A detailed evaluation of the current renal response criteria in AL amyloidosis: is it time for a revision?

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ABSTRACT

Organ response correlates with overall survival in patients with immunoglobulin light chain amyloidosis and is the goal of treatment. This study evaluates the current renal response criteria and their ability to predict overall survival. Patients with immunoglobulin light chain amyloidosis who underwent autologous stem cell transplantation between 1995 and 2010 were recruited. Eligibility criteria included >1 g/dL of proteinuria, dialysis independence at baseline and within the first year of autologous stem cell transplantation, and a minimum follow-up of 1 year. Responses were assessed by the best values after autologous stem cell transplantation. The difference between involved and uninvolved serum free light chain levels was used to determine hematologic response. Increases in serum creatinine were calculated from the highest creatinine after autologous stem cell transplantation. Inclusion and exclusion criteria were met by 141 patients. These patients had a median follow-up of 52 months. Superior overall survival was observed in patients with a >75% reduction in proteinuria and those who had a >95% reduction had additional benefits. The overall survival of patients with >50% to ≤75% proteinuria was similar to that of patients with ≤50% reduction. A rise in serum creatinine >25% was not associated with a poorer outcome in patients with a >75% reduction in proteinuria. Deeper hematologic responses were associated with higher rates of proteinuria reduction. These results suggest that further evaluation of the current renal response criteria is needed. In particular, discrimination of the renal response into complete and partial categories and modification of the serum creatinine requirement seem justified.

Introduction

Systemic immunoglobulin light chain amyloidosis (AL) is a fatal form of plasma cell dyscrasia characterized by the fibrillar deposits of monoclonal immunoglobulin light chains.[1] The deposition process results in progressive organ dysfunction leading to the death of the patient. Fortunately, over the past decade several therapies have been found to be effective against AL. These include high-dose melphalan followed by autologous stem cell transplantation (ASCT), melphalan-dexamethasone and regimens containing novel agents.[2]

Successful therapy in AL is characterized by hematologic response followed by organ response.[3,4] Organ response is essential since the majority of these patients do not have multiple myeloma and do not die from bone marrow failure.[5] Instead, they die of organ failure, most commonly heart failure. The importance of this is highlighted by the ability of cardiac biomarkers [high sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP)] to predict outcomes and tolerability of aggressive treatment such as ASCT.[6] Improvement in cardiac biomarkers has also been associated with better overall survival.[4]

The kidney is the most common organ involved in AL and may be the only organ involved in some patients. Proteinuria is present in up to 73% of patients and approximately 50% will have renal insufficiency.[5] Since measurements of creatinine and proteinuria are well standardized, the determination of renal response is quite easy and reliable. Indeed, renal response has been shown to correlate with overall survival.[3] Currently, renal response is defined as a 50% decrease in proteinuria in the absence of a 25% increase in serum creatinine (Scr) with a minimum of 0.5 mg/dL or a 25% decrease in glomerular filtration rate or creatinine clearance.[7] Unfortunately, these criteria do not differentiate patients with complete reversal of proteinuria from those who just had a 50% reduction. Furthermore, the importance of maintaining stable renal function in order to achieve a renal response has been called into question. This study was undertaken to study the individual renal response criteria in greater detail.

Design and Methods

This study was approved by the Institutional Review Board at the Mayo Foundation, in accordance with the Declaration of Helsinki Principles and the guidelines of the Health Insurance Portability and Accountability Act (HIPPA). Potential patients were identified by querying the Mayo Clinic AL Autologous Stem Cell Transplantation database for subjects transplanted between 1995 and December of 2010. The details of ASCT have been previously described.[8] To be included in this study, patients had to have a baseline proteinuria >1 g/dL and at least 1 year of follow-up after ASCT. Patients with missing relevant laboratory data (n=3), or who were dialysis dependent prior

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to ASCT (n=12) were excluded. Patients who developed end-stage renal disease requiring dialysis or within a year of ASCT or who had a kidney transplant (n=44) were excluded from the study. Patients who died (n=78) within 1 year of ASCT were also excluded. Anyone who developed a second malignancy (n=4) other than multiple myeloma was also excluded. Finally, since survival was measured from the day of stem cell infusion, patients who had received >4 months of chemotherapy prior to ASCT were also excluded (n=8).

