Am J Blood Res 2021;11(4):373-383
www.AJBlood.us /ISSN:2160-1992/AJBR0136189

Original Article

Ibrutinib in patients with relapsed/refractory mantle cell lymphoma: a real-life, retrospective, multicenter trial on behalf of the "RTL" (regional Tuscan lymphoma network)

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Received June 9, 2021; Accepted July 14, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Background: Relapsed or refractory (R/R) mantle-cell lymphoma (MCL) patients have a poor prognosis and their management is challenging, in absence of a golden standard as salvage treatment. Bruton's tyrosine kinase inhibitor ibrutinib represents an effective treatment for R/R MCL patients. We investigated ibrutinib efficacy and safety in daily clinical practice, together with factors that could predict disease outcome. Patients and methods: We retrospectively analyzed 69 consecutive R/R MCL patients managed in 10 Tuscan onco-hematological centers. The treatment regimen consisted of oral, continuous, single-agent ibrutinib, maximum dosage of 560 mg once per day, until disease progression. Results: Overall response rate was 62.3%, with a CR rate of 39.1%. After a median follow-up of 15.6 months, 40/69 patients (58%) were alive, the main cause of death was progressive disease (PD, 22/69 cases, 31.9%). Median progression-free survival (PFS) and overall survival (OS) were 17 and 34.8 months. Inferior PFS was associated with >1 prior line of therapy and B symptoms. Ibrutinib refractoriness was associated with inferior OS, median OS after ibrutinib failure was only 5 months. Discussion and conclusion: In this real-life setting ibrutinib treatment prolonged survival in R/R MCL patients, without unexpected adverse events. Patients receiving ibrutinib as 2nd line regimen had the most favorable outcome.

Keywords: Mantle cell lymphoma, ibrutinib, prognosis, safety, survival

Introduction

Mantle-cell lymphoma (MCL) represents a rare and aggressive subtype of non-Hodgkin lymphoma (NHL), frequently diagnosed in advanced-stage with bone marrow, nodal and extranodal involvement [1]. In most cases, clinical course is aggressive, while in a small proportion of patients MCL is characterized by a leukemic, non-nodal presentation and indolent clinical behavior [1, 2]. Even if first-line therapy is administered with curative intent, including high-dose (HD) cytarabine and autologous stem cell transplantation (ASCT) as consolidation, disease relapse is frequently reported and only a minority of cases achieves a durable response [3]. Recently, a significant survival improvement has been achieved with the addition of rituximab maintenance after ASCT or chemoimmunotherapy [1, 3, 4]. Relapsed or refractory (R/R) MCL patients have a poor prognosis and their management is challenging, in absence of a golden standard as salvage treatment [3, 4]. In recent years, many novel agents have been approved for R/R MCL such as mTOR inhibitors, proteasome inhibitors, immunomodulatory drugs and B-cell receptor (BCR) signalling inhibitors [5-9]. Bruton

tyrosine kinase (BTK) represents an important component of the BCR signalling pathway, which plays a critical role in MCL growth and progression [10]. Ibrutinib, an oral, first-in-class, covalent BTK inhibitor, inhibits BCR signalling and showed promising long-term efficacy in several lymphoproliferative malignancies, including MCL [11]. In the pivotal paper by Wang and colleagues, a daily dose of 560 mg obtained a durable efficacy, overall response rate (ORR) and complete response (CR) rate were 68% and 21%, with prolonged median progression-free survival (PFS), duration of response (DOR) and overall survival (OS) [12]. Overall, a manageable safety profile was reported, with a limited rate of discontinuation due to adverse events, including bleeding, diarrhea, infections, hypertension and atrial fibrillation (AF) [12, 13]. These promising results were confirmed in an analysis of 370 R/R MCL cases from three open-label studies, which extended follow-up analysis reported a better clinical outcome in patients receiving ibrutinib as 2nd line regimen [14, 15]. However, we recognize treatment response and prognosis in a real-life experience could be somewhat different from those observed in clinical trials and there are limited published studies about ibrutinib in a non-trial setting [16-21]. Hence, we retrospectively analysed data regarding ibrutinib efficacy and safety, together with factors that could predict outcome for R/R MCL patients receiving ibrutinib in daily clinical practice in Tuscany.

