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ORIGINAL ARTICLE

A real-life cohort study of immunoglobulin light-chain (AL) amyloidosis patients ineligible for autologous stem cell transplantation due to severe cardiac involvement or advanced disease

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ABSTRACT

Objective: To study the outcome of patients with AL amyloidosis who were ineligible for high dose melphalan (HDM) and autologous stem cell transplantation (ASCT).

Methods: A real-life retrospective observational cohort study of Dutch patients with AL amyloidosis ineligible for HDM and ASCT was performed at the University Medical Center Groningen from January 2001 until April 2017. Primary outcome measure was overall survival (OS). Secondary outcome measures were hematological response (HR), organ responses, and treatment toxicity.

Results: Eighty-four patients were included. Ineligibility was due to NYHA class III/IV ($n = 58$), otherwise advanced disease ($n = 11$), advanced age ($n = 14$), or treatment refusal ($n = 1$). Early death (<3 months) rate was high (44%). Median OS improved from 4 months in period 2001–2009 ($n = 36$) to 8 months in period 2009–2017 ($n = 48$, $p = .02$). HR was seen in 29%, and 42% of the patients, respectively. Median OS was 36 months after induction treatment with bortezomib ($n = 32$) and 18 months with immunomodulatory imide drug (IMID) ($n = 16$), both higher than median OS (7 months) with other regimens ($n = 27$). Incidence of toxicity was high (51%).

Conclusion: OS improved in this high-risk group over the years, especially after introduction of new treatment modalities. However, early death rate remains high, illustrating the need for more effective treatment.

Abbreviations: AL amyloidosis: immunoglobulin light chain amyloidosis; ANOVA: analysis of variance; ASCT: autologous stem cell transplantation; ATTR: amyloidosis: transthyretin amyloidosis; CR: complete remission; CTC: Cancer Institute Common terminology criteria; dFLC: difference between involved and uninvolved free light chain; FLC: immunoglobulin free light chains; HDM: high dose melphalan; HR: hematologic response; ISA: International Society of Amyloidosis; IMID: immunomodulatory imide drug; NYHA: New York Heart Association; OR: organ response; OS: overall survival; PR: partial response; SAP: serum amyloid-P component; s.c.: subcutaneous; VGPR: very good partial response; WHO: World Health Organization

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AL amyloidosis; cardiac amyloidosis; bortezomib; thalidomide; melphalan; survival outcome

Introduction

AL amyloidosis is an acquired disorder caused by the deposition of insoluble fibrils derived from soluble monoclonal immunoglobulin free light chains (FLCs) produced by abnormal, neoplastic CD38+ plasma cells in the bone marrow. Deposition of these amyloid fibrils in tissues and organs leads to organ dysfunction, progressive disability and, if left untreated, eventually to death [1]. Life expectancy in patients suffering from AL amyloidosis mainly depends on organ involvement, of which cardiac involvement is the most important prognostic factor [1,2]. The prognosis of patients with systemic AL amyloidosis has improved after the introduction of new therapeutic modalities [2–6]. The introduction of high-dose melphalan (HDM) treatment followed by autologous stem cell transplantation (ASCT) has drastically changed the outlook for patients [4,6]. Although HDM and ASCT are associated with improved survival, treatment-related toxicity is high, especially in patients with advanced disease [7]. Therefore, HDM and ASCT is not recommended in patients with severe cardiac involvement, renal failure, age >65–70, a poor performance score, or severe autonomic neuropathy

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[4]. After the introduction of ASCT, combination chemotherapy with bortezomib, a proteasome inhibitor, became available with the advantage of inducing a rapid hematologic response [8,9]. Prospective data on the efficacy of such combination chemotherapy regimens, however, are still scarce regarding patients with severe cardiac involvement (NYHA class III/IV) or with otherwise advanced disease. Treatment of such high-risk patients remains challenging due to a high risk of cardiac failure, of sudden death, or of unexpected adverse events related to toxicity of the treatment or to the huge amyloid burden in the body.

This real-life cohort study presents the treatment outcomes of patients with AL amyloidosis who are ineligible for HDM and ASCT, mainly due to severe cardiac involvement. The impact of different first-line chemotherapy regimens on response, overall survival and toxicity is evaluated.

