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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Molecular and Cytogenetic Evaluation in Systemic Mastocytosis

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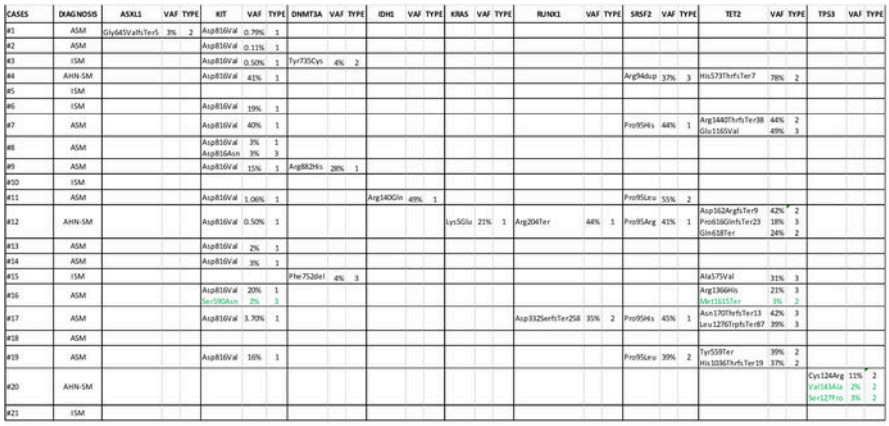
Systemic mastocytosis (SM) is a rare hematological neoplasm characterized by pleomorphic symptoms, related to mediators release from pathological mast cells. Tissue infiltration of liver, spleen, gastro-intestinal (GI) tract and osteolysis are present in aggressive disease. As KIT D816V mutation can be found in approximately 80% of patients, several additional somatic mutations of prognostic significance have been detected in a subset of patients.

We report on clinical, cytogenetic and molecular characteristic of 160 patients with SM diagnosed in the last 15 years at our center. Fourteen (8.9%) patients had cutaneous mastocytosis, 85 (53.5%) had indolent SM (ISM), 12 (7.5%) had smoldering SM (SSM), 27 (17%) had aggressive SM (ASM), 17 (10.5%) had SM with an associated hematological neoplasm (AHN-SM) and 1 (0.6%) had mast cell leukemia. Symptoms were mostly related to mediators release: itching and blistering (69, 43%), anaphylaxis (49, 30%), diarrhea/bloating (19, 12%), osteoporosis/bone fracture (10, 6%), constitutional symptoms (8, 5%), bone pain and myalgia (16, 10%), anaphylaxis from Hymenoptera venom (24, 15%). While SM patients were mostly treated with antihistamines and membrane stabilizers, 29 patients needed a disease modifying therapy. Four patients with ISM were treated with Interferon (IFN) for bone lytic alterations, while 1 patient with ISM started midostaurin for uncontrolled symptoms. Other 11 patients with ASM were treated with midostaurin: 4 responded, while 7 needed multiple lines of therapy including allogeneic transplant in 4 cases. Eleven patients with ASM were treated with tyrosin kinase inhibitors (TKI) before midostaurin became available, while 2 elderly patients were treated with low dose cytarabine and TKI for concomitant acute leukemia.

KIT D816V mutation was found in 111 of 131 (85%) evaluable patients with SM. Cytogenetics was normal in all but 2 patients with AHN-SM in which a chromosomal gain was reported. Among 6 patients with ISM, KIT mutation was found in only 2 cases. One patient had isolated KIT mutation and was treated with IFN for skin symptoms and bone fracture, and another patient had a DNMT3A associated mutation and was treated with imatinib. Moreover, 1 patient presented both DNMT3A and TET2 mutations and was treated with IFN for bone fracture. Among 12 ASM patients, 1 was negative for significant mutations: no disease control was achieved after target therapy, and bone marrow function slowly recovered after allogeneic transplant. The most frequently recorded mutations were SRSF2 and TET2: they were present in 4 patients each and recorded

together in 3 cases. Two patients with SRSF2 and TET2 mutations died after multiple lines of therapy: 1 patient for infection and graft versus host disease after allogeneic transplant and 1 for progressive disease. Moreover, the latter had additional RUNX1 mutation. Two patients with concomitant SRSF2 and IDH1 mutations and TET2 mutation respectively responded to midostaurin, while 1 with DNMT3A mutation received multiple lines of therapy and died for pneumonia. One patient with ASXL1 mutation responded to chemotherapy after 2 previous lines of treatment. Among 4 patients with isolated KIT mutation, 2 responded to midostaurin, 1 obtained a partial control of symptoms after 4 lines of treatment and 1 suddenly died after achieving stable disease after 2 lines of therapy. Among 3 patients with SM associated to myelodyplastic syndrome, 1 was negative for KIT but positive for TP53 mutations and died for natural event after symptoms directed therapy and continuing recombinant erythropoietin. The other 2 KIT positive patients presented multiple concomitant mutations. Additional TET2 and SRSF2 mutations were recorded in a patient who died few weeks after diagnosis, while additional TET2, SRSF2, RUNX1 and KRAS mutations were recorded in a patient treated with midostaurine and 2CDA before successful allogeneic transplant. Molecular characterization of SM has uncovered a complex landscape of somatic mutations other than KIT D816V. Although the prognostic significance of some recurrent mutations has been reported, prospective correlation with clinical response may highlighted their role in the pathogenesis of disease and possibly elucidate mechanism of resistance to treatment. On the other hand, cytogenetics might no be considered mandatory except for AHN-SM

Disclosures Pagano: *AstraZeneca:* Honoraria; *Menarini:* Honoraria; *Gilead:* Honoraria; *Janseen:* Honoraria; *Moderna:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Jazz:* Honoraria.