Methods

Study design

In this multicentre, single-arm, observational study we retrospectively analyzed a cohort of 69 consecutive, R/R MCL patients managed at 10 onco-hematological centers in Tuscany from 2005 to 2019. Diagnosis was made according to 2008 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. The study was firstly approved by the Institutional Review Board of the coordinating center of Siena (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana Sezione: AREA VASTA SUD EST) on 15th of June 2020 (protocol code Ibru_MCL, protocol number 17512) and subsequently by the ethics committees of the other adhering Institutions. All patients signed written informed consent in accordance with local Institutional Review Board requirements and the Declaration of Helsinki. A centralized database with clinical and follow-up data was collected at the University of Siena (with data cutoff as of 30th of September 2020). Patients were included if they had a MCL diagnosis, were ≥18 years old at diagnosis and received single-agent ibrutinib in the daily clinical practice after at least 1 prior systemic therapy, to which they were refractory, or after which their disease relapsed. Patients who received ibrutinib in combination with other anticancer drugs were excluded. Patients who received at least 1 cycle of therapy with ibrutinib were considered evaluable for safety. Response evaluation and survival analysis have been reported according to intention-to-treat, patients not evaluated for response due to early death were included in the denominator for ORR calculation and classified as non-responders. We have collected data about clinical outcome after ibrutinib failure, including non-responders and patients relapsed after an initial response, but excluding patients without response evaluation due to early death.

We identified PFS as primary endpoint, while OS, DOR, ORR and CR rate were secondary endpoints. We have used PFS as primary endpoint because it represents the primary endpoint in the main published studies in this field; in such a way as to make our study comparable with the others. PFS is the most reliable parameter for determining the effectiveness of a therapy, such as ibrutinib, approved until progression. Moreover, OS is influenced by subsequent therapies and median follow-up is too short to utilise OS as primary endpoint. We also investigated the potential predictive factors associated with disease response and survival. In addition, we analyzed overall toxicities and therapeutic strategies used in patients who relapsed during treatment.

Treatment regimen and concomitant medications

The treatment regimen consisted of oral, continuous, single-agent ibrutinib, maximum dosage of 560 mg once per day, until disease progression or unacceptable toxicity. Each course of therapy was considered of 30 days. Antimicrobial prophylaxis for Pneumocystis jiroveci

Table 1. Baseline characteristics of patients

Characteristic	Number of patients (%)
Age: median [range]	70 [41-89]
Male	45/69 (65.2%)
Female	24/69 (34.8%)
Blastoid/pleomorphic	7/69 (10.2%)
Stage IV at diagnosis	45/69 (65.2%)
Stage IV pre-ibrutinib	38/69 (55.1%)
B-symptoms	15/69 (21.7%)
High sMIPI score at diagnosis	29/69 (42%)
High sMIPI score pre-ibrutinib	21/69 (30.4%)
High-intensity front-line therapy (including high-dose cytarabine)	13/69 (12.8%)
Prior autologous stem cell transplantation	9/69 (13%)
ORR after front-line therapy	57/69 (82.6%)
CR	40/69 (58%)
PR	17/69 (24.6%)
Prior regimens pre-ibrutinib	
1	45/69 (65.2%)
≥2	24/69 (34.8%)

Abbreviations: sMIPI, simplified mantle-cell lymphoma International Prognostic Index; ORR, overall response rate; CR, complete response; PR, partial remission.

pneumonia with trimethoprim-sulfamethoxazole (160/800 mg twice a day, two times a week), granulocyte colony-stimulating factor (G-CSF) and erythropoietin stimulating agents (ESA) were used as concomitant medications according to the summary of product characteristics. All patients received baseline CT scan, 18F-FDG PET and bone marrow biopsy. Response to therapy was assessed by both CT scan and 18F-FDG PET according to the Lugano 2014 classification criteria, while bone marrow biopsy was repeated to confirm CR only if positive at baseline [22]; tumor evaluation was performed according to the single Institutions practice, but generally every 3 months in the 1st year of treatment and every 6 months thereafter. Patients achieving at least a partial remission (PR) were considered as responders, while patients achieving a stable disease (SD) or a progressive disease (PD) were considered as treatment failure. After treatment ending, whatever the reason, we have collected survival data and available information about subsequent therapies.

After each course of ibrutinib, hematological and extra-hematological toxicity was defined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4 criteria. It is a descriptive terminology which can be utilized for adverse events (AE) reporting. A grading (severity) scale is provided for each reported AE.

Statistical analysis

In this single arm, multicenter, observational study focused on R/R MCL patients, descriptive statistics was used to illustrate patients characteristics. Categorical variables were analyzed using Chi-square or Fisher's exact test; Fisher's exact test was preferred for small sample size, when the expected frequency was less than 5.

Time to response was defined as the time from the first day of treatment until first documented response. DOR was defined as the time from documented response (CR or PR) until disease progression or last follow-up (censored). PFS was defined as the time from the first day of treatment until disease progression, relapse, death for any cause or last follow-up (censored). OS was defined as the time from the first day of treatment until death for any cause or last follow-up (censored).

