DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

THE IMPACT OF CXCR4 MUTATION SUBTYPES IN THE RESPONSE AND PROGRESSION-FREE SURVIVAL OF PATIENTS WITH WALDENSTROM MACROGLOBULINEMIA TREATED WITH IBRUTINIB

Jorge J. Castillo, Joshua N. Gustine, Kirsten Meid, Toni E. Dubeau, Lian Xu, Guang Yang, Zachary R. Hunter, Steven P. Treon

Bing Center for Waldenstrom Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

INTRODUCTION

Ibrutinib is the only approved drug for the treatment of symptomatic Waldenstrom macroglobulinemia (WM), with a major response rate of 70% and a median progression-free survival (PFS) that has not yet been reached at 4 years of follow-up. CXCR4 mutations, which can be detected in up to 40% of patients with WM, have been associated with lower major response rates and shorter median PFS in patients treated with ibrutinib. However, over 40 CXCR4 mutation subtypes have been described in WM patients, and the impact of these mutations in clinical presentation, response and PFS on ibrutinib needs further study.

METHODS

We identified patients seen at our institution between May 2012 and December 2017 who met clinicopathological criteria for WM and received ibrutinib therapy. CXCR4 mutations were detected using Sanger sequencing. CXCR4 mutations were divided in 3 groups: wild-type (WT), frameshift (FS) and nonsense (NS). Response was defined based on IWWM6 criteria. PFS was defined as the time between ibrutinib initiation and disease progression or death from any cause. PFS curves were estimated using the Kaplan-Meier method, and compared using the log-rank test. P<0.05 was considered significant.

Table 1. Selected patients' characteristics, according to CXCR4 mutation subtype

	Total (n=180)	CXCR4^{WT} (n=112)	CXCR4^{NS} (n=49)	CXCR4^{FS} (n=19)	p
Age >65 years	102 (57%)	65 (58%)	27 (55%)	10 (53%)	0.88
Male sex	119 (66%)	77 (69%)	27 (55%)	15 (79%)	0.11
Hemoglobin ≤11.5 g/dl	125 (70%)	78 (70%)	31 (63%)	16 (84%)	0.24
Platelet count ≤100 K/uL	20 (11%)	6 (5%)	8 (17%)	6 (32%)	0.002
Serum B2M >3 mg/l (n=157)	107 (68%)	73 (74%)	24 (55%)	10 (71%)	0.07
Serum IgM >7000 mg/dl	11 (6%)	3 (3%)	6 (12%)	2 (11%)	0.04
Bone marrow ≥50% (n=171)	92 (54%)	52 (50%)	29 (59%)	11 (65%)	0.38
Previously treated	125 (69%)	78 (70%)	33 (67%)	14 (74%)	0.88
IPSSWM (n=156)					
Low-risk	36 (23%)	23 (23%)	11 (26%)	2 (14%)	
Intermediate-risk	49 (31%)	33 (33%)	13 (30%)	3 (21%)	0.67
High-risk	71 (46%)	43 (43%)	19 (44%)	9 (64%)	
Indications to treat (n=179)					
Anemia	101 (56%)	65 (59%)	23 (47%)	13 (68%)	0.21
Constitutional symptoms	62 (35%)	37 (33%)	19 (39%)	6 (32%)	0.77
Hyperviscosity	27 (15%)	10 (9%)	13 (27%)	4 (21%)	0.01
Extramedullary disease	19 (11%)	18 (16%)	1 (2%)	0 (0%)	0.008
Neuropathy	16 (9%)	11 (10%)	4 (8%)	1 (5%)	0.79
Other indications	7 (4%)	6 (5%)	1 (2%)	0 (0%)	0.39
Response to ibrutinib (n=176)					
Very good partial response	44 (25%)	36 (33%)	3 (6%)	5 (26%)	
Partial response	90 (51%)	56 (52%)	24 (49%)	10 (53%)	
Minor response	31 (18%)	13 (12%)	16 (33%)	2 (11%)	<0.001
No response	11 (6%)	3 (3%)	6 (12%)	2 (11%)	
Major response (≥partial)	134 (76%)	92 (85%)	27 (55%)	15 (79%)	<0.001

Figure 1. PFS estimates in all patients

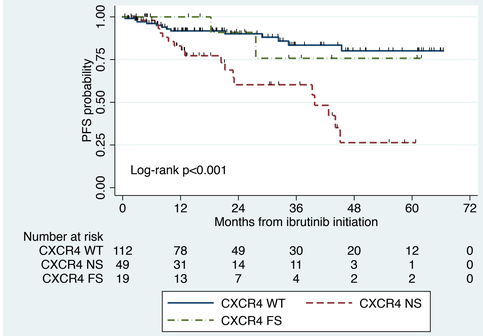

Figure 2. PFS estimates in previously untreated patients

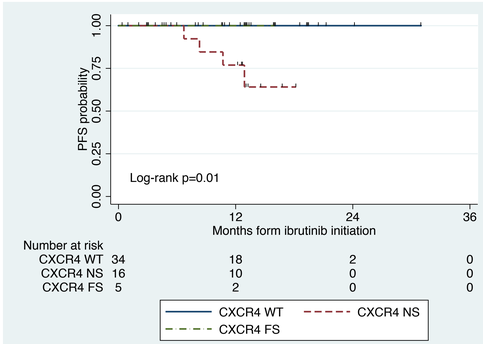

Figure 3. PFS estimates in previously treated patients

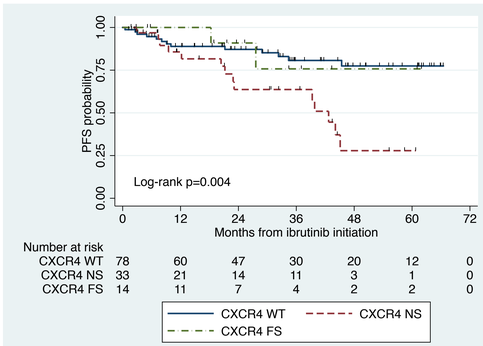

Table 2. Multivariate regression models for response and progression-free survival

Major response	OR (95% CI)	p
CXCR4^{WT}	1.00 (Ref)	
CXCR4^{NS}	0.20 (0.07-0.57)	0.002
CXCR4^{FS}	0.42 (0.09-2.01)	0.28
Progression-free survival	**HR (95% CI)**	**p**
CXCR4^{WT}	1.00 (Ref)	
CXCR4^{NS}	6.70 (2.70-16.7)	<0.001
CXCR4^{FS}	1.78 (0.34-9.27)	0.50

CONCLUSIONS

WM patients with CXCR4^{NS} were more likely to present with low platelets and high serum IgM level, and were less likely to have extramedullary disease than CXCR4^{FS} patients.

When treated with ibrutinib, WM patients with CXCR4^{NS} had lower odds of major response and worse PFS than CXCR^{WT} patients, while there were no detectable differences between CXCR4^{FS} and CXCR4^{WT} patients.

DISCLOSURES

JJC and SPT have received honoraria and/or research funds from Abbvie, Pharmacyclics Inc. and Janssen Pharmaceuticals.

REPRINTS

JORGEJ_CASTILLO@DFCI.HARVARD.EDU

DANA-FARBER CANCER INSTITUTE

BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

This is a PPT Template 1/2 of the final size

Please don't change the size

Your final poster print size will be 36"x 72"
including a white border all around