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Title

ACTIVITY WITH IBRUTINIB IN MANTLE CELL LYMPHOMA PATIENTS WITH CENTRAL NERVOUS SYSTEM RELAPSE

Running title

Ibrutinib in mantle cell lymphoma CNS relapse

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SUMMARY

The risk of central nervous system (CNS) dissemination in mantle cell lymphoma (MCL) is low and occurring late in the course of the disease. However, prognosis in such cases remains extremely poor despite high-dose antimetabolite chemotherapy. Among novel drugs used to treat relapsing MCL patients, ibrutinib, an oral inhibitor of Bruton’s tyrosine kinase, shows great promise. Here we report the clinical observation of three MCL patients with symptomatic CNS relapse treated with single agent ibrutinib. All three patients had dramatic and rapid responses with almost immediate symptoms recovery. We also confirmed that ibrutinib crosses the blood-brain barrier (BBB) with parallel pharmacokinetic analyses in plasma and cerebrospinal fluid using a validated LC-MS/MS method. All responses are ongoing after 2 months to 1 year of follow-up.

Key Points:

Ibrutinib induces a rapid, dramatic and sustained response in MCL patient with symptomatic CNS relapse

Ibrutinib penetration through the blood-brain barrier was confirmed using plasma and CSF pharmacokinetic analyses

INTRODUCTION

Mantle cell lymphoma (MCL) is a rare lymphoma, accounting for 5% of non-Hodgkin’s lymphomas. Central nervous system (CNS) dissemination occurs in 4.1% of these patients during the course of the disease. Median survival after diagnosis of CNS involvement is 3.7 months.

Ibrutinib, an oral Bruton’s tyrosine kinase (BTK) inhibitor, acts by blocking B-cell antigen receptor signaling, thereby reducing malignant proliferation of B-cells and inducing apoptosis. Ibrutinib is a highly active novel agent with durable single agent activity in relapsed and refractory MCL, giving a 68% response rate in a cohort of patients with relapsed/refractory MCL.
We report here the clinical observation of three MCL patients with CNS relapse treated with ibrutinib. All three patients presented with symptomatic CNS disease. Neuroimaging confirmed MCL infiltration in the cerebral parenchyma or the spinal cord, and cerebral spinal fluid (CSF) analysis was positive in one patient. We observed rapid responses in all three patients without any significant toxicity.

METHODS

Three MCL patients with CNS relapse presented for treatment in our unit between April 2014 and May 2015. MCL diagnosis was confirmed with cyclin D1 overexpression at diagnostic biopsy for the three patients. All patients had received at least one line of prior treatment, two having R-BEAM high-dose therapy followed by ASCT. All three patients presented with refractory or early relapsing MCL and measurable CNS disease (retro-orbital lesion, CSF infiltration, temporal mass, transverse myelitis). Patients and disease characteristics at ibrutinib initiation and responses to treatment are summarized in Table 1. Ibrutinib treatment was administered at a standard dose (560 mg/day) as a single agent. Patients were assessed for response (clinical exam, CSF, MRI, FDG-PET scan, Cheson criteria) and toxicity. Response assessment was specific to each patient, adapted for initial CNS lesion. Plasma and CSF pharmacokinetics analyses were performed (patients 2, 3 only). Blood samples for plasma pharmacokinetics were collected on day 8 at pre-dose, 1, 2, 4, 6 and 8 h post-dose. CSF collection was performed 2 to 4 h post-dose. Ibrutinib quantification in plasma and CSF was performed using a liquid chromatography coupled with mass tandem spectrometry (Thermo Quantum Ultra TQD) validated according to the bioanalytical method validation guidelines. Cmax (maximal concentration) was determined and area under the plasma concentration versus time curve (AUC0–t) was calculated according the trapezoidal rule.
RESULTS AND DISCUSSION

At 3 months, impressive responses had been obtained for all three patients (Figure 1). The first patient presented a CR for cerebral and extra-cerebral lesions according to Lugano classification criteria\textsuperscript{8} at 3 months which was maintained at 6 months, with a normal CT-scan and a negative FDG-PET of the CNS retro-ocular lesion. The follow-up for this patient is currently at 1 year and he is still in CR on FDG-PET, cerebral MRI and CT-scan. The second patient showed very early improvement in his neurologic exam (within 3 days). In parallel, we observed a reduction of CNS lesion on MRI at day 8, with a CR at 1 month on cerebral MRI, medullar MRI and FDG-PET. At 6 months, the CR was confirmed at both sites on cerebral and medullar MRI. The third patient presented a partial response (PR) in CSF (from 900 to 76 cells/ml) and retro-orbital lesion evaluation (cerebral MRI) with recovery of walking, decreased pain and improved performance status. All three responses occurred within 3 to 8 days of treatment initiation, with a significant improvement in the clinical exam. Response was confirmed in all cases by biological analysis and imaging. Only 2 cases (patients 2 and 3) were evaluated for CSF infiltration and one of them was positive. Patients obtained a clinical response in the 3 cases, with no consideration of CNS relapse site and CSF infiltration. We did not observe any secondary effect in term of bleeding or hematoma performing lumbar puncture under ibrutinib.

Treatment was well tolerated by all three patients with no severe toxicity, including heavily pretreated patients. Patient 2 had higher ibrutinib plasma exposure on day 8 (AUC\textsubscript{0-24h} 3119 ng*h/mL; C\textsubscript{max} 729 ng*mL\textsuperscript{-1}) compared to published data\textsuperscript{9,10} and ibrutinib CSF concentrations reached 50 ng/mL (equivalent to 113. 5 nmol/L). Patient 3 had ibrutinib plasma exposure on day 8 consistent with published data (AUC\textsubscript{0-24h} 1002 ng*h/mL; C\textsubscript{max} 188 ng/mL), and ibrutinib CSF concentrations reached 2 ng/mL (equivalent to 4.5 nmol/L) which was well above ibrutinib IC50 (0.46 nmol/L).