Survival curves were assessed using the method of Kaplan and Meier and log rank test for significant associations; a P value <0.05 was considered statistically significant. To investigate significant factors associated with survival, we used a Cox proportional hazards model. All statistical analyses were performed with Statistical Software MedCalc, version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

Study population

Clinical characteristics of enrolled patients are illustrated in **Table 1**. The median age was 70 years (range 41-89). All patients received

baseline physical examination, complete blood cell count and radiological assessment prior to therapy. There were 54/69 (78.3%) cases diagnosed with advanced stage disease (9/69, 13% stage III and 45/69, 65.3% stage IV) and 47/69 (68.1%) cases who had advanced stage disease before ibrutinib (14/69, 20.3% stage III and 33/69, 47.8% stage IV). Simplified MCL international prognostic index (sMIPI) was high at diagnosis and before ibrutinib in 29/69 (42%) and 21/69 (30.4%) patients, respectively. Disease relapse was histologically documented in 30/69 cases (43.5%).

Prior regimens before ibrutinib

Median number of prior therapies before ibrutinib was 1 (range 1-4), 45/69 (65.2%) patients received ibrutinib as 2nd line treatment. As front-line regimen, due to the advanced median age of our cohort at diagnosis, the most used regimen was represented by bendamustine in association with rituximab (BR, 29/69 cases, 42%). The association of bendamustine with rituximab and moderate doses of cytarabine (R-BAC, with rituximab 375 mg/m^2 day 1, bendamustine 70 mg/m^2 day 1-2, cytarabine 500 mg/m^2 day 1-3) was given to 8/69 cases (11.6%). Other rituximab-containing regimens were gathered as follows: (i) cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) alternating with rituximab, dexamethasone, cytarabine, oxaliplatin (R-DHAOx, 3/69 cases, 4.3%), R-DHAOx with reduced doses of cytarabine (1/69 case, 1.4%), the regimen administered in the FIL MCL0208 trial (5/69 cases, 7.3%), R-CHOP (7/69 cases, 10.2%, in 2 cases alternating with BR), other HD cytarabine containing regimens (4/69 cases, 5.8%) less intensive regimens including fludarabine and/or cyclophosphamide (7/69 cases, 10.2%), rituximab, cyclophosphamide, vincristine, prednisone (R-CVP, 3/69 cases, 4.3%), rituximab monotherapy (2/69 cases, 2.9%).

Overall, 13/69 cases (12.8%) received HD therapy and were eligible for ASCT, 9/13 received ASCT, in the remaining cases ASCT was not administered as consolidation because of chemorefractoriness or early disease relapse after 1st line therapy.

Most patients (57/69, 82.6%) responded well to 1st line therapy, CR rate was 58% (40/69 cases), while 12/69 cases (17.4%) were chemo-refractory. The progression of disease (POD) after 1st line regimen was after or within 24 months of diagnosis in 36/69 (52.2%) and 33/69 cases (47.8%), respectively (median 28.8 months, range 1-123).

Median DOR with prior lines was 13 months (range 1-84); DOR was longer than 24 months in 44 cases, less than 24 months in the remaining 25 patients. Out of 24 cases who received ibrutinib as ≥3rd line treatment, only 1 patient received an allogeneic SCT (allo-SCT) before ibrutinib, 3/69 cases had received lenalidomide, while there were no patients treated with bortezomib or temsirolimus.

Response to treatment

Response to treatment is summarized in **Table 2**. Most patients (55/69, 79.7%) received the starting recommended dose of ibrutinib (560 mg once daily), while reduced doses due to medical decision were administered to 14/69 cases (20.3%); in particular, 8 patients received 420 mg daily and 6 received 280 mg daily. Median duration of treatment was 9 cycles (range 1-45); 66/69 patients were evaluable for response (95.7%), the remaining 3 patients died within 3 months from the beginning of treatment due to infections (pulmonary infection, sepsis not otherwise specified and COVID-19, 1 case each) and therefore did not undergo disease restaging. In an intention-to-treat analysis, performed at the time of the data cut-off, 28/69 patients (40.6%) were still receiving treatment, while 41/69 (59.4%) had discontinued therapy. Reasons for treatment discontinuation were PD (30/69 cases, 43.5%, including 23 cases of treatment failure and 7 relapsed after an initial response), second malignancies (1 lung cancer, 1 prostate cancer), acute renal insufficiency (1 case, considered as unrelated to ibrutinib), treatment toxicity (8/69 cases, including infectious complications, 6 cases, skin toxicity and AF-related cardiac complications, 1 case each). Out of 11 patients who interrupted ibrutinib for reasons other than PD, 2 experienced disease relapse, 2 are alive and disease-free and the other 7 patients died (4 cases without evidence of disease and 3 cases in which disease restaging was not performed).