Methods

This real-life retrospective observational cohort study included consecutive patients with newly diagnosed systemic AL amyloidosis treated at our institution from January 2001 until April 2017. The survey ended 2 years later in April 2019. Patients included in our study had not been eligible for HDM and ASCT for the following reasons: New York Heart Association (NYHA) class >II [10], World Health Organization (WHO) performance status >2 [11], older than 65 years of age, or treatment refusal. Patients with a different type of amyloidosis or who had previously received chemotherapy for a plasma cell dyscrasia, were excluded. Before initiation of chemotherapy patients underwent a complete physical examination, electrocardiogram, echocardiography and serum amyloid P component (SAP) scan [12]. Kidney and liver function tests, cardiac biomarkers, serum albumin, FLC assay, urine and serum immunofixation, urine analysis on proteinuria, abdominal fat aspiration and bone marrow biopsy were performed. Cardiac biomarkers and the FLC assay were introduced in our hospital in 2004 and serum samples stored before 2004 were assessed afterwards. Organ involvement was assessed using the International Society of Amyloidosis (ISA) consensus criteria [13,14]. Involvement of the heart, liver, kidneys and peripheral nervous system was counted, yielding a maximum of 4 involved organs [15]. The revised Mayo clinic staging system was used to assess severity of the disease [14]. To classify the underlying plasma cell dyscrasia we divided the groups into patients with AL amyloidosis with less than 10% plasma cells, AL amyloidosis with more than 10% plasma cells, and patients with underlying multiple myeloma (MM), which was classified according to the updated criteria of the International Myeloma Working Group from 2014 [16].

Treatment regimens

Treatment regimens were patient-tailored and in line with the 2013 guidelines of the HOVON multiple myeloma working group [17]. Treatment of patients with underlying multiple myeloma was also in line with these guidelines. Rituximab was added to the treatment of patients with underlying Waldenström's disease.

Induction regimens changed over the years due to the availability of new classes of drugs. In our hospital, bortezomib was introduced in 2009 and lenalidomide in 2013. At the moment of implementation, bortezomib was administered intravenously. However, since the efficacy of subcutaneously administered bortezomib appeared to be non-inferior to intravenous administration, and with an improved safety profile, we switched to subcutaneous administration starting in 2012 [18]. Due to a considerable heterogeneity in treatment strategies (for induction, consolidation, and maintenance treatment) we decided to focus on induction treatment only.

Group comparison

Because treatment regimens changed over time, with the introduction of bortezomib in 2009, we performed a period-based analysis comparing patients treated from January 2001 until January 2009 with patients treated from January 2009 until April 2017.

Furthermore, to study the efficacy of the induction therapy, three different treatment regimens were compared: (1) bortezomib; (2) immunomodulatory imide drug (IMID) (containing thalidomide or lenalidomide as the main drug); and (3) other regimens (all regimens without bortezomib, thalidomide or lenalidomide, most of these containing melphalan as the main drug).

Outcome measures

Primary outcome measure was overall survival (OS) defined as the interval from the time of diagnosis to death from any cause or to the last follow-up moment [19]. Secondary outcome measures were hematologic response, organ responses, and toxicity. Evaluation of hematologic and organ responses was scheduled three months after start of treatment. Hematologic and organ responses were assessed using the international consensus criteria published in 2005 and modified in 2012 [13,14]. Toxicity was classified according to National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events, version 4.0 [20]. Toxicity data were obtained by retrospective chart analysis. Only adverse events that were deemed to be treatment-related were reported.

Statistical analysis

Clinical characteristics were shown as mean with standard deviation in case of normal distribution and median with interquartile range in case of non-normal distribution. The two period-based groups and the three treatment regimen groups were compared using the one-way analysis of variance (one-way ANOVA) for normally distributed variables and the Kruskal–Wallis test for the non-normally distributed variables. Significant differences in the one-way ANOVA analysis of the treatment regimen groups were

further analyzed with *post hoc* tests to correct for multiple comparisons using the Bonferroni *post hoc* test if data met the homogeneity of variances criteria and the Games Howell *post hoc* test if data did not meet these criteria. Dichotomous variables were compared using the chi-square test. Survival curves were constructed using the Kaplan–Meier method and all were mutually compared using the log-rank test (pairwise comparisons). A landmark analysis after 3 months (after response assessment) was performed to compare the survival of the responders with the non-responders after the first-line chemotherapy. $p < .05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS, version 23.0 (IBM, Armonk, NY).

