

Bendamustine or Fludarabine based immunochemotherapy as treatment of Bing Neel syndrome:

A French retrospective study

Arthur Coste^{1,2}, Cécile Tomowiak³, Emmanuelle Ferrant⁴, Marine Baron¹, Brieuc Cherel⁵, Inès Boussen¹, Adrien Grenier¹, Daphné Krzisch¹, Véronique Morel¹, Sylvain Choquet¹, Pierre Boncoeur⁶, Karim Maloum⁶, Eric Durot², Elise Chapiro⁶, Marine Armand⁶, Nicolas Gower⁷, Lise Willems⁸, Pierre-Edouard Debureaux⁹, Faustine Lhomme¹⁰, Magali Le Garff-Tavernier⁶, Steeve Chevreux¹¹, Damien Roos-Weil¹

1. Service d'hématologie clinique, Hôpital Universitaire Pitié Salpêtrière-Charles Foix, AP-HP, Sorbonne Université, Paris, France

2. Service d'hématologie clinique, Hôpital Robert Debré, CHU de Reims, Université de Reims Champagne Ardenne, France

3. Service d'hématologie clinique, CHU de Poitiers, France

4. Service d'hématologie clinique, Hospices civiles de Lyon, France

5. Service d'hématologie clinique, CH de Bretagne, France

6. Service d'hématologie biologique, Hôpital Universitaire Pitié Salpêtrière-Charles Foix, AP-HP, Sorbonne Université, Paris, France

7. Service d'hématologie clinique, CHU de Lille, France

8. Service d'hématologie clinique, Hôpital Cochin APHP, Paris, France

9. Service d'hématologie clinique, Hôpital Saint Louis APHP, Paris, France

10. Service d'hématologie clinique, CHU de Rennes, France

11. Service d'hématologie clinique, CHU de Dijon, France

Introduction

Bing-Neel syndrome (BNS) is a rare but severe neurological complication of Waldenström macroglobulinemia (WM), resulting from direct lymphoplasmacytic infiltration of the central and/or peripheral nervous system. Although covalent BTK inhibitors (cBTKi) and primary CNS lymphoma-based regimens are the most widely reported treatments, bendamustine and fludarabine represent attractive alternatives because of their ability to cross the blood-brain barrier and their established activity in WM. We report the largest multicenter study evaluating bendamustine-rituximab (BR) and fludarabine-rituximab (FR) in patients with BNS.

Methods

This nationwide retrospective multicenter study included patients with BNS treated with BR or FR between 2012 and 2026, either as first-line therapy or at relapse. Clinical, biological, radiological, molecular, treatment, and outcome data were collected retrospectively. Responses were assessed according to the IWWM-12 criteria. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. BR and FR consisted of six 28-day cycles of rituximab combined with bendamustine or fludarabine. The study was approved by the French national data protection authority (CNIL No. 2212382).

Results

Forty-three patients from 11 French centers were included. Median age at BNS diagnosis was 64 years, and 60% were male. Twenty-five patients (58%) had a prior diagnosis of WM, with a median interval of 5 years before BNS onset, and 17 (40%) had previously received WM-directed therapy.

All patients presented with neurological manifestations, most commonly sensory deficits (43%), cranial nerve involvement (38%), and motor impairment (30%). CSF analysis demonstrated lymphoplasmacytic infiltration by cytology and/or flow cytometry in all evaluable patients, with positive cytology in 69% and flow cytometry in 90%. *MYD88* L265P was detected in the CSF of 70% of tested patients. Brain and/or spinal MRI was abnormal in 63%.

Twenty-nine patients (67%) received BR and 14 (33%) FR; treatment was administered first line for BNS in 35 patients (81%). Among the eight patients treated at relapse, previous BNS therapies included high-dose methotrexate-based regimens (n=7) or a cBTKi (n=1).

According to IWWM-12 criteria, complete response was achieved in 16%, partial response in 65%, stable disease in 9%, and progressive disease in 7%, yielding an overall response rate of 81%. Three patients underwent consolidative autologous stem cell transplantation.

After a median follow-up of 4.9 years, 17 patients (40%) relapsed (BNS, n=11; WM, n=3; both, n=2; histological transformation, n=1). Median time to next treatment was 2.5 years. Median PFS was 4.5 years (4.1 years with BR and not reached with FR), while median OS was not reached and estimated 3-year OS was 95%. No significant differences were observed between BR and FR. No treatment-related deaths occurred.

Conclusion

BR and FR achieved high response rates and durable disease control in BNS, with excellent long-term survival despite the severity of this rare complication. These findings support rituximab-based chemoimmunotherapy as an effective treatment option for selected patients with BNS and provide the strongest evidence to date supporting the use of BR and FR in this setting.

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First Name: Damien

Last Name: Roos-Weil

Email: damien.roosweil@aphp.fr

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Abstract Title: Bendamustine or Fludarabine based immunochemotherapy as treatment of Bing Neel syndrome: a French retrospective study

Conference: IWWM13