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Comparison of bortesomib-based induction regimens with other treatment modalities in patients with newly diagnosed systemic light chain amyloidosis ineligible for autologous stem cell transplantation

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Summary

Systemic light chain (AL) amyloidosis is a form of plasma cell disorders, characterized by overproduction of immunoglobulin light chains by clonal plasma cells and their deposition in organs and tissues as an insoluble fibrillar protein-amyloid. Suppression of amyloid production is the main goal of therapy, whereas cardiac involvement is the main predictor of survival. Therapeutic regimen containing bortezomib, cyclophosphamide and dexamethasone (CyBorD) was recently introduced as the standard of care for newly diagnosed patients. However, there are only few longitudinal comparative studies of this regimen with evaluation of organ responses.

In our study we analyzed the response to induction therapy in 105 patients with newly diagnosed patients with systemic AL amyloidosis ineligible for autologous stem cell transplantation (ASCT). All the patients were divided into three groups: group 1 received CyBorD; group 2 was treated with other bortezomib-based regimens, and group 3 received bortezomib-free regimens.

The 3-year OS was 70.3% (95% CI 61-80) with the median follow-up of 27.8 months (22 days to 11 years). Unfavorable factors for OS were as follows: age >70 years (p=0.007), male gender (p=0.015), Mayo stage IIIb (p=0.07) and renal damage stage III (p<0.0001). In the multivariate analysis, all other treatments than CyBorD were associated with decreased 3-year OS values (HR 4.9, 95% CI 1.4-17.2, p=0.012). 3-year progression-free survival (PFS) in CyBorD group was 79% (95% CI 63-95), *vs* 48% (95% CI 35-61) in group 2, and 55% (95% CI 30-80) in group 3 (p=0.28). Overall response rate (ORR) was 70% (n=74). The percentage of patients who showed hematological response was significantly higher in the CyBoRD group, 94% *vs* 84% in group 2 and 63% in group 3 (p=0.033), and median time to response in this group was 9.6 (5.3-15) months. The organ response (OR) was assessed over a 3-year period. The percentage of heart and renal responses was higher in CyBorD group. For cardiac responses, the rate was 78% *vs* 55% *vs* 16% (p=0.05) for groups 1, 2 and 3 respectively. Renal responses were observed in 90% *vs* 92% *vs* 57% of the patients (p=0.01). Overall median time of hematologic response (median, 10 months) and renal response (median, 12 months) occurred earlier than cardiac and hepatic responses (median, 26 months).

In summary, our results are comparable with previously published studies, demonstrating faster hematological response and organ responses after CyBorD treatment, which is translated into improved overall survival. Organ responses were observed significantly later than hematologic response.

Keywords

Systemic AL amyloidosis, CyBoRD, bortezomib.

Introduction

Systemic light chain (AL) amyloidosis is a form of plasma cell disorders, characterized by overproduction of immunoglobulin light chains by clonal plasma cells (PS) or lymphocytes and their deposition in organs and tissues in the form of an insoluble fibrillar protein-amyloid. Cardiac involvement is the main predictor of patient outcome. The goal of therapy is to rapidly and profoundly suppress production of amyloidogenic light chains [1-2].

Autologous hematopoietic stem cell transplantation (ASCT) has been used in the treatment of systemic AL amyloidosis since 1994. Long-term follow-up demonstrate 15-year overall survival in 50% of patients who achieved complete hematological response (CR) after ASCT [3-4]. However, 80% of patients with newly diagnosed systemic AL amyloidosis are ineligible for ASCT.

For a long time, oral melphalan and dexamethasone (MDex) were considered a standard of care in AL amyloidosis, but the addition of proteasome inhibitor- bortezomib, significantly increased the efficacy of treatment [5]. However, bortezomib, cyclophosphamide and dexamethasone (CyBorD) regime currently is the standard of care for newly diagnosed patients. According to a large European retrospective study, the frequency of hematological response (HR) on CyBorD regime is 65%, cardiac response – 33%, renal response –15%, median overall survival (OS) was 72 months [6-8].

Despite higher frequency of clinical responses, the addition of bortezomib did not improve prognosis in the patients with IIIb heart stage, according to the Mayo Clinic classification (NT-proBNP >8500 ng/l), and 40% of these patients still die within 6 months after the diagnosis. Therefore, the question of the optimal regimens for these patients is still open.

