CANOMAD: a neurological monoclonal gammopathy of clinical significance that benefits from B-cell–targeted therapies

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CANOMAD: a neurological monoclonal gammopathy of clinical significance that benefits from B-cell targeted therapies

Short title: CANOMAD syndrome

Marie Le Cann[1*], Françoise Bouhour[2*], Karine Viala[3], Laurence Simon[1], Céline Tard[4], Cédric Rossi[5], Guillaume Morel[6], Emmeline Lagrange[7], Laurent Magy[8], Alain Créange[9], Maud Michaud[10], Jérôme Franques[11], Andoni Echaniz-Laguna[12], Jean-Christophe Antoine[13], Marine Baron[1], Bertrand Arnulf[14], Angela Puma[15], Emilien Delmont[16], Thierry Maisonobe[3], Véronique Leblond[1□], Damien Roos-Weil[1□], on behalf the French CIDP and FILO groups

1. Sorbonne Université, Service d'Hématologie Clinique, Hôpital Pitié-Salpêtrière, APHP, Paris, France
2. Service d’ENMG et Pathologies Neuromusculaires, Hôpital Neurologique, Hospices Civils de Lyon, Lyon, France
3. Sorbonne Université, Département de neurophysiologie clinique, Hôpital Pitié-Salpêtrière, APHP, Paris, France
4. Department of Neurology and Movement Disorders, U1172, CHU de Lille, Centre de référence des maladies neuromusculaires Nord Est Ile de France, Lille, France
5. Service d’Hématologie, CHU F. Mitterrand, Dijon, France
6. Département d'Oncologie et d'Hématologie, CHU Strasbourg, Hôpital de Hautepierre, Strasbourg, France
7. Service de Neurologie, Centre Hospitalier Universitaire de Grenoble, Grenoble, France
8. Department of Neurology, ALS Reference Center, CHU Tours (Bretonneau Hospital), Tours, France
9. EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, Créteil, France; Service de Neurologie, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris, Créteil, France
10. Nancy University Hospital, Department of Neurology, Nancy, France
11. Department of Neurology, La Casamance Hospital, Aubagne, France

12. Department of Neurology, APHP, CHU de Bicêtre, Le Kremlin Bicêtre, 94276, France; French National Reference Center for Rare Neuropathies (NNERF), Le Kremlin Bicêtre, 94276, France; INSERM U1195 & Paris-Saclay University, Le Kremlin Bicêtre, 94276, France
13. Department of Neurology. University Hospital of Saint-Etienne, France
14. Saint-Louis University Hospital AP-HP, Paris, France
15. Université Côte d'Azur, Peripheral Nervous System and Muscle Department, CHU Nice, France
16. Referral Centre for Neuromuscular Diseases and ALS, La Timone hospital, Marseille, France

* These authors are co-first authors

□ These authors are co-senior authors

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Correspondence:

Damien Roos-Weil, MD, PhD, Sorbonne Université, AP-HP, Hôpital Pitié-Salpêtrière, Service d'Hématologie Clinique, 47-83 Bd de l'Hôpital 75651 Paris Cedex, France, Phone: + 33.1.42161596, Fax: + 33.1.42162848; email: damien.roosweil@aphp.fr

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Abbreviations used: CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies; CIDP, chronic inflammatory demyelinating polyneuropathy; FILO, French Innovative Leukemia Organization; IVIg, intravenous immunoglobulins; MGCS: monoclonal gammopathy of clinical significance; WM, Waldenström macroglobulinemia.

Key points

- This largest study to date of CANOMAD patients revealed that one third harbored an overt hematologic malignancy, consisting mainly in WM.
- IVIg and rituximab-based regimens were the most effective therapies with a 50% response rate.

Abstract

CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies) is a rare syndrome characterized by chronic neuropathy with sensory ataxia, ocular and/or bulbar motor weakness, in the presence of a monoclonal IgM reacting against gangliosides containing disialosyl epitopes. Data regarding associated hematologic malignancies and effective therapies in CANOMAD are scarce. We conducted a French multicenter retrospective study that included 45 patients with serum IgM antibodies reacting against disialosyl epitopes in the context of evocating neurological symptoms. Main clinical features were sensitive symptoms (ataxia, paresthesia, hypoesthesia) (n=45, 100%), motor weakness (n=18, 40%), ophthalmoplegia (n=20, 45%) and bulbar symptoms (n=6, 13%). Forty five percent of the cohort had moderate to severe disability (modified Rankin score, 3-5). Cold agglutinins were identified in 15 (34%) patients. Electrophysiological studies showed a demyelinating or axonal pattern in respectively 60 and 27% of cases. All patients had serum monoclonal IgM gammopathy (median, 2.6 g/L; range, 0.1-40). Overt hematologic malignancies were diagnosed in 16 patients (36%), most frequently Waldenström macroglobulinemia (n=9, 20%). Forty-one patients (91%) required treatment for CANOMAD. Intravenous immunoglobulins (IVIg) and rituximab-based regimens were the most effective therapies with respectively 53 and 52% of partial or better clinical responses. Corticosteroids and immunosuppressive drugs were largely ineffective. Although more studies are warranted to better define the optimal therapeutic sequence, IVIg should be proposed as the standard of care for first-line and rituximab-based regimens for second-line treatment. These compiling data argue for CANOMAD to be included in neurological monoclonal gammopathy of clinical significance.

Introduction

Monoclonal gammopathy of unknown significance (MGUS) is a common age-related condition, defined by the presence in serum and/or urine of a monoclonal immunoglobulin (Ig) produced by an abnormal B-cell clone, in the absence of overt plasma cell or B-cell lymphoproliferative diseases. Though mainly asymptomatic, these quiescent clones can be responsible for potentially severe organ damage, due to the toxicity of the monoclonal Ig or to other mechanisms, defining monoclonal gammopathy of clinical significance (MGCS)[1]. This situation often requires therapeutic intervention, directed against the B-cell clone[2]. Along with the kidney and skin, the peripheral nerve is one of the most frequently involved organs.

