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ABSTRACT

Monoclonal immunoglobulin M (IgM) anti-myelin-associated glycoprotein (MAG) neuropathy is a rare disabling condition, most commonly treated with rituximab monotherapy (R), which leads to neurological improvement in only 30%-50% of patients. The combination of rituximab plus chemotherapy has been proven to improve the level of responses. We studied the outcomes of anti-MAG neuropathy patients treated either by R, or by immunochemotherapy (ICT) in our centre, focusing on the incidence of the first neurological response evaluated by the modified Rankin Scale (mRS). From 2011 to 2018, 64 patients were studied: 34 were treated with R and 30 with ICT. According to our treatment decision-making process, the median mRS was higher in the ICT group (mRS 2) compared to the R group **(**mRS 1). At 1 year, mRS improvement rates were 46% and 18% of the ICT and R groups of patients respectively, with a median time to response of 8 and 13 months ($p=0.023$). Adverse effects were higher in the ICT group: 62% vs 15% ($p<0.01$) all grades included. One secondary acute leukaemia occurred 5 years after treatment by ICT. In conclusion, ICT may be used as a valid option for patients with rapidly progressive and/or severe anti-MAG neuropathy symptoms.

INTRODUCTION

Monoclonal gammopathy of clinical significance (MGCS) is defined by the presence in the serum of monoclonal immunoglobulin (Ig) or monoclonal free light chain produced by indolent B-cell clones in the absence of overt tumour proliferation but responsible for organ damage because of toxicity of the monoclonal component.(1) Mechanisms of toxicity include deposition of all or part of the monoclonal Ig, immune complex formation, complement activation or autoantibody activity against a tissue antigen. Any antibody activity against myelin-associated glycoprotein (MAG) may be responsible for IgM anti-MAG antibody-related peripheral neuropathy which is a rare, disabling condition. Most frequently, there is no overt lymphoproliferative syndrome but monoclonal gammopathy of undetermined significance (MGUS) occurs. However, in 33% of cases, Waldenström macroglobulinemia (WM) or indolent B-cell lymphoma is present.(2) The ensuing neuropathy is characterized by mostly sensitive disorders and is generally slowly progressive but there is great heterogeneity of clinical presentation among patients, and progression can lead to irreversible secondary axonal loss with disabling neurological outcomes. Rarely, acute worsening can occur and lead to major and rapid disability. (3). It is estimated that 20%-45% of patients are disabled by severe progressive neuropathies that undermine their quality of life. (2,4) Thus, there is a need to develop effective treatments. The criteria required to initiate treatment are difficult to establish in anti-MAG neuropathy because of its rarity, its heterogeneous progressive course, the subjectivity of symptom presentations and the non-standardized evaluation criteria.(5,6) Usually, treatment is warranted in case of significant disability and should not be based on IgM and/or anti-MAG levels. There are no clearly established therapeutic recommendations and there is insufficient evidence from most pilot studies to recommend any particular treatment. Rituximab monotherapy use is more and more frequent although its effectiveness has not been demonstrated by all groups. (5,7–9) Clinical scales improvement with rituximab monotherapy is reported in 30% to 50% of cases with a median delay of improvement ranging from 9 to 12 months. (10)

In WM and other lymphoproliferative disorders, immunochemotherapy (ICT) yields better outcomes than rituximab monotherapy (11). In the context of MGCS, the treatment decision is based on the benefit-to-risk approach and frequently involves chemotherapy.(1) Indeed, rituximab may be combined with chemotherapy to target the underlying B-cell clone responsible for the production of anti-MAG antibodies and has been reported by several teams. (12–15). Our centre has shown that the addition of chemotherapy makes it possible to

obtain a faster clinical response, the median time to response being 5 months in the ICT group compared to 9.5 months in the rituximab group.(16) It is suggested that ICT may be preferred in case of rapid and/or severe neurological symptoms.

