LETTER TO THE EDITOR

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Real-world outcomes of ibrutinib therapy in Korean patients with relapsed or refractory mantle cell lymphoma: a multicenter, retrospective analysis

Dear Editor,

Despite the introduction of novel front-line therapies including rituximab plus high-dose cytarabine followed by consolidative autologous stem cell transplantation (ASCT) and salvage therapy with bendamustine, lenalidomide or bortezomib, mantle cell lymphoma (MCL) is still considered incurable and most patients experience relapse or refractory (RR) disease. Ibrutinib (Imbruvica®) is a first-in-class oral agent that mainly works by inhibiting Bruton's tyrosine kinase and is considered the standard of care for RR MCL. However, reports for outcomes and safety profiles of ibrutinib treatment in Asian RR MCL patients are limited as MCL accounts for less than 3% of Non-Hodgkin's lymphomas in Asia [1, 2]. To evaluate the real-world outcomes of ibrutinib therapy in RR MCL patients in Korea, we performed a retrospective analysis of patients with RR MCL who were treated with ibrutinib from 18 tertiary institutes (details are provided in the Supplementary Materials).

A total of 88 patients were analyzed. Their immunophenotypic and cytogenetics features at the time of diagnosis are shown in Supplementary Table S1. 71 (80.7%) patients were male. Three (3.4%) patients had blastoid variants MCL. At the time of initial diagnosis, their median age was 67 (range: 40-90) years. A total of 11 (12.5%) patients were classified as stage II and 77 (87.5%) as stage III-IV. All patients received combination chemotherapy with or without rituximab as front-line treatment. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was the most frequently used regimen ($n = 59$, 67.0%), followed by rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and

dexamethasone alternating with high-dose methotrexate and cytarabine (R-HyperCVAD/MA; $n = 10$, 11.4%); CHOP or HyperCVAD/MA without rituximab ($n = 7$, 8.0%); bendamustine and rituximab ($n = 6$, 6.8%); and bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone ($n = 3$, 3.4%). Upfront and salvage autologous stem cell transplantation (ASCT) was performed in 5 and 7 cases, respectively. No patient received rituximab maintenance therapy either after induction treatment or after ASCT. The median progression-free survival (PFS) from the front-line treatment was 24.0 months (95% confidence interval [CI]: 21.6-28.2 months), and the median duration of response was 26.7 months (95% CI: 22.5-31.1 months). Before ibrutinib treatment, the median number of prior lines of treatment was 1 (range 1-6).

At the time of ibrutinib treatment, the median age was 71 (range: 42-92) years. In terms of MIPI-risk group [3], 18 (20.5%), 34 (38.6%), and 36 (40.9%) patients were classified as low-, intermediate-, and high-risk MIPI groups, respectively (Supplementary Table S2). Fifty-seven (64.8%) patients received ibrutinib at 1st relapse, and 31 (35.2%) received ibrutinib in later lines. The overall response rate was 64.8% (95% CI: 55.5%-75.5%). At a median follow-up of 30.5 months (95% CI: 25.9-35.1 months), the estimated median PFS was 20.8 months (95% CI: 10.8-30.8 months) with the 2-year PFS rate being 48.2% (95% CI: 41.8%-54.6%) (Supplementary Figure S1A).

Patients in the low- or intermediate-risk group had superior PFS compared to the high-risk group (25.6 months vs. 11.7 months, $P = 0.004$), and patients with tumor size < 5 cm demonstrated trends for longer PFS, compared to those with tumor size ≥ 5 cm (25.6 months vs. 12.0 months, $P = 0.073$). Patients who had received ibrutinib at 1st relapse also showed trends for longer PFS compared to those who received ibrutinib in later lines of treatment (25.1 months vs. 11.1 months, $P = 0.078$). The median duration of response was 26.7 months (95% CI: 22.5-31.1 months) among responders (Supplementary Figure S1B) and the

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Abbreviations: AE, adverse event; ASCT, autologous stem cell transplantation; CI, confidence interval; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, relapsed or refractory; RT, radiation therapy

median overall survival (OS) was not reached but had a 2-year OS rate of 79.1% (95% CI: 74.0%-84.2%) (Supplementary Figure S1C). The median duration of treatment was 14.7 months (95% CI: 7.2-22.2) and, at the time of analysis, 45 (51.1%) patients remained on ibrutinib. Among the other 43 (48.9%) patients who stopped the treatment, 27 (62.8%) were due to disease progression, 6 (14.0%) were related to adverse events (3 heart problems, 2 infections, 1 bleeding) and 2 (4.7%) were due to ASCT. The other 8 patients were lost to follow-up.

