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Chapter 2

Effective treatment of
Bing Neel Syndrome with
oral fludarabine: A case series of
4 consecutive patients

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Direct central nervous system (CNS) involvement of Waldenstrom macroglobulinaemia (WM) is very rare and is referred to as Bing-Neel syndrome (BNS) (Bing & Neel, 1936; Ly et al, 2011). The incidence of BNS is unknown, but in a retrospective cohort of 1523 WM patients, only 13 patients with BNS were identified. (Kulkarni et al, 2013). The prognosis has typically been poor. Less than 50 cases have been published, mostly in a setting of relapsed WM (Malkani et al, 2010; Abdallah et al, 2013; Poulain et al, 2014). There is no consensus on the best treatment strategy and, thus far, there are no systematic reports on treatment in Bing-Neel Syndrome. Purine analogues (fludarabine, cladribine) are widely used and considered very effective in the treatment of WM (Leblond et al, 2013). Fludarabine is thought to cross the blood-brain barrier based on animal studies, and has induced remissions in CNS involvement of B-CLL. (Knop et al, 2005) There is only one published case of BNS treated with cladribine with good clinical effect (Richards, 1995). These considerations indicate that oral purine analogue therapy may be a promising option for BNS. We report our experience with fludarabine-based treatment in four consecutive patients with five episodes of BNS.

All consecutive BNS patients presenting at the University Medical Centre Utrecht between 2009 and 2013 were included in this study and all were treated with oral fludarabine-based therapy. Treatment consisted of six cycles of oral fludarabine 40 mg/m² on Days 1–5. Rituximab was given at a dose of 375 mg/m² i.v. on Day 1, in a 28-day cycle. The diagnosis of BNS was based on cytology and immunophenotyping of cerebrospinal fluid (CSF), Magnetic Resonance Imaging (MRI) and demonstration of WM in the bone marrow. Neurosurgical biopsy was not performed if CSF cytology and/or immunophenotyping were positive for WM cells. Data on response were collected based on a combination of haematological response [bone marrow sampling, detection of IgM M-protein in serum; (Owen et al, 2013)] and neurological response (CSF sampling, repeated MRI scan, functional improvement).

The clinical characteristics of the four patients are summarized in **Table I**. In all patients, BNS was the presenting symptom of WM. The treatment was generally well tolerated and no serious adverse events occurred, with the exception of a grade 3 reversible neutropenia (according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4) in Patient one after the second cycle of fludarabine.

Patient one presented with a 1-year history of symptomatic tonic-clonic seizures and cognitive complaints. She was first treated with i.t. methotrexate (MTX) without response. Monotherapy with oral fludarabine resulted in a complete remission (CR) of both the BNS and WM in the bone marrow and a full neurological recovery. BNS and WM relapsed 5 years later, with complaints of double vision. Treatment with rituximab-fludarabine resulted in a second haematological and neurological partial remission (PR), with residual slight cognitive disturbances. A second relapse 2 years later was refractory to rituximab-cladribine. The patient achieved a third CR following radiotherapy (40 Gy)

and remained in a stable clinical condition for 10 years after BNS was first diagnosed. She died due to a traumatic subdural haematoma.

Patient two presented with bradyphrenia, dysarthria and a rapidly progressive tetraparesis. He was treated with rituximab- fludarabine combined with i.t MTX (15 mg). A haematological CR combined with an impressive and fast full neurological recovery was reached: after only one cycle he went from tetraplegic to fully ambulatory. The MRI response for this patient is shown in **Fig 1**. On neurological examination only a slight bipyramidal syndrome remained. He has remained stable since then, with a follow-up of 3.5 years.

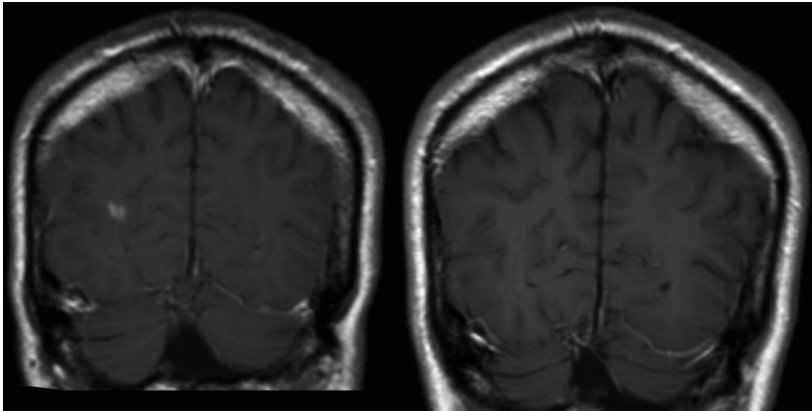


Figure 1: Brain MRI before and after treatment (patient 2)

Left image: coronal T1-weighted image with gadolinium at diagnosis demonstrate focal enhancement of the subcortical white matter; Right image: coronal T1-weighted image demonstrate resolution of areas of enhancement

Patient three presented with a 5-year history of mild paresthesias in the hands. IgM-related polyneuropathy was excluded based on the neurological evaluation. The CSF demonstrated infiltration of monotypic B cells. Treatment with rituximab-fludarabine resulted in a haematological PR with neurological improvement. She has remained stable since then, with a follow-up of 1.5 years.

