

Zanubrutinib in Light Chain Amyloidosis associated with Waldenström Macroglobulinemia and indolent B-cell lymphoma: tolerability and efficacy

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A previous version of this work was presented at EHA. Data have been extended since.

Background

Immunoglobulin light chain (AL) amyloidosis is rare. The majority is secondary to plasma cell dyscrasias, but up to 5-10% may be caused by indolent B-cell non-Hodgkin lymphomas (iNHL). When caused by iNHL, AL amyloidosis is often associated with IgM paraproteinemia in the context of Waldenström Macroglobulinemia (LPL/WM), although IgG and light chain only production also occur. Intensive chemotherapy is recommended to achieve a deep hematological response but is often too toxic due to age, amyloid-related morbidities or comorbidities. Bruton tyrosine kinase inhibitors (BTKi) are highly effective in iNHL, but showed only minor anti-clonal activity and were associated with severe cardiac side effects in a small case series with ibrutinib in IgM AL amyloidosis. Zanubrutinib, a BTKi associated with less (cardio)toxicity and a trend towards deeper responses, could potentially be a more feasible approach.

Methods

Between July 2022 and July 2024, data of all consecutive AL amyloidosis patients with underlying iNHL that took at least 1 dose of zanubrutinib were retrospectively collected across 6 hospitals (The Netherlands, UK and Germany). All patients signed informed consent. Data were collected for adverse events (AEs) and efficacy every 3 months up to zanubrutinib discontinuation. AEs were graded in accordance with CTCAE v5.0. Hematologic responses were assessed using published consensus criteria for AL amyloidosis¹.

Results

Ten patients were included (underlying disease and MYD88/CXCR4 mutational status: **Figure 1**). Median follow-up was 7.9 months (range 2.9 – 16.8) and median duration of therapy was 7.1 months (range 2.9 – 12.3) with treatment ongoing in 4 of 10 patients. Best hematologic response was a very good partial response (VGPR) in 4 out of 10 patients. Five patients have discontinued zanubrutinib

for reasons specified in **Figure 1**. Two patients are still on treatment and have not reached a response (patient 7 & 10; iFLC decrease of 9.9% and dFLC decrease of 10.7%, respectively), and 1 patient died of heart failure after 6 months of treatment.

Grade ≥ 3 AEs were reported in four individual patients; urosepsis, drug-induced liver injury (DILI), neutropenia and gastric hemorrhage. Temporary treatment discontinuation occurred for all grade ≥ 3 AEs except for the latter. Zanubrutinib was safely restarted in all cases, with dose reduction in the patient with DILI. The death related to heart failure occurred in the setting of preexistent cardiac amyloidosis (Mayo stage 2), it is unknown whether the use of zanubrutinib contributed to this. In the other 9 patients, 4 with cardiac amyloidosis, no cardiac AEs were reported.

Conclusion

Zanubrutinib led to a VGPR in at least 4 out of 10 patients. Longer follow-up is needed to assess organ response as well as the duration and deepening of the ongoing hematologic responses. Of importance, 9 out of 10 patients experienced no cardiac events. Based on these preliminary data, zanubrutinib might represent a treatment option for AL amyloidosis patients with underlying iNHL that are unfit (or non-responding) for intensive chemotherapy. Data collection and accrual is currently ongoing and will be updated at the time of the meeting.

Reference consensus criteria for AL amyloidosis:

¹ Comenzo RL, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia*. 2012;26(11):2317-25.

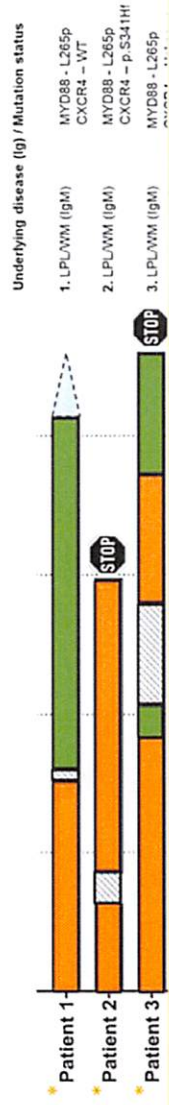


Figure 1. Clinical course of Light Chain Amyloidosis patients with underlying INHL treated with zanubrutinib.

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Dear Workshop chairs of the 12th International Workshop on Waldenström's Macroglobulinemia,

I hereby confirm that Mr. Wouter Verhaar is a delegate in training at the department of Hematology of Amsterdam UMC, location VUmc.

I hope to have informed you sufficiently.



Prof. Dr. Marie José Kersten