In the entire cohort, ORR and CR rate were 62.3% (43/69 cases) and 39.1% (27/69 cases), respectively; out of 26 patients considered as treatment-failure (37.7%), 8/69 (11.6%) and 15/69 (21.7%) achieved a SD and a PD, respectively. Simplified MIPI score at diagnosis and prior to ibrutinib, advanced-stage at diag-

Table 2. Treatment schedule and response to ibrutinib

	Entire cohort (n=69)	1 previous line (n=45)	≥2 previous lines (n=24)
CR	27 (39.1%)	19 (42.2%)	8 (33.3%)
PR	16 (23.2%)	14 (31.1%)	2 (8.3%)
ORR	43 (62.3%)	33 (73.3%)	10 (41.6%)
PD	15 (21.7%)	9 (20%)	6 (25%)
SD	8 (11.6%)	2 (4.4%)	6 (25%)
Not evaluable	3 (5.3%)	1 (2.2%)	2 (8.3%)
Starting recommended dose of ibrutinib (560 mg once daily)	55 (79.7%)	38 (84.5%)	17 (70.9%)
Median number of cycles [range]	9 (1-45)	9 (1-45)	6 (1-36)
Treatment ongoing at data cut-off	28 (40.6%)	22 (48.9%)	6 (25%)
Reasons for treatment discontinuation			
PD	30 (43.5%)	15 (33.3%)	15 (62.5%)
Toxicity	8 (11.6%)	6 (13.3%)	2 (8.3%%)
Second neoplasm	2 (2.9%)	2 (4.4%)	/
IRA (not related)	1 (1.4%)	/	1 (4.2%)

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial remission; PD, progressive disease; SD, stable disease; IRA, intravenous regional anaesthesia.

nosis and prior to ibrutinib, age, gender, presence of blastoid/pleomorphic variant, administration of intensive front-line regimen, prior ASCT as consolidation, the achievement of a CR/PR after induction therapy and a POD less than 24 months were not associated with response to ibrutinib therapy. The administration of more than 1 prior line of therapy was negatively associated with response to ibrutinib (P=0.04), while the presence of B symptoms showed a trend (P=0.05). The median time to first response was 4 cycles (range 1 to 12); 10/43 cases relapsed after an initial response. During treatment, 12/69 patients (17.4%) had a dose reduction. The reasons for dose reduction included infections, bleeding, diarrhea (2 cases each), neutropenia, renal toxicity, hypertension, cramps, peripheral neuropathy and medical decision (1 case each).

After a median follow-up for survival of 15.6 months in the whole cohort (range 1-54), 40/69 patients (58%) were alive and 29/69 patients (42%) had died; reasons were PD in 23 cases, infectious complications in 3 cases (including SARS-CoV-2 pneumonia in 1 patient), second malignancy, cardiac failure and acute renal insufficiency in 1 case each.

Median PFS was 17 months, median DOR was not reached (estimated 2-y DoR 68%), median OS was 34.8 months, as illustrated in **Figure 1A-C**.

As expected, OS was improved for patients who responded compared to those who did not respond to ibrutinib, with a median OS of 8.7 months in those who did not respond and not reached in the responding patients (estimated 2-y OS 77.3%, P<0.0001), as represented in **Figure 2**. Simplified MIPI score at diagnosis and prior to ibrutinib, advanced-stage at diagnosis and prior to ibrutinib, age, gender, presence of blastoid/pleomorphic variant, administration of intensive front-line regimen, prior ASCT as consolidation, the achievement of a CR/PR after induction therapy and a POD less than 24 months were not associated with PFS and OS, as showed in **Table 3**. The administration of more than 1 prior line of therapy (P=0.04) and the presence of B symptoms (P=0.01) were associated with reduced PFS (**Figure 3A**, **3B**). Stage IV disease at diagnosis, the administration of more than 1 prior line of therapy and the presence of B symptoms showed a trend towards a reduced OS, not statistically significant (Supplementary Figure 1, available on request).

Therapies and clinical outcome after ibrutinib failure

Out of 23 patients who had a treatment failure and 9 patients who relapsed after an initial response to ibrutinib, data about subsequent therapies were available for 14 cases. Subse-

