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Long term follow-up of rituximab for anti-myelin-associated glycoprotein demyelinating polyneuropathy in IgM gammopathies: clinical, hematological and neurophysiological correlations

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Abstract

Background and purpose. Anti-myelin-associated glycoprotein (MAG) demyelinating polyneuropathy (PNP) is a rare, underdiagnosed condition, associated with monoclonal Immunoglobulin M (IgM) gammopathy of undeterminate significance (MGUS) or Waldenstroem macroglobulinemia (WM), that might deeply compromise patients' quality of life (QoL). We here report updated, long-term clinical, hematological and neurophysiological results, with a novel series of patients.

Methods. Anti-MAG PNP patients were prospectively evaluated by a multidisciplinary team prior to, during and after treatment with RTX. Neurological evaluation included electromyography (EMG), INCATds, mISS, PGIC scales, serum anti-MAG titer, and physical examination. Hematological assessment included bone marrow biopsy (BMB) and BM aspirate, complete blood count, M protein quantification and serum immunofixation, serum IgM level; BM samples multiparameter flow cytometry (MFC) and droplet digital PCR for $MYD88^{L265P}$ gene mutation were performed. Diagnostics were based on IWWM criteria [Semin, Oncol 2003]. RTX (375 mg/m^2 weekly) was administered for 4 ("cohort 1") to 8 courses (4+4, "cohort 2"). Hematological and neurological evaluations (including CD19+ cells count in peripheral blood, PB) were performed before (T0), 1 year (T1) and 2 years (T2) after RTX. PNP relapse was defined as increase $\geq$1 point at INCAT-ds score or $\geq$2 points at mISS.

Results. Between 2017-2023, 41 pts with confirmed anti-MAG PNP and IgM gammopathy were treated with RTX at the Hematology Division of Torino University; of note, 7 pts had already received prior RTX while 35 were treatment naïve. Median age at the time of BMB was 71 years (range 50-82), 26 pts (63%) had WM vs 15 pts (37%) IgM MGUS. Median IgM baseline level 507 mg/dL (range 121-1479 mg/dL), and median anti-MAG titer of 1:60000 (range 1:5000-1:200000). Median invasion by lymphoplasmacytic lymphoma 20% (range 5-60%); 35 pts (92%) carried $MYD88^{L265P}$ mutation in BM with median level $5x10^{-3}$ (range $4.7x10^{-4}$ – $1x10^{-1}$). Interestingly, the median time between clinical PNP onset to RTX was 22 months (range 4-174). 22 patients received 4 cycles of RTX (cohort 1), 19 patients received 4+4 RTX cycles frontline (cohort 2). Major response rate (MRR) was 47% (T1), 58% (T2). Median baseline level of CD19+ B cells in PB in 7 evaluable patients was 67/µL (range 5-637/µL), after RTX 7/12 pts had no detectable CD19+ cells.

Neurological responses (EMG, clinical scales and QoL) were initially reported elsewhere [Parisi, EJN 2022], update will be after the follow-up completion.

Median follow-up (FU) was 79.5 months; 9 patients (22%) were retreated with RTX for clinical PNP relapse, median time to next treatment 27 months (range 11-65). Notably, REL pts median FU was longer, burden of $MYD88^{L265P}$ mutation lower and 7 vs 2 pts came from cohort 1 (p=.0535); 7 were WM and 2 MGUS.

One patient required additional treatment with zanubrutinib (PNP progression); another died for cardiovascular disease.

Conclusions. This study describes a homogeneous, consistent and well characterized series of patients affected by IgM gammopathies and anti-MAG PNP effectively treated with RTX in a single center with considerable FU. This work highlights how the cooperation between hematologists and neurologists might improve diagnostics, monitoring and outcome in this rare condition.

	All patient (n=41)	Non-relapsing patients (n=32)	Relapsing patients (n=9)
Median age	71	71	71
Male	28 (68%)	21 (65%)	7 (78%)
MGUS	15 (37%)	13 (40%)	2 (22%)
WM	26 (63%)	19 (60%)	7 (78%)
IgM-k	37 (90%)	31 (97%)	6 (67%)
IgM-l	3 (7%)	1	2 (22%)
IgM-k and IgM-l	1 (3%)	0	1
Median IgM baseline	507 mg/dL (range 121-1479)	543 mg/dL (121-1479)	507 mg/dL (range 195-788)
Median anti-MAG titer^	1:60000 (range 1:5000-1:200000)	1:50000 (range 1:5000-1:200000)	1:70000 (range 1:9000-1:200000)
Median BM invasion	20% (range 5-60%)	20% (range 5-60%)	10% (range 10-30)
Median clonal B lymphocyte (MFC)	0.17% (range 0-35%)	0.185% (range 0-35%)	0.185% (range 0-13%)
Median clonal PCs (MFC)	0% (range 0-2.34%)	0% (range 0-2%)	0% (0-2.34%)
MYD88^{L265P} mutation*	35 (92%)	27 (90%)	8 (100%)
MYD88^{WT}**	3 (7%)	3 (11%)	0
Median MYD88^{L265P} level	$5x10^{-3}$ (range $4.7x10^{-4}$-$1x10^{-1}$)	$6.85x10^{-3}$ (range $4.7x10^{-4}$-$1.16x10^{-1}$)	$8.88x10^{-4}$ (range $6.04x10^{-4}$-$3.72x10^{-2}$)
Median baseline CD19+ level§	67 c/μL (range 5-637 c/μL)	67 c/μL (range 5-637 c/μL)	Missing data
Median time between PNP onset to RTX	22 months (range 4-174)	20.5 months (range 4-153)	29 months (range 6-174)
4 RTX cycles (cohort 1)	22 (54%)	15 (47%)	7 (78%)
4+4 RTX cycles (cohort 2)	19 (46%)	17 (53%)	2 (22%)
Major response rate (MRR) (T1)	17/36 (47%)	14/29 (48%)	3/7 (43%)
Major response rate (MRR) (T2)	19/33 (58%)	15/26 (58%)	4/7 (57%)
Median follow-up	79.5 months (range 14-209)	62.5 months (range 14-180)	89 months (64-209)°

^ 1 pts had 1:100 anti-MAG titer (negative) but was positive for IgM anti-GD1b and IgM anti-GQ1b
* 3 missing pts
** 2 WM and 1 IgM MGUS
§ available in 7 pts
° REL Cohort 1: 89 months, REL cohort 2: 57 months

Letter of endorsement

To whom it may concern, I strongly support the abstract submission of Dr. Enrico Amaducci to the IWWM12 Workshop. Enrico is a smart hematology fellow who I had the pleasure to supervise in his clinical and research activity. Recently he has joined the multidisciplinary team involved in Torino in the IgM anti-MAG PNP research program. In thight collaboration he has updated and extended the results of our internal series, published in 2022 (REF), by writing the present abstract. I hope the committee might evaluate his work and consider his application for a travel grant.
Kind regards,

Torino, 15/07/2024

Firma
Dott. Simone Ferrero