Effectiveness of Bruton's Tyrosine Kinase Inhibitors in IgM related Amyloidosis with Underlying Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia

Bou Zerdan Maroun[1], Diacovo Julia[1], Elson Leah[1], Bilani Nadeem[1], Chieh-Lin Fu[1], Chaulagain Chakra[1]

[1]Department of Hematology-Oncology, Maroone Cancer Center, Cleveland Clinic Florida, Weston FL, USA

BACKGROUND

- Of the variety of immunoglobulin related amyloidosis (AL), immunoglobulin M (IgM) related AL represents around only 5% of affected patients, and around 10-22% of these reported cases are linked with Waldenström's macroglobulinemia (WM) or Multiple Myeloma (MM) (1).
- Ibrutinib, acalabrutinib and zanubrutinib are Bruton Tyrosine Kinase (BTK) inhibitors approved for certain indolent B cell Non-Hodgkin Lymphoma (NHL).
- The BTK is a non-receptor kinase involved in B-cell survival, proliferation and interaction with the microenvironment (2).

METHODS

In this IRB approved case series, we retrospectively evaluated the tolerability and effectiveness of BTK inhibitors ibrutinib and acalabrutib therapy in (n=4) patients with IgM related AL amyloidosis with underlying WM. The patient characteristics are presented in the table). The hematologic and organ response were assessed according to previously published consensus criteria (3) .

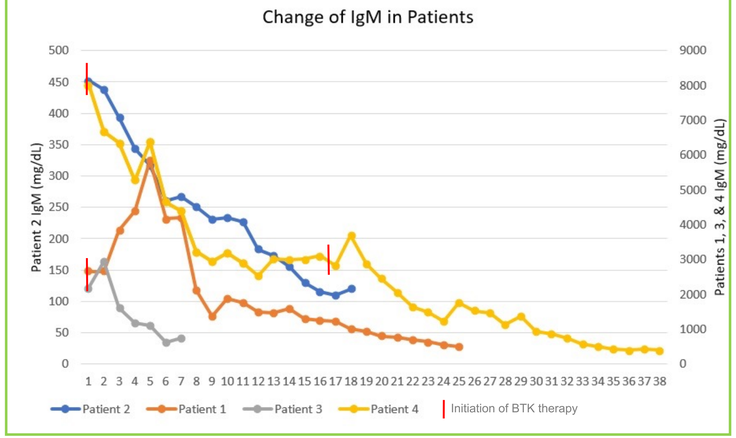


Figure 1: Change in difference of free light chains before and after BTK inhibitor therapy.

RESULTS

Clinical Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	74//M	67/F	91/F	60M
Date of diagnosis and initiation of anti-lymphoma treatment	7/2020, first line rituximab and Acalabrutinib	8/2019, first line Ibrutinib and rituximab	6/2019, Acalabrutinib	Diagnosed in 11/2016, 1st line: VDR 2nd line (4/2017-12/2017): Ibrutinib +rituximab
Clinical presentation leading to the diagnosis	Symptomatic hepatomegaly, diastolic CHF	Stage IV CKD, anemia, no significant proteinuria	Transfusion dependent anemia, CHF, stage IV CKD	Dyspnea on exertion, lymphadenopathy
Circulating monoclonal protein (g/dL)	IgM kappa, M spike 2.6	IgM lambda, M spike 0.4	IgM kappa, M spike 2.2	IgM lambda, M spike 4
IgM level at presentation (40 - 230 mg/dL)	2666	452	2949	8020
Serum free kappa (3.30 - 19.40 mg/L)	205	30	705	7
Serum free lambda (5.7 - 26.3 mg/L)	3	39	101	170
Kappa to lambda ratio	68	0.81	7	0.04
dFLC at presentation	202	9	604	163
Troponin T (0.000 - 0.029 ng/mL)	0.042	Not tested	0.1	0.047
NT pro BNP (0 - 450 pg/mL)	4928	650	10500	2300
Tissue biopsy confirming the diagnosis of AL amyloidosis	Liver, bone marrow and cardiac biopsy	Renal biopsy	Bone marrow biopsy	Lymph node biopsy showing both LPL and Amyloid
LC-MS/MS analysis	Main amyloidogenic component is kappa immunoglobulin light chains	Main amyloidogenic component is lambda immunoglobulin light chains	Not done, amyloid type confirmed with immunohistochemistry	Note done, amyloid type confirmed with immunohistochemistry
Bone marrow biopsy findings	40-50% involvement by LPL, Amyloid +	50% involvement by LPL, Amyloid -	90% involvement by LPL , gain of chromosomes 4 and 18	Not done
MYD88 status	Mutated	Mutated	Mutated	Mutated
Complications during treatment with BTK-I and rituximab	Rituximab flare, Thumb hematoma (Image 3) leading to 50% dose reduction of Acalabrutinib	None	None	Atrial fibrillation leading to discontinuation of Ibrutinib
Anti-lymphoma therapy prior to initiating BTK inhibitor-based regimen	None	None	Intolerance to rituximab and Bortezomib	First line (11/2016-3/2017: VDR with PR 2nd line (4/2017-12/2017): Ibrutinib +rituximab with VGPR 3rd line (1/2018 -6/2018): BR with stable disease 4th line: CAEL 101 +CyBorD (3/2020-present) with VGPR
Best response with BTK Inhibitor therapy/ duration of treatment	VGPR with hepatic and cardiac response/ 8 months	CR with renal response/ 12 months	VGPR with cardiac response/ 10 months	CR with cardiac response/ 9 months

