Pomalidomide and dexamethasone grant rapid hematologic responses in patients with relapsed and refractory AL amyloidosis: a European retrospective series of 153 patients.

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Abstract

Pomalidomide demonstrated activity in the treatment of AL amyloidosis in three phase II clinical trials. We evaluated safety and efficacy of 28-day cycles of pomalidomide and dexamethasone in 153 previously treated patients with systemic AL amyloidosis. Nighty-nine (65%) were refractory to the last line of therapy and 54 (35%) had relapsed. The median number of previous lines of therapy was 3 (range: 2-7): 143 patients (93%) previously received bortezomib, 124 (81%) lenalidomide, 114 (75%) oral melphalan and 37 (24%) underwent autologous stem cell transplant.

At completion of cycle 6, 68 (44%) patients obtained at least partial hematologic response, with 5 complete responses (CR, 3%), 35 very good partial responses (VGPR, 23%). Hematologic response resulted in improved overall survival in the whole cohort (median survival 40 vs. 25 months, P=0.007) in a 6 months landmark analysis. Obtaining at least partial response was also associated in a significant improvement of the progression free survival in the whole cohort (median PFS 26 vs. 16 months, P=0.013).

Pomalidomide was effective treatment in AL amyloidosis in a heavily pretreated population. Hematologic responses are associated with an overall survival advantage.

Introduction

The treatment of systemic immunoglobulin light chain (AL) amyloidosis is based on regimens developed for multiple myeloma (1). Those treatment strategies are adapted to the fragile population of patients with systemic AL amyloidosis based on risk assessment that is mainly related to cardiac biomarker staging (2-4). The relative rarity of this disease renders it difficult to perform prospective controlled clinical trials, and the design of the therapeutic strategy is mainly based on retrospective studies. Nevertheless, a wide consensus has been reached on upfront therapy. The few eligible patients are offered autologous stem cell transplant (ASCT) (5), sometimes preceded and followed by bortezomib based induction (6, 7) and consolidation (8, 9). Subjects who are not candidates to ASCT are mostly treated with chemotherapy based on bortezomib combined with cyclophosphamide (10, 11) or melphalan (12) and a subset underwent deferred high dose therapy (13). Response to upfront regimens is obtained in approximately two third to three fourth of patients.

The optimal treatment of subjects who are refractory to first line and also the best time to start second line regimens in patients who relapsed to previous treatment is not well established (14-16). Immunomodulatory agents (IMiDs), new proteasome inhibitors (17), bendamustine (18, 19) and antibody based regimens, i.e. daratumumab (20, 21), have been evaluated in this setting. Currently, in Europe, most patients receive IMiDs-based rescue therapy. Lenalidomide was combined with dexamethasone alone (22-24) or also with cyclophosphamide (25-27) and melphalan (28). Response rates in both first line and relapsed/refractory setting ranges from 46% to 68%. However, lenalidomide tends to act slowly, requires dose adjustments in patients with renal insufficiency and reductions of estimated glomerular filtration rate (eGFR) have been reported in patients with relevant proteinuria (29). Nevertheless, renal responses can be high in patients in long-term treatment with lenalidomide (24).

Fewer studies exist on the third generation IMiD pomalidomide. Three prospective phase II clinical trials reported response rates that ranging from 48% to 61% (30, 31) in relapsed/refractory patients. More recently, we reported a small series of patients receiving pomalidomide in standard clinical practice (32). However, the impact of pomalidomide in a real word setting remains largely unknown.

Aim of our study is to evaluate the efficacy of the combination of pomalidomide and dexamethasone in a large cohort of previously treated patients with long follow-up.

Methods

The prospectively maintained databases of the Pavia Amyloidosis Research and Treatment Center (Italy), the Heidelberg Amyloidosis Center (Germany) and the National Amyloidosis Center of London (United Kingdom) were searched for patients with a diagnosis of systemic AL amyloidosis treated with oral pomalidomide and dexamethasone between January 2009 and July 2018. All patients had a biopsy proven diagnosis of AL amyloidosis. In all cases the deposits were characterized as AL-type by immunohistochemistry (33), immune-electron microscopy (34) or proteomics (35). DNA analysis was performed in order to exclude hereditary forms of amyloidosis in selected cases. All patients gave written informed consent for their clinical data to be used for research purposes in accordance with the Declaration of Helsinki. Although outside the framework of a formal clinical trial, response and safety data were collected prospectively. Hematologic and organ responses were assessed according to the International Society of Amyloidosis criteria (36-38). The analysis of response was by intent-to-treat, and the patients who died before the evaluation of response were considered non-responders. Toxicity was assessed every two cycles and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NIH, USA). Overall survival was calculated from the start of pomalidomide treatment until death or last follow-up. Progression-free survival (PFS), defined as time to progression requiring treatment change, death or relapse requiring re-institution of treatment, was calculated in all patients from the start of pomalidomide therapy. Survival curves were plotted according to Kaplan-Meier and differences in survival tested by the log-rank test. MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Belgium) was used for computation.