Results

Patients

From January 2001 until April 2017, 225 patients with systemic AL amyloidosis were referred to our outpatient clinic. There were 141 patients excluded from the study for the following reasons: 58 patients were treated with HDM and ASCT; 79 patients were not treated in our hospital, but had been referred for disease evaluation, genetic testing or confirmation of the diagnosis; three patients had been previously treated with chemotherapy for a plasma cell dyscrasia; and one patient had a combined diagnosis of AL and wild-type ATTR amyloidosis.

Clinical characteristics

There were 84 patients included in the study of whom 36 were included in the period 2001-2009 and 48 patients in the period 2009–2017. The clinical characteristics are listed in Table 1. The mean age at diagnosis was 66 years. Forty patients (48%) were female. In 24 (29%) patients more than two major organs were involved. Seventy (83%) patients had cardiac involvement. Fifty-eight (69%) patients were classified as having severe heart failure (NYHA class > II). Fifty-one (61%) patients had renal involvement of which four (5%) were on hemodialysis at baseline. Four patients (5%) started hemodialysis during treatment: three patients developed complete renal failure due to disease progression and one patient due to treatment toxicity. Twelve patients (14%) were classified as having multiple myeloma, thirteen patients (15%) as having AL amyloidosis with more than 10% plasma cells, and two patients (2%) as having Waldenström's disease. Fifty-eight patients (69%) were ineligible for HDM and ASCT because of severe heart failure (NYHA > II); 11 patients (13%) because of a poor performance status (WHO performance status >2); 14 patients (17%) because of advanced age; and one patient (1%) because of treatment refusal. In 79 patients (94%) Mayo clinic stages could be determined, of whom 68 (81%) had Mayo stage >2. Except for the level of alkaline phosphatase, there were no significant differences between the period-based groups (Table 2). Among the three treatment groups, significant differences were seen for levels of serum creatinine and alkaline phosphatase (Table 2). However, after correction for multiple comparisons, no significant differences were found among the groups.

Table 1. Baseline demographics and clinical characteristics of AL-amyloidosis patients.

Characteristics	No. of patients (%)	Mean(SD), Median (IQR)[a]
Total	84 (100)	
Female	40 (48)	
Age (years)	84 (100)	66 (9)
dFLC (mg/l)	79 (94)	166 (86–480)
Plasma cell content bone marrow (%)	79 (94)	10 (5–17)
Serum creatinine (μmol/l)	84 (100)	99 (71–141)
Proteinuria (g/24 hours)	72 (86)	1.1 (0.3–7.0)
Beta-2 microglobulin (mg/l)	67 (80)	3.7 (2.6–6.6)
NT-proBNP (pg/ml)	79 (94)	5243 (1094–9472)
cTnT (ng/ml)	80 (95)	0.07 (0.03–0.12)
Septal thickness (mm)	78 (93)	13 (4)
Left ventricular ejection fraction (%)	82 (98)	54 (11)
Alkaline phosphatase (IU/l)	83 (99)	97 (69–151)
Serum albumin (g/l)	83 (99)	31 (9)
>2 major organs involved	24 (29)	
Heart involvement	70 (83)	
Kidney involvement	51 (61)	
Liver involvement	37 (44)	
Peripheral nerve involvement	11 (13)	
NYHA stage > II	58 (69)	
Mayo stage > II	68 (81)	
WHO performance score >2	67 (80)	
Multiple myeloma	12 (14)	
Waldenström's disease	2 (2)	

Number of patients (and percentage of total number) with a particular characteristic or in whom that characteristic has been analyzed. For the latter, the mean or median has been presented in the next column. dFLC: difference between involved and uninvolved free light chain; NT-proBNP: N-terminal pro-B-type natriuretic peptide; cTNT: cardiac troponin T; NYHA: New York Heart Association; WHO: World Health Organization.

[a]Data are expressed as median (interquartile range, from 25th percentile to 75th percentile, IQR) or mean (standard deviation, SD) where appropriate.