Patients and methods

We analyzed the response to induction therapy in 105 newly diagnosed patients with systemic AL amyloidosis, treated at RM Gorbacheva Research Institute within a period from 2004 to 2021 [6]. All the patients signed informed consent for the use of personal data for research purposes. Their median age was 63 years (31-81). The percentage of men and women was 53% and 47%, respectively. Isolated AL amyloidosis was documented in 72% (n=76) of cases; in combination with multiple myeloma, in 27% (n=29). At the time of diagnosis, 62% of patients had three or more organs involved. The incidence of organ involvement was as follows: kidneys, 88% (n=93); heart, 87% (n=92); liver, 40% (n=43); nervous system, 48% (n=51); gastrointestinal tract, (GIT) 27% (n=29); lungs, 11% (n=12), and other organs (thyroid gland, lymph nodes, adrenal glands, etc.), 20% (n=21). In the patients with established Mayo stage, the following distribution was observed: stage I, 22% (n=20); stage II, 52% (n=47); stage III, 26% (n=24). The median NT-proBNP level was 1892 ng/l (35 to 34772), 15 patients had IIIb stage (NT-proBNP >8500 ng/l). Renal involvement was documented in 94 patients at the following severity distribution: stage I, 23% (n=22); stage II, 48% (n=45); stage III, 29% (n=27).

In our study, we assessed the efficacy of CyBorD compared with other treatment regimens. All consecutive patients were divided into 3 groups: group 1 was treated with CyBorD (26%, n=28); group 2 received other bortezomib-based regimens (bortezomib/dexamethasone (VD), bortezomib/melphalan/dexamethasone (BMDex)), 59% (n=62); group 3 included bortezomib-free regimens (melphalan/dexamethasone (MDex), cyclophosphamide/prednisolone, corticosteroids), 14% (n=15). Patients with autologous ASCT were excluded. The median number of therapeutic rounds in all groups was 4. The main patients' characteristics are presented in Table 1.

Clinical definitions

Hematological response (HR) evaluation was based on serum and urine immunofixation and determination of the level of free light chains (FLC) by nephelometry. Complete remission (CR) definition included negative serum and urine immunofixation and normal FLC ratio, very good partial response (VGPR) was based on difference between involved and uninvolved concentrations of free light chains (dFLC) <40 mg/L. Partial response (PR) was defined as a decrease of dFLC by >50%. Organ response was evaluated by changes in biomarkers: NT-proBNP for the heart, proteinuria for the kidney and alkaline phosphatase for the liver. Relapse or progression was defined as loss of previously achieved response, or organ progression, or increase in dFLC by 50% from the best response.

Statistical analysis

Descriptive statistics was used for the patient data evaluation. Chi-square test was used to compare response between the groups. Kaplan-Meier method and log-rank test was used to compare survival estimates. Cumulative incidence estimates were used to evaluate hematologic and organ responses. Gray's test was applied to compare cumulative incidences between the groups. All the survival and cumulative incidence parameters were calculated from the date of systemic therapy initiation. For progression-free survival, the outcome measures were death or hematological relapse/progressive disease. Relapse/progressive disease were considered a competing risk for organ response. Multivariate analysis was done with proportional hazard analysis for survival estimates and Fyne-Gray regression for cumulative incidences. Variables with significance of <0.015 were selected for multivariate analysis.

Results

The 3-year OS was 70.3% (95% CI 61-80), the median follow-up was 27.8 months (22 days to 11 years). In the univariate analysis, unfavorable factors for OS were as follows: age over 70 years (p=0.007); male gender (p=0.015, 64% *versus* 86%); Mayo stage IIIb [OS was 48% (95% CI 21-75) *vs* 60% (95% CI 25-95) *vs* 72% (95% CI 59-85), and 79% (95% CI 58-100) in comparison with Mayo stages IIIa, II and I, respectively (p=0.07)]; renal injury stage III [65% (95% CI 46-84) *vs* 73% (95% CI 54-92) *vs* 79% (95% CI 68-90) compared with stages I and II, respectively, p<0.0001]. Improved 3-year OS was documented in the presence of hematological response [91% (95% CI 83-99) *vs* 40% (95% CI 25-54),

p<0.001] (Figure 1B) and organ responses [93% (95% CI 86-100) *vs* 55% (95% CI 38-72), p=0.0003] in patients with cardiac response *vs* non-responders, [92% (95% CI 85-99) *vs* 77% (95% CI 60-94), p<0.0001, and 100% *vs* 33% (95% CI 4-62), p=0.0002 in the patients with renal and liver responses, respectively. Assessment of overall survival risk factors is presented in Table 2.