Based on these findings, we investigated whether patients with anti-MAG neuropathy would benefit from more intensive treatments. Here, we report the outcomes of a retrospective **series** of patients treated with rituximab (R) or rituximab plus chemotherapy at a single centre**.**

MATERIALS AND METHODS

Patients

Recruitment was conducted retrospectively based on medical records. The inclusion criteria were patients with anti-MAG neuropathy treated with R alone or in combination with chemotherapy. The diagnosis was related to the association of demyelinating neuropathy based on EMG features, clinical data matching and monoclonal gammopathy of the IgM type with anti-MAG activity. Clinical evaluation was assessed with the modified Rankin Scale (mRS; **Table 1)**. IgM levels were assessed with protein electrophoresis and anti-MAG antibodies with ELISA (Bühlmann, Switzerland) using coated human MAG and peroxidase-conjugated anti-human IgM. Samples $\geq$ 5,000 BTU were considered as positive. Clinical data were obtained in accordance with the declaration of Helsinki and with ethical approval from national (CNIL 2212382) and local (CPP Ile-De-France 05/21/2014) ethics committees. All patients were informed and oral non opposition of each patient was recorded in medical files according with the ethical French law. Sixteen patients have been previously described with shorter follow-up. (16)

Treatments

The treatment decision was made according to the patient's symptoms, the impact on daily life and the natural course of the disease, independently of bone marrow evaluation. ICT was used to treat the patients with high mRS (3-4) and/ or acute or sub-acute ($\leq$ 6 months) neurological worsening of the disease, subject to the age and the general status. Patients treated with ICT received 6 cycles of: dexamethasone (20 mg day 1) plus R (375 mg/m^2 day 1) plus oral cyclophosphamide (300 mg/m^2 day 1 to 5) (DRC), or oral fludarabine (40 mg/m^2 day 1 to 3) plus oral cyclophosphamide (250 mg/m^2 day 1 to 3) plus R (37**5** mg/m^2 day 1) (FCR), or oral fludarabine (40 mg/m^2 day 1 to 5) plus R (375 mg/m^2 day 1) (FR), or bendamustine (90

mg/m^2 day 1 and 2) plus R (375 mg/m^2 day1) (BR). In the R group, R was given: 375 mg/m^2 intravenous every week for 4 weeks.

Outcomes

The study's primary endpoint was the incidence of the first mRS improvement. Improvement was defined as mRS decrease ≥1, stabilization as stable mRS, and progression as mRS increase ≥1. The secondary endpoint was the survival without initiation of a new treatment defined as the time from the start of treatment and initiation of a new treatment or death. We also evaluated the electrophysiological change (improvement, stability, worsening), according to Lunn and Nobile-Orazio, (17) the anti-MAG change (decrease defined as ≥ 25% titre decrease, increase defined as ≥ 25% titre increase, stability otherwise) and the IgM change (decrease defined as ≥ 25% level decrease, increase defined as ≥ 25% level increase, stability otherwise).

Statistical analysis

Characteristics of the study population were described in terms of frequencies for qualitative variables or medians and associated ranges for quantitative variables. Qualitative variables were compared using Chi-2 test (or Fisher exact test if appropriate), quantitative variables were compared using Student test (or non-parametric Wilcoxon test in case of non-normal distribution). The cutoff date for the analysis was 20/01/2020. Median follow-up was estimated using reverse Kaplan-Meier. (18)

Time to modified Rankin Score (mRS) improvement was defined as the delay between the start of treatment and the date of event. Patient alive without improvement of modified Rankin Score were censored at the date of their last known contact or death. Patient who died before an improvement of modified Rankin score were censored at the date of death. Survival analyses were performed using the Kaplan-Meier estimate. Incidence of the event was estimated using the following transformation F(t)= 1-S(t) where S(t) is the Kaplan-Meier estimate of survival functions.