Description of treatment combinations

Nine patients (11%) died before a treatment decision had been made. Of the remaining 75 patients, 32 patients (43%) were selected for the first-line chemotherapy with a bortezomib-based regimen, 16 patients (21%) for treatment with an IMID-based regimen, and 27 patients (36%) for treatment with another regimen. However, four patients died before treatment was started (one in the bortezomib group and three in the other regimen group). Therefore, 71 patients actually received chemotherapy: 31 patients in the bortezomib group, 16 patients in the IMID group and 24 patients in the other regimen group.

The median number of induction chemotherapy cycles was 3 (range 0–12). The median number of cycles used in the bortezomib group was 4 (range 0–9), in the IMID group 4 (range 1–12), and in the other treatment group 2 (range 0–12). Fourteen patients received a reduced dose which was modified at the physician's discretion. The small number of induction chemotherapy cycles is caused by the high rate of early death (<3 months, $n = 37$, 44%) and the high rate of patients that switched to a second line of treatment

Table 2. Baseline demographics and characteristics: inclusion period-based analysis and treatment-based analysis.

	1. Inclusion period-based analysis			2. Treatment-based analysis			
Characteristics	Period 2001–2009	Period 2009–2017	*p* Value	Bortezomib	IMID	Other	*p* Value
Patients included	36 (43)	48 (57)		NA	NA	NA	
Patients treatment selected	34 (40)	41 (49)		32 (43)	16 (21)	27(36)	
Patients treatment started	31 (37)	40 (48)		31 (41)	16 (21)	24 (32)	
Female	14 (39)	26 (54)	.523	17 (53)	7 (44)	12 (44)	.753
Age (years)	67 (9)	66 (9)	.169	64 (10)	66 (8)	68 (9)	.276
FLC diff (mg/L)	156 (57–549)	199 (93–432)	.556	225 (100–441)	151 (70–329)	126 (62–5614)	.587
Plasma cell bone marrow (%)	9 (6–11)	9 (5–16)	.997	9 (5–15)	10 (6–17)	9 (5–10)	.613
Serum creatinine (μmol/l)	102 (70–156)	84 (68–134)	.467	91 (69–149)	70 (64–92)	107 (91–173)	.033
Proteinuria (g/24 hours)	2.5 (0.5–7.7)	0.6 (0.2–5.7)	.256	1,4 (0.2–9.3)	0.6 (0.1–2.1)	3.2 (0.4–8.6)	.240
NT-proBNP (pg/ml)	3651 (1447–7577)	4564 (934–11,685)	.344	4637 (1089–10,646)	2631 (767–8764)	3651 (1241–6904)	.6629
cTnT (ng/ml)	0.05 (0.03–0.09)	0.07 (0.03–0.12)	.422	0.09 (0.04–0.13)	0.04 (0.01–0.08)	0.05 (0.03–0.08)	.266
Septal thickness (mm)	13 (4)	14 (3)	.082	14 (3)	14 (4)	13 (4)	.630
LV ejection fraction (%)	54 (9)	54 (12)	.558	53 (11)	56 (10)	55 (8)	.564
Alkaline phosphatase (IU/l)	122 (88–187)	75 (59–108)	.035	72 (61–100)	99 (61–126)	135 (87–230)	.048
NYHA class	2.5 (1.0)	2.5 (0.9)	.386	2,6 (0,9)	2,6 (1.0)	2,4 (1,02)	.852
WHO performance status	2.7 (0.9)	2.7 (0.9)	.887	2.6 (0.81)	2.7 (0.9)	2.7 (1.0)	.640
MAYO clinic stage	3.6 (0.7)	3.4 (0.7)	.774	3.5 (0.9)	3.3 (0.9)	3.5 (0.7)	.680

Data are expressed as number (percentage), mean (standard deviation, SD), or median (interquartile range, IRQ) where appropriate.
IMID: immunomodulatory imide drug; FLC diff: difference between involved and uninvolved free light chain; NT-proBNP: N-terminal pro-B-type natriuretic peptide; cTNT: cardiac troponin T; LV: left ventricle; NYHA: New York Heart Association; WHO: World Health Organization.

Table 3. Continuation after induction therapy per inclusion period.

	Treatment	Total	Acceptable HR	Death <3 months	Clinical deterioration	Consolidation	Second-line treatment
Period 2001–2009	Other	25	4	10	5	3	3
	IMID	9	2	4	1	1	1
Period 2009–2017	Other	2	0	1	0	1	0
	IMID	7	0	0	1	1	5
	Bortezomib	32	8	13	1	2	8

IMID: immunomodulatory imide drug; HR: hematologic response.

