Poor Overall Survival of Patients with Ibrutinib-Resistant Mantle Cell Lymphoma

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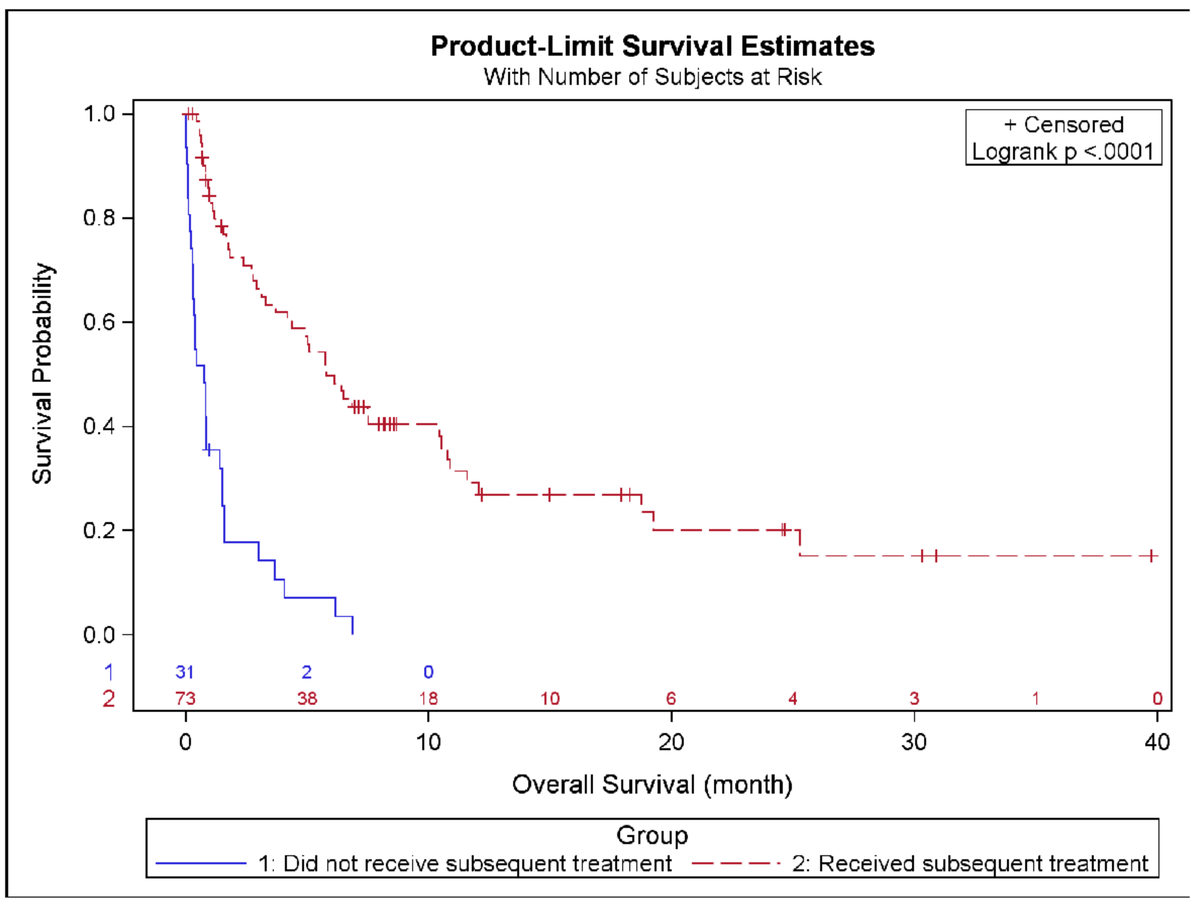
METHODS AND OBJECTIVES

We performed a retrospective cohort study of all patients with MCL that experienced disease progression while receiving ibrutinib across 15 international sites. Medical records were evaluated for clinical characteristics, therapies used pre and post ibrutinib, and pathology and radiology data. Time-to-event statistics were estimated using the Kaplan-Meier method. Cox proportional hazard regression was used to calculate hazard ratios and test statistical significance.

The primary objective was to describe the overall survival of patients with MCL following cessation of ibrutinib due to disease progression. The secondary objective was to determine the association between key clinical and treatment variables and overall survival.



RESULTS

Characteristics pre-ibrutinib	Number	
All	114	
Median Age	68 years	Range 46-85
Prior systemic therapies	3	Range 0-10
MIPI scores at start of ibrutinib		
High risk	46	39%
Intermediate risk	35	26%
Low risk	22	19%
Unknown	18	16%
Response to ibrutinib		
Complete response	13	11%
Partial response	45	39%
Stable disease	5	4%
Progressive disease	37	32%
Not reported/Not evaluable	14	12%
Duration of ibrutinib	4.7 mo.	95% CI 3.8-5.7 Range 0.7-43.6 mo.

Characteristics post-ibrutinib	Number	Percentage
All	104	100%
Received treatment post-ibrutinib	73	70%
Time from ibrutinib to next therapy	0.3 mo.	95% CI 0.2-0.5 mo.
MIPI scores at start of therapy		
High risk	35	48%
Intermediate risk	18	25%
Low risk	9	12%
Unknown	11	15%
Subsequent treatment		
Rituximab	39	53%
Lenalidomide	19	26%
Cytarabine	13	18%
Bendamustine	12	16%
Bortezomib	7	10%
Anthracycline	5	7%
PI3K inhibitor	4	5%

The median OS of all patients following cessation of ibrutinib was 2.9 months (95% C.I. 1.6-4.9). The cause of death was lymphoma in 79, treatment-related toxicity in 3, unrelated in 2, and not reported in 30. The median OS following ibrutinib cessation for patients that received subsequent treatment was 5.8 months (95% C.I. 3.7-10.4). Sixty-seven patients underwent a second post ibrutinib therapy. The median time from first to second subquent therapy was 2.4 months (95% C.I. 1.4-3.3). For patients that received subsequent treatment following ibrutinib failure, univariate Cox regression analysis of MIPI prior to ibrutinib, MIPI prior to first subsequent treatment, best response to ibrutinib, duration of ibrutinib, and subsequent treatment with bendamustine, cytarabine, or lenalidomide revealed that only MIPI prior to ibrutinib (HR 1.81, 95% C.I. 1.32 to 2.49, p=0.0002) and duration of ibrutinib (HR 0.96, 95% C.I. 0.93 to 1.00, p=0.0465) were associated with OS. Multivariate Cox regression analysis revealed that none of MIPI prior to first post-ibrutinib therapy, treatment with bendamustine, cytarabine, or lenalidomide was associated with overall survival from the start of the post-ibrutinib therapy.

CONCLUSIONS

Poor clinical outcomes were noted in majority of patients with primary or secondary ibrutinib resistance. Patients with a low-risk MIPI score prior to ibrutinib and a long duration of ibrutinib had longer survival following ibrutinib but we could not identify treatments that clearly improved outcomes. Future trials should focus on preventing ibrutinib resistance and on treatment following ibrutinib.

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