Monoclonal gammopathies associated with peripheral neuropathy are more commonly IgM than IgG or IgA. The prevalence of neuropathy in patients with monoclonal IgM ranges from 5 to 31%[3,4]. Pathophysiologic mechanisms that link gammopathy and neuropathy include: i) specific autoantibody activity of the IgM against different components of the nerve, ii) specific properties of circulating IgM, leading to cryoglobulinemic neuropathy, amyloid or endoneurial IgM deposits, iii) nerve infiltration or nerve damage mediated by cytokine secretion of tumoral cells[1,5]. Autoreactive IgM most frequently recognize myelin-associated glycoprotein (MAG), but gangliosides can also be targeted. This latter activity can be responsible for a neurological syndrome termed CANOMAD (Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM paraprotein, cold Agglutinins and Disialosyl antibodies), which is characterized by chronic neuropathy with sensory ataxia, and motor weakness involving oculomotor and bulbar muscles, occurring in the presence of monoclonal IgM directed against disialosyl ganglioside epitopes. As some of the symptoms defining CANOMAD are not observed in all patients[6,7], this acronym may be restrictive and the term CANDA (Chronic Ataxic Neuropathy with Disialosyl Antibodies) has also been proposed[8]. The first case of neuropathy associated with monoclonal IgM with anti-ganglioside auto-activity was described in 1985[9] and the largest series to date, published in 2001, comprised 18 patients[6]. Since then several case reports and small series have been reported in the literature, amounting to less than 50 cases[6,9-18]. Symptoms are dominated by progressive chronic neuropathy with marked sensory ataxia that can lead to severe disability. In some cases, fluctuating or fixed symptoms such as ocular, sensory or bulbar manifestations are reported together with ataxia. The presence of antibodies directed against gangliosides is constant. The most frequently targeted gangliosides are GD1b, GD3, GT1b and GQ1b, which all harbor disialosyl groups containing the sequence NeuNAc (α2–8) NeuNAc (α2–3) Gal. Such gangliosides are notably localized in the neurons of dorsal root ganglia and within the oculomotor nerves[19]. In contrast to anti-MAG neuropathy, which is a predominantly distal demyelinating neuropathy, both axonal and demyelinating patterns have been reported using electrophysiological studies and nerve biopsies.

Investigation of IgM-associated peripheral neuropathy require a well-defined strategy that combine (1) nerve conduction studies (NCS) to distinguish between demyelinating and axonal patterns; (2) detection of anti-MAG and anti-ganglioside antibodies; (3) screening for "red flag" features (that include pain, multifocal topography, rapidly evolving course, cranial nerve involvement, dysautonomia, weight loss, cutaneous signs, heart/kidney/lung involvement, and abnormal serum-free light-chain concentration and ratio) to orientate further investigations and rule out in particular cryoglobulinemic/amyloid neuropathy and tumor nerve infiltration[5,20].

There is actually no consensus for CANOMAD/CANDA treatment. Different therapeutic options have included intravenous immunoglobulins (IVIg), plasma exchange (PE), corticosteroids and immunosuppressive drugs[7]. More recently, small case series have reported encouraging results with rituximab[21-24]. Finally, although virtually all cases of CANOMAD/CANDA syndrome are associated with the presence of a monoclonal IgM, the spectrum of underlying hematologic malignancies and the efficacy of B-cell-targeting therapies have not been thoroughly investigated.

Main objectives of this retrospective study were to describe the clinical features of CANOMAD/CANDA syndrome, to identify associated hematologic malignancies and to gain insights into its optimal therapeutic management, while studying the largest patient cohort to date.

Patients, material and methods

Patients

This study is a national retrospective analysis of 45 patients, treated in 17 centers, which were included in a CANOMAD multicenter French registry between 2002 and 2018 on the basis of the positivity of at least one serum IgM antibody reacting against disialosyl epitopes (among GD1b, GD3, GT1b and GQ1b) and evocating neurological signs. A standardized questionnaire on demographics, clinical, biological, electrophysiological and therapeutic data was sent to all referring clinicians.

IVIg treatment consisted of a dose of 2 g/kg every 4 weeks. This interval between courses could be gradually increased by one week in case of clinical improvement. IVIg treatment could be stopped in case of clinical complete response. Administration schedules of single-agent rituximab were weekly infusions of 375 mg/m^2 for four weeks (n = 13) or two infusions of one g/m^2 on days 1 and 15 (n = 6).

Clinical data were obtained in accordance with the Declaration of Helsinki and its later amendments. All patients were informed and consented to participate in this study prior to inclusion in the registry.
Three cases have been published previously as case reports[21,25,26].

Investigations

Detection of monoclonal gammopathies, cold agglutinins and anti-ganglioside antibodies were performed locally and were part of variables collected in the standardized questionnaire. Methods testing for the presence of anti-disialosyl antibodies comprised enzyme-linked immunosorbent assay (ELISA)[6,27], “home-made” immunodots[28] or commercial tests (Generic Assays, Courtaboeuf, France). The Generic Assays commercial test (AntiGangliosidDot) is a line immunoassay used for the qualitative detection of IgM antibodies directed against 11 gangliosides (GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b) while “home-made” assay detect antibodies directed against 8 gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD2, GT1b, GQ1b). Routine screening investigations to exclude other causes of neuropathy followed recommendations previously published[5] and were negative. Electrophysiological studies were carried out locally in all cases and centrally reviewed. Axonal and/or demyelinating damages were defined according to the Ad Hoc Subcommittee of the American Academy of Neurology AIDS task Force’s demyelination criteria[29]. Bone marrow examination was performed in 31/45 (69%) patients.

Definitions

CANOMAD and CANDA were defined as described in the Introduction section and in previous publications[6,8]. Diagnoses of associated hematologic malignancies followed the WHO classification criteria[30].