($n = 17$; 20%) due to treatment failure ($n = 14$; 17%) or adverse events ($n = 3$; 4%). Further treatment depended on the degree of hematologic response. Fourteen patients (19% of the 75 patients who were selected for treatment) had a favorable response on induction chemotherapy. Treatment in these patients was continued until the maximum effect on the light chain level was reached, whereas sometimes a final consolidation course with a different kind of chemotherapy (mostly containing low dose melphalan) was given in order to maintain the achieved hematologic response. Eventually 8 patients (11%) received consolidation therapy with a median of 4 cycles (range 2–7); and 17 patients (23%) switched to the second-line therapy due to inadequate response to the first-line induction therapy. Eight patients (11%) did not receive further treatment due to clinical deterioration (Table 3).

Overall survival, hematologic response and organ response

Thirty-seven patients (44%) died within three months. The median overall survival (OS) of all patients was 7 months. Patients included from January 2001 until January 2009 ($n = 36$) had a worse OS, median 4 months, compared to patients included from January 2009 until April 2017 ($n = 48$), median OS 8 months, $p = .02$ (Figure 1(A)).

According to treatment regimen, median OS was 36 months for the bortezomib group, 18 months in the IMID group, and 7 months in the other regimen group. This resulted in a significant difference in OS between the bortezomib group and the other regimen group ($p = .003$), and between the IMID group and the other regimen group ($p = .010$). There was no significant difference in OS between the bortezomib and IMID group ($p = .923$, Figure 1(B)).

Survival curves according to Mayo stages II–IV are presented in Figure 1(C). Only one patient with Mayo stage I was included in the study (because of advanced age), with an individual survival of 41 months. Median OS for Mayo stages II, III, and IV were 49 months, 55 months, and 3 months, respectively, with a significant difference in OS between Mayo stages II and IV, $p = .020$, and stages III and IV, $p = .015$. There was no significant difference in OS between stages II and III.

Median overall survival seemed to differ among patients with AL amyloidosis with less than 10% plasma cells, AL amyloidosis with more than 10% plasma cells, multiple myeloma, or Waldenström's disease, with median OS of 12 months, 6 months, 1 month, and 2 months, respectively. However, there were no significant differences among the groups.

After exclusion of patients who were only included because of age ($n = 14$) or treatment refusal ($n = 1$) the trend

