EFFICACY AND SAFETY OF ASCIMINIB DOSE ESCALATION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML) WITHOUT OPTIMAL RESPONSE TO THE STANDARD DOSE

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INTRODUCTION

Asciminib (ASC) is a highly effective STAMP inhibitor for the treatment of patients (pts) in the chronic phase (CP) of chronic myeloid leukemia (CML). However, approximately half of pts previously treated with ≥2 tyrosine kinase inhibitors (TKIs) do not achieve an optimal response to the standard dose (SD = 80 mg/day) of the drug.

AIM

To evaluate the long-term efficacy and safety of increasing the dose of ASC in patients with CP CML without BCR::ABL^{T315I} mutation and no optimal response to SD.

METHOD

ASC dose was escalated up to 120-400mg in 10 patients (6 men) after at least 12 months SD therapy due to absence of any molecular response (MR= BCR::ABL >10%) in 4 Pts or a major molecular response (MMR) in 6 pts (5/6 pts were in MR2, but never reached MMR). At the time of ASC escalation: the median age of Pts was 54.4 (28-72) years, the median CML duration was 4,6 (2,9-15,1 years), the median number of previous TKIs was 3 (2-6) and the median duration of SD of ASC therapy was 18.7 (14-49.2) months (Tab.1). Mutations in the BCR::ABL gene were not detected in any of the patients; additional chromosomal abnormalities were detected in one case.

CONCLUSIONS

The ASC dose escalation was effective – half of our pts reach at least MMR. High dose of ASC was safe; It seems that ASC dose escalation should be suggested in CP CML pts without MMR on SD

RESULTS

At the time of date collection the median duration of high dose (HD) ASC therapy was 30.8 (7.9-37.7) months. Six (60%) pts are ongoing HD of ASC during 45.4 (17-73.1) months and 4 other pts were switched to other TKIs due to lack of optimal response after median 13.7 (7.9-33.9) months of HD ASC. Among pts with baseline no MR only 1/4 (25%) reach MMR after re-escalating ASC dose from 160mg to 400mg. Among Pts with lower initial level of BCR::ABL 4/6 (66.7%) reach stable MMR after 3, 6, 9 and 24 months of HD therapy. No new grade 3-4 AEs were recorded after the ASC dose escalation. Duration of follow up for the start of HD ASC was 38.9 months (26-43.9) months. All patients are alive without progression to the advanced phases of the disease.

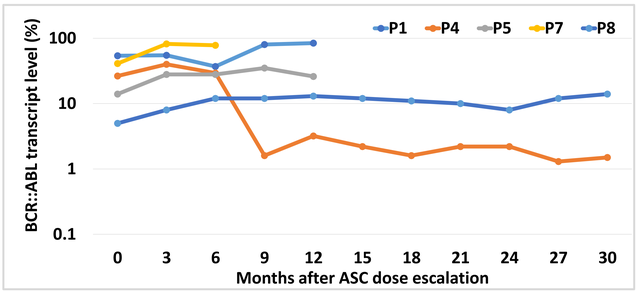
Table 1. Individual patient characteristics (n=10) before and after ASC dose escalation.

Patient number	Sex/ age (years)	Duration of SD ASC therapy (mos)	Doses of ACS after escala-tion (mg)	Duration of ASC therapy after dose escala-tion (mos)	BCR::ABL (%) p210 transcript level					Duration of observation from the start of ASC SD (+if ongoing)/or ASC discontinuation (months)	ASC treatment disconti-nuation
					The best response on the last TKI	At the start of ASC	The best response on SD of ASC	At the start of escalated dose of ASC	The best molecular response after ASC dose escalation		
P1	M/62	29.4	200	12.6	9.9	44.4	39	54	No MR	68.1/26.1	Yes
P2	W/72	16.7	120/200	31.2	0	0.007	0.2	0.9	MMR	47.9+	No
P3	M/28	20.3	160	30.7	7.4	42.9	0.15	0.17	MMR	51.0+	No
P4	M/44	49.2	160/400	31	2.3	20.0	9.2	26.5	MR1	80.2+	No
P5	W/56	33.3	200	14.7	25	32	1.2	14	No MR	77.3/29,3	Yes
P6	W/71	35.9	200/80	37.7	16	17.8	0.2	0.3	MMR	73.6+	No
P7	M/62	15.6	200	7.9	21.9	44	31	41	No MR	55.2/31.7	Yes
P8	W/54	15.8	200	33.9	12	16	5	5	No MR	52.9/3.2	Yes
P9	M/47	14.0	200/80	34.6	1.1	1.4	0.4	0.5	MR2	48.6+	No
P10	M/61	17.1	200	26	9	9	0.13	0.36	MMR	43.1+	No

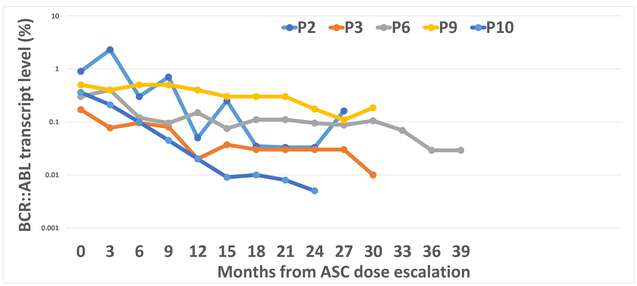
Abbreviations: ASC-asciminb, P-patient, M-male, W-woman, SD-standard dose, ESC-escalated dose, TKI-tirosine kinase inhibitor, MR-molecular response, No MR-BCR::ABL>10%, MR1-BCR::ABL>1-10%, MR2-BCR::ABL>0,1%-1%, MMR-major MR, BCR::ABL≤0,1%, mos-months

Dynamics of the BCR::ABL transcript level (log scale) After ASC dose escalation

A. among patients without MR2 a baseline



B. among patients with MR2 at baseline, but without MMR



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