Chemotherapy for renal AL amyloidosis: treatment results and outcomes in 49 patients from a single center

AL amyloidosis is actually known to be the most common form of systemic amyloidosis. Renal involvement is characteristic for AL amyloidosis and almost invariably results in proteinuria, more that 50% of patients present with nephrotic syndrome at diagnosis, about 20% of patients require dialysis over time. Beyond kidneys, the other most affected by AL amyloidosis organ is heart; other sites of damage include liver, peripheral and autonomous nervous system and soft tissues. Historically, combination of melphalan and prednisone was used for AL amyloidosis treatment, later combination of melphalan and dexamethasone and high dose melphalan with autologous stem cell transplantation were introduced, and recently regimens, including bortezomib-dexamethasone, cyclophosphamide-bortezomib-dexamethasone and others were adopted from multiple myeloma treatment protocols. Treatment outcomes depend on severity of renal and cardiac involvement.

In our retrospective study we aimed to evaluate treatment efficacy and long-term outcomes in 49 patients with biopsy-proven AL amyloidosis, treated in our unit with above mentioned chemotherapy regimens over last 15 years. At the time of kidney biopsy 81% of patients had nephrotic syndrome, 43% had impaired kidney function, and 30% presented with both nephrotic syndrome and renal dysfunction. In one third of patient's population kidneys were the only site of damage, others presented with kidneys and heart or multiorgan involvement.

Under chemotherapy 42.8% of patients achieved hematological remission, and 34.6% - both haematological and organ remission. The rate of hematological remissions was significantly higher those who received autologous stem cell transplantation. During follow-up period 12 [4; 29] months 14% of patients started dialysis and 41% died. 5-year cumulative survival reached 50% in patients, treated with bortezomib, in melphalan-based treatment subgroups and it was only 29-21-30%, however the differences were not significant. Bortezomib-based regimens also showed the tendency to better 5-year patients (69% vs 29-29-30%), but not kidney (72% vs 100-49-100%) survival.

Keywords: Renal amyloidosis, chemotherapy, melphalan, bortezomib, outcomes

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Introduction

AL amyloidosis is actually known to be the most common form of systemic amyloidosis in the Western countries [1, 2]. In this particular type of amyloidosis monoclonal immunoglobulin light chains, produced by plasma cell clone, undergo aggregation and form amyloid deposits, almost always systemically, and kidneys are one of the most frequent sites of amyloid deposition [3, 4, 5]. AL amyloidosis may occur in some patients with overt multiple myeloma, and rarely arise in association with Waldenström macroglobulinemia and non-Hodjkin lymphoma/leukaemia, but usually the degree of plasma cell proliferation in AL amyloidosis is low or even undetectable, thus for many years it used to be named "primary" amyloidosis, the term which is actually eliminated [6, 7, 8, 9, 10, 11, 12, 13].

Despite its non-malignant nature, so-called "primary" AL amyloidosis is associated with a high morbidity and mortality. In 2012 the term "monoclonal gammopathy of renal significance" (MGRS) was proposed by International Kidney and Monoclonal Gammopathy Research Group (IKMGRG) in order to stress the target-organ damage crucial significance in the group of "dangerous small B-cell clones"-driven diseases (AL amyloidosis, light/heavy chain deposition disease, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, immunotactoid glomerulonephritis), and discriminate them from "monoclonal gammopathy of undetermined significance" [3, 14, 15, 16].

Renal involvement in AL amyloidosis is most typical and almost invariably results in proteinuria, more that 50% of patients present with nephrotic syndrome (NS) at diagnosis. Renal insufficiency is not that frequent at diagnosis, but about 20% of patients develop ESRD over time and require dialysis. Beyond kidneys, the other most affected by AL amyloidosis organ is heart; other sites of damage include liver, intestine, peripheral and autonomous nervous system and soft tissues [17, 18, 19].

AL amyloidosis, as well as other MGRS conditions is diagnosed by demonstration of monoclonal deposits in the kidney. Kidney biopsy is usually indicated for significant proteinuria and/or renal insufficiency, but is even more important when a monoclonal gammopathy is present. Immunofluorescence study should be performed in all suspected cases. Monoclonal protein studies should be performed as well to match the monoclonal protein in circulation with the monoclonal deposits in the kidney. As AL amyloidosis is associated with high morbidity due to the severity of renal and systemic lesions induced by the amyloid deposition, early recognition is crucial, notably because the suppression of monoclonal immunoglobulin light chains secretion by chemotherapy often improves outcomes [16, 20].

