Annals of Oncology Advance Access published March 25, 2015

original article

Annals of Oncology 00: 1–5, 2015
doi:10.1093/annonc/mdv111

Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes

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Received 18 December 2014; revised 16 February 2015; accepted 18 February 2015

Background: Although ibrutinib is highly effective in patients with relapsed/refractory mantle cell lymphoma (MCL), a substantial proportion of patients have resistant disease. The subsequent outcomes of such patients are unknown.

Patients and methods: We carried out a retrospective review of all patients with MCL treated with ibrutinib at MD Anderson Cancer Center between January 2011 and January 2014 using pharmacy and clinical databases. Patients who had discontinued ibrutinib for any reason were included in the study.

Results: We identified 42 patients with MCL who discontinued therapy due to disease progression on treatment ($n = 28$), toxicity ($n = 6$), elective stem-cell transplant in remission ($n = 4$) or withdrawn consent ($n = 4$). The median age was 69 years, 35 (83%) were male; the median number of prior treatments was 2 (range 1–8) and the median time from initial diagnosis of MCL to commencing ibrutinib was 3.0 (range 0.5–15.5) years. Patients had received a median of 6.5 (range 1–43) cycles of ibrutinib. Among 31 patients who experienced disease progression following ibrutinib and underwent salvage therapy, the overall and complete response rates were 32% and 19%, respectively. After a median follow-up of 10.7 (range 2.4–38.9) months from discontinuation of ibrutinib, the median overall survival (OS) among patients with disease progression was 8.4 months. By univariate analysis, elevated serum lactate dehydrogenase at progression was associated with inferior OS.

Conclusion: The outcome of patients with MCL who experience disease progression following ibrutinib therapy is poor, with both low response rates to salvage therapy and short duration of responses. Further studies to better understand and overcome ibrutinib resistance are urgently needed.

Key words: mantle cell lymphoma, treatment, ibrutinib, Bruton's tyrosine kinase inhibitors, prognosis

introduction

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma (NHL) with distinctive pathologic, molecular and clinical features. Though generally considered incurable, advances such as the incorporation of high-dose cytarabine with induction therapy [1–3], high-dose consolidation with autologous stem-cell transplantation [4] (in younger patients) and rituximab maintenance [5] (in elderly patients) have resulted in improved survival. However, the prognosis of patients with relapsed/refractory disease has been poor. The first-in-class Bruton's tyrosine kinase inhibitor ibrutinib was recently shown to be highly effective in this population as a single agent, with phase II data showing an overall response rate (ORR) of 68% and median duration of response of 17.8 months [6]. However, both primary and secondary ibrutinib resistance have been observed and the outcome of these patients is not well described. We therefore reviewed our experience with MCL patients treated with ibrutinib who subsequently stopped therapy in order to determine their clinicopathologic characteristics, prognostic factors, response to salvage therapies and outcome.

patients and methods

We carried out a retrospective review of all patients with MCL treated with ibrutinib at MD Anderson Cancer Center (MDACC) between January 2011 and January 2014 using pharmacy and clinical databases. Patients who had discontinued ibrutinib for any reason were included in the study. There was

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no protocol-mandated treatment of patients who experienced disease progression on ibrutinib; therefore, subsequent treatment strategy was determined by treating clinician. Standard baseline, treatment and other variables were collected on chart review and verified by two investigators. Ki67 proliferation index was determined according to published consensus criteria [7]. Continuous variables were expressed as median and range and compared using the Mann–Whitney *U*-test. Categorical variables were reported as percentages, and compared using the χ^2 test. Responses were defined according to the Lugano Classification [8]. Overall survival (OS) was determined from date of stopping ibrutinib until death from any cause. Duration of response to salvage therapy was calculated from date of best response to salvage therapy and disease progression or death from any cause. Survival analyses were carried out using the method of Kaplan and Meier, with curve comparisons using log-rank analysis. *P* values were two sided and values <0.05 and were considered significant. Cox proportional hazard modeling was used to determine prognostic factors for OS by univariate analysis, and factors with *P* value of <0.2 were included in an exploratory multivariate analysis. This study was approved by the MD Anderson Cancer Center institutional review board (Protocol PA14-0694).

results

We identified 78 patients with MCL treated with ibrutinib at MDACC during the period specified, of whom 42 (54%) have discontinued therapy. Patients were treated on with ibrutinib alone ($n = 34$, 81%), or rituximab and ibrutinib ($n = 8$, 19%). The characteristics of the patients at time of commencing ibrutinib and at time of disease progression are presented in Table 1. The median time from initial diagnosis of MCL to commencing ibrutinib was 3.0 (range 0.5–15.5) years. Baseline cytogenetic analysis was available in 40 patients: 28 (70%) had normal karyotype and 12 abnormal, although features known to be associated with higher risk (3q gains or 9q deletions) were absent [9]. Although p53 mutations were not tested routinely, two patients were noted to have 17p deletions.