Baseline data were collected from the closest time prior to ASCT. Overall survival was calculated from the day of stem cell infusion. Proteinuria was calculated from 24-hour urine collections. The best proteinuria reduction was calculated from the lowest proteinuria measured after ASCT. Time to 50% reduction in proteinuria was measured in 3-month intervals between 12 and 24 months after transplantation. The change in Scr after ASCT was calculated from the highest (of at least two consecutive readings) stable Scr after ASCT. Hematologic response was determined using the new criteria.[9] Reduction of free light chain was assessed by both involved serum free light chain (sFLC) and the difference between involved and uninvolved free light chains (dFLC). According to the new hematologic response criteria, complete response was defined as having a normal sFLC ratio with no detectable monoclonal protein in the serum or urine. A very good partial response was defined as a dFLC of <40 mg/L. Reduction of dFLC by >50% was considered a partial response and a reduction <50% was considered no response. In this study, the best hematologic response was used for comparison. Receiver operator characteristic (ROC) curves were employed to determine cutoffs for various parameters. Overall survival was calculated using the Kaplan-Meier method. Multivariate analysis was performed using a proportional hazard model. *P* values <0.05 were deemed statistically significant.

Results

During the study period, 156 patients met the inclusion criteria. Three patients were excluded for not having both pre- and post-transplant sFLC measurements. Four patients developed another malignancy (1 acute myelogenous leukemia, 2 non-Hodgkin's lymphoma and 1 adenocarcinoma of the gut) and eight were excluded for having had >4 months of therapy prior to ASCT. The median follow up for the remaining 141 patients was 51.8 months. The median age was 58 (range 25 -72) years and 57.7% were male. Other baseline characteristics are listed in Table 1. Cardiac biomarkers were considered normal according to cardiac staging in 54.7% of patients in this study.[10] All patients in cardiac stage 2 in this study were classified in this stage as the result of abnormal NTproBNP.

Proteinuria was reduced by >50%, >75% and >95% in 73.1%, 58.2% and 34.0% of patients, respectively. The median time to 50% proteinuria reduction was 11.1 months and all renal responders had >50% reduction in proteinuria by 24 months. Scr increased >25% in 38.2%, and >25% with a minimum of 0.5 mg/dL in 24.1% of this cohort. According to the current definition, 61.0% met the criteria for renal response. The distribution of hematologic response was 53.9% with complete response, 34.7% with very good partial resposne, 8.5% with partial response and 2.8% with no response. A >50% reduction in sFLC was noted in 90.8% and a >90% reduction in 38.3% of patients. Serum albumin improved by 12 g/L after ASCT. Using the proportional hazard model, the best serum albumin achieved after ASCT was associated with improved overall survival (*P*=0.03) but the change in serum albumin was not (*P*=0.16). It was not an independent predictor of overall survival in the multivariate analysis.

Overall survival was significantly better in patients who achieved a renal response (*P*<0.001). To explore the effect of the depth of the renal response on overall survival, patients were further divided into smaller groups. In the subgroup analysis, overall survival was found to improve with increasing reduction in proteinuria (Figure 1A). Best overall survival was noted in patients with >95% reduction in proteinuria. Even within the group of patients with >75% proteinuria reduction, there was a statistically significant improvement in overall survival in those with >95% proteinuria reduction *versus* those with >75% to ≤95% reduction (not reached *versus* not reached, *P*=0.006). On the other hand, just having a >50% reduction in proteinuria had little impact on overall survival. There was no difference in overall survival between patients with >50% to ≤75% reduction in proteinuria (n=21) *versus* those (n=34) with ≤50% proteinuria reduction (72.8 months *versus* not reached, respectively, *P*=0.34, Figure 1B). Among the patients with a >50% reduction in proteinuria, overall survival was improved only in those who achieved >75% reduction in proteinuria (*P*=0.04, Figure 1C). A borderline improvement in overall survival was found in patients with 0 to ≤75% proteinuria reduction (n=50) as compared to those (n=8) with no proteinuria reduction (79.8 months *versus* 42.9 months, *P*=0.049). Of the 48 patients with >95% reduction in proteinuria, the proteinuria was normalized in 58.3%. Their overall survival was similar (not reached, *P*=0.40). ROC analysis suggested that patients with proteinuria <231 mg/day had the best overall survival [*P*=0.01, OR = 7.47 (CI 1.63 – 34.7)].