Results

A total of 164 patients were identified and 11 subjects (7%) were excluded from the analysis for incomplete dataset. One hundred and fifty-three patients (97 treated in Pavia, 28 in Heidelberg and 28 in London) were included in the study. Patients' characteristics are reported in the Table. All patients were previously treated with a median time from the diagnosis of AL amyloidosis to pomalidomide initiation of 44 months [interquartile range (IQR): 15-71 months]. Nighty-nine (65%) were refractory to the last line of therapy and 54 (35%) had relapsed at the time of pomalidomide initiation. Eighty-seven (57%) patients received at least three previous different lines of therapy [median number 3 (range: 2-7)]. In particular, 143 (93%) patients previously received bortezomib, 124 (81%) lenalidomide, 114 (75%) oral melphalan and 37 (24%) underwent autologous stem cell transplant.

All the patients received 28-days cycles of pomalidomide (administered from day 1 to 21) and oral dexamethasone (once a week). Pomalidomide was administered at the dose of 4 mg in 95 (62%) patients while a reduced dosage was used in the remaining patients, due to frailty of pre-existing cytopenia. Twenty (13%) received pomalidomide 3 mg, 35 patients (23%) 2 mg and 3 patients (2%) 1 mg. Dexamethasone was administered at the dose of 20 mg weekly in 137 patients (89%). A higher dose (40 mg once a week) was used in the remaining subjects 17 (11%). The median number of PDex cycles completed was 3 (range: 1-30).

Grade 3 adverse events were observed in 52 (33%) subjects. The more frequently reported were infections 15 (9%), cardiac failure in 12 (7%), creatinine increase in 9 (6%), cytopenia 4 (2%), cutaneous rash 3 (2%) and atrial fibrillation, suspect transient ischemic attack, atrial sinus block (pacemaker implantation required), gastritis and poor tolerability in one patient each. One patient experienced a sudden cardiac death during the first cycle (this patient had a baseline NT-proBNP of 10.499 ng/L with normal renal function and death was considered disease related). During the course of therapy, 30 patients (19%) had a reduction to a lower dose level of pomalidomide due to non-grade III cytopenia in 19 cases, worsening of kidney function and infections in 4 subjects each and cutaneous rash in 3 patients. The rate of adverse events was not greater in the subset of patients that underwent dialysis (5 out of 18 patients) during the course of pomalidomide treatment (P=0.311) and two of those subjects required a dose reduction due to cytopenia.

At 3 months, the overall hematologic response rate was 42%, 37 patients (24%) obtained a very good partial response and no complete responses were observed. At 6 months, the overall hematologic response rate was 44% with 5 patients (3%) who obtained complete response and 23

subjects (23%) who attained very good partial response. In 4 patients the hematologic partial response obtained at 3 months was not confirmed at 6 months. Notably, 7 out of 14 (50%) patients who failed to attain at least partial response but continue pomalidomide due to the lack of other available treatment options obtained a partial response at cycle 6. Among the subset of advanced cardiac disease patients (NT-proBNP >8500 ng/L), 5 out of 21 obtained at least partial hematologic response. Among those who failed to obtain a hematologic response, 3 subjects are still alive and were rescue by a subsequent treatment with daratumumab in all cases.

No difference was seen in the rate of hematologic response between patients who were refractory N=40 (40%) and relapsed N=28 (52%) after the last line of therapy administered before pomalidomide (P=0.089) and between the subgroup of patients treated with full dose pomalidomide (4 mg) compared to the reduced dose subgroup (49% vs. 37%, P= 0.084). The percentage of bone marrow plasma cell at diagnosis did not affect hematologic response rate.

Cardiac responses were observed in 7 of 62 patients (11%) with measurable NT-proBNP (>650 ng/L) at the time of PDex initiation, but this can be underestimated due to the immunomodulatory-related increase of NT-proBNP (39). Renal response was detected in 10 of the 49 evaluable patients (20%). Only one patient experienced a progression to end stage renal disease during the course of therapy.

Overall, 75 (49%) patients died during follow-up and the median follow-up of living patients was 32 months (95%CI: 32-40 months). Median overall survival from pomalidomide initiation was 29 months (Figure 1). Obtaining at least partial response at both 3 and 6 months was associated with a significant survival advantage (median 50 vs. 25 months, P <0.001, landmark analysis at 3 months, Figure 2A, and median 40 vs. 25 months, P=0.007, landmark analysis at 6 months, Figure 2B).

The median progression free survival (PFS) in the entire cohort was 8 months (95% CI: 5-13 months). Hematologic response after pomalidomide and dexamethasone was associated with a significant improvement in PFS (median PFS 26 vs. 16 months, P=0.013, Figure 3).