The median number of cycles of ibrutinib given was 6.5 (range 1–43, Figure 1). The main reason for discontinuation of therapy was disease progression on treatment, documented in 28 patients (67%). Ibrutinib resistance was primary in 8 patients (28%) and secondary in 20 patients (71%), with the latter group experiencing disease progression after an initial complete ($n = 6$) or partial ($n = 14$) response. Six patients (14%) discontinued ibrutinib because of toxicity: atrial fibrillation (AF, $n = 2$), bleeding, lung cancer, therapy-related myelodysplastic syndrome (MDS), prolonged hospitalization with respiratory infections in a patient with chronic obstructive pulmonary disease (each $n = 1$). The patient who developed MDS had received five prior treatments and had cytogenetic (but not morphologic) features consistent with MDS on bone marrow biopsy before commencing therapy with ibrutinib. Of patients stopping because of toxicity, three subsequently experienced disease progression. Three have remained in remission and are described in detail below. Of the patients who developed AF, one (who was in partial remission) received two cycles of hyper-fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with methotrexate/cytarabine (achieving complete response (CR)) followed by autologous stem-cell transplantation and remains in remission 3 months post-transplant. The other patient stopping therapy due to AF was in CR after six cycles of rituximab and ibrutinib, was observed and remains in remission 12 months after discontinuation of ibrutinib. One patient (in CR after nine cycles of rituximab and ibrutinib) stopped because of bleeding, was continued on 2-monthly rituximab maintenance

Table 1. Characteristics of patients who discontinued ibrutinib

Characteristic	At commencement of ibrutinib ($N = 42$)	At time of progression ($N = 34$)
	$n = 42$	($n = 34$)
Median age (range), years	69 (35–84)	69 (36–87)
	$n = 42$	$n = 34$
Male	35 (83%)	29 (85%)
Prior treatments	$n = 42$	–
1	14 (33%)	
2	12 (29%)	
3	5 (12%)	
4+	11 (26%)	
Prior therapies		
Rituximab	42 (100%)	–
CHOP	8 (19%)	
Hyper-CVAD	35 (83%)	
Lenalidomide	9 (21%)	
Bendamustine	13 (31%)	
Bortezomib	19 (45%)	
AlloSCT	4 (10%)	
Everolimus	4 (10%)	
Lactate dehydrogenase	$n = 38$	$n = 32$
Median normalized (range)	0.8 (0.5–1.8)	0.8 (0.5–2.0)
>Upper limit of normal	8 (21%)	4 (12.5%)
White cell count (range) $\times 10^9$/l	5.0 (2.2–11.3)	5.9 (1.8–24.6)
Performance status	$n = 40$	–
0	20 (50%)	
1	19 (48%)	
2	1 (2%)	
Morphology	$n = 37$	$n = 14$
Classical (nodular, diffuse)	25 (68%)	9 (64%)
Pleomorphic, blastoid	12 (32%)	5 (36%)
	$n = 21$	$n = 6$
Median Ki67 (range)	50% (5%–100%)	72% (30%–95%)
Ki67 ≥50%	11 (52%)	4 (67%)
Median duration on ibrutinib (range), months	–	$n = 34$ 6.5 (1.2–43.3)

Middle column: at time of commencing ibrutinib. Right column: at time of disease progression.
R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; alloSCT, allogeneic stem-cell transplantation; n/a, not available/applicable.