Previously, a rise of Scr >25% was an exclusion criterion for renal response. In this study, 24.1% of patients had a >25% rise in Scr (with a minimum of 0.5 mg/dL). There was an inverse relationship between proteinuria reduction and having a Scr >25%, *P*<0.001 (Table 2). An increase of >25% in Scr was associated with inferior overall survival

Table 1. Patients' baseline characteristics.

	Median	Range
Age	58	25-72
Sex (male)	57.4%	
Scr (mg/dL)	1.0	0.5-2.2
GFR (mL/min/1.73 m^2)	80	19-148
Proteinuria (g/day)	5.9	1.0-18.0
Involved sFLC (mg/L)	108	9.7-1130
Albumin (g/dL)	1.9	0.6-3.8
NTproBNP (pg/mL)	243	19.4-10529
cTnT (ng/mL)	0.01	0.01-0.35
BM plasma cell %	6.4	0.4-74
Cardiac staging[10]		
1	54.7%	
2	33.0%	
3	12.3%	

Scr: serum creatinine, GFR: glomerular filtration rate, NTproBNP: N terminal pro-brain natriuretic peptide, cTnT: cardiac troponin T, BM plasma cell%: bone marrow plasma cell percentage,

in the univariate analysis, although in the multivariate analysis, a >25% increase in Scr no longer had an impact on overall survival (*P*=0.13) in patients who had >75% reduction in proteinuria (*P*<0.001).

To understand how hematologic response affected renal response, the relationship between hematologic response and proteinuria reduction was explored. As the depth of hematologic response increased, so did the percentage of patients with current renal response (Table 3). Of the patients with a complete response 73.7% and 52.6% of patients achieved a >75% and >95% reduction in proteinuria, respectively. Only 25% of patients with a partial response had a >75% reduction in proteinuria and no patient with less than very good partial response had a >95% reduction in proteinuria. There was no difference in the rate of achieving a >75% reduction in proteinuria between patients who had a partial response or no response (*P*=0.16). There were, however, differences in the rates of achieving a >75% reduction in proteinuria between patients who had achieved a very good partial response *versus* no response (*P*=0.03) and complete response *versus* very good partial response (*P*=0.002). A ROC curve was used to determine the optimal hematologic response to ensure a renal response. Using a >75% reduction in proteinuria as the target, it was found that a >81% reduction of the involved sFLC (*P*=0.001) or > 86% reduction in dFLC (*P*=0.004) was needed to produce the reduction in proteinuria. Additionally, a sFLC <28.1 mg/L (odds ratio 1.07, CI 1.01 – 1.20, *P*=0.008) or a dFLC <7.45 mg/L (OR 1.09 CI 1.02 – 1.24, *P*=0.005) was associated with an increased frequency of achieving >75% reduction in proteinuria. As in previous studies, overall survival was associated with depth of hematologic response (Figure 2). However, only patients with a very good partial response did not have significantly better overall survival than patients with a partial response (*P*=0.14). Otherwise, overall survival was significantly longer for patients with a complete response than for those with a very good partial response (*P*=0.004) and, likewise, for those with a partial response compared to patients with no response (*P*<0.001).

