

Safety and efficacy of zanubrutinib in patients with IgM AL amyloidosis

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Introduction: Patients with IgM immunoglobulin light chain (IgM-AL) amyloidosis, are a rare and distinct population with unmet needs. Optimal treatment has not been determined yet, and these patients rarely achieve deep hematologic responses and have inferior outcomes. Zanubrutinib is a next generation covalent BTK-inhibitor, approved for WM, associated with higher VGPR rates and lower cardiovascular toxicity. There is limited data for zanubrutinib in IgM-AL with an underlying lymphoplasmacytic clone

Aim and methods: We present four patients with IgM-AL treated with Zanubrutinib.

Result: The clinical characteristics are shown in the Table. Prior to zanubrutinib initiation median dFLC was 151 mg/L, median NTproBNP 10240 ng/L and median eGFR 29.5 ml/min/1.73m². Three patients had cardiac and two renal involvement. Three patients had lambda and one kappa light chain type; median lymphoplasmacytic bone marrow infiltration at diagnosis was 35% (range 12-50); all had MYD88 mutation (L265P). All patients had received one prior line of therapy that included rituximab and bendamustine. Reason to start treatment with zanubrutinib was inadequate hematologic response (define as $\leq$ PR).

Median time from diagnosis to treatment with zanubrutinib was 8 months (range 3-12). Zanubrutinib was administered orally at 320 mg daily divided into two doses in combination with rituximab. VZV and PCP prophylaxis was administered according to standard protocols and one patient was already on immunoglobulin replacement therapy due to severe hypogammaglobulinemia. Median duration of treatment was 4.5 months (range 2-8). Regarding safety, three patients who also had severe renal dysfunction developed bleeding events. One patient, who was also on treatment with anticoagulant due to paroxysmal atrial fibrillation, developed spontaneous hematoma and was admitted to the hospital. Zanubrutinib was temporarily interrupted and reinitiated at a lower dose, however, hematoma re-occurred and zanubrutinib was permanently discontinued. The second patient developed epistaxis and hematuria gr1 leading to temporarily interruption of zanubrutinib and the third developed bruising and subconjunctival hemorrhage gr1, while she was also receiving anticoagulant as thromboprophylaxis, but zanubrutinib was not interrupted. Neutropenia gr3, requiring growth factor, occurred in one patient and anemia gr2 and gr3 in two patients. Notably none developed infections or cardiovascular events. Regarding efficacy, one patient achieved hematologic PR, while the other three patients did not achieve hematologic response. Among three patients with heart involvement two have achieved cardiac response (CarPR), and among the two patients with renal involvement one has renal progression and one has not achieved renal

response. None of the patients have hematologic progression. All patients are still alive; two are ongoing: one on hemPR and one with hemNR but with gradually fall of dFLC along with cardiac response; one patient discontinued treatment due to unacceptable toxicity and one due to inadequate hematologic response with organ progression.

Conclusions: Our series, although limited, demonstrates that treatment with zanubrutinib in combination with rituximab is feasible, even in patients with severe cardiac disease, without significant cardiotoxicity. However, the efficacy is low in patients with IgM-AL. Notably, patients with impaired renal function demonstrate high bleeding risk, especially in combination with anticoagulant, and tailored dose should be considered.

Table. Summary of baseline characteristics

Patient (age, gender)	Mayo stage	Organ involvement	Baseline dFLC (mg/L)	Baseline NTproBNP (ng/L)	Baseline proteinuria (gr/24h)	Baseline eGFR (ml/min/1.73m ²)	Prior lines	Hem response	Organ response
1 (73y, F)	1	Kidney	44.3	164	15470	29	1	NR	RenPD
2 (75y, F)	2	Kidney Heart	68.22	1055	67	8	1	NR	RenNR CarNR
3 (70y, F)	3a	Heart	350.9	28688	156	19	1	PR	CarPR
4 (71y, F)	3a	Heart	141.3	11052	75	62	1	NR	CarPR

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