Hazard ratios and their associated 95% confidence intervals were calculated using the Cox proportional hazard model. For multivariate analysis, we chose to adjust treatment effect on main confounding factors based on clinical knowledge: mRS at baseline evaluation and speed of worsening (fast/progressive) assessed before treatment initiation. The proportional hazards hypothesis was tested for each factor, with Schoenfeld's residuals test and plotting. All tests

were two-sided and used a significance threshold at 5%. Analyses were performed with the R software, version 3.6.3 (R Development Core Team, 2011).

RESULTS

Patients and treatment

From 2011 to 2018, 78 patients with a positive anti-MAG dosage were treated with R or ICT. Fourteen patients were excluded because of other concomitant indications of treatment (cryoglobulinemia, CANOMAD syndrome, active WM: n = 4) or lack of data (n = 10). Thus, 64 patients with anti-MAG neuropathy are reported here. Patient characteristics before treatment are summarized in **Table 2**. The median age at symptom onset was 63 years [IQR 55–69] and 55% of the patients were male. The median time between onset of neuropathy and treatment initiation was 4.3 years [IQR, 2-7].The most common symptoms were: sensory deficit (83%), paraesthesia and dysesthesia (70%) and ataxia (67%). Distal lower limbs motor deficit was reported for 25 patients (39%), neurological pain for 33 patients (52%) and tremor for 11 patients (18%).. The most frequent type of onset was chronic (>6 months) (81%) but 2 patients had acute progression (≤ 1 month).. The median mRS was 2 [IQR 1–2] in the overall population, and twelve patients (40%) of the ICT group had mRS of 3 or 4 versus 2 (6%) of the R group. The median monoclonal peak (for patients with measurable IgM peak, n = 43) and MAG antibody level (for n = 33 patients with anti-MAG dosage<70,000 BTU) were, respectively, 4 g/L [IQR 3–4] and 32,900 BTU [IQR 23,400–43,000]. Thirty-one patients had anti-MAG antibody levels >70,000 BTU. The kappa isotype was predominant in 81% of patients. There was no evidence of an overt haematological malignancy in 30/53 patients (57%) with available bone marrow evaluation. Among the other patients, 18 had WM and 5 patients had non-WM lymphoplasmacytic lymphoma. Thirty-four patients were treated with R and thirty with ICT, including 13 (43%) with DRC, 13 (43%) with FR, 3 (10%) with FCR and 1 (3%) with BR.

Modified Rankin Scale outcome and time to new treatment

The median follow-up was 5 years [IQR 3.9–6.4] for the whole cohort and was longer for the ICT group (6.6 years) than for the R group (4 years). The incidence of the first mRS improvement was statistically different between the ICT group and the R group (HR = 2.41 CI95% [1.10, 5.28], p = 0.023). Twelve months after treatment initiation, 46% (CI95% [26; 62]) of patients had mRS improvement in the ICT group versus 18% (CI95% [2; 26]) in the R group (**Fig. 1**). In addition, the mean change of mRS between start of treatment and 12

months was –0.64 in the ICT group versus –0.15 in the R group (p = 0.036) (**Fig. 2**). At 3 years, 57% (CI95% [35; 72]) of patients had mRS improvement in the ICT group vs 30% (CI95% [11; 45]) in the R group. Median time to first mRS improvement was 25.2 months (CI95% [8.4; NR]) in the ICT group but it was not reached in the R group as less than 50% of patient had a mRS improvement. For responder patients, the median time to first response was 8 months [IQR 6–10] in the ICT group versus 13 months [IQR 9–29] in the R group. After adjustment on baseline mRS score and the type of onset, incidence of the first mRs improvement was no longer significant between ICT and R groups (HR = 1.34, CI95%[0.58 ; 3.12]).