To assess treatment response, we used the modified Rankin score (RS) (a 7-point disability rating scale with scores from zero (no deficit) to six (death)) evaluating the degree of disability or dependence for daily activities[31]. Clinical response was defined as complete response (CR, complete clinical improvement from baseline, RS=0), partial response (PR, a clinical improvement defined as ≥ 1-point RS decrease), stable disease (SD, unchanged RS) and progression (≥ 1-point RS increase). The different lines of therapy were separately analyzed for each patient. Biological response was defined as CR (disappearance of IgM and negative immunofixation), PR (decrease in serum IgM levels > 50%), SD (increase < 25% or decrease < 25%) and progression (increase > 25%).

Statistics

Overall survival was calculated from date of diagnosis until last follow-up/death and time to next treatment from date of first- to second-line of treatment. Kaplan-Meier analysis was performed to construct survival curves and the log rank test used to determine differences between groups. The X^2 or Fisher's exact test were used to compare data distribution in different clinical or treatment subgroups. The significance level of $p < 0.05$ was applied and statistical analyses were performed using the SPSS software.

Data Sharing Statement

For original data, please contact damien.roosweil@aphp.fr.

Results

Clinical features

Main clinical characteristics are provided in **Table 1**. Of the 45 patients included in our study, 35 (78%) were male. Median age at onset of symptoms was 58 years (range, 37-81) and the median delay between onset of symptoms and diagnosis of CANOMAD/CANDA was 4.0 years (range, 0.1-27). The most frequent initial symptoms were sensory (paresthesia and ataxia in respectively 26 (58%) and 21 (47%) cases), ocular (n=6, 13%) and bulbar (n=3, 7%). Of note, the disease was revealed by isolated ophthalmoplegia in one patient. At CANOMAD/CANDA diagnosis, nearly half (n=19, 44%) of the cohort harbored significant disability (modified Rankin score of 3 to 5). Clinical outcome was mainly chronic progressive (n=30, 67%) or relapsing-remitting (n=14, 31%). One patient experienced one symptomatic flare-up that completely resolved after first-line therapy. The set of neurological symptoms observed during the course of the disease for the whole cohort are detailed in **Table 1**.

Serological analyses and others investigations

All patients had anti-ganglioside antibodies with IgM specificity, reacting against at least one out of four of the following disialosyl epitopes: GD1b, GD3, GT1b and GQ1b. Thirty (67%) and 21 (47%) patients had antibodies reacting against at least 3 or 4 out of 4 of the mentioned epitopes. Forty (89%) had also antibodies reacting against other gangliosides such as GM1, GM2, GM3, GD1a, GD2 or GT1a.

Regarding cerebrospinal fluid (CSF) analysis, the mean protein level was 0.9 g/L (range, 0-2) and cellularity was negative in 80% of cases (median, 0/mm^3; range, 0-4). Nerve conduction studies (NCS) showed a demyelinating or axonal pattern in respectively 27 (60%) and 12 patients (27%). Among the six patients for whom electrophysiological studies were normal, two had abnormal somatosensory evoked potential, corresponding to a particular form of peripheral neuropathy, characterized by demyelination involving the proximal part of the sensory nerves[32]; it could be undetectable by classical NCS. One patient had a form of small fiber neuropathy, which is also usually not detected by classical NCS. Two other patients had only very mild sensitive symptoms when NCS were performed. Fourteen nerve biopsies were performed revealing demyelinating, axonal and mixed features in respectively four, five and four cases. One patient had a normal nerve biopsy. Three cases presented additional abnormalities: endoneural fibrosis (n=1), IgM deposits identified by immunofluorescence (n=1), and epineural lymphocyte infiltrate without precision (n=1).

Associated hematologic and non-hematologic malignancies

All patients (n=45) harbored a monoclonal IgM gammopathy detected by immunofixation. The monoclonal light chain was kappa in 19/45 (42%) and lambda in 21/45 (49%) patients. Five patients had both monotypic kappa and lambda IgM. The median peak value was 2.6 g/L (range, 0.1-40). Cold agglutinins were identified in 15 out of the 44-screened cases (34%) but their specificity was not available in most cases. None had active hemolysis.

Overt associated hematologic malignancies were identified in 16 patients (36%). These diagnoses were made before, after or were concomitant to those of CANOMAD/CANDA in respectively four (25%), four (25%), and eight (50%) patients. One patient required treatment for B-cell malignancy before CANOMAD/CANDA diagnosis. The most frequent associated hematologic malignancy was Waldenström macroglobulinemia (WM) (n=9, 20%). Other documented hematologic neoplasms included diffuse large B-cell lymphoma (n=2, 4%, including one transformation of WM), monoclonal B lymphocytosis (n=2, 4%), chronic lymphocytic leukemia (n=1, 2%), marginal zone lymphoma (MZL) (n=1, 2%), unclassifiable small B-cell lymphoma (n=1, 2%) and mantle cell lymphoma (n=1, 2%) (**Table 2**). Clinical characteristics of CANOMAD/CANDA were largely similar between patients with or without an overt associated hematologic malignancy, notably in terms of ocular or bulbar involvement and degree of disability, and were no significantly associated with the level of IgM peak value (**Supplemental Table S1, S1bis and S1 ter**).

Three patients developed solid tumors during their follow-up, i.e. bronchopulmonary cancer (n=2) and glioblastoma (n=1). These diagnoses were concomitant in one case and largely posterior to those of CANOMAD/CANDA in two cases (6 and 18 years).

Treatment and outcomes

Forty-one (91%) patients received treatment for CANOMAD/CANDA, including two patients treated by CHOP regimen for concomitant symptomatic hematologic malignancy. Among the four patients that did not receive treatment, three had minor symptoms (modified Rankin score of 1) and a very indolent course with a follow-up of more than 5 years each. One patient had a very aggressive and disabling CANOMAD syndrome revealed by acute respiratory distress secondary to phrenic paralysis and died within a few weeks due to pulmonary complications.

