# A UK consensus algorithm for early treatment modification in newly diagnosed systemic AL amyloidosis

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**Abstract**

Depth of response is the critical determinant of prognosis in AL amyloidosis. Here, we aim to identify patients who are unlikely to improve response based on analysis of baseline characteristics and 1-month response. In a multivariate model, dFLC at diagnosis (dFLC > 400 mg/l, OR 4.051, p< 0.005) and no response at 1-month (OR 4.787, p< 0.005) were significant predictors of response non-improvement. Only 5% of patients with dFLC > 400 mg/l and no response at 1-month improved their response (p< 0.005). We suggest that these patients should switch treatment early, subject to their functional status.

## Introduction

Systemic immunoglobulin light chain (AL) amyloidosis is a multi-system disorder associated with an underlying plasma cell/B-cell dyscrasia. Outcomes have improved with the introduction of several novel agents. (1) Bortezomib-based combination therapy is the current global standard of care. (2-5) Daratumumab-CyBorD is licensed for the frontline treatment of AL but is not widely available. The depth of haematologic response is the critical determinant of survival. (6-8) We have shown that early deep (≥VGPR at 1-month) response translates to superior outcomes, and there is also a progressive response improvement with continued treatment (from 34.1% ≥VGPR at 1-month to 57.1% and 65% at 3 & 6-months, respectively).(9)

Our previous data raises an important question on managing patients with a sub-optimal early response. As a proportion of patients improve their response over time, factors predicting progressive responders vs those unlikely to respond would be a valuable clinical aid to avoid ineffective therapy and potential worsening organ function/toxicity in the group unlikely to respond.

Here, we report on a subgroup (<VGPR at 1-month) of 1276 newly diagnosed, upfront Bortezomib treated AL patients registered with the National Amyloidosis Centre, UK. We aim to identify patients who are unlikely to improve their response with continued Bortezomib treatment. We also propose a treatment algorithm based on the above analysis.

## Patients & methods

1276 patients received frontline Bortezomib from February 2010 to August 2019. All methods are as previously published. (9)

## Results

525 patients had < VGPR at 1-month and are included in this analysis. Patients excluded were: ≥VGPR – 404 patients; dFLC < 20 mg/l at diagnosis - 82 patients; deaths before 1-month – 78 patients; received 2$^{nd}$ line within initial six months – 65 patients and missing response data at 1-month - 122 patients (Consort diagram, Figure SA1, Supplementary Appendix). 212/525 (40.4%) improved response to ≥ VGPR and 313/525 (59.6%) did not improve response at 6-months [termed as response improved and response not improved, respectively]. The median dFLC of the entire cohort was 347.3 mg/l (range 24.6- 15898 mg/l). The dFLC corresponding to the 1$^{st}$, 2$^{nd,}$ and 3$^{rd}$ quartiles were 167.6, 347.3, and 636.1 mg/l, respectively. The interquartile range was 468.5 mg/l.

Table SA1 (supplementary appendix) compares the baseline characteristics of these two groups (response improved vs response not improved). Patients who did not improve their response had higher baseline NT-proBNP (1895 ng/l vs. 1467 ng/l, p=0.039), higher baseline dFLC (median 423.6 mg/l vs. 259.6 mg/l, p<0.005) and more advanced cardiac involvement (Mayo stage IIIb, 16.9% vs. 10.4%, p=0.03), respectively. 60% of the patients who improved response to ≥VGPR at 6-months had achieved at least a partial response at 1-month compared to only 33% in the cohort with <VGPR at 6-months (p< 0.005).

We used binary regression model to identify factors predicting response non-improvement. In univariate analysis, (Table SA2, Supplementary Appendix), NT-proBNP (p=0.04), Mayo stage IIIb (p=0.036), dFLC at diagnosis (p< 0.005), Kappa light chain isotype (p=0.043) and no response at 1-month were significant predictors of response non-improvement. We analysed the impact of baseline dFLC, stratifying into four quartile groups (rounded up to the nearest 100); < 200 mg/l, 201-400 mg/l, 401-700 mg/l and > 700 mg/l. Both 401-700 mg/l and > 700 mg/l were significant predictors of response non-improvement. Therefore, we clubbed these two categories and analysed dFLC stratified as < 400 mg/l and > 400 mg/l. In a multivariate model incorporating Mayo stage (European modification), dFLC at diagnosis (stratified into < 400 mg/l and > 400 mg/l), Kappa light chain isotype and haematologic response at 1-month, only dFLC at diagnosis (dFLC > 400 mg/l, OR 4.051, 95% CI 2.641-6.213, p< 0.005) and no response at 1-month (OR 4.787, 95% CI 3.146-7.285, p< 0.005) were significant predictors of response non-improvement.