Commented [WA1]: Can you please add the responses to IMiD refractory vs. not and also to those for IMiD exposed vs not – thanks

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Discussion

The present study describes the largest series of relapsed/refractory patients with AL amyloidosis reported so far. The subjects had been exposed to modern upfront therapy and received pomalidomide outside the framework of clinical trials in an international setting. Data were collected in prospectively-maintained databases at 3 major European referral centers. This allows an accurate and generalizable evaluation of the impact of rescue treatment with pomalidomide in patients with AL amyloidosis previously exposed to alkylators, bortezomib, lenalidomide and dexamethasone.

In this setting, pomalidomide toxicity was manageable, although dose reductions were required in almost 20% of patients. The previously reported phase II studies revealed a hematologic response rate of 48% in the Mayo study (30) and 50% in the Boston trial from Sanchorawala et al. (31). In our previous phase II trial, a higher hematologic response rate was noted (61%) probably due to the use of continuous schedule of pomalidomide (from day 1 to 28) and a high rate of subjects treated with full dose dexamethasone (40 mg) (40). In this report was noted a survival advantage for those who obtained a hematologic response to pomalidomide as we noted in our retrospective real-world cohort. Therefore, in the first retrospective series about the use of pomalidomide outside the clinical trail framework (32), the hematologic response rate (47%) was comparable to our observation in the present series where we found an overall hematologic response rate was 44%, and more than one fourth of patients obtained at least very good partial response. Although this is remarkable, considering that the patients were very heavily pretreated, there is the urgent need to improve the rate of response to rescue therapy in AL amyloidosis. Similar to multiple myeloma, three drug combinations can grant more frequent and deeper responses also in AL amyloidosis. Pomalidomide could be the backbone of these novel combinations also in AL amyloidosis. Different combinations could be considered. For example, a valuable option could be the use of pomalidomide and daratumumab, an antibody based drug, that was explored in multiple myeloma with a high degree of success in relapsed/refractory setting (41) and it will be evaluated in a phase II clinical trail that is about to begin at the Pavia Amyloidosis center. Another possible option that has to be investigated in the amyloidosis setting could be the use of elotuzumab, pomalidomide and dexamethasone that resulted effective in myeloma patients(42).

The present study also reports the largest series of homogeneously treated relapsed refractory patients with AL amyloidosis published so far. In this setting, hematologic response to anti plasma cell therapy was still able to improve survival. This emphasizes the utility of offering

potentially effective therapy to patients with AL amyloidosis who fail to respond to upfront therapy or who relapse. Moreover, being able to consistently predict survival, hematologic response is a robust surrogate endpoint also in relapsed / refractory patients and can be used for the design of clinical trials also in this setting. This is relevant because newer investigational agents are usually offered to previously treated patients.

In conclusion, pomalidomide and dexamethasone can be safely administered to relapsed/refractory patients with AL amyloidosis and grants a hematologic response in more than 40% of patients with extended survival. Novel combinations are urgently needed to further increase the rate of response to rescue therapy in this disease.

Author contributions

…designed the study, evaluated patients, collected data, analyzed data, wrote the manuscript and gave final approval.

Conflict of interests (please provide any relevant COI)

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Table. Patients' characteristics

Variable	N (%) / median (range)
Refractory to the last therapy	99 (65)
Relapsed after previous therapy	54 (35)
Male sex	94 (61)
Age, years	64 (IQR: 55-71)
Organ involvement	
Heart / kidney	93 (61) / 92 (60)
soft tissues / liver	41 (27) / 22 (14)
PNS / ANS / GI	18 (12) / 18 (12) / 15 (10)
Two or more organs involved	92 (60)
ECOG-PS (≥2)	56 (36)
NT-proBNP ng/L	1615 (IQR: 524-4917)
NT-proBNP >8500 ng/L	21 (14)
Cardiac stage (available in 99 patients)(2)	
I / II / IIIa / IIIb	20 (20) / 50 (50) / 19 (20) / 10 (10)
Renal Stage(43)	
I / II / III	65 (42) / 56 (36) / 14 (10)
Patients on dialysis	18 (12)
BMPC, %	18 (IQR: 10-27)
BMPC ≥10%	112 (73)
MC type	
IgG / IgA / IgM	73 (48) / 8 (5) / 1 (-)
Light chain-only MC	71 (45)
Kappa : lambda	50 (33) : 103 (67)
dFLC, mg/L	130 (IQR: 72-367)
dFLC >50 mg/L	122 (79)

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; PNS, peripheral nervous system; ANS, autonomic nervous system; GI, gastro-intestinal; NT-proBNP, N-terminal natriuretic peptide type B; BMPC, bone marrow plasma cells infiltrate; MC, monoclonal component; dFLC, difference between involved and uninvolved free light chains.