The median number of therapeutic lines was two (mean, 3.0; range, 1-7), corresponding to a cumulative number of 135 lines of treatment for the whole cohort. The median delay between CANOMAD/CANDA diagnosis and initiation of treatment was 4 months (range, 0-168). First-line treatment consisted in IVIg (n=20/41, 49%), corticosteroids (n=11/41, 27%), plasma exchange (PE) (n=3/41, 7%), chlorambucil (n=3/41, 7%), CHOP regimen (n=2/41, 5%), azathioprine (n=1/41, 2%) or rituximab (n=1/41, 2%) (**Table 3**). Of note, clinical characteristics, especially regarding the degree of disability before treatment, were similar between the two largest groups of first-line treatment (IVIg and corticosteroids) (data not shown). Overall clinical response was obtained in 18 (44%) patients, including four (10%) CR and 14 (34%) PR, while stable disease and progression were respectively observed in seven (17%) and 16 (39%) cases (**Table 3 and Supplemental Figure S1)**. Type of first-line treatment impacted quality of response as overall clinical responses were obtained in 60% of patients treated by IVIg and in only one patient (10%) with corticosteroids, correlating with a respective median decrease of 1 point (range, +1 to -4) and increase of 1 point (range, 0 to +2) in modified Rankin score.

Thirteen patients (32%) received only one line of treatment, which consisted in IVIg (n=9), single agent rituximab (n=1), plasma exchange (n=1) and CHOP regimen (n=1). Median time to next treatment was respectively 23 (range, 1-101) and 35 months (range, 4-101) for the whole cohort and first-line IVIg (**Supplemental Figure S3B** and **C**).

Different types of therapies used in first and subsequent lines of treatment (n=135) are summarized in **Table 4**. The most frequently used treatments were IVIg (n=55/135, 41%), rituximab-based regimens (n=19, 14%), corticosteroids (n=14, 10%), immunosuppressive therapies (n=14, 10%), plasma exchange (n=8, 6%), chlorambucil (n=6, 4%), and other chemotherapy regimens (n=5, 4%). While IVIg and rituximab-based regimens were associated with overall clinical responses of respectively 53 and 52%, corticosteroids and immunosuppressive therapies were largely ineffective with respectively 14 and 0% of overall clinical responses (**Table 4 and Supplemental Figure S2**).

With a median follow-up time from the onset of neurological symptoms of 127 months (range, 1-434) for the whole cohort, 30 (65%) patients were still alive at their last follow-up. The median OS of our cohort was not reached (range, 0.16-31 years) (**Supplemental Figure S3A**). Deaths were related to CANOMAD/CANDA, hematologic malignancies or other causes in respectively five (33%), three (20%) and seven (47%) cases. Others causes included progressive solid tumors (n=3, comprising the aforementioned bronchopulmonary cancer [n=2] and glioblastoma [n=1]), infectious (n=2) and cardiovascular (n=2) complications.

Rituximab-based regimens

Nineteen patients were treated with a regimen including rituximab, in first-line (n=1) or subsequent lines of treatment (n=18). Five patients received a rituximab-based regimen twice or more. The median line of treatment of rituximab-based regimens was three (range, 1-7). Tolerance of rituximab was excellent with the exception of one anaphylactic shock that resolved after corticosteroid therapy. No IgM flare was reported.

Rituximab-based regimens consisted in rituximab monotherapy (n=13), immunochemotherapy (ICT) combination (n=4) (rituximab-fludarabine, n=2; rituximab-cyclophosphamide-dexamethasone, n=2) or other regimens (rituximab-ibrutinib, n=1; rituximab-corticosteroids, n=1). ICT was used in patients with an overt hematologic malignancy (WM, n=3; MZL, n=1). Five patients were retreated with a second course of single-agent rituximab upon disease progression. This rechallenge led to similar or improved clinical responses. Biological responses to rituximab-based regimens were available or interpretable (pre-treatment IgM peak value above 0.5 g/L) in 14/19 cases, correlated well to clinical responses and were distributed as follows: two CR (corresponding to one clinical CR and one clinical PR), six PR (corresponding to five clinical PR and one clinical PR), five SD (corresponding to four clinical SD and one clinical progression) and one progression (corresponding to one clinical progression) (**Figure 1** and **Supplemental Table S2**). Considering first-use of rituximab-based regimens (n=14), median time to next treatment was 45 months (range, 2-100) (**Supplemental Figure S3D**).

Five additional patients received both single agent rituximab and IVIg that precluded single evaluation of each drug efficacy (**Table 3**).

Discussion

To our knowledge, this is the largest retrospective series of CANOMAD/CANDA available to date. In this series, we confirmed many of the already published clinical features, extended our knowledge of different clinical presentations, characterized the spectrum of associated hematologic malignancies and highlighted IVIg and rituximab-based regimens efficacy.

Consistent with previous studies, most patients were male, in the fifth decade of life and were disabled by sensory ataxia. However, even if sensory symptoms were predominant, they were not specific and clinical presentation in our series was less homogeneous than previously described[6]. Only 19/45 (42%) patients recapitulated all the features of CANOMAD. Ophthalmoplegia was only observed in 44% and severe forms (modified Rankin score of 4-5) were not rare (27%). Also, in keeping with others studies, all patients had anti-ganglioside antibodies with IgM specificity, reacting against GD1b, GD3, GT1b or GQ1b, and around half of the cohort had antibodies directed against these four disialosyl epitopes, emphasizing that they are key biological elements for diagnosis. All the data mentioned above plead for a more extensive entity that the acronym CANDA (chronic ataxic neuropathy with disialosyl antibodies) could better encompass, as previously suggested[8]. From a practical point of view, CANOMAD/CANDA must be suspected in case of sensory symptoms associated with ocular or bulbar motor disorders but also in case of isolated sensory forms especially if: i) there is ataxia (present in half of cases), ii) the disease progresses in flare-ups, and/or iii) anti-MAG antibodies are negative. This also emphasizes the need for cooperation between hematologist and neurologist in difficult cases.

