Ibrutinib penetrates the blood brain barrier and shows efficacy in the therapy of Bing Neel syndrome

Bing Neel syndrome (BNS) is a rare complication of Waldenström macroglobulinemia (WM) (Bing & Neel, 1936). BNS is characterized by central nervous system (CNS) infiltration by clonal lymphoplasmacytic cells with or without cerebrospinal fluid (CSF) hyperglobulinaemia. Intrathecal chemotherapy alone, high dose methotrexate and other systemic chemotherapies are used to treat BNS with variable success (Castillo *et al*, 2016).

Ibrutinib is a Bruton Tyrosine Kinase (BTK) inhibitor that was approved by the US Food and Drug Administration and the European Medicines Agency for treating WM following a prospective, multicentre study that showed an overall response rate of 91% and 2-year progression-free survival rate of 69% in previously treated patients (Treon *et al*, 2015). Patients with BNS were excluded from this study, and both *MYD88* and *CXCR4* mutation status impacted systemic ibrutinib responses (Treon *et al*, 2015). The potential for ibrutinib to impact CNS disease is supported by rodent studies that show brain and spinal cord drug uptake (McGinn, 2013). Herein, we report on a WM patient with BNS whose CNS disease progressed despite multiple regimens, responded to ibrutinib and had synchronous plasma and CSF drug levels determined to evaluate for CNS drug penetration.

The patient, a 59-year-old male was diagnosed with WM and a pleural amyloidoma in 2009. He was treated initially with rituximab, cyclophosphamide and dexamethasone and had a partial response. In March, 2011, he developed right ear congestion unresponsive to antibiotics. Computerized tomography (CT) scans and brain magnectic resonance imaging (MRI) revealed extensive tumour in the parapharyngeal space, right cavernous sinus, right ear, bilateral frontal parietal areas, right fifth cranial nerve, and bilateral parotid nodules. CSF examination revealed a total protein of 2·09 g/l (normal 0·15–0·45 g/l), and lambda light chain restricted monoclonal B cells ($CD19^+$, $CD20^+$, $CD23^+$, $FMC7^+$). CSF immunoelectrophoresis revealed an IgM M-spike (0·0385 g/l; normal <0·001 g/l). CT scans showed diffuse adenopathy, pulmonary nodules and a right pleural mass. Serum IgM level was 13·6 g/l (normal 0·4–2·3 g/l) and the IgM M-spike was 6·0 g/l. Molecular testing revealed tumour cells were positive for *MYD88* L265P and wild-type for *CXCR4* (Hunter *et al*, 2014).

The patient was diagnosed with BNS and received 2 cycles of high-dose methotrexate and rituximab in August 2011. Despite treatment, he had systemic and CNS disease progression. Bendamustine was added and a peripheral partial remission with stable CNS disease was achieved after 2 cycles. He remained asymptomatic except for right-sided hearing loss and aural congestion. An Ommaya reservoir was placed in February 2013, and liposomal encapsulated cytosine

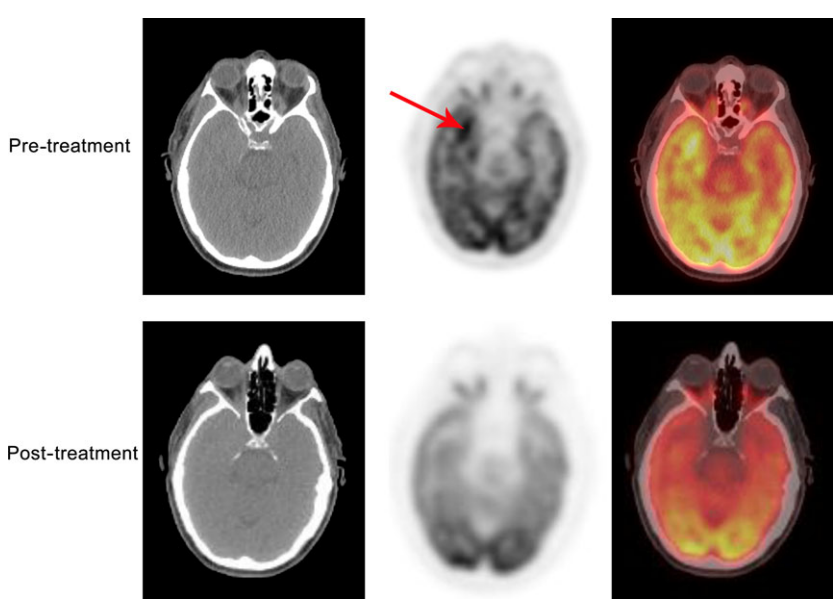

Fig 1. Pre- and post-treatment F-18, ^{18}F-FDG-PET/CT scans. Pre- and post-treatment, ^{18}F-fluorodeoxyglucose positron emission tomography/computerized tomography (FDG-PET/CT) scans in a Bing Neel syndrome patient, showing a hypermetabolic focus of disease in the right middle cranial fossa (red arrow) at baseline which resolved after ibrutinib treatment.

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Table I. Plasma and CSF concentrations for ibrutinib and its metabolite PCI-45227.

