved a cardiac response achieved a CR within 1 month. There was cardiac progression in 7

(36.8%) cases – of these 4/7 (57.1%) were on IRd at time of response assessment. The remaining 11 (57.9%) did not respond. Ten patients (25.0%) had liver involvement based on alkaline phosphatase (ALP) of which 7 (70%) were evaluable (2 not reached 6 months, 1 missing data); 4/7 (57.1%) progressed and 3/7 (42.9%) did not respond. Of the patients who demonstrated liver progression, 3 were non-responders and 1 achieved a PR.

Renal involvement was recorded in 28 (70.0%) patients. 13/28 (46.4%) were not evaluable: 3 not reached 6 months, 3 data missing, 4 on dialysis prior to IRd, 2 died and 1 baseline protein <0.5g/24h. Of 15 evaluable patients, 2/15 (13.3%) responded, 7/15 (46.7%) progressed and 6/15 (40.0%) were non-responders. Of the 7 patients who progressed, 3/7 (42.9%) had reductions in proteinuria sufficient to constitute a response but had a creatinine rise >25%. Two of these 3 patients achieved a CR and the third, a VGPR. Of the 4 patients who progressed based on an increase in proteinuria, hematological responses were 1 (25%) VGPR, 3 (75%) stable/progressive disease. One patient with renal progression required dialysis.

Median follow up was 10.5 months (range 2-35 months). During the period of follow up, 8/40 (20.0%) patients died, 14/40 (35.0%) patients have stopped treatment, 17/40 (42.5%) continue on IRd and 1/40 (2.5%) has been lost to follow up. One patient stopped treatment after developing a grade 3 rash following the first dose of ixazomib. Of the remainder, 4/14 stopped due to grade 3/4 toxicity (2 infection, 1 renal, 1 bradyarrythmic cardiac arrest), 2/14 decision to palliate due to advanced disease with poor quality of life and 7/14 suboptimal hematological response. Of these 7 patients, 4 commenced next line therapy (daratumumab x2, melphalan-prednisolone, pomalidomide respectively).

The AEs are detailed in table 3. During treatment, serious adverse events were seen in 35.0% of patients - there were 15 admissions in 12/40 (30.0%) patients: infection (6/15, 40.0%), fluid overload (5/15, 33.3%), cardiac arrhythmia (2/15, 13.3%), renal dysfunction (1/15, 6.6%) and for a blood transfusion (1/15, 6.6%).

Discussion

Patients with AL amyloidosis almost always relapse after initial therapy. The treatment of relapsed patients has been studied typically with doublet regimes or doublets combined with alkylators. Novel agent triplets, which are now a standard of care in multiple myeloma, remain poorly studied – particularly the combination of immunomodulatory agents combined with proteasome inhibitors. This cohort reports the efficacy and toxicity of a novel agent triplet combination of oral proteasome inhibitor, ixazomib, in combination with an immunomodulatory drug, lenalidomide, and dexamethasone for the first time in patients with AL amyloidosis; confirming that IRd regimen is efficacious, with the ability to achieve deep clonal responses alongside acceptable tolerability using real world data.

Ixazomib, a next generation proteasome inhibitor, appeared to show promise as single agent in AL amyloidosis in early phase I study. However, a pivotal phase III study of Ixazomib-Dexamethasone vs. physicians choice was closed after failing to reach its primary end points (15) suggesting limited activity for the doublet (Ixazomib-dexamethasone). Lenalidomide has been extensively used in AL amyloidosis in the relapse refractory setting typically in combination dexamethasone but also with additional alkylators (9, 10, 16). Hematological response and survival data for other regimens including lenalidomide or ixazomib are documented in Table 3. The main challenge in use of lenalidomide is the poor tolerance in patients with amyloidosis, especially those with cardiac involvement, for reasons that remain unclear. Additionally, there is potential for worsening renal function with lenalidomide. Full dose lenalidomide can be rarely used in patients with AL amyloidosis. In the current cohort treated with IRd, the overall hematological response rate (65.8%) compared with responses to ixazomib (52%)(11) in phase I studies and 51% (17) and 61% (8) with lenalidomide. There was suggestion that IRd achieved a deep response (CR/VGPR) in nearly half of all the treated patients (47.4%) compared to just less than a third with lenalidomide-dexamethasone (28%). A small phase I study of ixazomib seemed show a good response in 42.9% (11).