The 3-year OS in CyBorD group was 95% (95% CI 85-99) *versus* 85% (95% CI 73-97) in other bortezomib-containing regimens, and 63% (95% CI 44-82) in non-bortezomib regimens (p=0.0337). In the multivariate analysis, when corrected for other confounding factors, any treatment except CyBorD was associated with worse 3-year OS (HR 4.9, 95% CI 1.4-17.2, p=0.012). Other factors which impacted the survival were: bone marrow plasma cell (BMPC) counts >2.5% (HR 0.2, 95% CI 0.1-0.5, p=0.0002), and NtproBNP levels >2500 ng/l OS (HR 4.6, 95% CI 1.0-20.6, p=0.04, Figure 2A).

The 3-year progression-free survival (PFS) in CyBorD group was 79% (95%CI 63-95), *versus* 48% (95%CI 35-61) in group 2, and 55% (95%CI 30-80) in group 3 (p=0.28).

Table 1. Patients characteristics

Parameters	Median (range) or n (%)
Age, years median (range)	62 (31-81)
Gender, n (%)	
Male	56 (53)
Female	49 (47)
Cardiac biomarkers level	
NT-proBNP, ng/L	1892 (35-34772)
High-sensitivity cardiac troponin I, ng/L	0.036 (0.0-1.6)
Amyloid light-chain type	
κ	37 (36)
λ	65 (64)
Combination with multiple myeloma	
AL	76 (72)
AL + MM	29 (27)
Percentage of plasma cells	
<10%	70 (67)
>10%	33 (32)
Involved organs	
Heart	92 (87)
Kidney	93 (88)
Liver	43 (40)
Nervous system	51 (48)
GIT	29 (27)
Lungs	12 (11)
Other (tongue, soft tissue, lymph nodes, adrenal glands and other)	21 (20)
Number of organs	
1	9 (8.5)
2	30 (28)
3	29 (27)
>3	37 (35)
Mayo stage	
I	20 (21)
II	48 (52)
IIIa, NT-proBNP ≤8500 ng/L	9 (9.7)
IIIb, NT-proBNP >8500 ng/L	15 (15)
Renal stage	
I	22 (23)
II	45 (48)
III	27 (29)
Therapy	
VD	53 (50.5)
CyBorD	28 (26)
MD	13 (12)
Bmeldex	8 (7.6)
other (CP)	2 (1.9)
Number of courses, mediane (range)	
Group 1 (CyBorD)	4 (1-11)
Group 2 (other bortezomib-based regimens)	4 (1-12)
Group 3 (non- bortezomib-based regimens)	4 (1-9)

Table 2. Risk factors assessment for 3-year overall survival

		n (%)	3-year OS	(95% CI)	P-value
Age	<50 50-70 >70	10 78 17	60% 79% 34%	(38-81) (70-88) (9-59)	P=0.007
Gender	Male Female	56 49	59% 82%	(46-72) (71-93)	P=0.015
Mayo stage	I II IIIa IIIb	20 (21) 48 (52) 9 (9.7) 15 (15)	79% 72% 60% 48%	(5-100) (59-85) (25-95) (21-75)	P=0.07
Renal stage	I II III	22 (23) 45 (48) 27 (29)	73% 79% 65%	(54-92) (68-90) (46-84)	P<0.0001
Percentage of plasma cells	<10% >10%	70 (66) 33 (31)	76% 53%	(67-85) (34-72)	P=0.06
Amyloid light-chain type	K λ	37 (36) 65 (64)	77% 66%	(62-92) (54-78)	P=0.16
NS involvement	Yes No	51 (49) 54 (51)	67% 72%	(54-80) (61-83)	P=0.48
GIT involvement	Yes No	29 (28) 76 (72)	68% 70%	(51-85) (61-79)	P=0.83
Lungs involvement	Yes No	12 (11) 93 (89)	71% 70%	(44-98) (61-79)	P=0.73
Lymph nodes involvement	Yes No	6 (6) 99 (94)	83% 70%	(54-99) (61-79)	P=0.9
Number of organs	1 2 ≥3	9 (9) 30 (28) 66 (63)	88% 67% 68%	(69-99) (50-84) (57-79)	P=0.53
Any hematologic response	Yes No	65 (70) 40 (30)	91% 40%	(83-99) (25-54)	P<0.001
Heart response	Yes No	38 (49) 39 (51)	93% 55%	(86-100) (38-72)	P=0.0003
Renal response	Yes No	46 (63) 24 (32)	92% 77%	(85-99) (60-94)	P<0.001
Liver response	Yes No	15 (62) 9 (38)	100% 33%	 (4-62)	P=0.0002
Treatment group	1 2 3	28 (26) 62 (54) 15 (14)	83% 68% 55%	(66-100) (57-79) (28-82)	P<0.16