Parameters of hematologic response and renal response were significantly associated with overall survival. In univariate analysis, proteinuria reduction (*P*<0.001), sFLC reduction (*P*=0.01), dFLC reduction (*P*<0.001), <25% increase in Scr (*P*=0.003), hematologic response (*P*<0.001) and a 50% proteinuria reduction within 24 months of

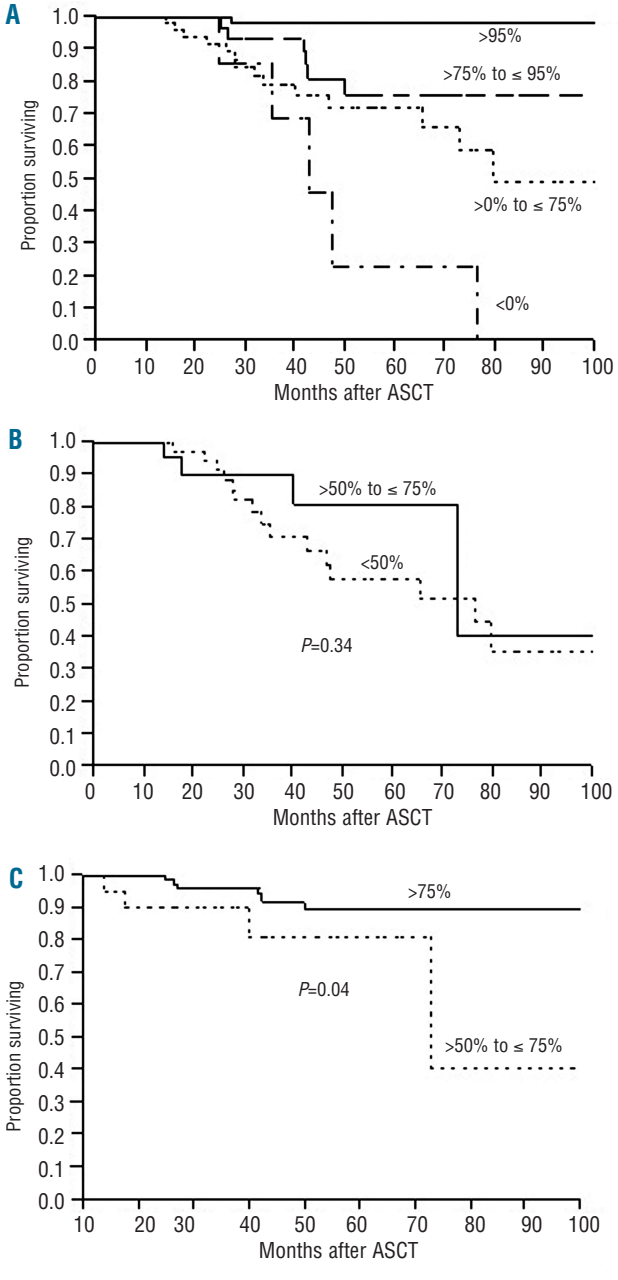

Figure 1. (A) Overall survival (OS) of the 141 patients measured from the time of autologous stem cell transplantation (ASCT). Groups were assigned by level of best proteinuria reduction, >95%, ≤95% to >75%, ≤75% to > 0% and <0%. OS was significantly better in patients with >95% reduction in proteinuria *vs.* those with ≤95% to >75% (*P*=0.006). Borderline improvement in OS was noted between patients with ≤75% to >0% and those with no proteinuria reduction (*P*=0.049). (B) No difference in OS was noted between patients who had ≤75% to >50% *vs.* <50% reduction in proteinuria (*P*=0.34). (C) There was a difference in OS between patients who had >75% reduction in proteinuria *vs.* ≤75% to >50% (*P*=0.04).

Table 2. Relationship between proteinuria reduction and increased serum creatinine.

Proteinuria reduction	Patients with rise in Scr >25%*
> 95%	4.2%
>75% ≤ 95%	29.4%
> 0% ≤ 75%	35.3%
< 0%	50.0%

**With a minimum of 0.5 mg/dL-*

Table 3. Renal response by hematologic response.

Hematologic response	Renal response	Proteinuria reduction >75%	Proteinuria reduction >95%
CR	72.4%	73.7%	52.6%
VGPR	55.1%	46.9%	16.3%
PR	25%	25%	0%
NR	25%	0%	0%

Hematologic response was significantly associated with renal response (P=0.004), >75% reduction in proteinuria (P<0.001) and >95% reduction in proteinuria (P<0.001).CR: complete response, VGPR: very good partial response, PR: partial response, NR: no response.

treatment (P=0.03) were associated with better overall survival. In the multivariate analysis using a proportional hazard model, dFLC reduction (P=0.02) and proteinuria reduction (P=0.02) were independent predictors of overall survival. If the depth of hematologic response was considered, then very good partial response or better (P=0.001) and >75% reduction in proteinuria (P=0.001) were independent predictors of overall survival (Figure 3). Elevation in Scr did not have a significant effect in the multivariate analysis in any of the models.