Whilst the studies are not directly comparable, the data is encouraging that more frequent deep responses are used with the triplet combination is used over the doublets. The clonal responses were rapid with median time to best response was 2 months. It appears that responses deepen with continuing therapy (similar to that documented with IRd in myeloma) (18)- 6 patients improved their response beyond 3 months including 2 patients who improved from PR to a CR and VGPR, respectively. Conversely, patients with a poor response 3 months did not improve their responses significantly with continued therapy; non-responders at 3 months should prompt consideration of switching to next line therapy. Encouragingly, patients who had prior exposure to lenalidomide (but not refractory) had good responses whilst three out of four patients in the series refractory to lenalidomide failed to respond. IRd appears to be a useful option of patients relapsing after prior lenalidomide treatment but may have a limited role in lenalidomide refractory patients.

The PFS in this cohort was good at 17.0 months but the PFS for patients responding to IRd was excellent at over 2 years. There is limited data on PFS with Ixazomib alone and in the small phase I cohort was 14.8 months (11). Lenalidomide combinations including cyclophosphamide and melphalan are reported to have a superior PFS of 25.1 (16) and 28.3 (9) months respectively; however, both trialled these therapies in new patients with limited exposure to other novel agent based therapies whereas, in this study, patients had a median of 2 prior lines of chemotherapy. A further study reporting on lenalidomide in combination with melphalan reported significantly worse outcomes (10) but did include 92% patients with cardiac involvement, a negative predictor of survival (19). The overall survival of our cohort was 29.1 months. However, there was no significant difference in OS between deep responders and those achieving ≤PR. The lack of difference in OS can be explained by a relatively short duration of follow up and the availability of effective next line agents such as daratumumab. Further work is required comparing different lenalidomide-containing regimens in comparable patients to ascertain their relative efficacy.

The toxicity of this regime was manageable but not insignificant. Just over one third of the patients experience serious adverse events – mainly infection and fluid retention. Grade 1-2 thrombocytopenia was common. Details of exact dose reduction from cycle to cycle are unavailable and remain a limitation of this study. These are not dissimilar from the reported grade 3/4 toxicity reported with the individual drugs: 81% with ixazomib (11) and 27% with lenalidomide alone (8). We acknowledge the limitations due to retrospective nature of the study. Lenalidomide has been linked to renal dysfunction in AL amyloidosis (20) but there are no renal toxicities reported with ixazomib in AL amyloidosis (11). Kastritis and colleagues did report transient increases (to grade 1) in renal failure and 5.5% developed acute renal failure requiring dialysis (17). In this study, 17.5% of patients developed acute kidney injury of which 1 patient required dialysis.

In summary, this real-world data of the use of ixazomib-lenalidomide-dexamethasone gives a first look at outcomes and toxicities in patients with relapsed AL amyloidosis who had received prior bortezomib and lenalidomide showing encouraging deep responses. The regime has the advantage of an all oral outpatient regime. Patients achieving CR/VGPR has excellent PFS of 28 months. This study is limited by the small sample size and retrospective data collection. These results support further larger prospective studies to evaluate either IRd alone or in addition of a monoclonal antibody.

Author Contributions

OCC and AW conceived the study, analysed data and wrote the manuscript. FS, JDG, HL, SS, SM, MF, CW, AMN, CK, NR, RP KY, SC, RS, and PH contributed to the manuscript and provided critical input. All authors reviewed the final version of the manuscript.

