Acknowledgments
This work was supported by the Wellcome Trust Strategic Award in Medical Mycology and Fungal Immunology (G097377) (A.B., A.W.), by an MRC Clinical Research Fellowship (MR/K002708/1) (A.S.), by the MRC Centre for Medical Mycology (MR/N006364/1) at the University of Aberdeen (A.W.), and by a Wellcome Trust Seed Award (204566/Z/16/Z) (D.A.-J.).

Authorship
Contribution: D.A.-J., A.W., and A.B. conceived the study; A.B., T.C., and A.S. performed the experiments; and A.B., T.C., A.S., A.W., and D.A.-J. wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profile: D.A.-J., 0000-0002-1014-7343.

Correspondence: Darius Armstrong-James, Fungal Pathogens Laboratory, Sir Alexander Fleming Building, National Heart and Lung Institute, Imperial College London, SWZ 2AZ, London, United Kingdom; e-mail: d.armstrong@imperial.ac.uk.

Footnotes
The online version of this article contains a data supplement.

There is a Blood Commentary on this article in this issue.

REFERENCES

DOI 10.1182/blood-2017-12-823393
© 2018 by The American Society of Hematology

TO THE EDITOR:

Treatment of AL amyloidosis with bendamustine: a study of 122 patients

Paolo Milani,1,2,* Stefano Schönland,3,4 Giampaolo Merlini,1,2 Christoph Kimmich,3 Andrea Foli,1,2 Tobias Dittrich,3 Marco Basset,1,2 Carsten Müller-Tidow,3 Tilmann Bochtler,3 Giovanni Palladini,1,2,† and Ute Hegenbart3,†

1Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 2Department of Molecular Medicine, University of Pavia, Pavia, Italy; and 3Department of Internal Medicine V, Hematology/Oncology/Rheumatology, Amyloidosis Center, University of Heidelberg, Heidelberg, Germany

Chemotherapy for light chain (AL) amyloidosis is based on combinations developed for multiple myeloma.1 A better understanding of susceptibility of the AL underlying clone to specific types of treatments2 and the ability to identify cytogenetic patterns with different clinical outcomes3,4 are beginning to change the approach to this rare and still fatal disease. Despite the high response rates to first-line regimens, treatment of relapsed/refractory patients remains an important unmet need.5 Relapsed patients may have a good outcome if treated before organ progression.5,7 Light chain amyloidosis caused by immunoglobulin M–producing clones (IgM-AL amyloidosis) is a distinct clinical entity and poses additional problems in the design of the therapeutic strategy.8 Rituximab- and bortezomib-based regimens developed for Waldenström macroglobulinemia9 have been evaluated in IgM-AL amyloidosis and are considered first-line options for these patients,9,10 and bendamustine is being evaluated in a phase 2 trial in relapsed AL amyloidosis.11

© 2018 by The American Society of Hematology

LETTERS TO BLOOD

1988 | 1 NOVEMBER 2018 | VOLUME 132, NUMBER 18

The prospectively maintained databases of the Pavia and Heidelberg amyloidosis centers were systematically searched for AL amyloidosis patients treated with bendamustine between 2005 and 2015. Organ involvement was defined according to the 2005 International Society of Amyloidosis criteria. All patients gave written informed consent for their clinical data to be used in retrospective studies as approved by institutional ethics committees, in accordance with the Declaration of Helsinki.

All patients received IV bendamustine (60-100 mg/m², days 1-2) and oral prednisone (100 mg, days 1-4) in 28-day cycles; bendamustine dose was adjusted according to renal failure in the Pavia cohort, the presence of cytopenia, and the severity of heart involvement at the time of treatment initiation. All patients with IgM-AL amyloidosis additionally received rituximab (375 mg/m², day 1).

Hematologic and organ response was assessed according to current validated criteria. The analysis of response was by intent to treat, and the patients who died before the evaluation of response were considered nonresponders.

Toxicity was assessed every 2 cycles and graded according to the Common Terminology Criteria for Adverse Events version 4.03 (National Institutes of Health). Overall survival was calculated from the start of bendamustine treatment until death or last follow-up. A 3-month landmark analysis of survival was performed to assess the impact of response on outcome. Progression-free survival (PFS), defined as time to progression requiring treatment change, death, or relapse requiring reintervention of treatment, was calculated in all patients from the start of bendamustine therapy. The occurrence of an organ progression only was not considered as a progression if therapy was not reintegrated. Survival curves were plotted according to Kaplan-Meier method, and differences in survival tested by the log-rank test. MedCalc Software version 16.8.4 (MedCalc bvba, Belgium) was used for computation.

A total of 130 patients were identified, and 8 subjects were excluded from the analysis for incomplete data set (61 treated in Pavia and Heidelberg, respectively). Twelve patients (10%) were newly diagnosed (all IgM-AL amyloidosis patients except 1), 77 (63%) were refractory to previous lines of treatment, and 84 (68%) received at least 2 prior lines of therapy. In relapsed/refractory patients, median time from diagnosis to bendamustine initiation was 27.4 months (interquartile range [IQR], 10-64). The median number of cycles of bendamustine in the whole cohort was 3 (range 1-6). No difference in overall survival was seen in patients treated with a reduced dose of bendamustine (<90 mg/m² vs ≥90 mg/m², median survival 14 vs 23 months, P = .295).