Discussion

One of the biggest differences between AL and multiple myeloma is in the sequelae of the plasma cell disorder. Patients with AL die of organ failure, particularly heart failure, whereas patients with multiple myeloma die of bone marrow failure and its consequences, including infection. It is, therefore, important to realize that while hematologic response is a primary endpoint in the treatment of both AL and MM, the ultimate goal of treatment in AL is organ response. Achievement of a complete response is associated with a higher rate of organ response, but by no means is it a guarantee nor is it always necessary. Accurate assessment of organ response is crucial for the monitoring and decision making on the treatment of these patients.

The results of our study confirmed that renal response remains an excellent marker of overall survival. Patients who achieved a renal response had a significantly longer overall survival than those who did not. More detailed evaluation revealed some discrepancies between our results and the current renal response criteria. First, even though it appeared that reduction of proteinuria by >50% was associated with better overall survival, the improvement in overall survival was limited to patients with a >75% reduction in proteinuria. In fact, the overall survival of patients who had a >50% but ≤75% reduction in proteinuria was similar to that of patients with a <50% proteinuria reduction. Moreover, a further improvement in overall survival was observed in those who had a >95% proteinuria reduction, suggesting that there are different levels of response. Finally, while there was an association between increase in Scr and poorer outcomes in the univariate analysis, in the multivariate analysis a rise of Scr of >25% did not affect survival in those patients who had a >75% reduction in proteinuria. To achieve a renal response, patients must first achieve a hematologic response. Deeper hematologic responses translated into higher rates of achieving a >75% reduction in proteinuria. The highest rate of proteinuria reduction was seen in patients with complete responses. ROC analysis revealed a reduction in sFLC and dFLC by >86% was strongly associated with a >75% reduction in proteinuria. Reducing the involved sFLC to 28.1 mg/L or the dFLC to 7.45 mg/L also improved the odds of achieving a >75% reduction in proteinuria.

These results clearly showed that a gradation of renal response exists. The best outcomes were observed in those with a >95% reduction of proteinuria followed by those with a >75% reduction. Patients who had any proteinuria reduction up to 75% did better than those without any reduction. This suggests that the single category of 50% reduction in proteinuria currently in use may not be sufficient. Obviously, these results need to be validated in larger AL populations. If confirmed, they suggests that the creation of a category of complete renal response (CRenal) to describe patients with a >95% reduction in proteinuria and a category of partial renal response (PRenal) for those who achieve a >75% reduction in proteinuria would be justified. There was also some benefit in patients who had <75% reduction in proteinuria as compared to those with no reduction and hence patients with >50% reduction could be categorized as having a minimal renal response (MRenal). The use of 50% reduction in proteinuria would hopefully reduce biological and laboratory variations.

The analyses also showed that a rise in Scr (>25%) did not negatively affect overall survival in patients once they achieved a >75% reduction in proteinuria. One way to interpret this is that reductions in proteinuria by >75%

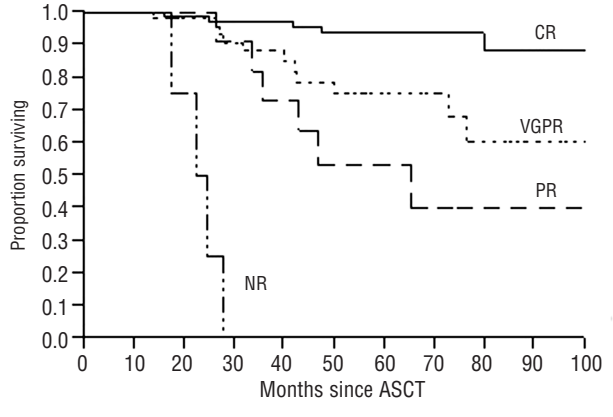

Figure 2. Overall survival (OS) of 141 patients by hematologic response. OS increased with deeper hematologic response (P<0.001). The median survival of patients with a complete response (CR) and a very good partial response (VGPR) was not reached. The median survival of patients with partial response (PR) was 79.8 months *vs.* 42.9 months in patients with no response (NR).