At 5 years, 36% (CI95% [11; 45]) of ICT group patients have started a new line of treatment or died versus 39% (CI95% [12; 57]) of R group patients (p=0.675) (**Fig. 3)**. Of note, 5 patients, all in the ICT group, continued to decrease their mRS after the first response. The mRS profile of each patient over time is reported in **Fig. 4**.

Other outcomes

Twelve months after treatment initiation, electrophysiological improvement occurred in 22/52 patients (42%) and its rate was higher in the ICT group (65%) vs the R group (24%) (p = 0.007). The electrophysiological improvement was concordant with the clinical mRS improvement in 88% of cases (**Fig. 5A**). Finally, decreases in anti-MAG and IgM were observed respectively in 27/39 (69%) and 19/48 (40%) patients, and we did not observe any statistical association between biological and mRS responses (**Fig. 5B-C**). Indeed, mRS improvement occurred in only 41% of patients with IgM decrease and in 32% of patients with anti-MAG decrease.

Tolerance

The ICT regimen was associated with higher adverse events including all grades: 62% in the ICT group versus 15% in the R group (p<0.01), but no toxic death was reported (**Table 3**). Rituximab-related infusion reactions were all classified as grade 1–2 and occurred in 6% of the patients. Grade 3–4 cytopenia and nausea/vomiting occurred, respectively, in 5 and 1 patients, all in the ICT group. Infectious complications were reported in 4 patients in the ICT group versus 1in the R group. They included 3 bacterial infections 1 septic shock, 1 febrile neutropenia and 1 parvovirus B19 infection (1 patient experienced 2 different infectious adverse events). Notably, 1 patient in the R group developed, after the fourth R injection, a grade 4 non-viral cytolytic hepatitis associated with neurological flare. Modified RS increased

from 1 to 4 and the patient temporarily required a wheelchair. In parallel, EMG and anti-MAG antibody assays worsened. The patient gradually recovered his baseline clinical condition 9 months later. Finally, 1 patient in the ICT group died from secondary acute leukaemia diagnosed 5 years after treatment (DRC and then FR).

DISCUSSION

Here, we report the outcomes of the largest cohort of anti-MAG neuropathy patients treated with ICT or R monotherapy. As expected, clinical characteristics assessed with mRS were different in the 2 treatment groups as follows: patients in the ICT group were more disabled than those in the R group**.** Indeed, in our centre, patients with severe or rapidly progressive neuropathy are more prone to be treated with ICT as a result of our previous experiences. (16) We assume that there is a major bias when comparing the efficacy of 2 treatment types but it reflects the heterogeneous presentation of the disease and the complexity of randomized trials in rare patient populations. Nevertheless, the time between onset of neuropathy and treatment initiation was similar between the 2 groups**.** In our cohort, the response rate at 1 year was higher (46% vs 18%) and the time to response (8 vs 13 months) shorter in the ICT group compared to the R group. In case of rapid neurological worsening with severe symptoms, a fast response is of great interest because, while waiting for the treatment to take effect, patients continue to become disabled, and the consequences may be irreversible. In the case of very slow disease progression, the patients may develop secondary axonal changes with loss of neurons. As a result, they are less likely to respond than patients with more recent disease, suggesting that, as previously noted by other authors, (19–21) a well-tolerated treatment such as R monotherapy may be proposed earlier during the disease progression in this slow context. Of note, ICT benefit was no longer significant in multivariate analysis. Taking into account confusion factors is useful in retrospective analysis. In rare patients population where randomized trials are not possible, estimating an hazard ratio at 1.34 may be clinically interesting without having the necessary power to be significant in the study. However, we cannot exclude that the effect of ICT vs. R is inferior due to residual confusion.

One way to improve treatment efficacy without adding adverse effects may be the use of new drugs targeting B cells, such as Bruton Tyrosine Kinase inhibitor (BTKi), but very few data are available in the specific context of anti-MAG neuropathy. In the study by Treon et al., 9 patients received ibrutinib for progressive neuropathy, 3 of whom had anti-MAG antibodies.