Overall hematologic response was not significantly different in the 2 groups (P = .535), and no difference was seen in terms of PFS (median PFS 10 vs 8 months, P = .323). Severe (grade 3 or 4) adverse events were observed in 34 (26%) subjects (supplemental Table 1; available on the Blood Web site). No difference in terms of total number of severe adverse events was seen between patients treated with full dose/reduced dose of bendamustine (P = .226).

The overall hematologic response rate to bendamustine in the whole cohort was 35%, with very good partial response complete responses (VGPR/CR) in 10 (8%)/2 (2%) of subjects. In patients with non-IgM-AL amyloidosis, the overall hematologic response rate to bendamustine in the whole cohort was 21%.
response rate was 28% (1 patient obtained CR, and 3 obtained VGPR; supplemental Table 2). In IgM-AL amyloidosis patients, hematologic response was obtained in 21 (58%) subjects with CR in 1 patient (2%) and VGPR in 7 (19%). Interestingly, the addition of bendamustine to rituximab was able to induce response in 9 (64%) of the 14 patients with IgM-AL amyloidosis who were refractory to previous rituximab-containing regimens. In the previously treated group, 32% of subjects exposed to alkylating agents and 26% of those exposed to bortezomib responded to bendamustine. Twelve (24%) patients who were refractory to proteasome inhibitor responded to bendamustine, and 9 (21%) who were refractory to immunomodulatory drugs. Only 6 of 36 (13%) patients who were refractory to both responded to bendamustine. No differences in overall survival or PFS were detected between the proteasome inhibitor/immunomodulatory/dual refractory patients groups.

At the time of evaluation of hematologic response, cardiac response was observed in 6 (12%) of 51 and renal response in 13 (31%) of 41 evaluable subjects.

Overall, 75 (58%) patients died during follow-up, and median overall survival from bendamustine initiation was 21 months (95% confidence interval [CI], 16-39). The median follow-up of living patients was 31 months (IQR, 17-46). Mayo stage III patients had a significant reduced outcome (median survival of stage II, 26 months vs stage III, 5 months; \( P < .001 \)).

The median PFS in the entire cohort was 9 months (95% CI, 6-15), and in previously treated patients 8 months (95% CI, 5-13). Hematologic response after bendamustine was associated with a significant improvement in PFS and overall survival (Figure 1A-B).

The present study reports the largest cohort of patients with AL amyloidosis treated with bendamustine published so far. The overall hematologic response rate in the subset of previously treated patients (32%; 95% CI, 24-41) was slightly lower compared with the results of a recently reported phase 2 trial in relapsed/refractory patients (45%; 95% CI, 29-62).\(^\text{11}\) This might be partly because of the selection criteria of the phase 2 trial, which excluded patients with relevant cardiac involvement.
In conclusion, bendamustine is a valuable rescue therapy in AL amyloidosis, being able to improve survival in responders even in heavily pretreated patients. This drug is particularly promising in IgM-AL amyloidosis patients in combination with rituximab and warrants further investigation in this setting.

Acknowledgments
This work was supported in part by “Associazione Italiana per la Ricerca sul Cancro–Special Program Molecular Clinical Oncology 5 per mille” (grant 9965). CARIPLO “Structure-function relation of amyloid: understanding the molecular bases of protein misfolding diseases to design new treatments” (grant 2013-0964), and the Italian Ministry of Health target project (grant RF-2013-02355259). G.P. is supported in part by the Bart Barlogie Young Investigator Award from the International Myeloma Society.

Authorship
Contribution: P.M., S.S., U.H., and G.P. designed the study, evaluated patients, collected data, analyzed data, wrote the manuscript, and gave final approval; G.M. designed the study, evaluated patients, critically reviewed the manuscript, and gave final approval; and C.K., A.F., T.D., C.M.-T., and T.B. evaluated patients, critically reviewed the manuscript, and gave final approval.

Conflict-of-interest disclosure: S.S. is on advisory boards for Prothena, Janssen, and Takeda; receives financial support for scientific projects from Janssen and Sanofi; receives honoraria from Janssen and Prothena; and receives support for congress participation from Janssen and Medac. G.M. is a consultant for Millennium Pharmaceuticals Inc., Pfizer, Janssen, Prothena, and IONIS. G.P. receives honoraria from Janssen, honoraria and travel support from Prothena, and travel support from Celgene. U.H. is on advisory boards for Pfizer and Prothena, receives honoraria from Janssen, and receives support for congress participation from Janssen and Jazz. The remaining authors declare no competing financial interests.

ORCID profiles: P.M., 0000-0002-2268-9422; G.P., 0000-0001-5994-5138.

Correspondence: Giovanni Palladini, Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy; e-mail: giovanni.palladini@unipv.it; and Ute Hegenbart, Amyloidosis Center, Heidelberg University Hospital, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany; e-mail: ute.hegenbart@med.uni-heidelberg.de.

Footnotes
*P.M. and S.S. are joint first authors.
†G.P. and U.H. are joint senior authors.

The online version of this article contains a data supplement.

REFERENCES

DOI 10.1182/blood-2018-04-845396
© 2018 by The American Society of Hematology

LETTERS TO BLOOD