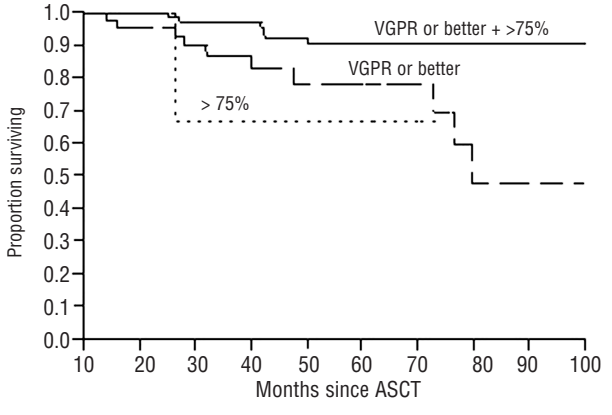

Figure 3. Overall survival (OS) of patients based on achievement of a very good partial response (VGPR) or better, >75% proteinuria reduction or both. Patients who had both >75% reduction in proteinuria and VGPR or better had an additional improvement in OS than patients who had a >75% reduction in proteinuria or VGPR or better alone (P=0.007).

can overcome the negative impact of a rise in Scr. However, an alternative explanation is that a proteinuria reduction of >75% strongly indicates that the kidney is recovering from the deleterious effects of amyloidosis. Thus, the elevation in Scr is unlikely to be due to AL and would not have the same impact on survival as progression of AL. Again, confirmation of this would require changes to the 2005 criteria.

Patients who achieved a hematologic very good partial response or better were more likely to have better outcomes than those with a partial response or less. Despite that, a >75% reduction in proteinuria was an independent predictor of survival in these patients. This again emphasizes the importance of organ response in order to guide treatment. In some patients, a deeper hematologic response may be required in order to achieve organ response. Recently, the National Amyloidosis Center in London reported that a >90% reduction of dFLC was associated with a higher probability of renal response.[11] This was similar to results of a previous study in which it was found that a sFLC reduction of >90% was equivalent to a complete response.[12] These findings resemble ours as reductions of >81% of sFLC and >86% of dFLC were needed to achieve adequate reduction of proteinuria.

Several limitations of our study should be highlighted. First and foremost is the nature of the organ response. An organ response takes time and, therefore, the patient must live long enough for it to occur. In this population, the median time for a 50% reduction in proteinuria was 11 months. We, therefore, chose to include only those patients that had more than 12 months of follow-up and excluded those who died or developed end-stage renal disease within the first 12 months. While it is possible that a small number of these patients may have achieved some renal response before they died, based on our previous study the number would be extremely low.[3] The renal response is dynamic and improves over time. This study only looked at the best response after ASCT. In some patients, the best response has yet to occur while others had already relapsed. This study was not designed to evaluate those patients but rather the impact that a certain renal response had on overall survival. Cardiac biomarkers were not included in the analysis in this study. There is no doubt that cardiac biomarkers are quite useful as markers of response in AL, but not all patients have cardiac involvement and this study was designed to evaluate whether renal response can also be used a surrogate of response. In this regard, it performed well even without input from cardiac biomarkers. Finally, these patients all underwent ASCT. While some patients did receive other treatments, whether our findings also apply to patients who never undergo ASCT is not known.

In conclusion, this study confirms that renal response is a good marker of response after treatment in AL patients. Renal response may be useful in patients who do not have alterations in their cardiac biomarkers and presents with predominantly renal manifestations. Our data showed an improvement in overall survival correlated with degree of proteinuria reduction. A rise in Scr >25% in the setting of proteinuria reduction was not associated with worse overall survival. These results suggest that refinement of the current renal response criteria is indicated. At minimum, it supports larger studies to confirm the findings.

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Authorship and Disclosures

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