Conflicts of Interest

None

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Table 1. Patient Characteristics

	N(%)/Median(range)
Age, median (range)	66, 42-80 years
Male, N (%)	24 (60.0)
Disease Isotype	
IgG	18 (45.0)
Light Chain Only	15 (37.5)
IgA	5 (12.5)
IgM	2 (5.0)
Light chain isotype Lambda	31 (77.5)
dFLC (mg/L)	51.5 (0-100)
Mayo Stage at Presentation	
1	9 (22.5)
2	14 (35.0)
3A	14 (35.0)
3B	3 (7.5)
Organ Involvement	
Renal	29 (72.5)
Cardiac	26 (65.0)
Liver	11 (27.5)
Peripheral Nerve	1 (2.5)
Autonomic Nerve	6 (15.0)
Soft Tissue	12 (30.0)
Gastrointestinal	1 (2.5)
Baseline Organ Function	
Median eGFR ml/min per 1.73m^2	56 (>90-<15)
Proteinuria, g per 24h,	2.35 (0.1-16.4)
NT-proBNP, ng/L, median (range)	2445 (50-51661)
ALP, IU/L, median (range)	91.5 (13-1203)
Albumin, g/L, median (range)	35.5 (16.0-49.0)
Prior Lines of Therapy	
Median (range)	2 (1-4)
Bortezomib	40 (100.0)
Lenalidomide	12 (30.0)
ASCT	10 (25.0)
Lenalidomide refractory, N (%)	4 (10.0)

Baseline demographics and disease characteristics. dFLC: difference between involved and uninvolved 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 2: Toxicity of Ixazomib-Lenalidomide-Dexamethasone

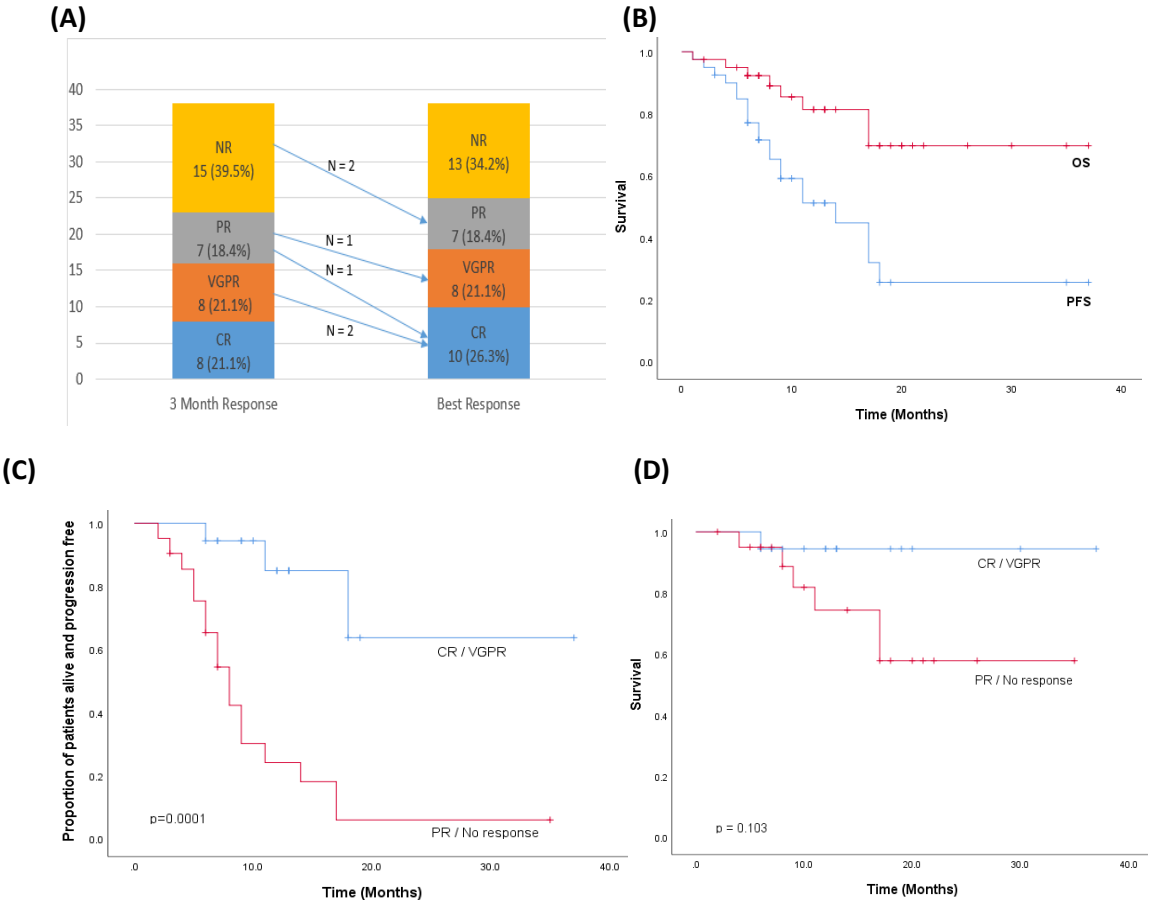
Toxicity	Adverse events – n(%)	Grade 3-4 events – n(%)
Thrombocytopenia	17 (42.5)	1 (2.5)
Fatigue	15 (37.5)	-
Constipation	10 (25.0)	-
Infection	9 (22.5)	6 (15.0)
Anaemia	9 (22.5)	2 (5.0)
Edema	9 (22.5)	5 (12.5)
Neutropenia	9 (22.5)	-
Acute kidney injury	7 (17.5)	1 (2.5)
Diarrhoea	6 (15.0)	-
Muscle / Bone Pain	6 (15.0)	-
Peripheral neuropathy	3 (7.5)	-
Nausea	3 (7.5)	-
Rash	2 (5.0)	1 (2.5)
Cardiac arrhythmia	2 (5.0)	2 (5.0)
Blurred vision	2 (5.0)	-
Insomnia	1 (2.5)	-