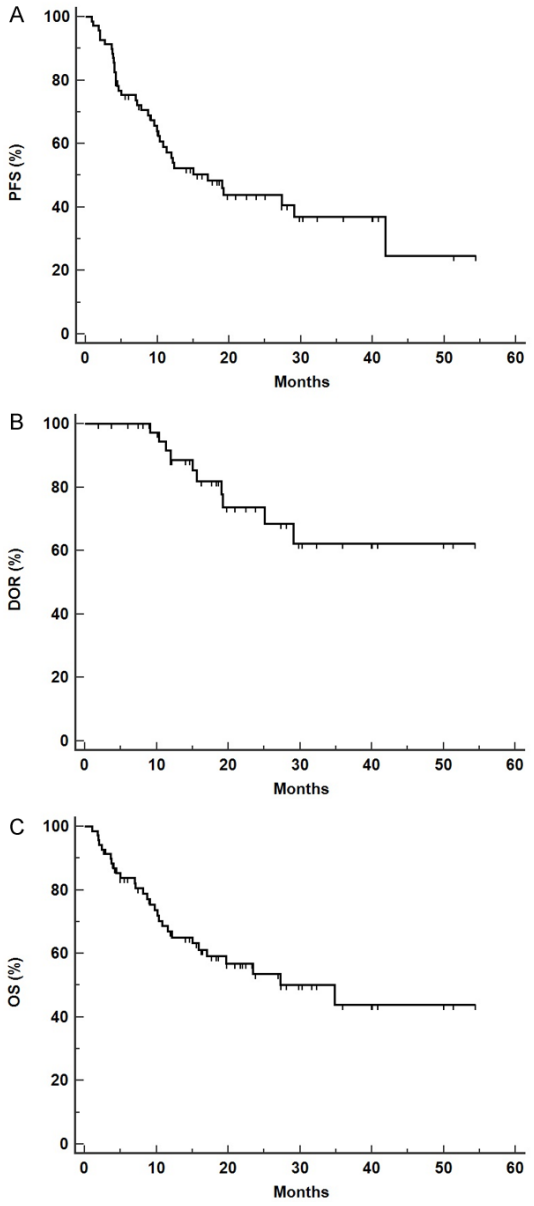

Figure 1. Survival analysis for the entire cohort. (A) Progression-free survival, (B) duration of response, (C) overall survival.

quent regimens included bortezomib (3 cases, as single-agent, together with rituximab or bendamustine, 1 case each), lenalidomide, R-BAC and BR (2 cases each), carfilzomib, lenalidomide, dexamethasone (KRD), venetoclax, rituximab and chlorambucil, HD-cytarabine, R-COMP (1 case each). As expected, ORR was 28.6% (4/14 cases), while most patients (10/14) experienced progression and died. For the entire cohort, regardless of further therapies, OS after ibrutinib failure was poor; median OS was 5 months (Supplementary Figure 2, available on request).

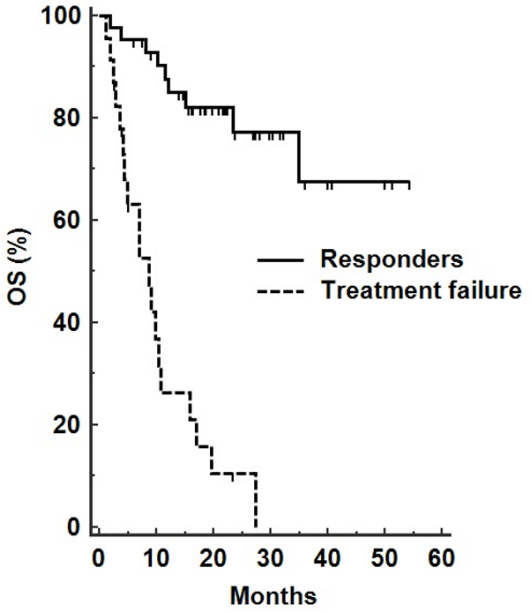

Figure 2. Overall survival for patients who had an initial response to ibrutinib compared to those who did not respond.

Toxicity

As represented in Supplementary Table 1 (available on request), the majority of the AE were mild to moderate (grade 1-2). A decrease in neutrophils count was observed in 11/69 cases (15.9%), while grade 3-4 neutropenia occurred in 7/69 cases (10.1%). Grade 1-2 thrombocytopenia and anemia occurred in 6/69 (8.7%) and 2/69 cases (2.9%), respectively.

Nonhematologic AE included diarrhea (8/69 cases, 11.6%), upper respiratory tract infections (9/69 cases, 13%), AF (2/69 cases, 2.9%), bleeding (4/69 cases, 5.8%), arthralgya (4/69 cases, 5.8%) and hypertension (1/69 cases, 1.4%). No grade 3-4 infections were observed, but 3 grade 5 infections were reported (due to septic shock not otherwise specified, Klebsiella KPC and SARS-CoV-2 infection, 1 case each). Second malignancies were observed in 2/69 cases (2.9%) and included lung cancer and prostate cancer (1 case each).

Discussion

In this study we observed that i) ibrutinib single-agent was very effective with manageable toxicity for R/R MCL patients in a real-life population, ii) treatment efficacy was higher in patients receiving ibrutinib as a 2nd line regi-