Different treatment regimens had been used since 1997, when melphalan was shown to be beneficial compared to colchicine [21]. Melphalan and prednisone (MP), melphalan and dexamethasone (MD), high dose melphalan with autologous stem cell transplantation (ASCT) were introduced first, and then novel therapies, including cyclophosphamide-thalidomide-dexamethasone (CTD), bortezomib-dexamethasone (BD), cyclophosphamide-bortezomib-dexamethasone(CBD) regimens, with relatively fast haematological response, were adopted from multiple myeloma treatment protocols. However long-term outcome data are lacking for the novel therapies. In most cases, the overall survival of patients with AL amyloidosis is better than that of multiple myeloma, but the renal outcomes are not. The exception is patients with AL amyloidosis with cardiac involvement, in which death can occur rapidly [16, 21-28].

Current recommendations from IKMGRG [29] for Al amyloidosis suggest, that for patients without severe cardiac involvement (stage I and II according to Mayo Clinic criteria), the first line treatment should be based on MD, with rapidly introducing bortezomib after 1 or 2 courses of MD in the absence of a clonal response. In patients with advanced CKD, cyclophosphamide is preferred to melphalan, and regimens such as CBD may be used. Another option is to use CTD regimen. Patients with stage III cardiac involvement represent a therapeutic challenge because their median survival remains poor. In selected patients (mainly stage I and II), ASCT should be considered, in the absence of overt renal insufficiency and the absence of other advanced organ failure [28, 29].

We aimed to evaluate treatment efficacy and long-term outcomes in patients with AL amyloidosis with kidney involvement, treated in our unit with different chemotherapy regimens over last 15 years.

Materials and Methods

Using electronic database and purposely designed chart, we searched and analysed data for 164 patients with biopsy-proven paraprotein-related kidney damage, treated in our centre in 2001-2015. As for this retrospective study the data were extracted from archive charts and entered into the study database anonymously, no informed consent from the patients was obtained.

Indications for kidney biopsy included NS, proteinuria (>0.3 g/24h) and/or haematuria and/or impaired kidney function. Kidney core biopsy was taken with BARD-Magnum biopsy guidance facility. Obtained specimens were divided into two or three parts and processed for light microscopy, immunohistology, and (in selected cases) electron microscopy. Formalin fixed/paraffin embedded sections for light microscopies were stained with haematoxylin and eosin, Masson's trichrome, periodic acid-Shiff and Congo red. Unfixed cryo-sections were routinely stained for IgA, IgG, IgM, C3, C1q, kappa and lamda light chains and fibrinogen. In selected cases immunofluorescence on formalin fixed/paraffin embedded sections with FITC-conjugated anti IgA, IgG, IgM, C1q, C3, fibrinogen, λ and λ light chains antibodies, and immunoperoxidase staining for amyloid A-protein was performed. Also in selected cases Toluidune blue stained semi-thick sections were examined and 1 glomerulus was identified for electron microscopic study (by external pathologist).

Work-up, beyond routine, included serum and urine immunoelectrophoresis; peripheral blood immunophenotyping; abdomen, kidneys and peripheral lymph nodes ultrasound; skeletal X-ray; chest and abdomen CT; bone marrow aspiration and/or biopsy; and/or lymph node biopsy with light microscopy and immunohistochemistry.

Patients with overt lymphoproliferative malignancies and with rare variants of MGRS were excluded from analysis, and 86 patients with AL amyloidosis were evaluated. 37 patients out of 86, who received only supportive treatment - those who could not tolerate chemotherapy due to multiorgan failure or refused chemotherapy - were excluded from further analysis. Study group included 49 AL amyloidosis patients treated with chemotherapy.

Treatment options varied over 15-years period, thus study group was divided in 4 subgroups: subgroup 1 - 7(14.2%) patients received ASCT; subgroup 2 – 10 (20.5%) patients treated with MP; subgroup 3 – 10 (20.4%) patients treated with MD; and subgroup 4 - 22 (44.8%) patients treated with bortezomib-based regimens (B), we used either CBD or BD options.