We then created a model incorporating dFLC at diagnosis and response at 1-month. We allocated scores to the two variables as follows - dFLC > 400 mg/l =1 point; no response at 1-month = 1 point; dFLC < 400 mg/l = 0 point; and partial response at 1-month = 0 point. Based on this model, all patients were allocated a response predictor score (RPS) (score range 0-2). 100/525 (19%), 324/525 (61.7%) & 101/525 (19.3%) patients had RPS 0, 1, and 2, respectively.

We compared survival amongst the three groups of patients in the above classifier model. Patients with a lower score had a significantly superior survival compared to those with higher scores- median survival 75 months (score =0) vs 50 months (score

=1) vs 23 months (score =2), respectively (p< 0.005) (Figure SA2, Supplementary Appendix).

We performed a decision tree analysis using the RPS (Figure 1) to predict response improvement. Only 5% of patients with RPS = 2 improved their response. In contrast, 43.5% patients with RPS = 1 and 66% patients with RPS = 0 improved their response (p< 0.005). We repeated the analysis in patients with RPS 0-1 (i.e. excluding those with RPS 2) based on a 3-month response. Only 23% of patients with < VGPR at 3-months improved their response by 6-months. In contrast, 88.1% patients with ≥VGPR at 3-months were in a continuing deep response at 6-months (p< 0.005). In this sub-group (patients with score 0-1), as expected, patients who improved their response (≥VGPR at 6-months) had significantly superior survival to those who did not improve their response- median OS 19 months vs 79 months, p<0.005 (Figure SA3, Supplementary Appendix).

**Discussion**

The above data shows that patients with baseline dFLC > 400 mg/l and no haematologic response at 1-month are extremely unlikely to improve their response; they should be switched to a suitable 2$^{nd}$ line regimen early, depending on their functional status. Patients who achieve at least a PR at one month and improve to ≥VGPR at 3-months mostly do not require a change in treatment. Any patient not achieving at least a VGPR by 3-months needs to change to 2$^{nd}$ line regimen (this is generally the practice in most amyloidosis patients at present). Using this algorithm, nearly 19% of the patients would be recommended for treatment modification at one

month, 61% would be monitored for another two months and considered for modification of therapy if the response did not deepen.

The depth of response at 6-months is the most critical determinant of survival in AL amyloidosis. (6-8) We have recently shown that patients who achieve a deep early response (at 1-month) have a superior survival, and the benefit is seen across all Mayo stages. (9) In our previous study, we showed that around 1/3$^{rd}$ of our cohort achieved an early deep response, another 1/3$^{rd}$ improved their response with continued treatment and, a third of the patients did not improve their response. The lack of response likely reflects the biology of the underlying clone or the delivery of treatment in very advanced patients. (10, 11) Patients with AL amyloidosis have a significant burden of organ dysfunction at diagnosis, and lack of response will result in ongoing proteotoxicity and amyloid fibril formation. Most guidance in amyloidosis suggests switching therapy at 3-moths in poor responders. Earlier switching may help a proportion of patients.

Studies have shown that deep light chain suppression improves outcomes in AL. (7, 8) The current data cannot address the question of the next therapy for patients who do not achieve a deep light chain response (dFLC < 10 mg/l or iFLC < 20 mg/l) at 6-months. The consensus is that patients with ≥VGPR who have an organ response may not need additional treatment. But those without an organ response may need to improve the depth of response based on functional status and tolerance. There is emerging data that measurable residual disease maybe a useful tool in calibrating treatment in patients without an organ response.(12, 13) Based on this and the above data, we propose a treatment algorithm described in Figure 2.

The above data provides clinicians with clear and objective criteria to aid decisions about switching treatments in poor responders. However, clinical consideration is paramount. For example, in patients with advanced cardiac disease, three months without a deep response may be very long, and earlier switching may be beneficial. Conversely, patients with cardiac stage II or without cardiac involvement could have a longer trial of 1$^{st}$ line treatment.

Daratumumab-CyBorD is now a licensed treatment for AL amyloidosis. This combination produces a more rapid and deeper haematologic response. (14) The proposed algorithm may not be fully applicable to patients treated with Daratumumab-based combination therapy upfront. The present data identify a high-risk group of patients with a particularly bad prognosis, despite treatment with Bortezomib based therapy. Treatment options for this group are limited (IMiDs/Anti CD38 antibody/bispecific antibody); clinical trials are required to refine the treatment paradigm for this high-risk group.