Cardiac stage based on troponins level and NT-proBNP: thresholds for cTnT, cTnI, hs-cTnT, and NT-proBNP are <0.035 μg/L, <0.1 μg/L, <77 ng/L, and <332 ng/L, respectively. Stage III cardiac involvement is defined at a cTnT >0.035 ng/mL or a cTnI >0.1ng/mL or a hs-cTnT >77 ng/L, and NT-proBNP >332 ng/L (provided their NT-proBNP is <8500 ng/L). Stage II patients have one value of either troponin or NT-proBNP above the thresholds. Stage I patients have troponin and NT-proBNP below the thresholds.
Renal stage based on proteinuria and estimated glomerular filtration rate (eGFR) levels: thresholds for proteinuria >5 g/24h and eGFR <50 mL/min per 1.73 m^2. Stage I, both proteinuria ≤5 g/24h and eGFR ≥50 mL/min per 1.73 m^2; stage II, either proteinuria >5 g/24h or eGFR <50 mL/min per 1.73 m^2; stage III, both proteinuria >5 g/24h and eGFR <50 mL/min per 1.73 m^2.

Figure 1. Survival from pomalidomide initiation

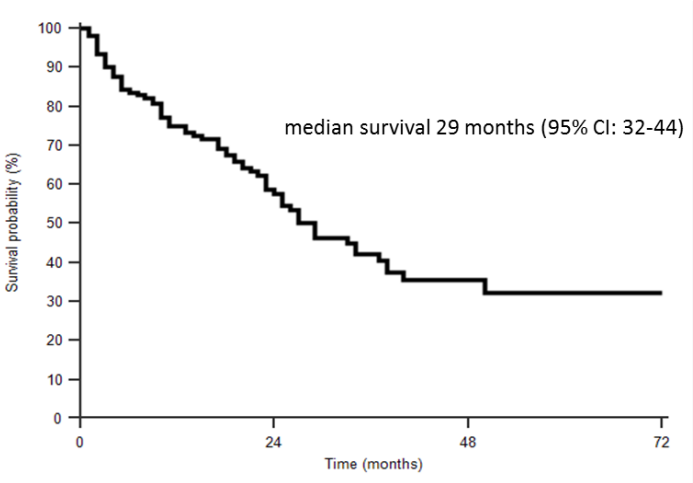

Figure 2A. Survival according to response at 3 months

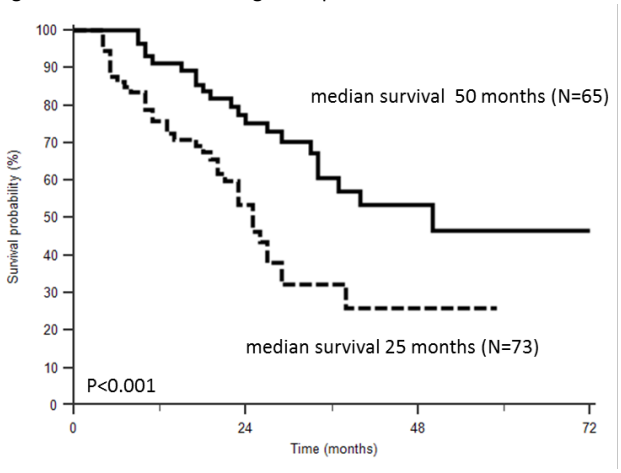

Figure 2B. Survival according to response at 6 months

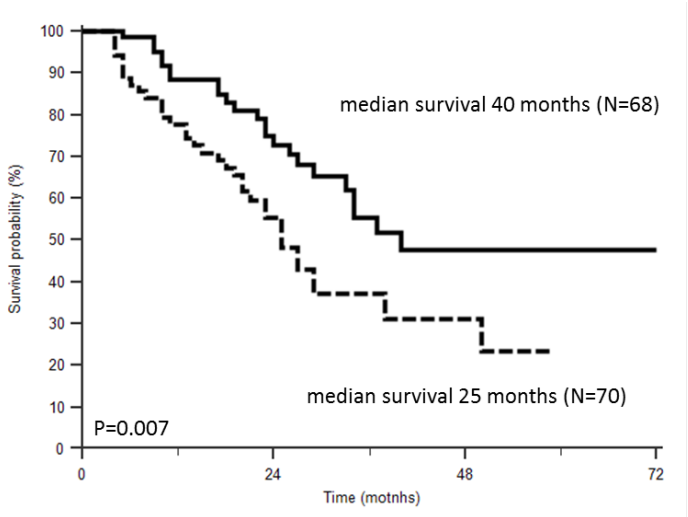

Figure 3. Progression free survival according to at least a partial response to pomalidomide (landmark analysis at 3 months).