Statistical analysis was performed using SPSS 11.5 program package. Normally distributed variables presented as the median and 25 and 75 percentile range. Comparison between median data performed using Student criteria. Differences significance for categorical variables was evaluated by Fisher's exact test and λ^2 test. For abnormally distributed variables median value and interquartile range were calculated, Mann-Whitney test and Kruskall-Wallis test were used for comparison of these variables. P-value<0.05 was defined for statistical significance.

Results

Study group comprised 56.9% of biopsy-proven AL amyloidosis cases, and included 49 patients, 25 (51%) males and 24 (49%) females, median age 58 [48; 64.5] years. Median duration from the disease onset to the time of kidney biopsy and start of chemotherapy was 12 [6; 23] months. Clinical presentation at the time of kidney biopsy is shown in the TABLE 1. Multiorgan lesions included liver, spleen, intestine, adrenal glands, salivary glands, lymph nodes and skin in different combinations.

Further analysis in the subgroups showed that median proteinuria was the lowest in the subgroup 1 - 3.2 [3.0; 4.3] g/L. In the subgroups 2, 3 and 4 median proteinuria was 6.0 [3.0; 5.8]; 6.0 [3.4; 7.6] and 5.5 [3.7; 8.2] g/L respectively, however the difference was statistically significant only between the subgroups 1 and 2 (FIGURE 1).

Table 1. Clinical presentation in the study group at the time of diagnosis

Kidneys only pts n (%)	16 (32.6)
Kidneys and heart pts n (%)	10 (20.4)
Kidneys, heart and other organs pts n (%)	23 (46.9)
Median proteinuria g/L	5.5 [3.3; 6.9]
Nephrotic syndrome n(%)	40 (81.6)
Median serum creatinine µmol/L	117.0 [90.0; 174.5]
CKD stage 2-4 pts n (%)	21 (42.8)
Neprotic syndrome and CKD sage 2-4 pts n (%)	15 (30.6)

CKD, Chronic kidney disease

Median plasma creatinine was highest in the subgroup 4 - 151.5 [100.0; 246.0] µmol/L. In the subgroup 1, 2 and 3 it was 90.0 [88.0; 112.07]; 111.0 [88.0; 200.0] and 109.0 [87.0; 162.0] µmol/L respectively, the differences were significant between subgroups 4 and 1 and subgroups 4 and 3 (FIGURE 2).

Kidneys only were affected in 42.8%, 50%, 30% and 22% in the subgroups 1, 2, 3 and 4 respectively. Kidneys and heart involvement was diagnosed in 28.5%, 20%, 20% and 18% in the subgroups 1, 2, 3 and 4 respectively. Multiorgan involvement presented in 28.5%, 30%, 50% and 59% of patients in the subgroups 1, 2, 3 and 4 respectively. Thus about a half of patients had only renal involvement in the subgroups 1 and 2, whereas in the subgroups 3 and 4 proportion of isolated renal amyloidosis was much lower - less than one third. However, these differences were not statistically significant.

Treatment results and outcomes are shown in the TABLE 2. Evaluation of treatment results demonstrated that totally 42.8%f of patients achieved haematological remission (HR), and 34.6% - also organ remission (OR). Further analysis of the subgroups showed that the rate of HR was significantly higher in the subgroup 1 compared to the subgroup 2 (85.7% vs 20% respectively, p<0.05), however the rate of OR did not differ significantly between any of the subgroups (FIGURE 3).

Median follow-up duration was 12 [4; 29] months. At the end of follow-up period 22.4% of patients were alive and did not need renal replacement therapy, 2 of them - as long as for 113-126 months.