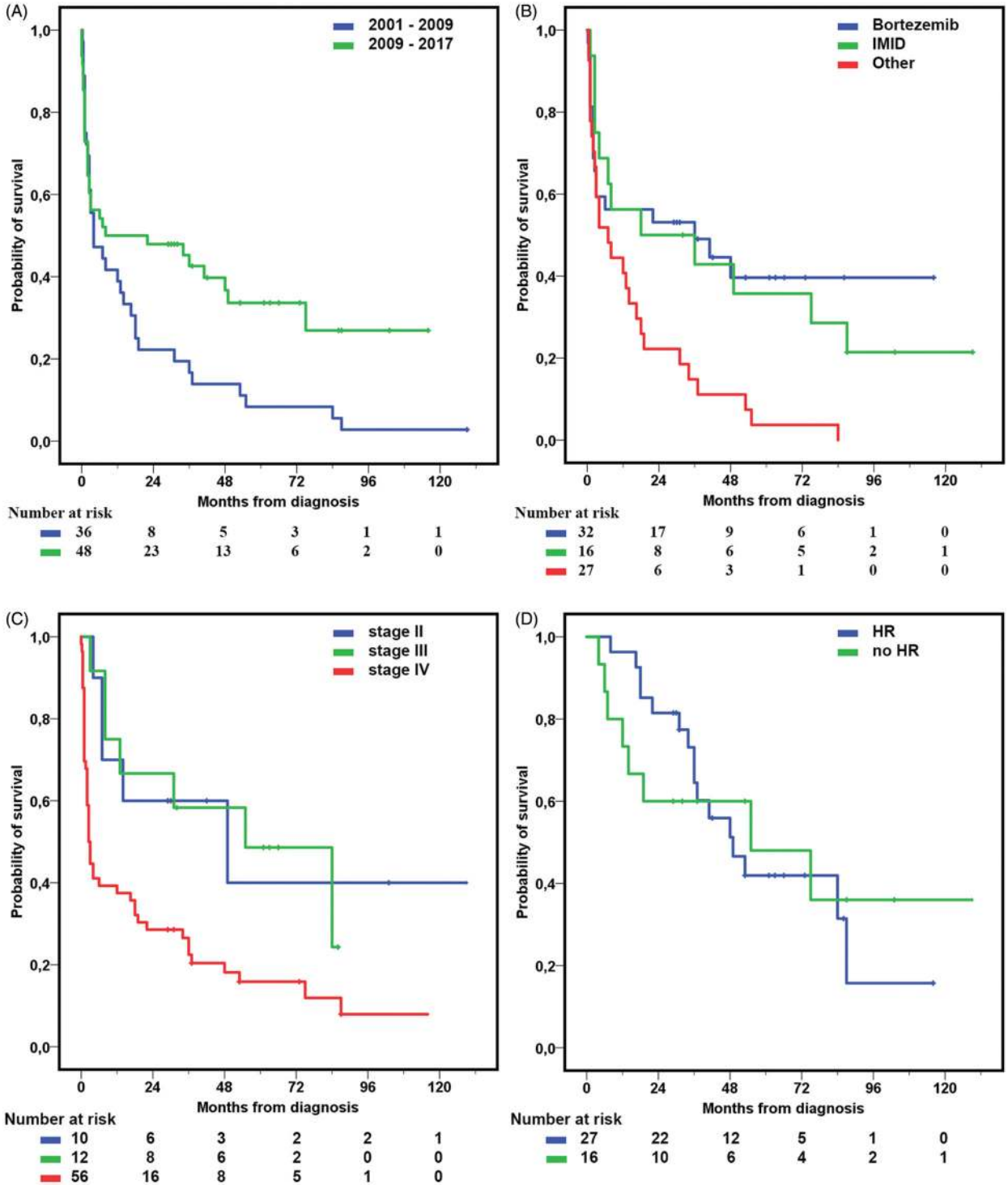

Figure 1. Kaplan–Meier curves of overall survival. (A) Two treatment periods: inclusion from 2001 to 2009 (blue, $N = 36$) and inclusion from 2009 to 2017 (green, $N = 48$). (B) Three treatment regimens: bortezomib-based (blue, $N = 32$), IMID-based (green, $N = 16$), and other treatment (red, $N = 27$). (C) Mayo clinic stage: stage II (blue, $N = 10$), stage III (green, $N = 12$), and stage IV (red, $N = 56$). (D) Landmark analysis after 3 months. Quality of hematologic responses: hematologic response (blue, $N = 27$) and no hematologic response (green, $N = 16$).

of the OS curves remained similar with an almost significant difference in OS between the first and the second period ($p = .056$) and significant differences, between the bortezomib group and the other regimen group ($p = .023$) and the IMID group and the other regimen group ($p = .027$).

In the landmark analysis at 3 months, hematologic response was assessed in 43 patients (57%). In 37 patients (49%) hematologic response was not assessed because of early death (within 3 months). Four patients (5%) were not assessed because of clinical deterioration. Patients with hematologic response (complete remission (CR); very good partial response (VGPR); partial response (PR)) ($n = 27$) had an overall survival median of 49 months. CR was reached in 8 patients (11%), VGPR in 10 (13%), and PR in 9 (12%) (Table 4). In patients without hematologic response (stable disease or progression) ($N = 16$) median

Table 4. Number of patients (%) with hematologic and organ response rates to first-line treatment: overall, per period and for the three different treatment regimens.

Characteristic	Overall	Period 2001–2009	Period 2009–2017	Bortezomib	IMID	Other
Patients, *N* (%)	75	34	41	32	16	27
Hematologic response						
Overall	27 (36)	10 (29)	17 (42)	15 (47)	4 (25)	8 (30)
CR	8	3	5	4	1	3
VGPR	10	3	7	6	1	3
PR	9	4	5	5	2	2
No hematologic response						
Overall	16 (21)	6 (18)	10 (24)	4 (13)	7 (44)	5 (19)
Stable disease	12	5	7	3	6	3
Progression	4	1	3	1	1	2
Organ response						
Organ response	8	1	7	6	2	0
Stable disease	23	8	15	10	6	7
Progression	12	7	5	3	3	6
Not evaluated	32	18	14	13	5	14

IMID: immunomodulatory imide drug; N: number; CR: complete response; PR: partial response; VGPR: very good partial response.