Patient four presented with a bilateral paresis of the upper extremity. Treatment with rituximab-fludarabine resulted in a haematological PR and clear neurological improvement. She has remained stable with a follow-up of 1.5 year.

To our knowledge this is the first consecutive case series of patients with BNS treated with a systematic therapeutic approach. There is no established first-line therapy for BNS. Based on the available case reports, i.t. MTX alone does not seem to be very effective, as was also the case in Patient 1. Radiotherapy seems effective in reversing neurological symptoms and achieving a MRI response, but there is concern about the long-term

Table 1. Characteristics of BNS patients.

Case	Age (years)/ Sex	Previous medical history	Symptoms	IgM paraprotein-aemia (g/l)	Bone marrow localization of WM	MRI results at diagnosis	CSF leucocyte-count (x10 ⁶ /l)/ Total protein (TP; g/l)	CSF cytology	CSF flowcytometry	Treatment	BNS response	WM response
1a	62/F	None	Cognitive decline, epilepsy	16	Yes	Meningeal enhancement	L 5.7/TP 0.76	Suspect	Positive	6x fludarabine	CSF and MRI; CR	CR
1b	67		Diplopia	4.5	Yes	White matter abnormalities, hyperintense T2 FLAIR lesions, meningeal enhancement	L 35/TP 0.61	Suspect	Positive	6x rituximab-fludarabine	CSF and MRI; CR. Clinical; partial recovery	PR
2	41/M	None	Bradyphrenia, dysarthria and tetraparesis	17	Yes	Cerebral and spinal white matter lesions	L 177/TP 0.95	Suspect	Failed	6x rituximab-fludarabine +5x MTX i.t.	CSF and MRI; CR. Clinical; full recovery	CR
3	70/F	Breast cancer: surgical treatment	Paresthesias	8.5	Yes	No abnormalities	L 62/TP 3	Suspect	Positive	6x rituximab-fludarabine	CSF CR. Clinical; full recovery	PR
4	58/F	Breast cancer surgery, radiotherapy, chemohormonal therapy	Bilateral paresis of upper extremity	4	Yes	No abnormalities	L 2/TP 0.4	Negative	Positive	6x rituximab-fludarabine	CSF; CR. Clinical; partial recovery	PR

BNS, Bing-Neel Syndrome; WM, Waldenström's Macroglobulinaemia; MRI, magnetic resonance imaging; CSF, central nervous system; F, female; M, male; T2 FLAIR, T2-weighted fluid attenuated inversion recovery; L, leucocytes; TP, total protein; MTX, methotrexate; CR, complete remission; PR, partial remission.

neurotoxicity and it also leaves the WM activity in the bone marrow untreated. High dose systemic chemotherapy using MTX and cytarabine, analogous to the treatment of the aggressive primary CNS lymphoma, has led to good responses, including CRs lasting from several months to several years. Due to publication bias, these incidental case reports could overestimate the therapeutic effect. In the only available retrospective case series of BNS, seven patients were treated with high-dose MTX, of whom only two responded. (Kulkarni et al, 2013). Compared to high-dose therapy, low-dose fludarabine has the advantage of a favourable toxicity profile and oral availability. There are concerns regarding the long-term toxic effects of purine analogues; however, this was not confirmed in a recent large randomized trial in WM (Leblond et al, 2013), and the follow-up in our patients is too short to comment on this. Of importance, all patients cleared their CSF monoclonal B-cells, three of them without intrathecal or high dose therapy. This suggests that low-dose fludarabine has the capacity to penetrate the CNS compartment. Despite uncertainty about the ability of rituximab to cross the blood-brain-barrier, data in patients with aggressive CNS lymphoma have shown that it does have clinical activity. In addition, rituximab is a known active agent in the control of systemic WM activity. In conclusion, we demonstrated that low dose oral fludarabine- based therapy is effective and well tolerated in patients with BNS. We propose that rituximab-fludarabine should be considered as a first-line treatment option for BNS patients.

Author contributions: All authors have made substantial contributions to design of this case series, drafting and/or revising the paper and approved of all submitted versions. JMIV helped in design of the study, data collection and wrote the paper. MJK helped in design of the study and critically revising the paper. WK helped with data collection and critically revised the paper. ONG and CL helped with data collection and writing the paper. STP helped with data collection and critically revised the paper. MCM helped in design of the study, data collection and writing the paper

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