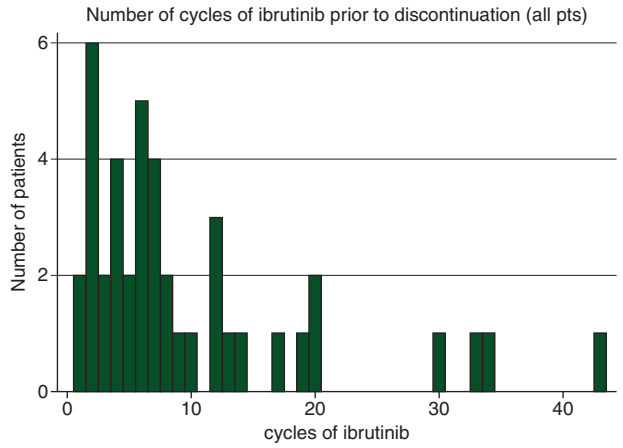

Figure 1. Histogram depicting the distribution and numbers of patients with respect to the number of cycles of ibrutinib administered before discontinuation of therapy (for any reason).

and remains in remission 6 months after discontinuation of ibrutinib. Four patients (12%) electively stopped ibrutinib in remission to pursue consolidative stem-cell transplantation after 4, 4, 8 and 10 cycles of therapy. Three received autologous, and one haploidentical allogeneic, stem-cell transplantation. All were alive and free from disease progression at time of reporting 3, 4, 5 and 38 months post-transplantation. Four patients (7%) withdrew consent for different reasons: financial difficulty, inability to travel, severe psychiatric illness and cause unknown. Three of these patients have subsequently experienced disease progression since stopping ibrutinib; one recommenced ibrutinib after it became commercially available.

Thirty-one patients with disease progression post ibrutinib received salvage chemoimmunotherapy. The ORR to first salvage regimen was 32% and CRR 19%; outcomes were poor irrespective of the regimen used (Table 2). After a median follow-up of 10.7 (range 2.4–38.9) months, the estimated 1-year OS was 22.1% (95% CI 8.3% to 40.2%) and the median OS was 8.4 months. The ORR among patients who had received ≤2 treatments before ibrutinib had an ORR of 35% (7/20) while patients with >2 prior treatments had an ORR of 25% (3/12), $P = 0.70$. Among the 10 patients who achieved a response to any salvage therapy, the median duration of response was 5.8 (range 0.9–10.1) months. Seven patients who achieved responses to salvage therapy underwent stem-cell transplantation (five allogeneic, two autologous). Among the patients receiving allogeneic transplantation, three have died (pneumonia, day +6, systemic and central nervous system progression, day +86 and acute graft versus host disease, day +129). The other two patients remain alive in remission at 7 and 10 months post-transplant. Of the patients treated with autologous stem-cell transplantation, one died from disease progression and the other is alive in remission 4 months post-transplant.

Prognostic factor analysis for OS was restricted to patients who experienced disease progression and received active therapy (Table 3). Elevated serum lactate dehydrogenase (LDH) at time of disease progression was adversely prognostic by univariate analysis (Figure 2A), while high MIPI, Ki67 ≥50% before the commencement of ibrutinib and lack of response to salvage

Table 2. Treatment regimens and response rates among patients treated for disease progression following discontinuation of ibrutinib

Regimen	*N*	ORR	CRR	mOS (months)
Hyper-CVAD	8	3 (37%)	2 (25%)	7.3
Bendamustine based	6	2 (33%)	2 (33%)	10.0
Investigational agent	3	2 (66%)	1 (33%)	NR
Lenalidomide based	3	1 (33%)	0 (0%)	10.5
Bortezomib based	3	0 (0%)	0 (0%)	6.9
Platinum based	2	1 (50%)	1 (50%)	8.2
Radiation	4	1 (25%)	0 (0%)	5.6
Fludarabine based	2	0 (0%)	0 (0%)	2.7
Overall	31	10 (32%)	6 (19%)	8.4

All salvage chemotherapy regimens contained rituximab.
hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; ORR, objective response rate; CRR, complete response rate; mOS, median overall survival.

Table 3. Univariate analysis of prognostic factors for overall survival using Cox proportional hazards model

