Ibrutinib for central nervous system lymphoma: the Australasian Lymphoma Alliance/MD Anderson Cancer Center experience

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Abstract:

Primary and secondary central nervous system lymphomas (PCNSL/SCNSL) are aggressive rare malignancies with dismal outcomes. Encouraging data has emerged from phase I/II clinical trials treating relapsed/refractory PCNSL/SCNSL with ibrutinib. We analysed 33 patients who received ibrutinib, alone or with other therapies, for PCNSL(n=9) or SCNSL(n=24). The objective response rate was 58% (complete response 55%). Median PFS and OS for PCNSL patients were both 3.1 months; for SCNSL, 10.2 and 11.5 months respectively. Only one invasive fungal infection was observed, despite concurrent or recent use of dexamethasone 8-16mg daily in 14 pts (42%). Ibrutinib has encouraging activity in these aggressive malignancies.
Primary central nervous system lymphoma (PCNSL) is a rare extranodal disease, typically with diffuse large B-cell lymphoma (DLBCL) histology and inferior prognosis to its nodal counterpart. (Grommes and DeAngelis 2017) Outcomes for patients with relapsed/refractory disease are poor, with median progression free survival (PFS) 2-5 months. (Grommes and DeAngelis 2017) Secondary central nervous system lymphoma (SCNSL) - CNS involvement in a patient with prior extracranial lymphoma - is typically an early and catastrophic event. (El-Galaly, et al. 2018) Favourable response rates have been reported using sequential high-dose chemotherapy followed by autologous stem cell transplantation in small phase II trials. (Ferreri, et al. 2019, Korfel, et al. 2013) However in clinical practice many patients are unsuitable for this intensive treatment due to age or comorbidities. (Cheah, et al 2017) Therefore, novel treatment approaches are needed.

In preclinical studies, Davis et al demonstrated increased survival of activated B-cell (ABC), but not germinal centre (GCB), DLBCL cell lines with nuclear factor kappa B (NF-κB) activity. (Davis, et al 2001) BCR and MYD88L265P mutations activate the NFkB pathway (Ngo, et al 2011) and are present in up to 90% of PCNSL but are less prevalent in non-GCB cell-of-origin SCNSL. (Kersten, et al 2014) Ibrutinib is a covalent BTK inhibitor that reduces NF-κB pathway activity (Yang, et al 2012) and has activity in a range of B-cell lymphomas. Wilson et al treated 80 patients with relapsed/refractory systemic DLBCL and reported a higher objective response rate (ORR) in ABC compared with GCB cell-of-origin (ORR 37% vs 5%) although PFS was short (Wilson, et al 2015). In phase I/II studies of ibrutinib monotherapy in relapsed/refractory PCNSL and SCNSL, investigators have demonstrated response rates of up to 78% irrespective of BCR and MYD88 status. (Grommes, et al 2017, Soussain, et al 2019) In a phase II study of 44 patients with relapsed/refractory CNS lymphoma (29 PCNSL, 15 SCNSL) Grommes et al demonstrated superior response with ibrutinib in patients with PCNSL (ORR 81%) compared with SCNSL (ORR 69%). (Grommes, et al 2018) Ibrutinib has also been combined with rituximab and methotrexate in phase I trials with promising results. (Grommes, et al 2019) However, high rates of invasive fungal infection and death were observed when ibrutinib was combined with intensive combination chemotherapy regimens. (Lionakis, et al 2017)

As the availability of clinical trials for patients with CNS lymphoma is scarce, and patients with CNS lymphoma can be challenging to enrol, we performed a multicentre, retrospective analysis of PCNSL/SCNSL patients who received ibrutinib for this indication.

Patients with PCNSL/SCNSL >18 years of age who received ibrutinib outside of clinical trials prior to 1st February 2019 were identified using institutional records at six Australian, one New Zealand and one US center. Patient characteristics were analysed using descriptive statistics and survival times were calculated using the method of Kaplan and Meier. All responses were defined using magnetic resonance imaging ± cerebrospinal fluid cytology/flow cytometry. Median follow-up was determined using surviving patients at last follow-up. Statistical analysis was performed using STATA 15.1 (StataCorp, College Station, TX, USA).

Thirty-three eligible patients were identified: 9 (27%) PCNSL and 24 (73%) SCNSL. Baseline patient characteristics are shown in Table 1. All PCNSL patients had DLBCL histology, with varied histologic...
subtypes of SCNSL. Frequent prior therapies were systemic methotrexate (67%), rituximab (61%),
cytarabine (42%), radiotherapy (32%) and thiopeta (16%).