Notes: *NS, nervous system; GIT, gastrointestinal tract*

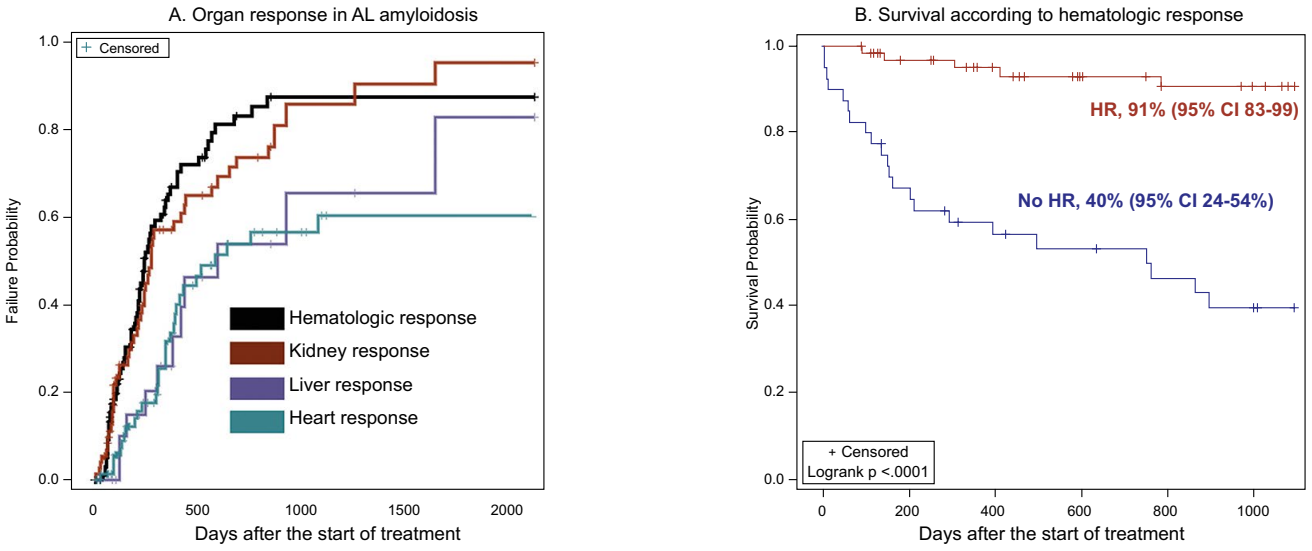
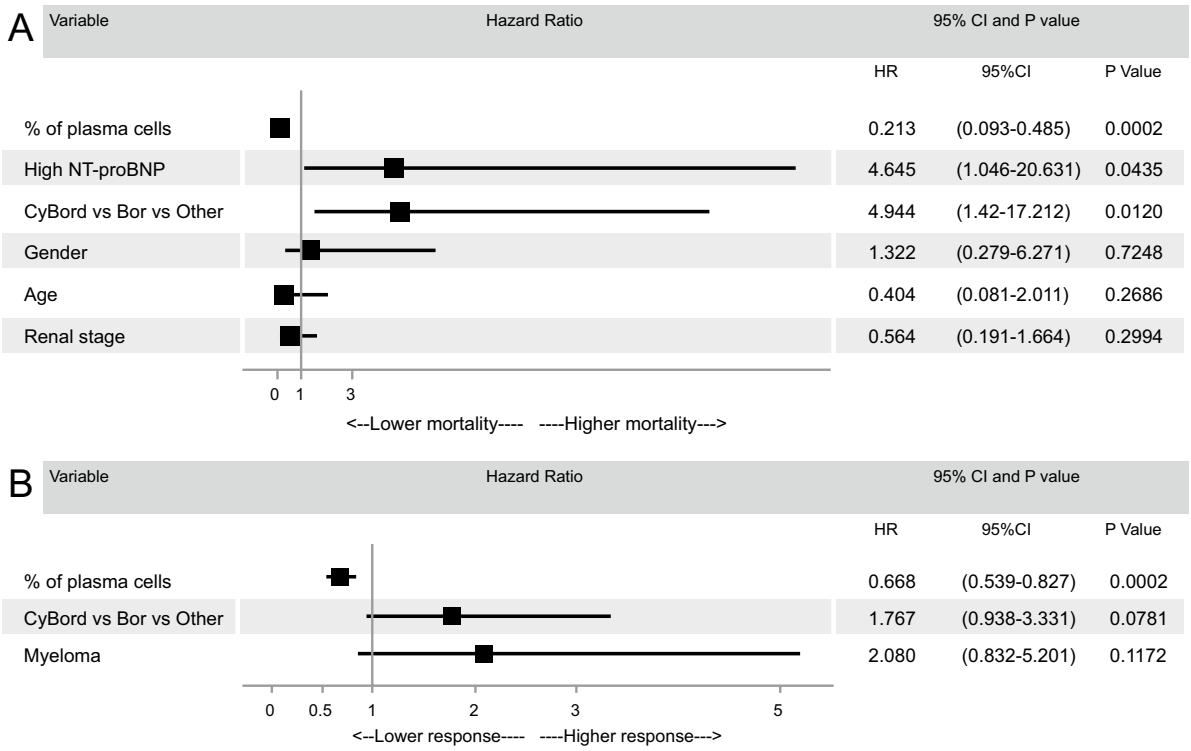