(22) Subjective improvement occurred in 5 patients and 4 remained stable. In a subsequent study, 4 patients with neuropathy were treated with ibrutinib: 2 had subjective improvement and 2 remained stable. (23) More recently, ibrutinib demonstrated objective improvement occurring early in the first 3 months in 3 patients with anti-MAG neuropathy. (24) These results suggest that BTKi should be considered for anti-MAG neuropathy patients in future clinical trials and that the delay of improvement may be short.

One concern with anti-MAG neuropathy is that international consensus on assessing response to treatment is still lacking and clinical evaluation is difficult because of inadequate scores. Rankin and ONLS scores are disability scales and cannot effectively capture small functional changes that can greatly impact quality of life. The only-well defined sensory score available in clinical trials is the INCAT sensory score, but it is insufficiently sensitive to detect the small functional changes or sensory improvement concerning paraesthesia or pain for example. (25,26). Also, it highlighted that we probably underestimated the clinical impact of treatment because of lack of sensitivity of the neurological score and that we need to develop more sensitive scores. On the biological side, disease markers may not be suitable for assessing treatment efficacy. Indeed, we confirmed that anti-MAG antibody evolution was not correlated to the clinical response. (27,28) A possible explanation for this observation is that differences in the anti-MAG antibody titre are no longer detectable above a certain threshold. We cannot detect changes in patients with anti-MAG titres ≥70,000 BTU at baseline. Moreover, the plasma anti-MAG antibody titre does not reflect its binding capacity in the nerve tissue and does not inform on its affinity. This is why anti-MAG antibody titre is of crucial interest for demyelinating neuropathy diagnosis but not for treatment evaluation. Similarly, we did not find a correlation between the IgM response and the clinical response. This may be explained in part by the low level of IgM monoclonal gammopathy that do not allow a correct assessment of peak reduction after treatment.

Finally, different treatment options were used according to the successive WM international guidelines. Purine-analogs based regimens were frequently used at the beginning of the twenties but are less used because of the risk of long-lasting cytopenia and myelodysplasia. (29) DRC is effective, well tolerated and is one of the most used treatment option. (11,30) More recently, bendamustine plus rituximab have demonstrated a superior overall responses and progression-free survival with superior time to best response compared to DRC and BDR (bortezomib plus dexamethasone plus rituximab). (31,32) Thus, we recommend the use of

alkylating based regimen in aggressive anti MAG neuropathy: BR in fit patients, and DRC in less fit or unfit patients .

In conclusion, our data suggest that treatment of anti-MAG neuropathy patients can be adapted to the heterogeneous clinical presentations and that ICT can be used to treat severe or rapidly progressive neurological symptoms in order to obtain a higher response rate with a shorter time to response.

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TABLES

Table 1. Modified Rankin Scale.

Scale	Symptoms
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

Table 2. Baseline clinical and biological characteristics of the patients before treatment.

