Effective treatment of Bing-Neel Syndrome with oral fludarabine: a case series of four consecutive patients

Direct central nervous system (CNS) involvement of Waldenström 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/m^2 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.

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 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 lead to good responses, including CRs

Table I. Characteristics of BNS patients.

Case	Age (years)/Sex	Previous medical history	Symptoms	IgM para-proteinaemia (g/l)	Bone marrow localization of WM	MRI results at diagnosis	CSF leucocyte count ($\times 10^6$/l)/TP (g/l)	CSF cytology	CSF flow-cytometry	Treatment	BNS response	WM response
1a	62/F	None	Cognitive decline, epilepsy	16	Yes	Meningeal enhancement	L 57/TP 0.76	Suspect	Positive	6x fludarabine	CSF and MRI: CR Clinical; full recovery	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, dysartria and tetraparesis	17	Yes	Cerebral and spinal white matter lesions	L177/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 treatment; surgery, radio-therapy, 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 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.

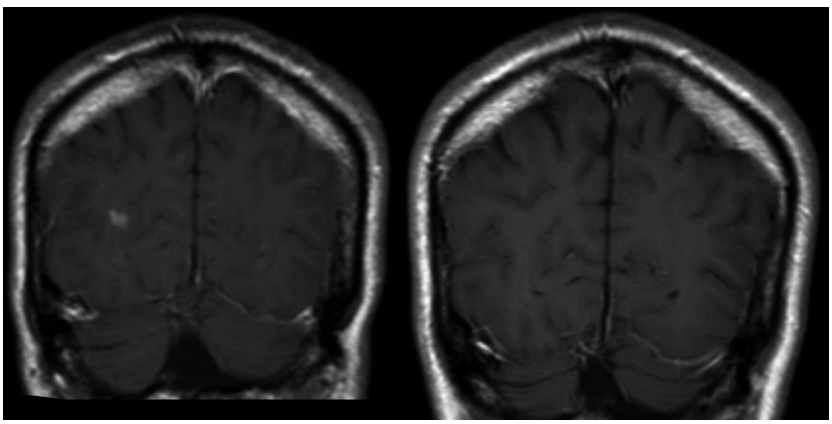

Fig 1. Brain MRI before and after treatment (Patient 2) Left image: coronal T1-weighted image with gadolinium at diagnosis demonstrating focal enhancement of the subcortical white matter; Right image: coronal T1-weighted image demonstrating resolution of areas of enhancement.

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. Josephine MI Vos helped in design of the study, data collection and wrote the paper. Marie Jose Kersten helped in design of the study and critically revising the paper. Willem Kraan helped with data collection and critically revised the paper. Onno N Groeneveld helped with data collection and writing the paper. Cisca Linn helped with data collection and writing the paper. Steven T Pals helped with data collection and critically revised the paper. Monique C Minnema helped in design of the study, data collection and writing the paper.

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References

Abdallah, A.O., Atrash, S., Muzaffar, J., Abdallah, M., Kumar, M., Van Rhee, F. & Barlogie, B. (2013) Successful treatment of Bing-Neel syndrome using intrathecal chemotherapy and systemic combination chemotherapy followed by BEAM auto-transplant: A case report and review of literature. *Clinical Lymphoma, Myeloma & Leukemia*, **13**, 502–506.

Bing, J. & Neel, A. (1936) Two cases of hyperglobulinemia with affection of the central nervous system on a toxi-infection. *Acta Medica Scandinavica*, **88**, 492–506.

Knop, S., Herrlinger, U., Ernemann, U., Kanz, L. & Hebart, H. (2005) Fludarabine may induce durable remission in patients with leptomeningeal involvement of chronic lymphocytic leukemia. *Leukemia & Lymphoma*, **46**, 1593–1598.

Kulkarni, T., Treon, S.P., Manning, R., Xu, L., Rinne, M., Lee, E.Q., Ghobrial, I.M., Norden, A., Kluk, M.J. & Nayak, L. (2013). Clinical characteristics and treatment outcome of CNS involvement (Bing-Neel Syndrome) in Walden-

strom's macroglobulinemia. *Blood* (ASH Annual Meeting Abstracts) **122**, 5090 (meeting abstract)

Leblond, V., Johnson, S., Chevret, S., Copplestone, A., Rule, S., Tournilhac, O., Seymour, J.F., Patmore, R.D., Wright, D., Morel, P., Dilhuydy, M.S., Willoughby, S., Dartigeas, C., Malphettes, M., Royer, B., Ewings, M., Pratt, G., Lejeune, J., Nguyen-Khac, F., Choquet, S. & Owen, R.G. (2013) Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. *Journal of Clinical Oncology*, **31**, 301–307.

Ly, K.I., Fintelmann, F., Forghani, R., Schaefer, P.W., Hochberg, E.P. & Hochberg, F.H. (2011) Novel diagnostic approaches in Bing-Neel syndrome. *Clinical Lymphoma Myeloma & Leukemia*, **11**, 180–183.