Long-term outcomes analysis results are

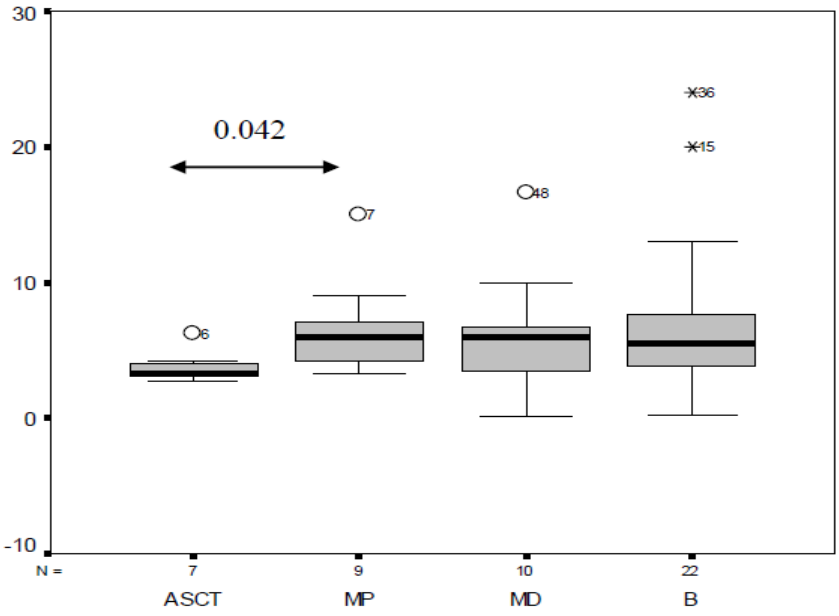

Figure 1. Proteinuria level in the treatment subgroups.ASCT, Autologous stem cell transplantation; MP, Melphalan-prednisone; MD, Melphalan-dexamethasone; B, Bortezomib

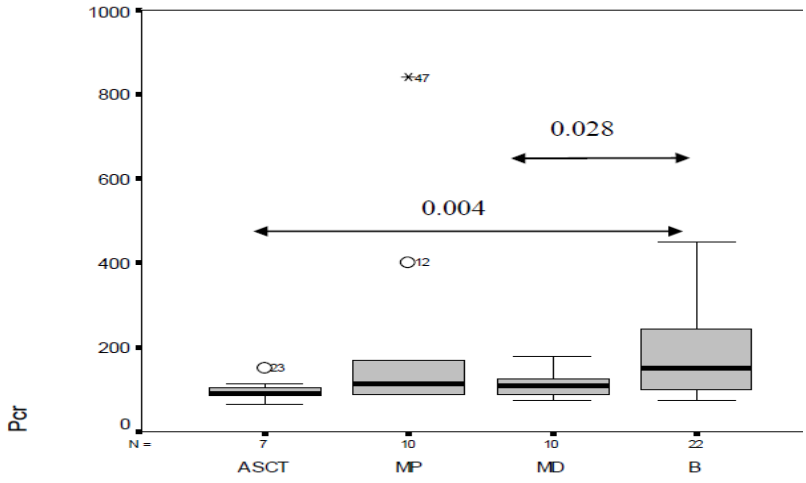

Figure 2. Plasma creatinine level in the treatment subgroups. Pcr, Plasma creatinine; ASCT, Autologous stem cell transplantation; MP, Melphalan-prednisone; MD, Melphalan-dexamethasone; B, Bortezomib

shown in the TABLE 3. Cumulative 5-year patients and kidney survival did not differ significantly between the subgroups (FIGURE 4).

5-year patients survival (FIGURE 5) tended to be better in the subgroup 4; however the difference was not significant. Same way, there was a trend for better kidney survival in the subgroups 1 and 3 compared to the subgroup 2, but the differences again did not reach statistical significance (FIGURE 6).

Discussion

In our retrospective study sample size in the treatment subgroups varied, which might influence the results of analysis. MP subgroup includeed 10 patients, treated some 15-11 years ago, at that time MP was the only regimen available in our institution and diagnostic algorithm was not fully applicable. Since 2006 MP regimen was replaced by MD, but only 10 patients received this treatment, as in patients with seriously impaired kidney function we started to use bortezomib-based modalities as soon as bortezomib became available in 2009. Bortezomib treatment subgroup thus included 22 patients, and in this subgroup median serum creatinine was significantly higher than in MD and ASCT subgroups. Only 7 of patients with less sever renal damage were selected for ASCT, in this subgroup median proteinuria and median serum creatinine were significantly lower, compared to the MP and Bortezomib subgroups respectively. Detailed analysis of the extrarenal amyloidosis-related damage was not the aim of our study; however patients without cardiac and other organs involvement clearly dominated among the subgroup, selected for ASCT.