This study is the first to describe comprehensively the spectrum of hematologic malignancies associated with CANOMAD/CANDA. All patients had detectable serum monoclonal IgM. Although no monotypic light chain predominance was observed, there is a possible bias toward lambda expression (49%) in our cohort in comparison to the 70-80% of monotypic kappa expression usually reported in IgM MGUS[33]. As anticipated by the presence of monoclonal IgM, the identified associated hematologic malignancies were B-cell lymphoproliferative disorders, which accounted for around one third of the cohort and mainly consisted of WM (56%). Of note, only 31 (69%) patients of our cohort had bone marrow examination, possibly underestimating the proportion of patients with overt associated hematologic malignancy.

Clinical features of CANOMAD/CANDA can precede, be concurrent to or appear during follow-up of a previously treated hematologic malignancy. The clinical course was highly variable with some patients being wheelchair users after few months despite therapeutic intervention and others remaining mobile after more than 10 years of follow-up without any treatment. Treatments used in our CANOMAD/CANDA series were very heterogeneous (> 10) but most of them corresponded to those used in chronic inflammatory demyelinating polyneuropathy (CIDP). Indeed, as for CIDP, IVIg and corticosteroids (31/41, 75%) represented the most frequent first-line treatments. Global overall clinical responses to first-line treatment in our cohort was 44% and was mostly seen in patients treated with IVIg (60%). Efficacy rate of IVIg was in accordance with those reported in previous studies in CIDP (40-60%)[34] and CANOMAD/CANDA (55-68%)[7,23]. Of note, the efficacy of IVIg was similar whether used as first-line treatment or in the relapse/refractory setting, with overall clinical responses obtained in around half of the cases. In contrast to its observed efficacy in CIDP (40-60%)[34] and previous experiences in CANOMAD/CANDA (30-50%)[7,23], corticosteroids were very rarely effective (13%) in our series. Although less frequently used, plasma exchange efficacy was also similar to previous reports with clinical responses observed in 40-50% of cases.

Considering the constant presence of a monoclonal IgM that produces the anti-ganglioside antibody activity and recapitulates clinical features, CANOMAD/CANDA should be considered as a neurological subtype of MGCS[1]. In this regard, our data highlighted the benefit of targeting the B-cell clone in CANOMAD/CANDA as it is already done in other types of MGCS. Rituximab-based regimens showed an efficacy rate of 53%, similar to the one observed with IVIg. They were mostly used in second or subsequent lines of treatment in patients that already experimented IVIg. Efficacy of rituximab-based regimens was comparable in patients with or without an associated hematologic malignancy. These results are in line with the efficacy reported with rituximab in anti-MAG neuropathy[35,36] and in non-CANOMAD/CANDA CIDP associated with hematologic malignancies[37].

This study has limitations due in part to its retrospective design encompassing a long period of time. Data is lacking regarding delay of response to treatment, preventing us from drawing conclusions as to which treatment could be better suited to patients with rapidly progressive disease. Additionally, clinical evaluation was not centrally reviewed, although all patients were followed up in CANOMAD neurological reference centers.

Several questions remain unanswered about the management of CANOMAD/CANDA patients. Further studies will determine if rituximab can allow safe withdrawal of IVIg in responding but dependent patients. For patients whose response to rituximab is insufficient, immunochemotherapy with adjunction of alkylating agents may improve outcomes obtained with single agent rituximab, as it has been reported for anti-MAG neuropathy[38]. Alternatively, more recently developed targeted B-cell drugs such as BTK and BCL2 inhibitors, that have demonstrated clinical efficacy in treatment of WM and other B-cell lymphoproliferative disorders[39,40], could be of potential benefit.

Based on our cohort and systematic analysis of the literature, we propose a therapeutic algorithm for CANOMAD/CANDA management (**Figure 2**). First-line IVIg treatment appears to be the most efficient and validated therapeutic option. IVIg refractory or relapsed forms require rituximab-based regimens as single-agent or in association with alkylating agents. IVIg rechallenge could be proposed in case of long-lasting remission after first-line IVIg treatment.

In conclusion, CANOMAD/CANDA is a rare, frequently debilitating and probably underdiagnosed syndrome, which is associated with an overt hematologic malignancy, mainly WM, in one third of patients. IVIg and rituximab-based regimens are the most effective therapies. Corticosteroids and immunosuppressive drugs should not be used. Similar to anti-MAG neuropathy, CANOMAD/CANDA should be considered as neurological subtype of MGCS and therefore could benefit from B-cell directed therapies. More studies are warranted to better characterize the correlation between clinical and biological responses and define the optimal therapeutic options and sequence.

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Tables

Table 1. Main clinical and electrophysiological characteristics of CANOMAD/CANDA patients.

Characteristics	No. (%)	
Total	45 (100)	
Male	35 (78)	
Age at CANOMAD/CANDA diagnosis, years		
Median (range)		62 (38-81)
Time from onset of symptoms to CANOMAD/CANDA diagnosis, years		
Median (range)		4 (0.1-27)
Type of onset		
Acute	8 (18)	
Subacute (rapidly progressive)	7 (15)	
Chronic (slowly progressive)	30 (67)	
Neurological symptoms at diagnosis		
Sensory symptoms	35 (78)	
Paresthesia	26 (58)	
Ataxia	21 (47)	
Ophthalmoplegia	6 (13)	
Bulbar symptoms	3 (7)	
Others	14 (31)	
Painful limb	6 (13)	
Motor weakness/myoclonus	3 (7)	
Acrocyanosis/livedo	2 (4)	
Dyspnea	1 (2)	
Facial nerve paralysis	1 (2)	
Neurological symptoms during the course of the disease		
Sensory ataxia	34 (76)	
Paresthesia	35 (78)	
Hypoesthesia	42 (93)	
Upper and lower limbs	24 (53)	
Lower limbs only	18 (40)	
Ophthalmoplegia	20 (44)	
Bulbar symptoms	6 (13)	

Motor weakness	18 (40)
Upper and lower limbs	13 (29)
Lower limbs only	5 (11)
Areflexia	42 (93)
Facial nerve paralysis	3 (7)
Dysautonomic signs	2 (4)
Acute respiratory distress	3 (7)
Modified Rankin score at diagnosis	/42
0 (asymptomatic)	0 (0)
1 (symptomatic but no significant disability)	15 (36)
2 (slight disability)	8 (19)
3 (moderate disability)	7 (17)
4 (moderately severe disability)	10 (24)
5 (severe disability)	2 (5)
Electrophysiological findings, pattern	
Demyelinating	27 (60)
Axonal	12 (27)
Normal	6 (3)
Type of evolution	
Relapsing-remitting	14 (31)
Chronic progressive	30 (67)
Isolated symptomatic flare-up	1 (2)

Table 2. Hematologic neoplasms associated with CANOMAD/CANDA syndrome.