Prognostic factor	Hazard ratio	*P* value
At commencement of ibrutinib		
Age (≥68 versus <68 years)	0.94 (0.39–2.24)	0.88
Serum lactate dehydrogenase (elevated versus normal)	1.56 (0.52–4.72)	0.45
White cell count (elevated versus normal)	1.50 (0.34–6.57)	0.60
MIPI		
Low	–	–
Intermediate	0.25 (0.03–1.90)	0.12
High	1.84 (0.60–5.67)	0.28
Performance status (≥1 versus 0)	0.83 (0.33–2.12)	0.51
Morphology (pleomorphic/blastoid versus classical)	1.95 (0.78–4.90)	0.16
Ki67 (≥50 versus <50%)	5.32 (0.64–44.5)	0.06
Number of prior therapies (≥3 versus <3)	0.88 (0.31–1.95)	0.59
Type of ibrutinib resistance (primary versus secondary)	1.55 (0.51–4.67)	0.41
At disease progression		
Hemoglobin (<100 versus ≥100 g/l)	2.07 (0.74–5.78)	0.19
White cell count (elevated versus normal)	0.35 (0.11–1.06)	0.08
Serum lactate dehydrogenase (elevated versus normal)	3.67 (1.19–11.33)	0.035
B symptoms (yes versus no)	2.49 (0.31–19.67)	0.44
Morphology (pleomorphic/blastoid versus classical)	1.21 (0.34–4.39)	0.77
Number of cycles of ibrutinib (<6 versus ≥6 cycles)	1.64 (0.69–3.92)	0.25
Response to salvage therapy (yes versus no)	0.42 (0.14–1.27)	0.098

MIPI, mantle cell lymphoma international prognostic index.