Image 1. Bone marrow clot H&E 10x: bone marrow spicules diffusely involved by small atypical lymphoid cells from lymphoplasmacytic lymphoma (Patient 1).

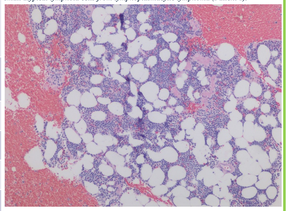
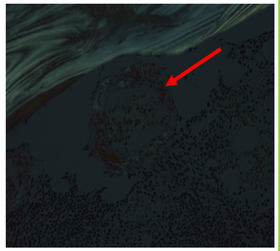


Image 2: Subungual Hematoma after a trivial trauma (Patient 1).

Image 3. Bone Marrow Congo red stain 20X: amyloid deposition on vessel wall with apple green birefringence under polarized light (Patient 1).



M: Male, F: Female, BR: bendamustine and rituximab, BTK-I=Bruton's Tyrosine Kinase Inhibitor, CKD: Chronic kidney disease, CHF: Congestive heart failure, dFLC=difference in free light chain levels, CR: complete response, LC-MS/MS: Liquid Chromatography with tandem mass spectrometry, CyBorD: cyclophosphamide, bortezomib and dexamethasone, LPL: lymphoplasmacytic lymphoma, VGPR: very good partial response, VDR: bortezomib, lenalidomide, and dexamethasone

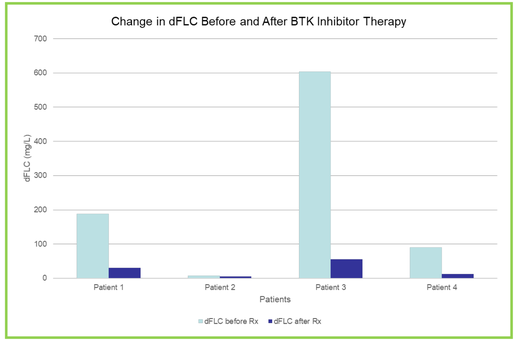


Figure 2 Change in difference of free light chains before and after Bruton's Tyrosine Kinase inhibitor therapy.

CONCLUSIONS

- In our small retrospective series, BTK inhibitors, ibrutinib and acalabrutinib, were well tolerated with both hematologic and organ response in patients with AL amyloidosis in the setting of WM.
- Atrial fibrillation led to discontinuation of ibrutinib in one patient and acalbrutinib caused significant thumb hematoma needing dose reduction in another patient.
- All patients evaluated had MYD88 mutation. This may explain good response to BTK inhibitors therapy in our series (4).
- BTK inhibitors should be further investigated in larger prospective studies for treatment of AL amyloidosis in patients with lymphoplasmacytic lymphoma/WM.

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There are no relevant conflicts of interest to disclose.