Thirteen patients received ibrutinib as monotherapy, (PCNSL 3/9 [33%], SCNSL 10/24 [42%]). Six
received concurrent radiotherapy (PCNSL 3/9 [33%], SCNSL 3/24 [13%]) and ten received ibrutinib
with other systemic therapies. Combination regimens were heterogeneous (Table 1). Four (12%)
patients received concurrent steroids, with an additional 10 (30%) having received steroids within 28
days of commencing ibrutinib. Two (6%) with vitreoretinal lymphoma received concurrent intravitreal
methotrexate. The daily dose of ibrutinib was 420-560mg daily in the majority of patients.

The ORR for the entire cohort was 58% (19/33), with CR rate 55% (18/33). Four patients (44%) with
PCNSL experienced an objective response; all CR. The ORR for SCNSL was 63% (15/24) with CR rate
58% (14/24). Response rates in the most frequently represented SCNSL histologic subtypes were:
DLBCL 44% (4/9), mantle cell lymphoma 40%, (2/5) and chronic lymphocytic leukemia/small
lymphocytic lymphoma 100% (3/3). One patient with SCNSL (DLBCL) had unconfirmed disease
response status, but remained on ibrutinib without clinical disease progression at last follow-up. The
median time to best response for responding patients was 3.3 months (range 0.8-9.5). Disease
responses and CRs were observed in all histologic subtypes with the exception of one patient with
Richter’s transformation who died prior to response assessment and was considered a non-responder.

The ORR for ibrutinib monotherapy was 54% (7/13; [PCNSL 1/3, SCNSL 6/10]), with all but one
responding patient with SCNSL (DLBCL) attaining a CR. Numerically, the highest response rate was
observed for ibrutinib in combination with radiotherapy (5/6; PCNSL 2/3, SCNSL 3/3), all CR. Both
patients with vitreoretinal SCNSL attained CR; 1 with ibrutinib monotherapy and 1 with concurrent
intravitreal methotrexate and combination chemotherapy (Rituximab, Ifosphamide, carboplatin and
etoposide [R-ICE]). Systemic therapy administered concurrently with ibrutinib were heterogeneous and
numbers are too small to draw definitive conclusions regarding efficacy of individual combinations.
Three patients, two with PCNSL and one with SCNSL (MZL histology) were tested for the MYD88L265P
mutation prior to ibrutinib. The mutation was detected in all three patients; all attained CR.

With a median follow up of 16.6 months (range 0.5-61.5), the 12-month PFS rate was 48% for the entire
cohort. Twenty-one (64%) patients have experienced PFS >6 months (maximum 61.5 months). The
median PFS, overall survival (OS) and duration of response for the entire cohort was 10.2, 11.5 and
10.5 months respectively, with no differences between PCNSL and SCNSL. (Figure 1) Patients who
achieved a response had superior PFS (14 vs 1.5 months, p<0.001) and OS (14 vs 3 months, p<0.001),
(Figure 1). Twelve (36%) patients remain on ibrutinib.

Twenty-one patients (64%) have discontinued therapy - due to progressive disease (14), toxicity (atrial
fibrillation [2] and cytopenia [1]); physician choice to switch therapy to lenalidomide (1), and three in
remission; two patients in remission ceased ibrutinib to undergo autologous stem cell transplant (ASCT)
and one has not had documented follow up since ibrutinib was ceased. One patient experienced
disease relapse 5 months following ASCT; the other two patients remain in continuous remission. Dose
interruptions or reductions occurred in 9 patients (27%), due to infection (12%; 4/33 bleeding (2/33;

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6%), neutropenia (2/33; 6%) and unsafe swallow (1/33; 3%). One patient with SCNSL (CLL) and no prior fungal infection developed probable pulmonary aspergillosis after 3 months of ibrutinib monotherapy 420mg daily, without recent steroid exposure. Aspergillosis was diagnosed following development of hypoxia and right upper lobe ground glass shadowing. Subsequent serum galactamanan assay was strongly positive, but there was no confirmatory bronchoalveolar testing. The patient received systemic antifungal therapy and recovered. Ibrutinib was initially continued, but later ceased due to atrial fibrillation. The patient remains alive and in remission off all therapy. No other invasive fungal infections were observed despite use of dexamethasone (dose ranges 8-16mg daily) prior to or during ibrutinib in 14 patients (42%). Grade 3/4 adverse events were observed in 13 patients (39%) and included non-neutropenic infection (5/33; 15%), neutropenia (4/33; 12%), two each (6%) of febrile neutropenia, thrombocytopenia and bleeding, and one each (3%) of aspergillus infection, atrial fibrillation, and anaemia.