Figure 1. Kinetics of hematologic and organ responses in the study group (A). Impact of hematologic response on overall survival (B)



Overall response rate (ORR) was 70% (n=74), and median time to HR was 10.3 (9-14.6) months.

The percentage of patients who had HR was significantly higher in the CyBoRD group, 94% (95% CI 84-99) *vs* 84% in group 2 (95% CI 73-95), and 63% in group 3 (95% CI 26-100), p=0.033. The HR was achieved earlier at the bortezomib-containing regimens, with median time to response of 9.6 (5.3-15), and 10 (7.7-12.4) months in groups 1 and 2 *vs* 32.7 (6.4-32.7) months in group 3.

The frequency of CR was comparable between the groups: 52% (11/21), 76% (30/39) and 60% (3/5). VGPR was achieved in 19% (4/21), 8% (3/39), 20% (1/5) and PR 28% (6/21), 15% (6/39), 20% (1/5), in groups 1, 2 and 3 respectively (Fig. 3, p>0.05).

In the univariate analysis, gender, age, number of affected organs, presence of multiple myeloma did not affect frequency of hematological remission. Surprisingly, in the multivariate analysis, the cumulative HR incidence was significantly lower in patients with the presence of PC >2.5% (HR 0.67, 95%CI 0.54-0.83, p=0.0002) and it was the only significant factor (Fig. 2B).

The organ response (OR) was assessed over a 3-year period from the start of therapy (Fig. 1A). Assessment of heart response by cardiac biomarkers was possible in 77 patients (23, 45 and 9 patients in groups 1, 2, and 3, respectively). Cardiac responses were observed in 38 (49%) cases. The median time to response was 19.3 (12.8-70) months.

The percentage of cardiac responses was higher in CyBorD group, i.e., 78% (95% CI 59-97) *vs* 55% (95% CI 36-74) and 16 % (95% CI 16-44), in groups 2 and 3, respectively (p=0.050). In CyBorD group, the time to cardiac response was also shorter: 13 months *versus* 36 months *versus* not reached (p=0.050).

Renal responses were observed in 46 (63%) of 73 patients with median time to response 12 (9.5-18.3) months. The frequency of responses in groups 1, 2 and 3 was the following: 90% (95% CI 73-99), 92% (95% CI 81-99, and 57% (95% CI 22-92), p=0.01. The shortest median time to response was also in CyBorD group, i.e., 7 (2.7-11.9) *vs* 16.5 (10-29) months in group 2. For the group 3, median response was not reached at 3-year interval. Liver responses were documented in 11 (45%) of 24 patients, median time to response was 25.5 (13.3-70.7) months. The frequency of response in groups 1, 2 and 3 was 40% (95% CI 40-81), 77% (95% CI 42-99) and 100%, p=0.084. The median time to liver response was comparable among groups.