Table 3: Review of ixazomib or lenalidomide containing treatment regimens

Study	Chemotherapy	Patient No.	Haematological response (CR)	Median PFS	Median OS
Current study*	Ixazomib-Lenalidomide-Dexamethasone	40	66% (26.3%)	17.0m	29.1m
Mahmood *et al* 2014 (21)	Lenalidomide-dexamethasone	84	61% (20%)	73% (2 yr)	84% (2 yr)
Kastritis *et al* 2018 (22)	Lenalidomide-dexamethasone	55	51% (6%)		25m
Kumar *et al* 2012 (9)	Cyclophosphamide-lenalidomide-dexamethasone	35	60% (11%)	28.3m	37.8m
Dinner *et al* (2013) (10)	Lenalidomide-melphalan-dexamethasone	25	58% (8%)	3.1m	58% (1 yr), Median NR
Hegenbart *et al* 2017 (16)	Lenalidomide-melphalan-dexamethasone	50	68% (18%)	25.1m	67.5m
Sanchorawala *et al* 2017 (11)	Ixazomib-Dexamethasone	27	52% (10%)	14.8m	85% (1 yr)

*A 28-day cycle was used. Ixazomib was given at a dose of 4mg on days 1, 8 and 15. Lenalidomide was given at a dose of 15mg on days 1-21. Dexamethasone was given at a dose of 40mg weekly. Calculation of median progression-free survival (PFS) and median overall survival (OS) were not uniform and have been reported in either months of percentage (%) survival.CR: complete response; NR: not reached.

Figure 1: Haematological response and survival



(A) Haematological remission at 3 months and best response after commencement of ixazomib-lenalidomide-dexamethasone. Demonstrates deepening of response in 6 patients. NR: no response; PR: partial response; VGPR: very good partial response; CR: complete response.

(B) Survival of patients with ixazomib-lenalidomide-dexamethasone. Progression-free survival (PFS) and overall survival (OS).

(C) Estimated progression-free survival in relation to the haematological response. CR: complete response; VGPR: very good partial response; PR: partial response.

(D) Estimated overall survival (OS) in relation to the haematological response. CR: complete response; VGPR: very good partial response; PR: partial response.