Malkani, R.G., Tallman, M., Gottardi-Littell, N., Karpus, W., Marszalek, L., Variakojis, D., Kaden, B., Walker, M., Levy, R.M. & Raizer, J.J. (2010) Bing-Neel syndrome: an illustrative case and a comprehensive review of the published literature. *Journal of Neuro-Oncology*, **96**, 301–312.

Owen, R.G., Kyle, R.A., Stone, M.J., Rawstron, A.C., Leblond, V., Merlini, G., Garcia-Sanz, R., Ocio, E.M., Morra, E., Morel, P., Anderson, K.C., Patterson, C.J., Munshi, N.C., Tedeschi, A., Joshua, D.E., Kastritis, E., Terpos, E., Ghobrial, I.M., Leleu, X., Gertz, M.A., Ansell, S.M., Morice, W.G., Kimby, E. & Treon, S.P. (2013) VIth International Workshop on Waldenström macroglobulinaemia Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. *British Journal of Haematology.*, **160**, 171–176.

Poulain, S., Boyle, E.M., Roumier, C., Demarquette, H., Wemeau, M., Geffroy, S., Herbaux, C., Bertrand, E., Hivert, B., Terriou, L., Verrier, A., Pollet, J.P., Maurage, C.A., Onraed, B., Morschhauser, F., Quesnel, B., Duthilleul, P., Preudhomme, C. & Leleu, X. (2014) MYD88 L265P mutation contributes to the diagnosis of Bing Neel syndrome. *British Journal of Haematology*, **167**, 506–513.

Richards, A.I. (1995) Response of meningeal Waldenström's macroglobulinemia to 2-chlorodeoxyadenosine. *Journal of Clinical Oncology.*, **13**, 2476.

A rapid test (STic Expert®) for the diagnosis of heparin-induced thrombocytopenia

We read with great interest the recently published report (Leroux *et al*, 2014) on the evaluation of a rapid nano-particle based flow immunoassay (STic Expert® HIT) for the diagnosis of heparin-induced thrombocytopenia (HIT). The diagnosis of HIT is very difficult and relies on clinical and laboratory data. The prognosis depends on the early recognition of the disorder, and as this adverse drug reaction causes great mortality, it is extremely important that initial HIT screening methods have an optimal sensitivity.

We would like to report our results from a similar study. We collected citrated plasma samples of 153 patients suspected with HIT between May 2006 and January 2014 (stored at −80°C).

Samples were thawed at 37°C in a warm water bath before analysis with STic Expert® HIT (Diagnostica Stago, Asnières sur Seine, France) and enzyme-linked immonosorbent assay (ELISA; Asserachrom® HPIA IgG; Diagnostica Stago), according to the manufacturer's instructions. Results for STic Expert® HIT were read by three readers and confirmed with a flow-cytometric CD62p (p-selectin) functional assay (Tomer, 1997; Tomer *et al*, 1999; Denys *et al*, 2008), which identified 20 HIT-positive samples (13·07%). For the ELISA, a cut-off was calculated for each run as advised by the manufacturer. The risk of HIT was estimated by the Warkentin 4T score (Greinacher & Warkentin, 2006) and accordingly classified as low, intermediate and high risk (Table I).

As described by Leroux *et al* (2014) we also found 2 HIT patients in the low risk group (4T score of 3 for both cases), indicating that HIT cannot be totally excluded by a low 4T score. As opposed to the report by Leroux *et al* (2014), our HIT cases did not include cardiac surgery patients but a patient receiving heparin therapy for port-a-cath®-related thrombosis and a patient receiving low molecular weight heparin after non-orthopaedic surgery.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for STic Expert® HIT and ELISA were determined using Bayesian analysis (MedCalc® Online diagnostic test calculator, http://www.medcalc.org/calc/diagnostic_test.php). The inter-reader agreement for STic Expert® HIT was calculated on the basis of kappa agreement (SPSS STATISTICS 22.0; IBM, Armonk, NY, USA and R: a language for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

Asserachrom® HPIA IgG showed an excellent sensitivity of 100·00% [95% confidence interval (CI) 83·01–100·00] and a good specificity of 80·45% [72·68–86·81]. PPV and NPV were 43·48% [28·94–58·89] and 100·00% [96·58–100·00] respectively.

The inter-reader reproducibility for STic Expert® HIT (kappa ratio) varied from 0·800 to 0·983 between readers. Overall Fleiss' kappa agreement between the three readers was 0·875. This is lower than that obtained by Leroux *et al* (2014). Sensitivity was 95·00% [75·05–99·17] for all readers and specificity for different readers varied from 83·46% [76·03–89·33] to 84·21% [76·88–89·95]. In our study, STic Expert® was negative for the 3 readers in 112 cases, but the diagnosis of HIT could only be excluded in 111. The sensitivity for this assay was therefore 95·00% [75·05–99·17] with a NPV of 99·15% [95·35–99·86], which is similar to the 99·6% reported by Leroux *et al* (2014) who attributed their only false negative result in the plasma sample group to a probable error of the operator by forgetting to add the patient sample to the cassette.

Our only false negative result was considered negative by the 3 readers. The sample concerned the earlier mentioned