As our study is retrospective, we have to stress that treatment choice in vast majority of cases was made before recommendations from IKMGRG [29] were created and published, which empirically confirm these recommendations applicability in the real clinical practice.

Treatment results demonstrated that more than one third of patients achieved both HR and OR despite late treatment start (mostly due to the late referral). Our findings are in agreement with literature data [22-25, 27]. Significantly higher rate of HR in the ASCT subgroup is also concordant with previously published data [23].

During the follow-up period totally 14.2% of patients started dialysis, and 40.8% died, this proportions do not differ from the literature data. Main causes of death were heart failure and multiorgan failure, confirming the impact of extrarenal lesions to the treatment outcomes. That again stresses the crucial role of early diagnostics and timely treatment for improving outcomes [20] disrespectful to the treatment modality.

1-year cumulative patient's and kidney survival varied in the range 45-71%, 3-year cumulative survival – in the range 21-50%, and 5-year cumulative survival-in the range 21-50% without significant differences between the treatment subgroups. Interestingly, 3-year and

Table 2. Treatment results and outcomes in the study group and treatment subgroups					
	Overall n 49	Subgroup 1 n 7	Subgroup 2 n 10	Subgroup 3 n 10	Subgroup 4 n 22
Hematological remission (%)	42.8	85.7	20	40	41
Organ remission (%)	34.6	42.9	20	40	36.4
Treatment failure (%)	57.1	14.3	80	60	59
Alive not on dialysis n (%)	11 (22.4)	2 (28.5)	1 (10)	2 (20)	6 (27.2)
Lost for the follow-up n (%)	11 (22.4)	0 (0)	2 (20)	2 (20)	7 (31.8)
Started dialysis n (%)	7 (14.2)	0 (0)	4 (25)	0 (0)	3 (13.6)
Died n (%)	20 (40.8)	5 (71.4)	3 (30)	6 (60)	6 (27.2)
Multiorgan failure	6	1	1	2	2
Heart failure	6	0	0	2	4
Stroke	2	0	1	1	0
Sepsis	3	2	0	1	0
Cancer	3	2	1	0	0

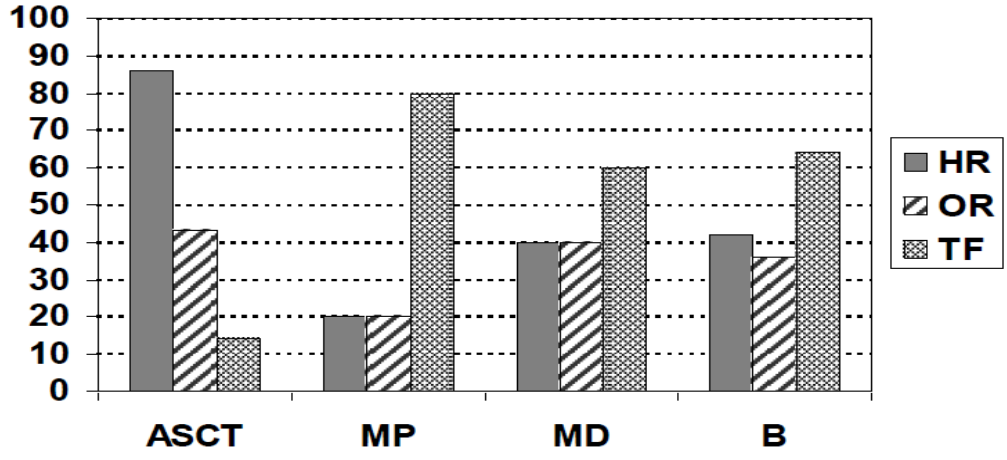

Figure 3. Proportion of remissions in the treatment subgroups. ASCT, Autologous stem cell transplantation; MP, Melphalan-prednisone; MD, Melphalan-dexamethasone; B, Bortezomib; HR, Hematologic remission; OR, Organ remission; TF, Treatment failure

5-year cumulative survival was almost equal, which means that if patient achieve OR and survive over 2 years, the long-term prognosis tends to be favorable.