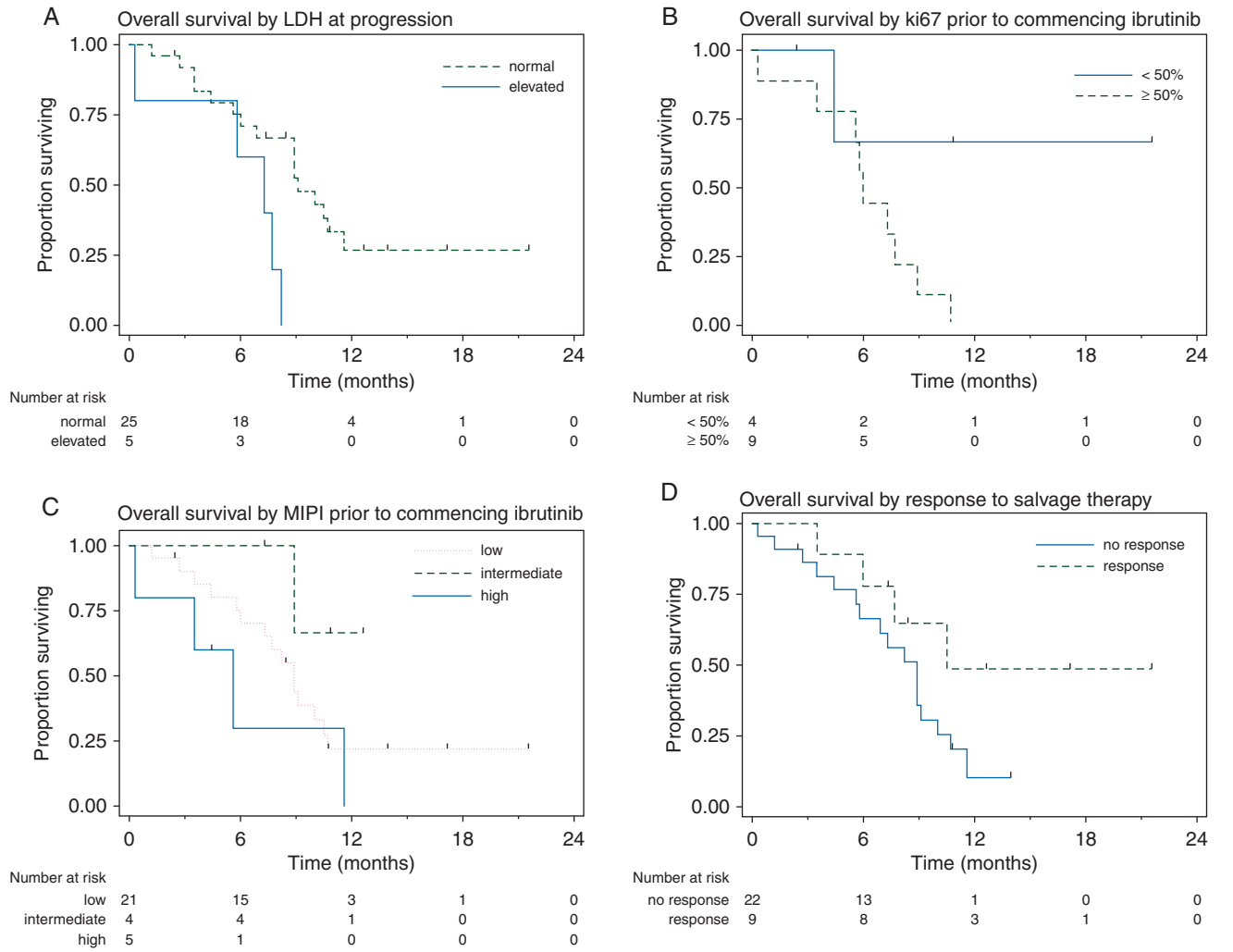

Figure 2. Overall survival from progression on ibrutinib among patients who received active salvage treatment ($n = 31$): (A) by lactate dehydrogenase at time of progression on ibrutinib; (B) by Ki67 proliferation index at biopsy before commencement of ibrutinib; (C) by MIPI before commencing ibrutinib; (D) by response to salvage therapy.

therapy were associated with a nonsignificant trend toward inferior OS (Figure 2B–D). Ki67 on biopsies at the time of progression on ibrutinib was only available in six patients, limiting further analysis. Exploratory multivariate analysis including pre-ibrutinib factors (MIPI, morphology and Ki67) and factors from time of progression (hemoglobin, white cell count and LDH) found none retained significance (data not shown). The remainder of potential factors examined including age, B symptoms, performance status, number of prior therapies, type of ibrutinib resistance (primary versus secondary), duration of ibrutinib and response to salvage therapy were not associated with OS.

We compared disease morphology in 14 patients who had biopsies pre- and post-ibrutinib: 6 (43%) were classical histology and remained unchanged at progression; 3 (21%) transformed from classical to blastoid; 3 (21%) with blastoid morphology pre-ibrutinib were classical at progression and 2 (14%) with blastoid histology remained blastoid at progression. Of the six biopsies carried out at progression in which Ki67 staining was carried out, pre-ibrutinib-paired Ki67 data were available for comparison. Ki67 was higher at post-ibrutinib progression in two cases (40% → 60%, 50% → 85%), similar in two cases (100% → 95%, 40% → 40%) and lower in one case (70% → 30%).

discussion

This report emphasizes the poor prognosis of patients with MCL who progress following treatment with ibrutinib. Even among the one-third of patients who respond to salvage therapies, duration of response was brief. With the exception of elevated serum LDH at time of progression, prognostic factors established in patients treated with chemoimmunotherapy or factors related to ibrutinib were unable to predict outcome. A handful of patients who achieved response did survive to undergo stem-cell transplantation; however, only two of seven remain alive. In contrast, the four patients who electively stopped ibrutinib in remission raise the possibility that ibrutinib may be used as a 'bridging' strategy to transplant; however, a larger cohort with longer follow-up is required to confirm this.

These data are in agreement with the only other data to our knowledge describing the outcomes of this patient population, reported by Martin et al. who studied 32 patients with ibrutinib resistance and found a similar ORR to salvage therapy of 6/17 response-evaluable patients (35%) and median OS of 4 months [10]. The clear message from both studies is that patients with relapsed MCL who exhibit primary or secondary ibrutinib resistance represent the greatest unmet medical need in this disease at present. Understanding the mechanism by which ibrutinib resistance occurs is of critical importance. In CLL patients with ibrutinib resistance, point substitutions in *BTK* (C481S) and *PLCG2* (R665W) have been described [11]. In contrast, Balasubramanian et al. carried out deep sequencing mutational analysis of 97 genes of interest on tumor biopsies of 25 patients with primary ibrutinib resistance (defined as PD at first response assessment on therapy) on paired samples pretreatment and at time of progression and identified recurrent mutations in *MLL2*, *CREBBP*, *PIM1* and *ERBB4* [12]. *MLL2* and *CREBBP* have been implicated in the pathogenesis of DLBCL [13]. Further studies to better understand ibrutinib resistance and devise means to prevent or circumvent it are required. Recent data suggest the HSP90 inhibitor AUY922 has promising activity in ibrutinib-resistant MCL murine xenograft model [14]. However, clinical trials using novel agents in this patient population are urgently needed to improve outcomes for these patients.

acknowledgement

CYC acknowledges his wife Kylie for her unending support.

disclosure

MLW reports receiving grant support through his institution from Pharmacyclics and Janssen Biotech. All remaining co-authors have declared no conflicts of interest.

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