There are no published studies evaluating the impact of rapid switching of treatment- on the eventual haematologic response and survival. The present data needs validation, both in other large retrospective cohorts and prospective trials. This study is retrospective, and we are unable to model the impact of organ involvement in the decision-making process (we don't have NT-proBNP and other organ function data at each month during follow-up). We do not have cytogenetic data from the bone marrow at diagnosis. All patients in our cohort were treated at their local centers, and data on the dose intensity of the treatment is lacking. We acknowledge these limitations of our data.

In conclusion, patients with dFLC >400 mg/l at diagnosis and who do not achieve at least a PR at 1-month should be considered for a suitable 2nd line regimen early. Our study provides clinicians with an algorithm to modify chemotherapy based on the haematologic response at different time points. This algorithm needs evaluation in other patient cohorts and prospective studies.

***Authorship declaration***

*SR designed the study, collected/analysed the data, and wrote the manuscript.*

*SM, BW, SS, RP, NR, HL, KR, SH, CK, JG, KY, PH, GJ, & GP reviewed and approved the manuscript.*

*ADW supervised the study and approved the manuscript.*

***Conflict of Interests***

*ADW has received honoraria from Janssen, GSK, Celgene, and Takeda. The other authors do not have any conflict of interest to disclose.*

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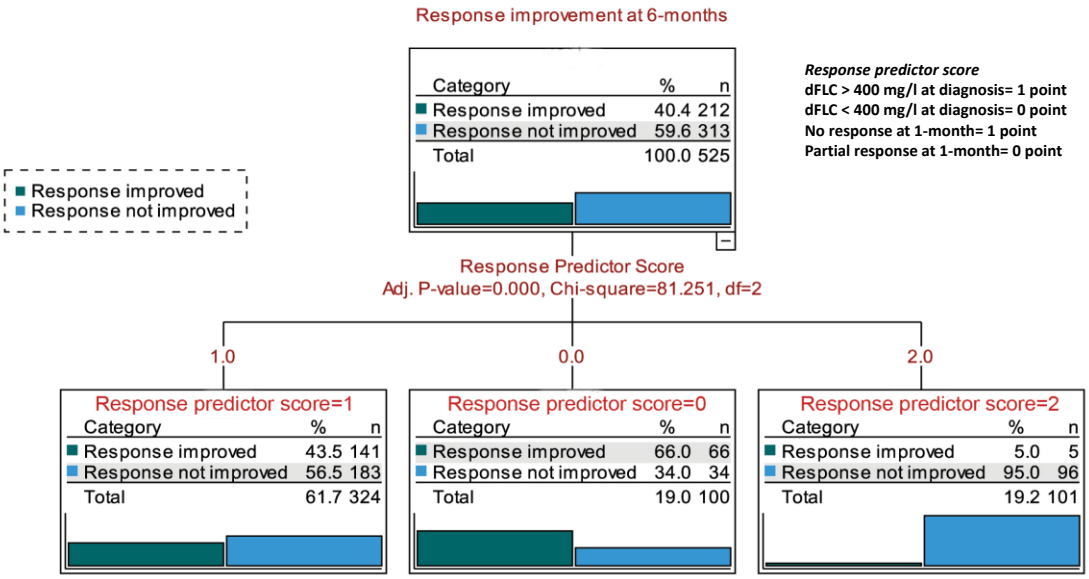
## Figure Legends

**Figure 1:** Shows a decision tree to predict a 6-month response using a response predictor score (classifier model). Patients with a response predictor score of 2 have a significantly poorer chance of improving their response at 6-months- only 5% of patients improved their response. In contrast, 43.5% of patients with a response predictor score of 1 and 66% of patients with a response predictor score of 0 improved their response by 6-months ($p< 0.005$).

**Figure 2:** Shows a proposed treatment algorithm for newly diagnosed AL patients. All newly diagnosed AL patients should be offered treatment with upfront Bortezomib, and response assessed at 1-month. Patients who achieve ≥VGPR at 1-month can continue treatment with Bortezomib with regular monitoring of haematologic & organ response. Patients with < VGPR at 1-month could be risk-stratified using the proposed classifier model. An early switch of treatment should be considered in those with a response predictor score = 2. Patients with scores 0 or 1 could continue frontline Bortezomib and their response was re-assessed at 3-months. Patients < VGPR at 3-months should be considered for 2$^{nd}$ line treatment. Patients ≥VGPR at 3-months could continue frontline Bortezomib with regular monitoring of haematologic & organ response. Patients who achieve ≥ VGPR at 6-month, but who do not have an organ response could be considered for further treatment.