		Ibrutinib (nM)			PCI-45227 (nM)		
Study Day	Time post-dose (h)	CSF	Plasma	%CSF/Plasma	CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA	BLQ	BLQ	NA
	2	34	1133	3·0	31	502	6·2
1 Month	3	16	463	3·5	32	331	8·4
4 Months	2·5	7	318	2·2	10	405	2·5

Plasma and CSF samples (from an Ommaya shunt) were collected 2–3 h following administration of 560 mg ibrutinib on Day 1, and at 1 and 4 months. Following collection, samples were frozen at −80°C within 1 h of collection. Concentrations of ibrutinib and its metabolite, PCI-45227, were determined using a qualified liquid chromatography-tandem mass spectrometry assay (Pharmacyclics Inc., Sunnyvale, CA, USA). Limit of detection of the assays for ibrutinib and PCI-45227 is 0·7 nmol/l for CSF and 2·3 nmol/l for plasma.
CSF, Cerebrospinal fluid; NA, Not applicable; BLQ, Below the limit of quantitation of the assay.

arabinoside was given intrathecally for 4 months with stable disease.

In early 2014, he developed increasing lymphadenopathy and progressive anaemia (Hb 77 g/l). Serum IgM level was 12·50 g/l, and IgM M-spike was 8·0 g/l. Brain MRI revealed increased oedema and mass effect. CT/positron emission tomography (PET) scans showed markedly progressive diffuse lymphadenopathy and a new right middle cranial fossa extra-axial lesion (Fig 1). CSF total protein was 0·49 g/l, IgM level was 0·0089 g/l, and an IgMλ paraprotein was identified on immunoelectrophoresis. Ibrutinib (560 mg/d) was initiated. After 3 months of therapy, his hemoglobin level improved to 139 g/l, serum IgM decreased to 2·75 g/l, and IgM M-spike decreased to 5·0 g/l. A repeat MRI showed decreased nodular enhancement along the right middle cranial fossa floor with decreased right temporal vasogenic edema. Repeat CT/PET scan also showed resolved right middle cranial fossa hypermetabolism (Fig 1), and decreased peripheral adenopathy. Repeat CSF studies 4 months after ibrutinib start showed no clonal B-cells by flow cytometry, a total protein of 0·29 g/l, IgM level below the limit of detection, and no IgM M-spike. The serum IgM level was 2·31 g/l, while the IgM M-spike decreased to 2·0 g/l. The patient continues to do well in partial remission and remains on ibrutinib at 23 months.

Synchronous plasma and CSF concentrations of ibrutinib and its active metabolite PCI-45227 during the course of therapy were determined (Table I) and demonstrated that ibrutinib penetrated the blood brain barrier. PCI-45227, an active metabolite of ibrutinib, was also detected in the CSF. The ibrutinib level detected in the CSF was above the 50% inhibitory concentration (IC_{50}) for BTK inhibition (0·5 nmol/l) (MacGlashan *et al*, 2011). The documented objective CNS response and demonstration of therapeutic CSF drug levels suggests that ibrutinib is a candidate for treating BNS, and possibly other ibrutinib responsive CNS lymphoproliferative disorders. The presence of the *MYD88* L265P mutation and absence of a *CXCR4* mutation may have favourably impacted this patient's response (Treon *et al*, 2015). Two recent publications have reported ibrutinib activity in BNS, but CSF drug levels in these patients were not measured (Cabannes-Hamy *et al*, 2016; Castillo *et al*, 2016). A higher dose of ibrutinib (560 mg/d) than typically used in WM (420 mg/d) was administered to our patient and may have contributed to measurable CSF ibrutinib and PCI-45227 drug levels, and BNS response. Bernard *et al* (2015) recently reported CNS responses in 3 mantle cell lymphoma patients who received 560 mg/d of ibrutinib. Ibrutinib levels in excess of the IC_{50} for BTK inhibition were also recognized in the CSF of these patients. At the National Institutes of Health, Dunleavy *et al* (2015) are exploring ibrutinib at 560–840 mg/d to treat primary CNS lymphoma (PCNSL), which, like WM, shows high rates of activating *MYD88* mutations (Yamada *et al*, 2015). Ibrutinib was observed in the CSF of these patients at concentratons that exceeded the IC_{50} for BTK inhibition, and were maintained for a median of 4 and 8·5 h at the 560 mg and 700 mg doses, respectively. With ibrutinib alone, 7 of 8 of the evaluable PCNSL patients achieved partial responses before combination chemotherapy was introduced (Dunleavy *et al*, 2015). Taken together, these studies demonstrate that ibrutinib crosses the blood brain barrier in patients with various B-cell malignancies, including WM, and can impact CNS disease in ibrutinib sensitive lymphomas. The optimal dose and schedule of ibrutinib treatment in CNS disease remains to be clarified.

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Contributions

CM provided patient care and wrote the manuscript; SS provided patient care and reviewed the manuscript; JJC analysed the data and reviewed the manuscript. LX performed

experiments and analysed the data; SPT provided patient care, designed the research, analysed the data and reviewed the manuscript; SLA provided patient care, designed the research, analysed the data and wrote the manuscript.

Conflict of interest

SPT has received grant funding from Pharmacyclics, and consulting fees from Pharmacyclics and Janssen Oncology. The remaining authors have no conflicts of interest to declare.

Christopher Mason[1]
Steven Savona[1]
Josephine N. Rini[2,3]
Jorge J. Castillo[4]
Lian Xu[4]
Zachary R. Hunter[4]
Steven P. Treon[4]
Steven L. Allen[1]

[1]Division of Hematology, Northwell Health Cancer Institute, [2]Hofstra Northwell School of Medicine, [3]Department of Radiology, Hofstra Northwell School of Medicine, Lake Success, NY, and [4]Bing Center for Waldenstrom's Macroglobulinemia, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA.
E-mail: steven_treon@dfci.harvard.edu

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