	No. (%)
Monoclonal gammopathy	45 (100)
IgM	45 (100)
kappa	19 (42)
lambda	21 (49)
kappa and lambda	5 (11)
Associated hematologic malignancies	17 (38)
Waldenström macroglobulinemia	9 (20)
Diffuse large B-cell lymphoma	2 (4)
Monoclonal B lymphocytosis	2 (4)
Marginal zone lymphoma	1 (2)
Chronic lymphocytic leukemia	1 (2)
Unclassifiable small B-cell lymphoma	1 (2)
Mantle cell lymphoma	1 (2)

Table 3. First-line therapies and clinical responses.

		Clinical responses, n (%)			
First-line	**n**	**CR**	**PR**	**SD**	**Progression**
IVIg	20	4 (20)	8 (40)	6 (35)	2 (10)
Corticosteroids	11	0 (0)	1 (10)	0 (0)	10 (90)
Chlorambucil	3	0 (0)	1 (33)	0 (0)	2 (67)
Plasma exchange	3	0 (0)	2 (67)	0 (0)	1 (33)

CHOP regimen	2	0 (0)	1 (50)	0 (0)	1 (50)
Azathioprine	1	0 (0)	0 (0)	1 (100)	0 (0)
Rituximab	1	0 (0)	1 (100)	0 (0)	0 (0)
Total	41	4 (10)	14 (34)	7 (17)	16 (39)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease

Table 4. Therapies used in first-line and subsequent lines of treatment and clinical responses

		Clinical responses, n (%)			
All lines of treatment	**n**	**CR**	**PR**	**SD**	**Progression**
IVIg	**55**	**5 (9)**	**24 (44)**	**16 (29)**	**10 (18)**
IVIg and rituximab	7	1 (14)	1 (14)	4 (58)	1 (14)
Rituximab-based regimens	**19**	**3 (16)**	**7 (36)**	**6 (32)**	**3 (16)**
Monotherapy	13	1 (8)	6 (46)	4 (31)	2 (15)
Rituximab, cyclophosphamide	2	0 (0)	1 (50)	0 (0)	1 (50)
Rituximab, fludarabine	2	1 (50)	0 (0)	1 (50)	0 (0)
Rituximab, corticoids	1	1 (100)	0 (0)	0 (0)	0 (0)
Rituximab, ibrutinib	1	0 (0)	0 (0)	1 (100)	0 (0)
Corticosteroids	**15**	**0 (0)**	**2 (13)**	**2 (13)**	**11 (74)**
Immunosuppressive therapies	**15**	**0 (0)**	**0 (0)**	**4 (27)**	**11 (73)**
Azathioprine	6	0 (0)	0 (0)	2 (33)	4 (67)
Cyclophosphamide	6	0 (0)	0 (0)	2 (33)	4 (67)
Cyclosporine	1	0 (0)	0 (0)	0 (0)	1 (100)
Mycophenolate mofetil	1	0 (0)	0 (0)	0 (0)	1 (100)
Methotrexate	1	0 (0)	0 (0)	0 (0)	1 (100)
Plasma exchange	**10**	**1 (10)**	**3 (30)**	**0 (0)**	**6 (60)**
Chlorambucil	**9**	**0 (0)**	**3 (33)**	**0 (0)**	**6 (67)**
Other chemotherapy regimens	**5**	**0 (0)**	**2 (67)**	**1 (33)**	**0 (0)**
CHOP	3	0 (0)	1 (100)	0 (0)	0 (0)
Fludarabine, cyclophosphamide	1	0 (0)	1 (100)	0 (0)	0 (0)
Ibrutinib	1	0 (0)	0 (0)	1 (100)	0 (0)
Total	135	10 (8)	42 (32)	33 (25)	48 (35)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease

Figure legends

Figure 1. Evaluation of clinical responses (bottom) according to biological responses (top) for patients that received rituximab-based regimens. CR, complete response; PR, partial response; SD, stable disease. Fourteen patients were evaluable for biological response (see **Supplemental Table S2**).

Figure 2. Therapeutic algorithm for CANOMAD/CANDA management. CR, complete response; IVIg, intravenous immunoglobulin; PE, plasma exchange; PR, partial response; SD, stable disease.