Figure 1

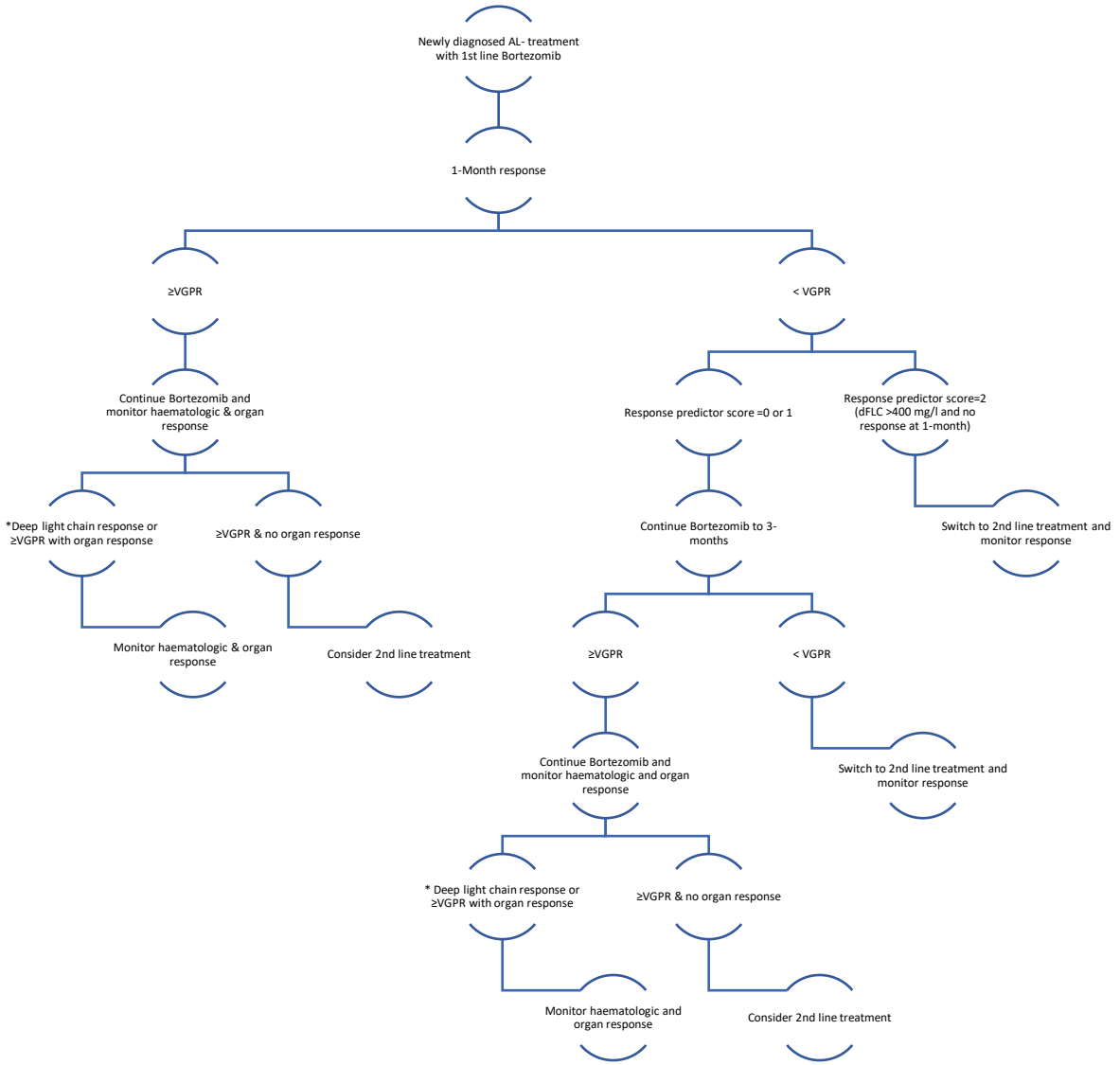
**Predicting response improvement using response predictor score**




***Response predictor score***
**dFLC > 400 mg/l at diagnosis= 1 point**
**dFLC < 400 mg/l at diagnosis= 0 point**
**No response at 1-month= 1 point**
**Partial response at 1-month= 0 point**

**Figure 2**

## Treatment algorithm for newly diagnosed AL Amyloidosis




**Response predictor score**

**dFLC > 400 mg/l at diagnosis= 1 point**

**dFLC < 400 mg/l at diagnosis= 0 point**

**No response at 1-month= 1 point**

**Partial response at 1-month= 0 point**

**Deep light chain response= dFLC < 10 mg/l or iFLC < 20 mg/l**