Ibrutinib for the Treatment of Bing-Neel Syndrome

Gilad Itchaki, MD[1], Jonas Paludo, MD[2], Maria Lia Palomba, MD[3], Marzia Varettoni, MD[4], Dipti Talaulikar, PhD, FRACP[5], Julio C Chavez, MD[6], Christian Buske, MD[7], Alessandra Tedeschi, MD[8], David Simpson, MBChB, FRACP[9], Constantine S Tam, MBBS, MD, FRACP[10], Samar Issa, FRACP[11], Stephen M Ansell, MD, PhD[2], Steven P Treon, MD, PhD, FRCP[1] and Jorge J Castillo, MD[1]

[1]Bing Center for Waldenstrom's Macroglobulinemia, Dana Farber Cancer Institute, Boston, MA, USA [2]Mayo Clinic, Rochester, MN, USA [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA [4]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [5]The Canberra Hospital, Red Hill, Australia [6]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA [7]Comprehensive Cancer Center Ulm, Ulm, Germany, [8]Niguarda Cancer Center, Milan, Italy, [9]North Shore Hospital, Auckland, New Zealand [10]Peter MacCallum Institute, Melbourne, Australia [11]Middlemore Hospital, Auckland, New Zealand

Background

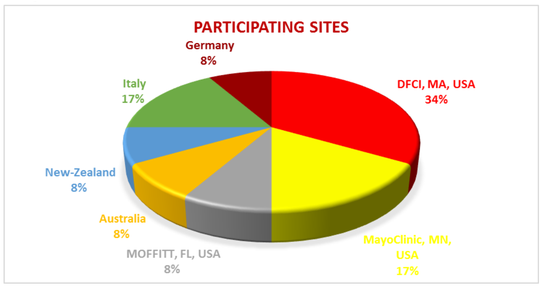
- Bing-Neel syndrome (BNS) is a rare complication of Waldenstrom macroglobulinemia (WM), in which WM cells gain access to the CNS causing neurological deficits[1].
- Treatment options in patients with BNS are limited
- Ibrutinib, an oral BTK-inhibitor, and the only approved therapy in WM, can penetrate into the CNS[2], but data on BNS is lacking.

Aim

To evaluate the efficacy of ibrutinib in patients with BNS

Methods

- A multicenter retrospective study
- Diagnosis of BNS was established in pts with WM by radiological and/or cytological evidence of CNS involvement by WM
- Ibrutinib was given at 420-560 mg PO qd until disease progression or intolerable toxicity
- Response was assessed based on recently published criteria[3]
- Events were defined as death from any cause, progression of disease, and stopping ibrutinib from any reason. Time-to-events were estimated using the Kaplan-Meier method.



Results – Patients Characteristics

24 pts are reported

WM Dx: median age 60 years (38-76); 58% ♂

- *Median time to BNS Dx was 4 years (0-27)*
- *Median lines of therapy was 1 (0-7), including anti-CD20 antibodies (n=15), alkylators (13), nucleoside analogues (8), proteasome inhibitors (3), immunomodulators (2), and autologous transplant (1).*
- *9 pts (38%) were untreated prior to BNS*

BNS Dx: median age 65 years (38-80)

- BNS symptoms @ presentation were cognitive deficits (n=10), sensory deficits (8), ataxia/falls (8), motor deficits (6), headache (5), and seizures (5).
- MRI findings demonstrated leptomeningeal enhancement (n=16) and/or brain masses (5), and were normal in 4.
- CSF flow cytometry was positive in 19 pts (79%)
- Brain biopsies were performed in 5 pts (21%)
- Tissue not obtained in 1 pt with pathological MRI
- Median serum IgM (n=20) prior to ibrutinib initiation was 1,294 mg/dl (125-5,938); 2 pts secreted IgG
- Median hemoglobin level was 11.9 g/dl (7.7-15.2)

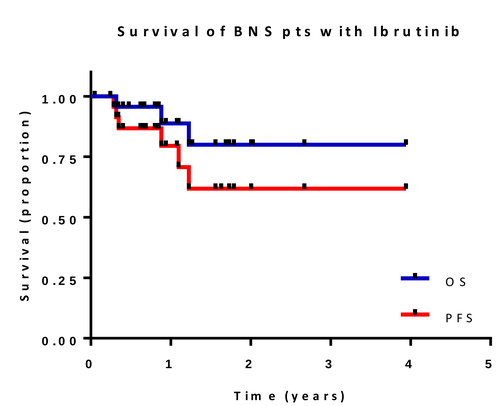
- *Median lines of BNS therapy prior to ibrutinib was 1 (0-5), including i.th. chemotherapy (n=9), high-dose methotrexate (6), bendamustine (3) and radiation therapy (3).*
- *Ibrutinib was the 1st BNS therapy in 7 pts (29%)*

Ibrutinib Rx:

10 pts (42%) received ibrutinib 560 mg qd and 14 (58%) 420 mg

Results – Response Assessment

- Median follow-up was 13 months (95% CI 8-21 months)
- At best response –
- Median serum IgM and hemoglobin levels were 340 mg/dl (82-3,330) and 14.6 g/dl (9.2-16.0).
- Based on consensus BNS response criteria, CR was attained in 2 pts (8%), PR in 14 (58%) and clinical improvement in 3 (13%).
- 5 pts stopped ibrutinib: 3 due to BNS progression, 1 due to grade 3 muscle cramps and 1 due to arrhythmia.
- 3 patients have died - 2 from infection and 1 from BNS progression.
- The median event-free survival (EFS) from ibrutinib initiation was not yet reached.



- 1-year & 2-year EFS rates were 71% (95% CI 46-86%) and 52% (23-75%).
- 2-year OS rate was 80%

Conclusion

Ibrutinib is a safe and effective treatment option for patients with BNS

References

[1]Castillo et al. Br J Haematol 2016; [2]Mason et al. Br J Haematol 2016; [3]Minnema et al. Haematologica 2016

Corresponding author: JorgeJ_Castillo@dfci.harvard.edu

There are no relevant relationships to disclose. Please see attached COI for details.