CNS relapse is probably the most dramatic complication in B-cell malignancies. Although infrequent, it has rapidly fatal consequences with a poor median survival\textsuperscript{2}. CNS relapse in MCL is a significant unmet medical need and the very poor prognosis with current treatment options\textsuperscript{11} highlights the urgent need for alternative therapeutic approaches. This is the first report describing the efficacy of ibrutinib in MCL patients with CNS relapse. The highly active therapeutic activity for these patients following single oral agent ibrutinib therapy, with clinical and objective responses within 3
months, seems very promising. Survival after CNS relapse diagnosis for these patients is already substantially higher than the median 3.7 months reported, and for two of them, follow-up at 1 year and at 9 months showed a persisting CR, confirming the efficacy of ibrutinib.

In the relapse setting, numerous phase II studies have proven the efficacy of ibrutinib monotherapy in B-cell malignancies, not only in MCL and in chronic lymphocytic leukemia where FDA approval has already been obtained following an accelerated process (in November 2013 and February 2014, respectively), but also in follicular lymphoma, Waldenström’s disease and diffuse large B-cell lymphoma (DLBCL).

In the first-line setting, ibrutinib is currently being evaluated in phase Ib trials in combination with standard first line treatment in DLBCL. Based on this observation, we postulate that this association opens new perspectives in terms of CNS relapse prevention in B-cell malignancies. Moreover the safety and simplicity of daily oral treatment with ibrutinib offers greater comfort to patients compared to intrathecal injections.

We have shown that a low CSF to plasma ibrutinib concentration ratio (ranging from 1% to 7%) was observed. Ibrutinib CSF distribution may rely on an active influx transport across the BBB or a simple diffusion limited by the high plasma protein binding of ibrutinib. Further preclinical studies are needed to determine precisely the mechanism involved.

In conclusion, ibrutinib is emerging as a promising targeted therapy approach for MCL patients with CNS relapse, whatever the form of CNS relapse is. Our clinical, biological, and pharmacokinetic results, confirm the ability of ibrutinib to cross the BBB. The use of ibrutinib to manage CNS relapses of MCL likely constitutes an efficient solution for this unmet medical need, and should be considered for others B-cell malignancies. Based on these data, one may speculate on the potential of a prophylactic activity on CNS relapse for ibrutinib in B-cell malignancies at diagnosis, by considering the proprieties of each of these entities. This observation about 3 patients opens new perspectives in the utility of ibrutinib in MCL disease but needs to be confirm with others studies.
Acknowledgements

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Authorship

SB and CT designed the research. SB, LG, SA, PB, JB, EDK, SM HS CT. analyzed data. SB and CT wrote the paper. LG, SA, PB, JB, EDK, SM, and HS reviewed the manuscript.

Conflict of Interest Disclosure

CT has participated to advisory committees for Gilead, Janssen and Roche. PB has participated to advisory committees for Takeda.

References

17. FDA. Clinical Pharmacology Reviews Ibrutinib 205552Orig1s000 2013.
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<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<td>Age/sex</td>
<td>61/M</td>
<td>62/M</td>
<td>77/F</td>
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<tr>
<td>MIPI score</td>
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<td>5.8 (intermediate risk)</td>
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<tr>
<td>Ki67</td>
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<tr>
<td>Prior HDT + ASCT</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
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<td>Clinical disease symptoms</td>
<td>- Proptosis - Ipsilateral optic nerve infiltration - Complete right blindness</td>
<td>- Complete motor deficit (lower limbs) - Impaired bladder bowel control</td>
<td>- Bilateral motor deficit - Severe pain (lower limbs)</td>
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<td>Intra-cerebral lesion</td>
<td>Right retro-orbital mass (30x32 mm) with intradural infiltration</td>
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<td>Asymptomatic left extradural retro-orbital mass (12x14mm)</td>
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<td>Intra-spinal lesion</td>
<td>No</td>
<td>Transverse myelitis (MRI): 90 mm with contrast enhancement</td>
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<td>CSF involvement</td>
<td>Not assessed</td>
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<td>- Left subclavian nodes - Left axillary mass (74x55 mm) - Subcutaneous nodes</td>
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ASCT, autologous stem cell transplantation; CNS, central nervous system; CR = complete response; CSF, cerebrospinal fluid; HDT, high-dose therapy; LDH, lactate dehydrogenase; PR = partial response.
Figure legends

**Figure 1. Neuroimaging in Patient 1 and Patient 2 under ibrutinib treatment.** 1a. Patient 1. CT without contrast and FDG-PET of the orbits at baseline, at months 3 and 9. Assessment at 3 months showed a complete response. A clinical response was observed after 2 weeks of initiation of ibrutinib. 1B and 1C. Patient 2 Contrast-enhanced T1-weighted (top) and T2-weighted (bottom) MRI of the spine (1B), and contrast-enhanced T1-weighted (top) and FLAIR images (bottom) of the brain (1C), at baseline, day 8, months 1, 3 and 6. At Day 8, complete response was observed in the spine and the brain without remaining contrast enhancement. Anomalies on T2-weighted images took up to 6 months to clear in the brain.
Activity with ibrutinib in mantle cell lymphoma patients with central nervous system relapse

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