Characteristic	Total	ICT	Rituximab	P value
No. of patients	64	30	34	
Median age [IQR]	63 [55-69]	63 [57-72]	62 [54-68]	0.641
Gender, n. (%)	Male: 35 (55) Female: 29 (45)	Male: 19 (63) Female: 11 (37)	Male: 16 (47) Female: 18 (53)	0.192
Underlying hematological malignancy* (n=53), n. (%) - IgM MGCS - WM - Other lymphoproliferative disorder	 30 (57) 18 (34) 5 (9)	 17 (63) 6 (22) 4 (15)	 13 (50) 12 (46) 1 (4)	0.131
Clinical presentation, n. (%) - Sensory deficit - Paresthesia/ dysesthesia - Ataxia - Pain - Motor deficit	 53 (83) 45 (70) 43 (67) 33 (52) 25 (39)	 27 (90) 15 (50) 26 (87) 12 (40) 19 (63)	 26 (77) 30 (88) 17 (50) 21 (62) 6 (18)	 0.152 **0.001** **0.002** 0.082 **<0.001**
Median time between neuropathy onset and treatment initiation, years [IQR]	4.3 [2.1-7.4]	4.2 [1.8-7.2]	4.8 [2.4-9.5]	0.1563
Type of onset, n. (%) - Acute/ Sub-acute - Chronic	 12 (19) 52 (81)	 10 (33) 20 (67)	 2 (6) 32 (94)	**0.005**
Modified Rankin Scale - Median [IQR] - mRS 1-2 (%) - mRS 3-4 (%)	 2 [1-2] 50 (78) 14 (22)	 2 [2-3] 18 (60) 12 (40)	 1 [1-2] 32 (94) 2 (6)	**0.001**
Spike IgM level, g/L [IQR]	4 [3-4]	6 [5-8]	4 [3-8]	**<0.001**
Kappa isotype, n. (%)	51 (81)	25 (83)	26 (79)	0.202
Anti-MAG titer - >70,000 BTU, n (%)	 31(48)	 16 (53)	 15 (44)	 0,462

- BTU [IQR]	32,900 [23,400-43,000]	40,600 [33,500-45,850]	23,700 [20,250-41,012]	**0.041**

Abbreviations. ICT, immunochemotherapy; No., number; MGCS, monoclonal gammopathy of clinical significance; mRS, modified Rankin Scale.

*Underlying hemopathy was assessed with bone marrow evaluation and was available for n=53 patients. Acute delay of degradation means ≤3 months, sub-acute between 3 and 6 months, progressive > 6 months from the diagnosis.

	Overall		ICT		Rituximab	
Adverse events	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher
Infusion reaction	4	0	2	0	2	0
Flare effect	1	1	0	0	1	1
Infectious complication	6	1	5	1	1	0
Anemia	0	3	0	3	0	0
Thrombocytopenia	3	1	3	1	0	0
Neutropenia	3	2	3	2	0	0
Aplasia	1	1	1	1	0	0
Nausea, vomiting	4	1	4	1	0	0
Hepatitis	0	1	0	0	0	1

Table 3. Treatment-induced toxicities.

Secondary malignancy	NS	1	NS	1	NS	0
Toxic death	NS	0	NS	0	NS	0

Abbreviations. ICT, immunochemotherapy; NS: not suitable.

FIGURE LEGENDS

Figure 1. Incidence functions of mRS response. Modified RS response was defined as a decrease ≥ 1 point under treatment. Purple line denotes patients treated with immunochemotherapy (ICT), green line denotes patients treated with rituximab alone (R).

Figure 2. Mean modified Rankin Scale at baseline and 12 months after treatment initiation. Red lines denote mRS mean, bold lines denote mRS median.**Figure 3. Probability of survival without a new treatment was started**. Purple line denotes patients treated with immunochemotherapy (ICT), green line denotes patients treated with rituximab alone (R).

Figure 4. Modified Rankin Scale profile of each patient under and after treatment. A. Immunochemotherapy (ICT) group, **B**. Rituximab (R) group. Vertical blue (for R group) and red (for ICT group) dotted lines denote the time point of 12 months after treatment initiation.

Figure 5. Concordance between mRS response and other outcomes. **A**. EMG change, **B**. Anti-MAG change, **C**. IgM change. The EMG change was reported according to Lunn and Nobile-Orazio (5) (improvement, stability or worsening). The anti-MAG change was defined as a decrease in case of ≥ 25% titer decrease, an increase in case of ≥25% titer increase and a stability in the other cases. The IgM change was defined as a decrease in case of ≥ 25% level decrease, an increase in case of ≥ 25% level increase and a stability in the other cases. The x axis denotes the neurological responder patients according to mRS improvement (yes) or not (no). The y axis denotes the frequency of improvement or increase (yellow color), stability (orange color) and worsening or increase (red color) according to the other parameters.