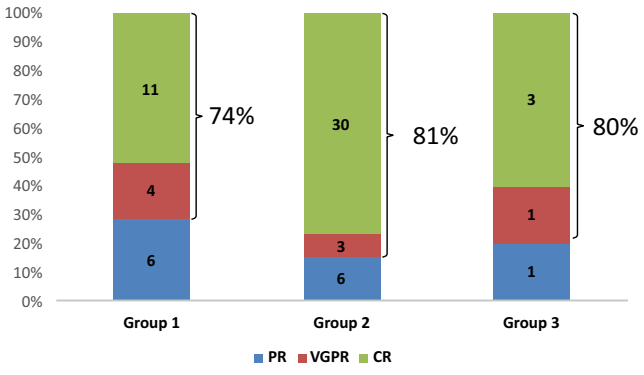


Figure 3. Summary of the best hematologic responses according to the study groups

Group 1: CyBorD; group 2: other bortezomib-containing regimens; group 3: non-bortezomib treatments.
Abbreviations: *Partial response (PR); Very good partial response (VGPR); Complete response (CR)*

Discussion

According to the previous studies, overall response rate (ORR) to bortezomib-based treatment varies from 60% to 94%, and CR rates vary from 23% to 71%. Multicenter retrospective European study included 230 AL amyloidosis patients, and concluded that upfront CyBorD was unable to overcome poor outcomes in Mayo stage III patients, with median OS of 4.6 months. Also, long-term organ responses are rarely reported for bortezomib-based treatments [7].

A recent prospective observational study data, with 915 systemic AL amyloidosis patients, showed that upfront bortezomib confers durable hematologic responses [9]. The main goal of this study was to assess the impact of deep HR upon the patients' outcomes. A dFLC <10 mg/L was evaluated as a new predictor of response depth ("stringent dFLC response"). All the patients were treated with bortezomib, and it was CyBorD regimen in 94.9% of cases. The median age, gender, number of therapy courses was comparable to our group of patients. The only difference was higher percentage of patients with stage III heart disease (50%), while percentage of patients with stage IIIb was comparable to our study (13%). In this retrospective study, median OS was 72 months. Overall response rate was 65%, with 49% of deep responses (CR, VGPR, stringent dFLC responses). Median time to next treatment (TNT) was not reached, and 55% had not proceeded to further treatment at 7 years [9]. Patients with stringent dFLC responses had significantly better OS and TNT and impressive organ responses than did those with lesser responses. The incidence of cardiac response was 61% compared to 45% with lesser responses (p=0.005).

Therefore, achievement of a stringent dFLC response may be a potential new therapy goal in AL. Our results are comparable to published data, and show a highly frequent HR, organ responses and improvement in OS with bortezomib-based treatments. Of note, like in the other studies [6, 10], we demonstrated that CyBorD was superior to other bortezomib-containing regimens not only in terms of time to organ response and probability of such response, but also for OS. Nonetheless, patients with IIIb stage still have a significantly lower OS.

The main limitation of our study were the absence of FLC analysis and cardiac biomarkers in some patients at the time of diagnosis and at the moment of data evaluation thus complicating the Mayo stage assessment, depth of hematological response and heart response, and could explain statistical insignificance for some comparisons.

However, absence of effective second-line treatments for a long time limited practical applications of the response criteria. Recent advances with introduction of daratumumab make the evaluation of response crucial for the prognosis and planning of therapies. According to the ANDROMEDA study, addition of daratumumab to the CyBorD regimen increased the rate of HR and organ response. Cardiac and renal response was achieved in the first 6 months of therapy with daratumumab in 41.5% *versus* 22.2% and 53.0% *versus* 23.9%, respectively [11].