In this population of patients with predominantly relapsed/refractory CNS lymphoma, ibrutinib was active with durable responses and no unexpected toxicity. This study has limitations inherent to its modest sample size, retrospective, multicenter design and substantial heterogeneity in patient population and therapy. Nevertheless, the data remain useful given limited experience outside of clinical trials. Based on favourable responses we have observed in this cohort administering radiotherapy concurrently with ibrutinib in both PCNSL and SCNSL, we propose that this combination is of interest to explore further. Further prospective studies are required to define the optimal dosing strategy and combinations for ibrutinib in this difficult-to-treat population.

**Acknowledgements:** No acknowledgements

**Authorship contributions:**

KLL and CYC designed research, analysed statistics and wrote the paper.

CKC, KM, JC, NH, JC, S-JH, SI, AG, PW, MKG, BD, LN, EAH contributed study data and wrote the paper

**Conflict of interest disclosures:**

KLL: consulting/advisory/honoraria – Roche; travel expenses – Janssen, Novartis

CKC: No disclosures

KM: travel – Bristol-Myers Squibb

JC: No disclosures

NH: No disclosures

JC: No disclosures

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S-JH: No disclosures
SI: No disclosures
AG: No disclosures
PW: No disclosures
MKG: Personal fees and other from MSD, grants and personal fees - Gilead, Janssen, Celgene, BMS, personal fees - Amgen
BD: No disclosures
LN: Honorarium- Bayer, Celgene, Gamida Cell, Genentech, Gilead/KITE, Janssen, Novartis, TG Therapeutics; Research- Celgene, Genentech, Janssen, Karus Therapeutics, TG Therapeutics
EAH: consulting/advisory/honoraria – Roche, Janssen, MSD, Gilead, Astra Zeneca; research funding – Bristol Myers Squibb, Merck KgA, Astra Zeneca, MSD, Celgene, Roche, travel expenses – Janssen, Roche.
CYC: consulting/advisory/honoraria – Roche, Janssen, MSD, Gilead, Ascentage Pharma, Acerta, Loxo Oncology, TG therapeutics; research funding – Celgene, Roche, Abbvie; travel expenses – Roche.

References


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Recurrent/Refractory Primary (PCNSL) and Secondary CNS Lymphoma (SCNSL). *Blood*, **132**, 2965-2965.


Figure legends:

Table 1: Table of patient characteristics. ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system; DLBCL = diffuse large B cell lymphoma; MCL = mantle cell lymphoma; SLL= small lymphocytic lymphoma; CLL=chronic lymphocytic leukemia; FL= follicular lymphoma; HGBL NOS= high grade B-cell lymphoma, not otherwise specified; MZL=marginal zone lymphoma; HCL=hairy cell leukemia; WM=Waldenstrom's macroglobulinaemia; SD=stable disease; PD=progressive disease; MTX= methotrexate; R-ICE= rituximab/ifosphamide/carboplatin/etoposide; DA-TEDDI-R= dose-adjusted temozolomide/etoposide/doxorubicin/dexamethasone/rituximab

Figure 1: Kaplan Meier survival curves a) Progression free survival Primary central nervous system lymphoma (PCNSL) vs Secondary central nervous system lymphoma (SCNSL); b) Overall survival PCNSL vs SCNSL; c) Progression free survival in responders vs non-responders to ibrutinib; d) Overall survival in responders vs non-responders to ibrutinib.
References


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Wilson, W.H., Young, R.M., Schmitz, R., Yang, Y., Pittaluga, S., Wright, G., Lih, C.J., Williams, P.M.,
Shaffer, A.L., Gerecitano, J., de Vos, S., Goy, A., Kenkre, V.P., Barr, P.M., Blum, K.A.,
Barrientos, J.C., McGreivy, J., Fardis, M., Chang, B.Y., Clow, F., Munneke, B., Moussa, D.,
Beaupre, D.M. & Staudt, L.M. (2015) Targeting B cell receptor signaling with ibrutinib in

Yang, Y., Shaffer, A.L., 3rd, Emre, N.C., Ceribelli, M., Zhang, M., Wright, G., Xiao, W., Powell, J.,
Platig, J., Kohlhammer, H., Young, R.M., Zhao, H., Yang, Y., Xu, W., Buggy, J.J.,
Balasubramanian, S., Mathews, L.A., Shinn, P., Guha, R., Ferrer, M., Thomas, C.,
Table 1:

<table>
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<tr>
<th>Characteristic</th>
<th>Study patient cohort, n (%)</th>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>23 (70%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (30%)</td>
</tr>
<tr>
<td><strong>Median age (years) at starting ibrutinib (range)</strong></td>
<td>64 (22-85)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Relapsed Primary CNS lymphoma</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Relapsed Secondary CNS lymphoma</td>
<td>23 (70%)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>MCL</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>SLL/CLL</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Transformed FL</td>
<td>1 (3%)</td>
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<tr>
<td>Richter’s transformation to HGBL NOS</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>MZL</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>HCL</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>WM</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Treatment naïve Primary CNS lymphoma</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Treatment naïve Secondary CNS lymphoma</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>EBV+ immunosuppression related</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Site of CNS disease</strong></td>
<td></td>
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<tr>
<td>Parenchymal</td>
<td>15 (46%)</td>
</tr>
<tr>
<td>Leptomeningeval</td>
<td>11 (33%)</td>
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<tr>
<td>Vitreoretinal/primary vitreal</td>
<td>2 (6%)</td>
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<tr>
<td>Combination</td>
<td>5 (15%)</td>
</tr>
<tr>
<td><strong>ECOG performance status at starting ibrutinib</strong></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>13 (39%)</td>
</tr>
<tr>
<td>2-4</td>
<td>15 (46%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (15%)</td>
</tr>
<tr>
<td><strong>B symptoms at starting ibrutinib</strong></td>
<td>3 (9%)</td>
</tr>
<tr>
<td><strong>Median no. of prior therapies for CNS lymphoma (range)</strong></td>
<td>1 (0-5)</td>
</tr>
<tr>
<td><strong>Prior autologous stem cell transplant</strong></td>
<td>6 (15%)</td>
</tr>
<tr>
<td><strong>Refractory to most recent prior therapy (SD/PD)</strong></td>
<td>8/31 (26%)</td>
</tr>
<tr>
<td><strong>Ibrutinib total daily dose</strong></td>
<td></td>
</tr>
<tr>
<td>140mg</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>420mg</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>560mg</td>
<td>22 (67%)</td>
</tr>
<tr>
<td>840mg</td>
<td>1 (3%)</td>
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**Therapy details**
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<th>PCNSL (n=9)</th>
<th>SCNSL (n=24)</th>
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<tr>
<td>Prior high dose methotrexate</td>
<td>7 (78%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Ibrutinib monotherapy</td>
<td>3 (33%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Concurrent therapy with ibrutinib</td>
<td>6 (67%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>3 (33%)</td>
<td>3 (13%)</td>
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<tr>
<td>Intravitreal methotrexate</td>
<td></td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Combination chemotherapy</td>
<td></td>
<td>4 (17%)</td>
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<tr>
<td>R-ICE</td>
<td></td>
<td>2 (8%)</td>
</tr>
<tr>
<td>DA-TEDD-R</td>
<td></td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Rituximab/temozolomide</td>
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<td>1 (4%)</td>
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<tr>
<td>Non-chemotherapy systemic agents</td>
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<td>3 (13%)</td>
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<tr>
<td>Rituximab/lenalidomide</td>
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<td>1 (4%)</td>
</tr>
<tr>
<td>Ofatumumab</td>
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<td>1 (4%)</td>
</tr>
<tr>
<td>Venetoclax/obinutuzumab</td>
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<td>1 (4%)</td>
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<tr>
<td>Rituximab monotherapy</td>
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<td>1 (4%)</td>
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<tr>
<td>EBV third party T cells</td>
<td>1 (11%)</td>
<td>1 (4%)</td>
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<tr>
<td>Steroids alone without other systemic therapy</td>
<td>2 (22%)</td>
<td>1 (4%)</td>
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<tr>
<td>Dexamethasone concurrently or within 28 days</td>
<td>6 (67%)</td>
<td>8 (33%)</td>
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<td>commencing ibrutinib</td>
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Lewis, KL; Chin, CK; Manos, K; Casey, J; Hamad, N; Crawford, J; Ho, S-J; Issa, S; Grigg, A; Wood, P; Gandhi, MK; Do, B; Nastoupil, L; Hawkes, EA; Cheah, CY

Title:
Ibrutinib for central nervous system lymphoma: the Australasian Lymphoma Alliance/MD Anderson Cancer Center experience

Date:
2021-03

Citation:

Persistent Link:
http://hdl.handle.net/11343/276019