During ibrutinib treatment, 20 (22.7%) patients experienced temporary treatment interruption. Fatigue was the most frequent cause of treatment interruption ($n = 7$; 35.0%), followed by dermatologic events including pruritus, skin rash and onycholysis ($n = 5$; 25.0%), bone marrow suppression ($n = 4$; 20.0%), diarrhea ($n = 2$; 10.0%), and infection ($n = 2$; 10.0%). The cumulative duration of treatment interruption ranged from 1 week ($n = 5$) to 28 weeks ($n = 1$). A total of 19 (21.6%) patients required dose reduction for further treatment and eight of them also experienced treatment interruption. Among all patients who started ibrutinib at a dose of 560 mg once a day, 12 (63.2%) patients had dose reduction to 420 mg once a day, 6 (31.5%) patients to 280 mg once a day, and one patient to 140 mg once a day. Bone marrow suppression was the most frequent cause of dose reduction ($n = 6$; 31.5%), followed by fatigue ($n = 5$; 26.3%), and diarrhea ($n = 4$; 21.1%). Collectively, 31 (35.2%; excluding 8 who experienced both treatment delay and dose reduction) patients experienced either a delay in treatment or dose reduction (Supplementary Table S3).

A total of 33 patients (27 patients due to progressive disease, 6 patients due to adverse events) failed to ibrutinib treatment. After ibrutinib failure, 16 (48.5%) patients received subsequent treatment, and the other 17 (51.5%) patients did not receive treatment because of rapid deterioration ($n = 11$; 64.7%) and patients' refusal ($n = 6$; 35.3%). Bendamustine-based therapy and high-dose cytarabine-based therapy were administered in 9 (56.3%) and 3 (18.8%) patients, respectively. The rest of the patients received bortezomib, doxorubicin, fludarabine, and etoposide-based treatment, each ($n = 1$; 6.3%). The estimated median post-ibrutinib PFS was 4.9 months (95% CI: 0.0-10.0 months) and OS was 19.4 months (95% CI: 0.0-46.4 months).

There have been several prospective [4] and real-world data [5–8] describing the safety and efficacy of ibrutinib in RR MLC. Collectively, an overall response rate (ORR) of ~65% and a median PFS of ~12 months were observed. Compared to these Western data, the present study showed that the clinical outcomes were similar or slightly better, especially in PFS and OS. This may be explained by the lower number of heavily treated patients being included

TABLE 1 Cross-trials comparison of prospective and retrospective studies dealing with RR MCL patients treated with ibrutinib (median (range) for age and prior lines of therapy; median [95% CI] for DoR, PFS, and OS)

Trials	Number of patients	Age (year, [median, range])	Prior lines	Prognostic indices	ORR (%)	DoR (months)	PFS (months)	OS (months)	Discontinue therapy due to AEs (%)
Pooled analysis of three prospective trials [4]	370	N/A	2 (1-9)	31.8% high-risk simplified MIPI	69.7	21.8 (17.2-26.4)	12.5 (9.8-16.6)	26.7 (22.5-38.4)	10.3
US retrospective trial [5]	97	63 (39-87)	2 (1-8)	27% high-risk MIPI	65	17	15	22	N/A
Italian retrospective trial [6]	77	68.6 (38.5-83.7)	3 (1-10)	N/A	36.4	36	12.9	16	16.9
French observational trial [7]	106	74 (49-88)	1 (39%); 2 (31%); ≥3 (30%);	N/A	76.4	27.4 (17.3 – N/A)	23.7 (18.3-30.4)	29.9 (23.2-39.2)	9.3
US retrospective trial [8]	159	71 (48-90)	2 (1-3)	N/A	N/A	N/A	19.6 (16.5 – 24.3)	25.8 (19.9 – not reached)	25.6
Current study	88	71 (42-92)	1 (1-6)	40.9% high-risk MIPI	64.8	26.7 (22.5-31.1)	20.8 (10.8-30.8)	2-year OS rate 79.5%	6.8

N/A, not available; CI, confidence interval

in our cohort, compared to previous studies. In 51 (58.0%) patients, ibrutinib was the second-line treatment and in 6 (6.8%) patients, ibrutinib was the second treatment after upfront ASCT or RT. The PFS of these 57 (64.8%) patients was 25.1 months (95% CI 18.9-31.3 months) [4], which was similar to that of a pooled analysis from three prospective trials (25.4 months). This earlier use of ibrutinib could have contributed to an overall better PFS. Another explanation is that our patients tolerated better the ibrutinib treatment, which resulted in a longer duration of treatment (Table 1). Based on the favorable outcomes, a recent consensus guideline recommended the use of ibrutinib in the second-line rather than later-line setting [9].

Compared to previous studies [10], the post-ibrutinib OS was more favorable in the present study at 19.4 months (vs. 5.8 months). The patients in our cohort were less heavily treated and even after ibrutinib failure, some viable options such as cytarabine or bendamustine may have been available.

In summary, the clinical outcomes of ibrutinib therapy for Korean MCL patients were comparable to those of Western data. The efficacy and safety data shown in this present study provides additional evidence to support the use of ibrutinib in RR MCL, especially as an earlier line of treatment.

DECLARATIONS

AUTHORS' CONTRIBUTIONS

JHY performed the analysis and writing draft;

SJK, DH Yoon, DH Yang, and WSK were involved in planning, data analysis, and supervised the work;

MHC, JCJ, SYH, JOL, JHK, SHH, SSL, JYK, SHK, DSK, JHL, HMR, HJK collected data;

CS, HSE, SYO aided in interpreting the results;

All authors discussed the results and commented on the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee. Institutional review boards approved the study protocol at the respective sites.

AVAILABILITY OF DATA AND MATERIALS

Data and materials can be provided upon reasonable request to the corresponding author.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

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