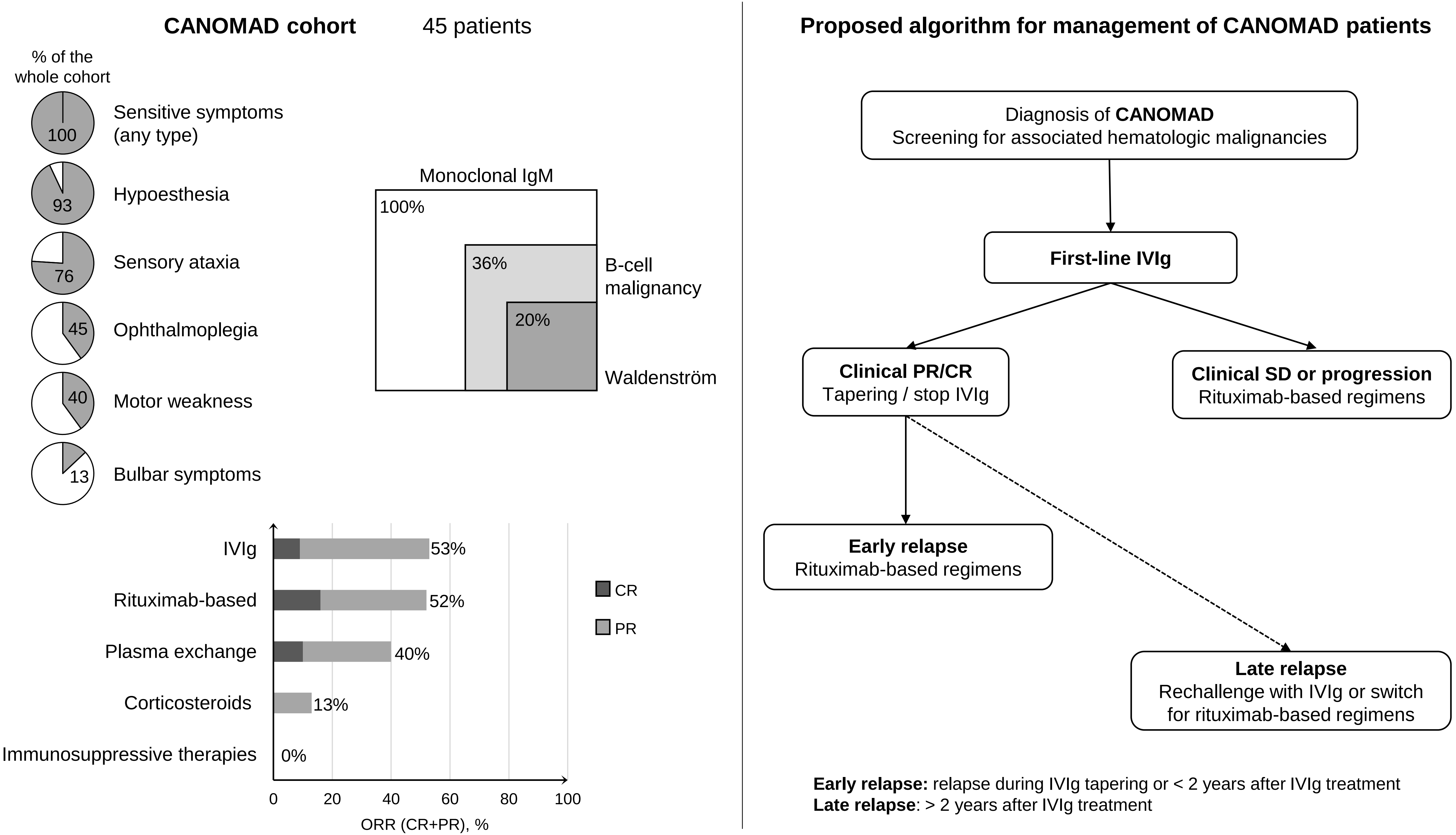
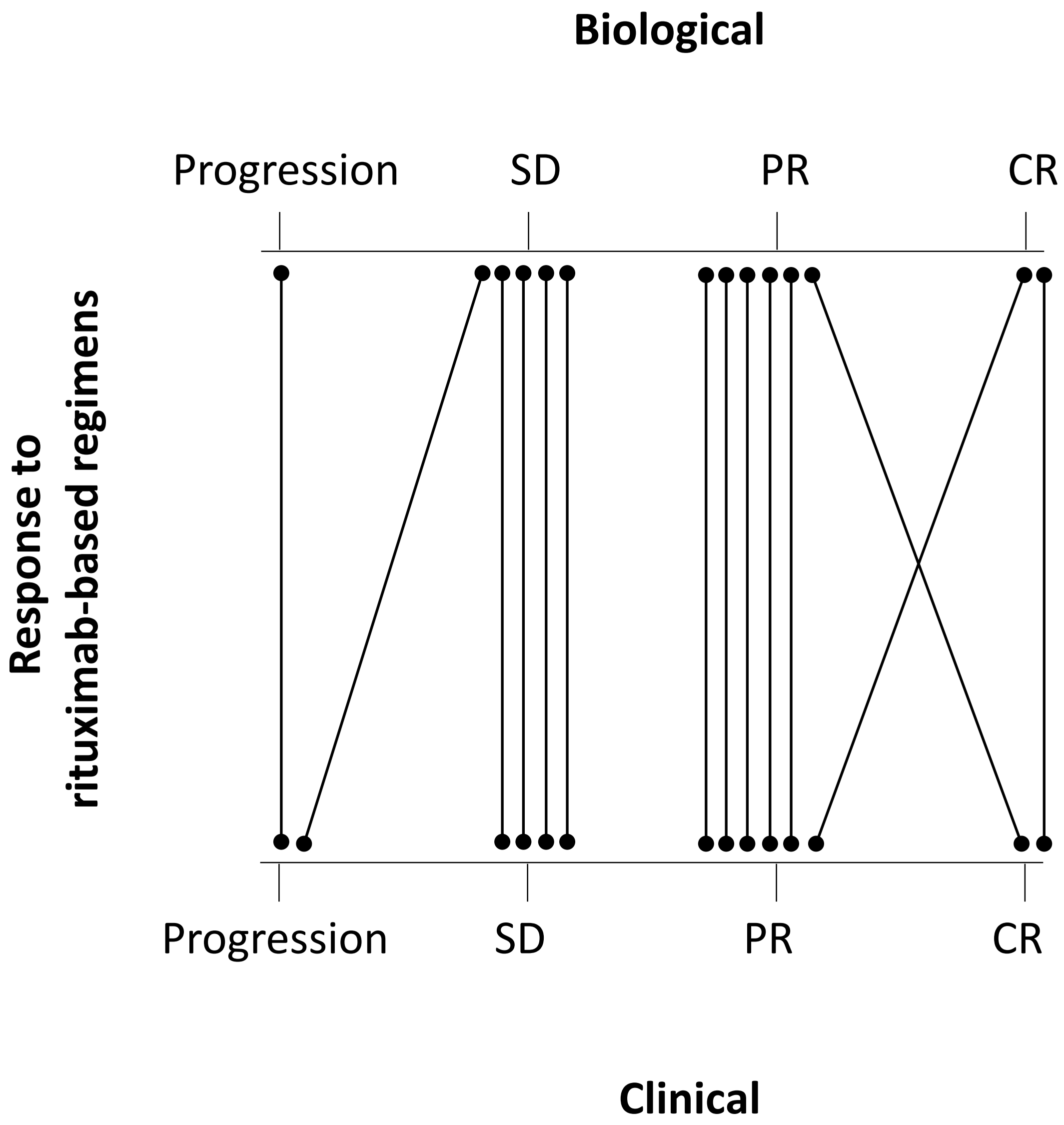
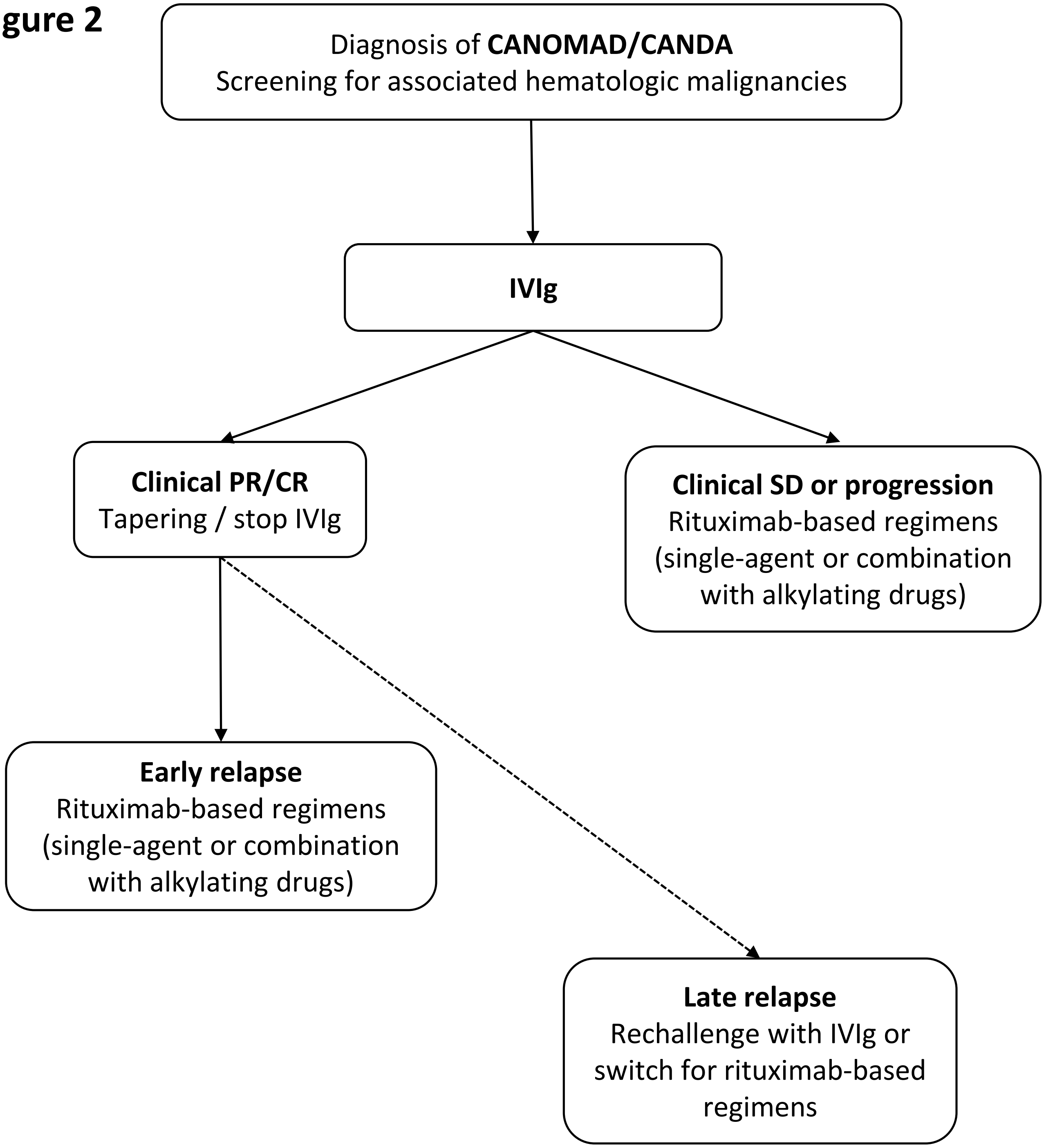