Even though the differences were not statistically significant, we observed that the higher 5-year cumulative survival (50%) was achieved in the bortezomib-treated subgroup, while in three melphalan-based treatment subgroups and it was only 29-21-30% respectively. Bortezomib-based regimens also showed the tendency to better 5-year patient's (69% vs 29-29-30% respectively), but not kidney (72% vs 100-49-100% respectively) survival, which reflect more advanced renal dysfunction at the time of diagnosis and treatment start in this particular subgroup. ASCT and MD subgroups tended to have higher kidney survival, which is not surprising, given baseline better kidney function in patients, selected for these treatment options.

We conclude that the efficacy of currently recommended by IKMGRG [29] AL amyloidosis treatment modalities was similarly effective in terms of cumulative patient's and kidney survival despite the higher rate of haematological remissions in patients, who received high dose melphalan with autologous stem cell transplantation.

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Table 3. Cumulative, patient's, and kidney 1-year, 3-year and 5-year survival												
	Cumulative survival				Patient's survival				Kidney survival			
Subgroups	1	2	3	4	1	2	3	4	1	2	3	4
1 year	71	63	45	61	71	88	45	69	100	65	100	87
3 years	43	21	45	50	43	29	45	69	100	49	100	72
5 years	29	21	30	50	29	29	30	69	100	49	100	72

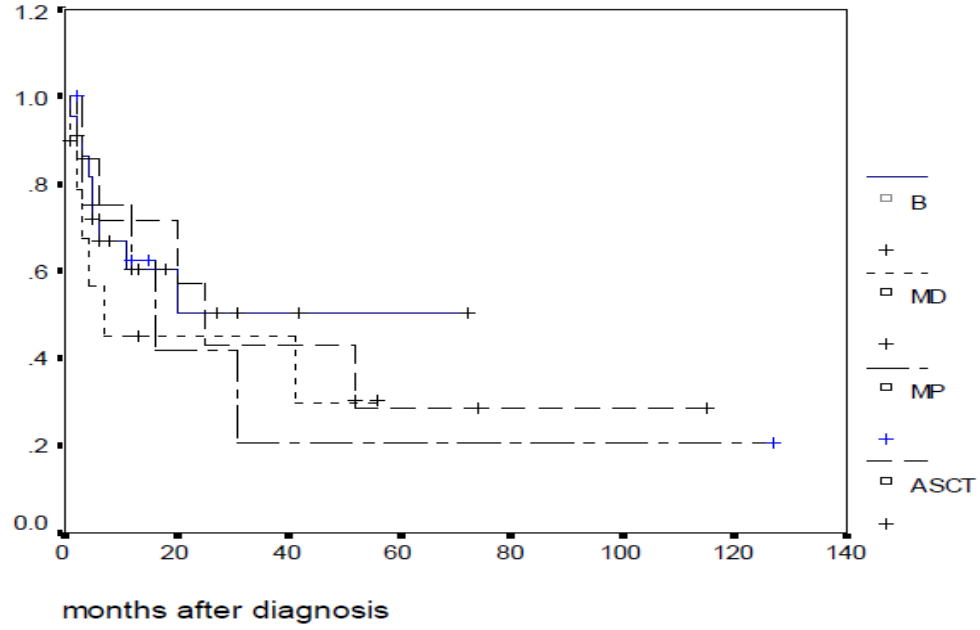

Figure 4. Cumulative patients and kidney survival in the treatment subgroups. Cum survival, Cumulative survival; ASCT, Autologous stem cell transplantation; MP, Melphalan-prednisone; MD, Melphalan-dexamethasone; B, Bortezomib