Table 5. Number of patients with observed treatment-related toxicity.

Toxicity (CTC grade ≥ 3)	Bortezomib	IMID	Other
Patients treated	31	16	24
Patients with toxicity	15 (48%)	9 (55%)	12 (50%)
Heart failure	5	3	1
Polyneuropathy	4	1	0
Kidney failure	0	0	1
Orthostasis	2	0	0
Infection	1	1	3
Malaise	1	2	4
Hematologic	3	1	4
Lung embolism	0	1	0
Constipation	2	0	0
Diarrhea	1	1	1
Hyperglycemia	2	0	0
Angioedema	1	0	0

IMID: immunomodulatory imide drug; CTC: National Cancer Institute Common terminology criteria for Adverse Events.

overall survival was 55 months ($p = .958$) (Figure 1(D)). Organ response was seen in 8 patients (11%) and organ progression in 12 patients (16%). All 8 patients with organ response had a hematologic response: CR in 3 patients, VGPR in 3 patients and PR in 2 patients. Of the 12 patients with organ progression, 4 patients also had hematologic progression and 4 patients had stable hematologic disease. The remaining 4 patients had a hematologic response: PR in 2 patients, VGPR in 1 patient and CR in 1 patient.

Toxicity

Treatment-related toxicity grade 3 or more was observed in 36 (51%) of the 71 patients that eventually received chemotherapy (Table 5). Of the 31 patients treated with bortezomib, 15 patients (48%) developed toxicity grade 3 or more. Bortezomib was discontinued in 6 patients (19%). Three patients (9%) were switched from a bortezomib- to a lenalidomide-based regimen. Three patients (9%) (all with amyloid cardiomyopathy) developed severe heart failure, leading to death. Nine of the 16 patients treated with an IMID (55%) developed toxicity grade 3 or more, of which 3 patients (19%) discontinued treatment. Twelve of the 27 patients treated with other regimens (44%) developed toxicity grade 3 or more. Treatment was discontinued in 5 patients (19%) and postponed in 2 patients (7%). One patient (4%) (with renal involvement) developed end-stage renal failure, for which hemodialysis was started, but eventually still led to death. One patient (4%) (with amyloid cardiomyopathy) developed severe heart failure, leading to death.

Discussion

This real-life observational cohort study shows that the survival of patients suffering from AL amyloidosis who were ineligible for HDM and ASCT has improved from 4 to 8 months in recent decades. The improved overall survival may largely be attributed to the introduction of novel drugs including bortezomib (median OS of 36 months in this treatment group) which can achieve a rapid and deep hematologic response in patients who tolerate this treatment [8,9,21]. The wider spectrum of available chemotherapeutics enables switching to a potentially effective second-line treatment in cases where a hematologic response to the first-line treatment has been inadequate or will take too much time. However, other factors probably also contribute to the observed improved OS, such as improvement in supportive care, earlier and more rapid diagnosis, the introduction of cardiac makers and the FLC assay in 2004, and – by influencing the composition of the study group – changes in criteria for selecting candidates for HDM and ASCT. All these changes occurred in recent decades. However, early mortality in this high-risk patient group of 84 patients remains high, as illustrated in Figure 1(A) by the 37 deaths (44%) within 3 months, of which 11 already occurred (13%) within two weeks after diagnosis.

Our findings are in line with previous studies indicating that treatment of patients having high-risk cardiac AL amyloidosis (Mayo stage III or IV) with bortezomib-containing chemotherapy improves the OS [22,23]. In the study of Jaccard et al., the median OS was not reached within a relatively short follow-up period of 11.7 months [22]. Shen et al. showed the median OS improving from 2 months to 30 months when patients were treated with bortezomib-containing chemotherapy instead of supportive treatment

only [23]. Comparing the findings of the IMID group is difficult, since patients with advanced disease were excluded in previous studies. Therefore, it is not surprising that the median OS of 18 months in the current study is lower compared to earlier reports [20,24]. The OS of 7 months in the patients treated with other regimens was also lower compared to the 10.5 months reported in 2008 [25] and 17 months reported in 2010 [26]. The lower OS in the current study is probably related to the poor clinical condition of the referred patients and the real-life setting of the study, in which all admitted patients participated.