Another unusual finding of this study is a correlation between the BMPC infiltration and outcomes in patients with AL amyloidosis. Upon analysis of our subgroups, higher percentage of BMPC was a significant factor of improved OS but negative factor for HR (p=0.0002). The significance of increased BMPCs in biology of AL amyloidosis is not clear. According to the literature, the patients with more than 10% BMPC had more frequent cardiac involvement (86% *vs* 63%), a significantly shorter PFS time (18 *vs* 48 months), and reduced OS (33 months *vs* not reached) [13]. However, in our study the high BMPC infiltration in patients with multiple myeloma and AL amyloidosis had an opposite effect on OS survival and HR rate, probably, due to low frequency of multiple myeloma cases in the study group. The issue of amyloidosis biology with high BMPC, but without multiple myeloma, should be yet to be understood.

Conclusions

CyBorD is an effective upfront option for the patients with systemic AL amyloidosis. However, the presence of a progressive heart damage remains a predictor of early mortality in these patients. Currently, only early diagnosis can improve the outcomes of these patients, so we need a good collaboration between hematologists, general physician, cardiologists and nephrologists, to recognize the disease before advanced stages. Risk stratification and response monitoring should be based on measurements of cardiac markers and markers of hematologic response.

Appropriate treatment should begin as soon as possible with rapidly acting regimens.

Acknowledgments

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The authors declare no conflicts of interest.

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Сравнение бортезомиб-содержащих режимов с другими вариантами терапии для лечения первичных пациентов с системным амилоидозом легких цепей, не подлежащих аутологичной трансплантации костного мозга

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Резюме

Системный амилоидоз легких цепей (AL) – одна из форм плазмоклеточных дискразий, характеризующаяся гиперпродукцией свободных легких цепей иммуноглобулинов клональными плазматическими клетками и их отложением в органах и тканях в виде нерастворимого фибриллярного белка-амилоида. Основная цель терапии – быстрое и глубокое подавление продукции амилоидогенных легких цепей, а поражение сердца при этом заболевании является основным предиктором выживаемости пациентов. Терапия на основе бортезомиба, циклофосфамида и дексаметазона (CyBorD) в последнее время считается стандартом лечения впервые выявленных пациентов. Однако, количество исследований режима CyBorD с оценкой долгосрочного гематологического и органного ответа ограничено.

В нашем исследовании мы проанализировали ответ на индукционную терапию у 105 пациентов с впервые выявленным системным AL амилоидозом, не являющихся кандидатами на проведение аутологичной трансплантации гемопоэтических стволовых клеток (АТГСК). Вся терапия была разделена на 3 группы: 1 – CyBorD, 2 – другие схемы на основе бортезомиба и 3 группа – схемы без бортезомиба.

Общая 3-х летняя выживаемость составила 70,3% с медианой наблюдения 27,8 месяцев (22 дня-11 лет). Неблагоприятными факторами в отношении прогноза при однофакторном анализе были возраст старше 70 лет (p=0,007), мужской пол (p=0,015), стадия Mayo IIIb (p=0,07) и III (p<0,0001) стадия поражения почек. В многофакторном анализе применение любых других режимов, помимо CyBorD, негативно сказывалось на показателях 3-х летней выживаемости (ОР 4,9, 95% CI 1,4-17,2, p=0,012). 3-летняя беспрогрессивная выживаемость при использовании схемы CyBorD составила 79% против 48% в группе 2, и 55% в группе 3 (p=0,28). Общая частота ответов составила 70% (n=74). Процент пациентов с гематологическим ответом был достоверно выше в группе CyBoRD, 94% против 84% и 63% в группах 2 и 3, соответственно (p=0,033), как и медиана времени до ответа (9,6, 95% ДИ 5,3-15 месяцев). Органные ответы были оценены за 3-х летний период от начала терапии. Процент кардиальных и почечных ответов так же был выше в группе CyBorD: для сердца он составил 78% против 55% и 16% (p=0,050) в 1, 2, 3 группах соответственно, а для почек 90% против 92% против 57% (p=0,01). В общей группе, гематологический (медиана 10 месяцев) и почечный ответ (медиана 12 месяцев) наблюдались раньше, чем кардиальный и печеночный ответы (медиана 26 месяцев). Наши результаты сопоставимы с ранее опубликованными данными европейских исследований и показывают высокую частоту ГО и органных ответов, улучшение общей выживаемости при использовании схемы CyBorD. Органные ответы при этом наблюдались существенно позже, чем гематологические.

Ключевые слова

Системный AL амилоидоз, CyBoRD, бортезомиб.