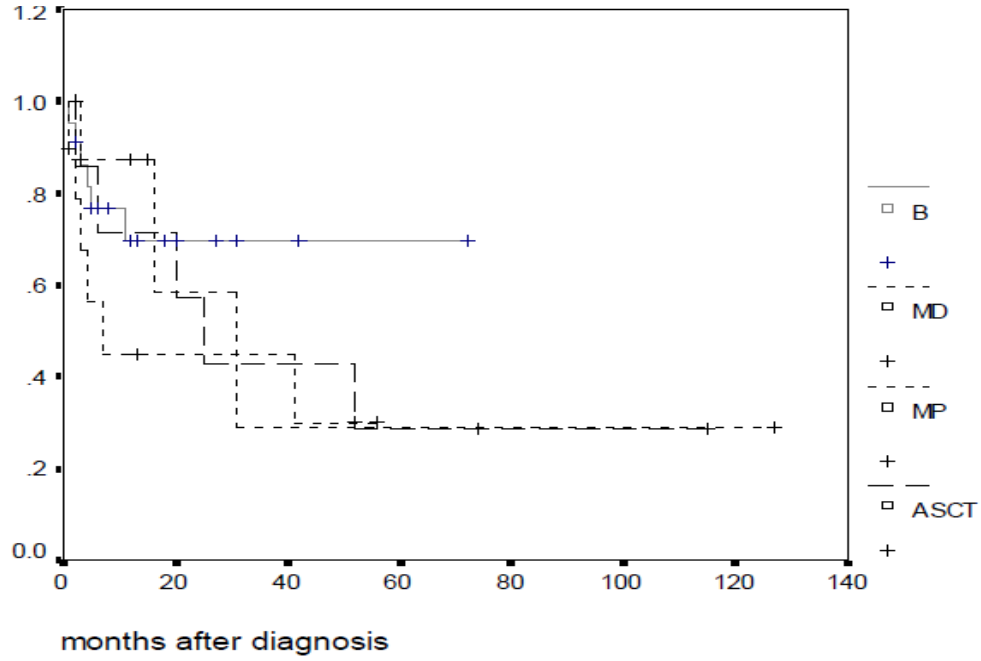

Figure 5. Patients survival in the treatment subgroups. ASCT, Autologous stem cell transplantation; MP, Melphalan-prednisone; MD, Melphalan-dexamethasone; B, Bortezomib

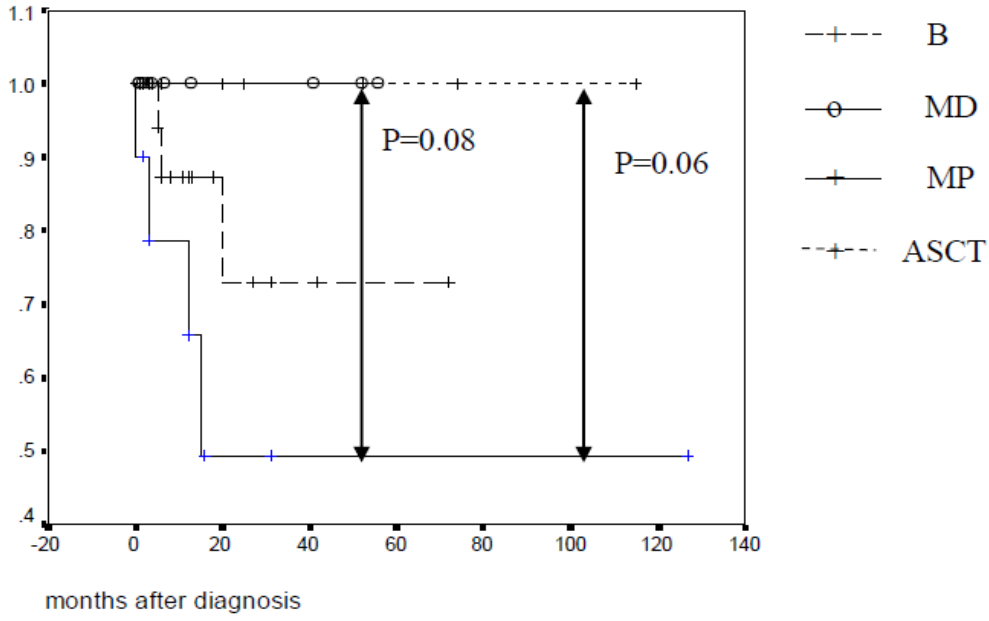

Figure 6. Kidney survival in the treatment subgroups. ASCT, Autologous stem cell transplantation; MP, Melphalan-prednisone; MD, Melphalan-dexamethasone; B, Bortezomib

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