The overall hematologic response of 36% was lower compared to previously reported responses of 59% and 68% in high-risk patients with cardiac AL amyloidosis [22,23]. This may also be related to the real-life setting in which severely diseased cases are referred to a tertiary care center. When looking at the different treatment-regimens the best hematologic response was obtained with bortezomib (47%) compared to IMID (25%) and other treatment regimens (30%). The relatively good hematologic responses in patients treated with bortezomib are in line with previous reports [5,8,9,19,24,27,28]. Lenalidomide was chosen as the first-line treatment only in two patients suffering from severe polyneuropathy and autonomic neuropathy.

Earlier studies showed that the depth of the hematologic response, especially CR, is predictive for organ response and prolonged survival [24,29]. We indeed found that all 8 patients with organ response had also achieved a hematologic response and 8 of 12 patients with organ progression had not achieved a hematologic response.

However, landmark analysis showed a median OS of 49 months in responders and of 55 months in non-responders: no difference in survival could be detected between patients with and without a hematologic response after the first-line chemotherapy. This lack of difference in survival is contrary to what was expected. However, it should be taken into account that the first-line chemotherapy was only the start of a much longer course of treatment in non-responders. If possible, non-responders sequentially received second lines of treatment with the aim of obtaining CR. Over time this change to the second-line chemotherapy was being opted for earlier. In patients with an adequate hematologic response to the first-line therapy, treatment was continued until the maximum effect on the light chain level was reached and sometimes a final consolidation course was given. Our findings may suggest that continuation with maintenance therapy retaining maximum HR could be important in this high-risk group to further improve survival.

Incidence of toxicity in this cohort is high (51%), even somewhat higher than previously reported [3]. However, this is not really surprising when considering the poor clinical condition of these patients. Besides, it should be noted that toxicity of the treatment is sometimes hard to distinguish from progressive disease due to the amyloid burden itself. Disease severity was to a certain extent reflected in the different Mayo stages. Only a difference between stages II and IV and between stages III and IV could be detected, probably due to the small number of patients classified with Mayo stages I–III.

Due to the retrospective nature of this cohort study, the results should be interpreted with caution. However, the real-life aspect of this study is an advantage compared to studies in which a group of carefully selected patients no longer represent patients encountered in real-life clinical practice. A second limitation is the possible confounding of disease severity due to the exclusion of patients from HDM and ASCT solely due to age (>65 years) or treatment refusal. Event-free survival curves have limited advantage in this population due to the high rate of early deaths and the frequent switch to the second-line treatment. In an attempt to rule out confounding factors, subgroup analysis was performed after excluding the age-related group. This did not affect the trend of the OS curves observed for the different groups.

In conclusion, the high rate of early deaths in this cohort shows the need for new treatment regimens that provide a rapid and deep (hematologic) response. The advantage of such treatment regimens must be balanced against the risk of toxicity to preserve a patient's chance of surviving long enough to benefit from clonal control. Daratumumab, a human IgG1k monoclonal antibody targeting the CD38 surface marker on plasma cells, is a promising drug especially when administrated subcutaneously (s.c.) thereby limiting the volume load [30,31]. After using daratumumab a hematologic response was seen in 76% of patients, with a median response time of one month. Moreover, treatment was well tolerated even in patients with cardiac involvement. Currently, daratumumab s.c. added to a backbone consisting of cyclophosphamide, bortezomib, and dexamethasone is under study [32]. In addition, the applicability of monoclonal antibodies, small compounds, or fusion proteins to clear amyloid deposits using immunological mechanisms is being explored [33–36]. It has yet to be demonstrated whether or not these new agents will be safe and can help to overcome the poor survival and high rates of early death in this high-risk group of patients. Also doxycycline, which may have a cardioprotective effect and may lead to reduced fibril formation, should be studied for its clinical potential in this high-risk population [37–39]. Finally, early diagnosis of the disease remains crucial, since early treatment is associated with better survival outcomes. Early diagnosis depends on awareness of the disease in daily clinical practice [40]. Therefore, increasing awareness should be the first and principal step to improve the situation of these patients.

Disclosure statement

The authors report no conflicts of interest.

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