Table 3. Predictive factors of survival

Variable	OS		PFS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male	1	n.s.	1	n.s.
Female	0,7934 (0,3715-1,6944)		1,1303 (0,5851-2,1837)	
Age ≥70 years	1	n.s.	1	n.s.
Age <70 years	1,3267 (0,6404-2,7484)		1,5641 (0,8276-2,9561)	
No B-symptoms	1	n.s.	1	0,0164
B-symptoms	1,8611 (0,7061-4,9053)		2,2887 (0,9420-5,5609)	
Classic	1	n.s.	1	n.s.
Blastoid-pleomorphic	1,3140 (0,3454-4,9987)		0,9519 (0,2999-3,0211)	
High-intensity front-line therapy	1	n.s.	1	n.s.
No High-intensity front-line therapy	0,9769 (0,4002-2,3846)		0,8981 (0,4061-1,9857)	
No ASCT	1	n.s.	1	n.s.
ASCT	0,8674 (0,2800-2,6870)		1,0518 (0,3655-3,0268)	
sMIPI low-intermediate	1	n.s.	1	n.s.
sMIPI high	1,1147 (0,4988-2,4910)		1,2181 (0,5975-2,4832)	
Ibrutinib 2nd line	1	n.s.	1	0,0393
Ibrutinib later lines	1,8958 (0,8742-4,1113)		1,9293 (0,9748-3,8184)	
Ibrutinib response	1	<0.0001	1	<0.0001
Ibrutinib no response	8,2137 (3,2785-20,577)		7,4910 (3,2373-17,3338)	
Stage I-III	1	n.s.	1	n.s.
Stage IV	1,9006 (0,9159-3,9437)		1,6206 (0,8578-3,0617)	
POD<24 mesi	1	n.s.	1	n.s.
POD>24 mesi	0,6855 (0,3310-1,4195)		0,9302 (0,4923-1,7576)	

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ASCT, autologous stem cell transplantation; sMIPI, simplified mantle-cell lymphoma International Prognostic Index; POD, progression of disease.

men, iii) survival outcome was poor after ibrutinib failure.

Management of R/R MCL is challenging, response to therapy is often unsatisfactory with reduced survival. In the PCYC-1104 trial, 111 R/R MCL cases received ibrutinib monotherapy, with a promising median PFS, DoR and OS of 13, 17.5 and 22.5 months, respectively [12]. The phase III multicenter, randomized RAY study definitely demonstrated the superior efficacy of ibrutinib compared to temsirolimus; median PFS was 14.6 and 6.2 months, respectively (P<0.0001) [23, 24]. In a long-term follow-up pooled analysis from 3 open-label studies (PCYC-1104, SPARK and RAY), median PFS was 12.8 months; interestingly, patients receiving ibrutinib as 2nd line regimen had the longest PFS compared with patients who had received more than 2 prior therapies [14]. These findings were confirmed in an extended 3.5-y pooled follow-up analysis, in which median PFS and OS for patients receiving ibrutinib in 2nd line were significantly prolonged compared with those treated in later lines (25.4 vs 10.3 months and not reached vs 22.5 months, respectively) [15].

Unexpectedly, there are only a few real-life published studies. Epperla and colleagues retrospectively analyzed 97 MCL patients, ORR was 65%, the median DoR, PFS and OS were 17, 15 and 22 months, respectively; ibrutinib response, sMIPI score, the presence of primary refractory disease were associated with PFS [16]. In an Italian retrospective study 77 patients were enrolled, who granted ibrutinib by compassionate use in a Named Patient Program (NPP). MCL patients were heavily pretreated (median number of prior regimens was 3), ORR was 36.4% (CR rate 18.2%), median PFS and OS were 12.9 and 16 months, respectively [17]. Another study enrolled 65 R/R MCL cases receiving ibrutinib in a NPP within the UK and Ireland. In the 5-y follow-up report, ibrutinib was well tolerated, without unexpected AE, the main reason for discontinuation was PD; median PFS and OS were 12 and 18.5

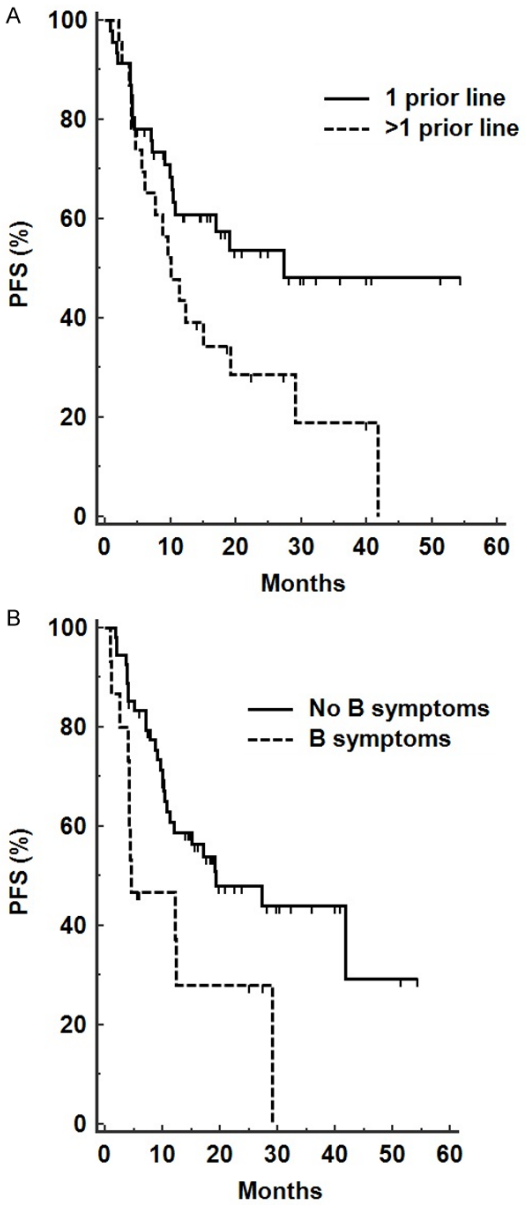

Figure 3. Progression-free survival for patients with one or more than 1 prior line of therapy before ibrutinib (A) and for patients with or without B-symptoms (B).