CANOMAD cohort
45 patients
% of the whole cohort
100
Sensitive symptoms (any type)
93
Hypoesthesia
76
Sensory ataxia
45
Ophthalmoplegia
40
Motor weakness
13
Bulbar symptoms
Monoclonal IgM
100%
36%
B-cell malignancy
20%
Waldenström
IVIg
53%
Rituximab-based
52%
Plasma exchange
40%
Corticosteroids
13%
Immunosuppressive therapies
0%
CR
PR
0
20
40
60
80
100
ORR (CR+PR), %
Proposed algorithm for management of CANOMAD patients
Diagnosis of CANOMAD
Screening for associated hematologic malignancies
First-line IVIg
Clinical PR/CR
Tapering / stop IVIg
Clinical SD or progression
Rituximab-based regimens
Early relapse
Rituximab-based regimens
Late relapse
Rechallenge with IVIg or switch for rituximab-based regimens
Early relapse: relapse during IVIg tapering or < 2 years after IVIg treatment
Late relapse: > 2 years after IVIg treatment

Figure 1



Biological
Progression
SD
PR
CR
Response to
rituximab-based regimens
Progression
SD
PR
CR
Clinical

Figure 2



Early relapse: relapse during IVIg tapering or < 2 years after IVIg treatment
Late relapse: > 2 years after IVIg treatment