months, respectively [18]. Sharman and colleagues retrospectively analyzed data from the US Oncology Network electronic medical records database [20]. Out of 159 R/R MCL patients, median PFS and OS were 19.55 and 25.82 months, respectively; OS after ibrutinib interruption was only 9.2 months [20].

In our study, ORR and CR rate were 62.3% and 39.1%, with a median PFS and OS of 17 months and 34.8 months, respectively. Treatment response and survival are consistent with those highlighted in the pooled analysis from 3 open-label studies by Rule and colleagues, particularly in terms of ORR (66% vs 62.3%), with a slightly improvement in our study of median PFS (12.8 vs 17 months) and OS (25 vs 34.8 months) [15]. If we compare our study with previously published retrospective experiences, first of all, we would like to report the difference in the median number of prior therapies; in the other studies 2 or 3 lines were administered before ibrutinib, while in the our cohort (as in the recent study within the UK) most cases received treatment as 2nd line (Supplementary Table 2). It could justify the increased DoR and CR rate and the reduced incidence of primary resistance in our population. In our opinion, an increased number of prior therapies could increase the risk of developing resistance to any treatment. The rate of treatment discontinuation was consistent with literature data; however, in our population, in most cases, ibrutinib was interrupted due to PD rather than toxicity.

Remarkably, our study confirms a higher efficacy, with improved PFS, when ibrutinib is administered as 2nd line rather than in subsequent lines, as reported in the aforementioned pooled analysis. The lack of statistically significant OS improvement in our population could be due to the reduced sample size.

In our study, as previously reported by Epperla and colleagues, the prognostic role of well-established variables associated with poor outcome, such as age, high MIPI score and the presence of a blastoid/pleomorphic variant, was not confirmed [16]. This issue could be due to the heterogeneity of patient characteristics and pre-ibrutinib therapies, as well as a reduced sample size compared with clinical trials. Unlike most of the other series, in our study the presence of B symptoms at diagnosis was associated with a reduced PFS.

Overall toxicity was consistent with literature data; as commonly observed in a retrospective study, AE incidence was lower than reported in clinical trials. Safety profile was manageable and only a minority of cases discontinued treatment due to an AE. These data allow confirming the handling of the drug and the favorable risk to benefit profile in daily clinical practice.

The strength of our study is represented by the achievement of data in homogeneously treated, unselected patients, indicative of daily clinical practice, managed in 10 Tuscan onco-hematologic Divisions.

Study shortcomings are represented by the retrospective nature and by the reduced sample size (even if comparable with previous experiences), who could have contributed to the lack of prognostic value for well-established clinical and biological variables. The median follow up is short but it is comparable with other retrospective studies and it is due to the aggressive nature of MCL, with many patients who finally die because of PD.

Finally, as previously reported in at least 2 published studies, we can confirm disease outcome is extremely poor after ibrutinib failure, with a median OS of less than 1 year and an unsatisfactory response to further therapies [25, 26]. In this setting, promising results were recently obtained with the R-BAC regimen, ORR was 83%, with a CR rate of 60% and a median PFS and OS of 10.1 and 12.5 months, respectively [27]. This regimen could represent a bridge to allo-SCT for eligible patients [27, 28]. Another opportunity for patients with an initial disease relapse or a suboptimal efficacy could be represented by combination strategies, such as ibrutinib in association with R, BR or venetoclax [29-32].

Conclusion

In this study we suggest ibrutinib single-agent could represent a suitable treatment option for R/R MCL patients in clinical daily practice, with similar outcomes as those reported in clinical trials and manageable toxicity. PFS and OS were durable and DoR was very prolonged for responsive patients. Disease outcome was particularly favorable for patients receiving treatment as 2nd line. Unfortunately, patients experiencing ibrutinib failure have limited survival and represent an unmet medical need. The manageable profile of the drug could permit to conceive combination strategies, especially for high-risk patients.

Disclosure of conflict of interest

None.

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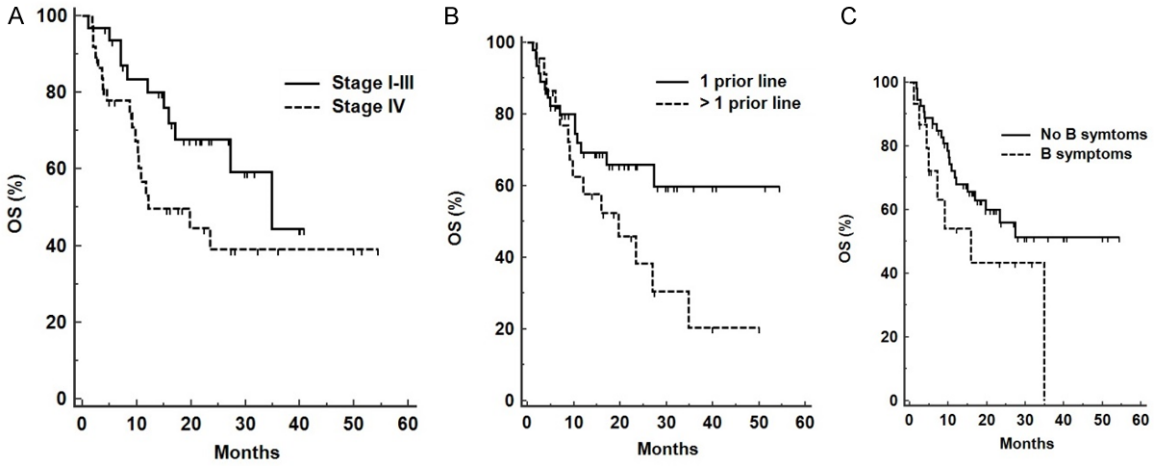
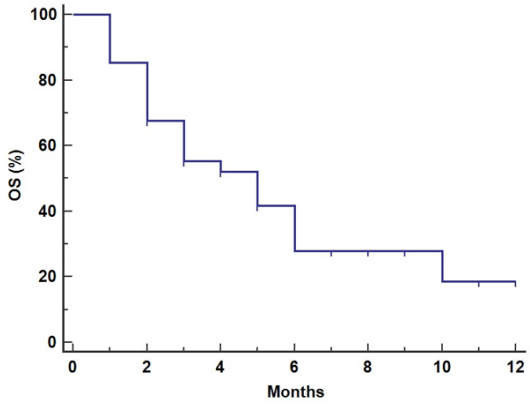


Supplementary Figure 1. Variables associate with a trend towards a reduced OS: (A) stage IV disease at diagnosis, (B) the administration of more than 1 prior line of therapy, (C) the presence of B symptoms.



Supplementary Figure 2. Overall survival after ibrutinib failure.

Supplementary Table 1. Treatment toxicity

	Overall (%)	Grade 3-5 (%)
Hematological toxicity		
Neutropenia	11/69 (15.9%)	7/69 (10.1%)
Thrombocytopenia	6/69 (8.7%)	1/69 (1.4%)
Anemia	2/69 (2.9%)	/
Diarrhea	8/69 (11.6%)	/
Respiratory tract infections	9/69 (13%)	3/69 (5.3%)
Atrial fibrillation	2/69 (2.9%)	/
Bleeding	(4/69 cases, 5.8%)	/
Neuro-muscular complications	(4/69 cases, 5.8%)	/
Hypertension	(1/69 cases, 1.4%)	/

Supplementary Table 2. Clinical results of ibrutinib for relapsed/refractory MCL outside clinical trials

	Sharman et al. [20]	Tucker et al. [18]	Jeon et al. [19]	Epperla et al. [16]	Broccoli et al. [17]	McCulloch et al. [21]	This study
Patients, *n*	159	65	33	97	77	211	69
Median prior treatments (range)	2 (1-3)	2 (1-6)	2 (1-4)	2 (1-8)	3 (1-10)	1	1 (1-4)
Median cycles (range)	7.8 (Q1-Q3 2.6-23.1)	10	16 (3-69)	N.A.	6 (1-20)	N.R.	9 (1-45)
ORR/CR	N.A.	N.A.	64%/15%	65%/33%	36.4%/18.2%	69%/27%	62.3%/39.1%
Ibrutinib discontinuation	83.6%	80%	51.6%	50.5%	78%	72%	59.4%
PD	35%	56%	36.4%	46.4%	53.3%	66%	43.5%
Toxicity	25.6%	13.8%	9.1%	4.1%	16.9%	7%	11.6%
Other	23%	10.2%	6.1%	/	7.8%	27%	5.3%
Median DoR	N.A.	N.A.	33.4 months	17 months	N.R. (79.2% at 40 months)	N.R.	N.R. (68% at 2-years)
Median PFS	19.55 months	12 months	27.4 months	15 months	12.9 months	17.8 months	17 months
Median OS	25.82 months	18.5 months	35.1 months	22 months	16 months	23.9 months	34.8 months

Abbreviations: ORR, overall response rate; CR, complete response; PD, progressive disease; DoR, duration of response; PFS, progression-free survival; OS, overall survival; N.R., not reported.