CASES	DIAGNOSIS	ASXL1	VAF	TYPE	KIT	VAF	TYPE	DNMT3A	VAF	TYPE	IDH1	VAF	TYPE	KRAS	VAF	TYPE	RUNX1	VAF	TYPE	SRSF2	VAF	TYPE	TET2	VAF	TYPE	TP53	VAF	TYPE
#1	ASM	Gly645ValfsTer5	3%	2	Asp816Val	0.79%	1																					
#2	ASM				Asp816Val	0.11%	1																					
#3	ISM				Asp816Val	0.50%	1	Tyr735Cys	4%	2																	
#4	AHN-SM				Asp816Val	41%	1													Arg94dup	37%	3	His573ThrfsTer7	78%	2			
#5	ISM																											
#6	ISM				Asp816Val	19%	1																					
#7	ASM				Asp816Val	40%	1													Pro95His	44%	1	Arg1440ThrfsTer38 Glu1165Val	44% 49%	2 3			
#8	ASM				Asp816Val Asp816Asn	3% 3%	1 3																					
#9	ASM				Asp816Val	15%	1	Arg882His	28%	1																	
#10	ISM																											
#11	ASM				Asp816Val	1.06%	1				Arg140Gln	49%	1							Pro95Leu	55%	2						
#12	AHN-SM				Asp816Val	0.50%	1							Lys5Glu	21%	1	Arg204Ter	44%	1	Pro95Arg	41%	1	Asp162ArgfsTer9 Pro616GlnfsTer23 Gln618Ter	42% 18% 24%	2 3 2			
#13	ASM				Asp816Val	2%	1																					
#14	ASM				Asp816Val	3%	1																					
#15	ISM							Phe752del	4%	3													Ala575Val	31%	3			
#16	ASM				Asp816Val Ser590Asn	20% 2%	1 3																	Arg1366His Met1161STer	21% 3%	3 2			
#17	ASM				Asp816Val	3.70%	1										Asp332SerfsTer258	35%	2	Pro95His	45%	1	Asn170ThrfsTer13 Leu1276TrpfsTer87	42% 39%	3 3			
#18	ASM																											
#19	ASM				Asp816Val	16%	1													Pro95Leu	39%	2	Tyr559Ter His1036ThrfsTer19	39% 37%	2 2			
#20	AHN-SM																									Cys124Arg Val143Ala Ser127Pro	11% 2% 3%	2 2 2
#21	ISM																											

CASES	Age	Sex	Diagnosis	Symptoms	Serum triptase	Treatment	Response	Status	Cause of death
#1	62	F	ASM	Itching, blistering, urticaria, bone fracture, gastric involvement	35	IFN, TKI, 2CDA	Symptoms remission, reduction of bone involvement	Alive	
#2	65	F	ASM	Myalgia, blistering, bone fracture, malabsorption	49.4	2CDA, TKI	Stable disease	Death	Sudden death
#3	48	M	ISM	Itching, blistering, urticaria	15	TKI	Symptoms remission, reduction of bone involvement and skin lesion	Alive	
#4	80	M	AHN-SM	Costitutional symptoms, diarrhea, cytopenia	14	TKI	No response	Death	Progression disease
#5	62	M	ISM	Bone fracture	97	IFN	Stable disease	Alive	
#6	72	M	ISM	Itching, blistering, urticaria, bone fracture	105	IFN	Stable disease	Alive	
#7	75	F	ASM	Anaphylaxis, cytopenia, gastric involvement	146	2CDA, TKI	Symptoms remission, reduction of bone involvement	Alive	
#8	53	M	ASM	Itching, blistering, urticaria, intestinal involvement, weight loss	165	Midostaurine	Symptoms remission, reduction of bone involvement and skin lesion	Alive	
#9	58	M	ASM	Itching, blistering, urticaria, osteoporosis, intestinal involvement, weight loss, anaphylaxis	384	Midostaurine, 2CDA, avapritinib	Symptoms control, persistence of bone involvement	Death	Infection
#10	46	F	ISM	Recurrent anaphylaxis, bloating, anorexia, diarrhea, hypotension	24	Midostaurine	Improvement of symptoms	Alive	
#11	63	M	ASM	Liver and spleen enlargement, cytopenia	123	Midostaurine	Improvement of bone marrow function, normalization of liver and spleen	Alive	
#12	51	F	AHN-SM	Costitutional symptoms, cytopenia, osteolysis, gastric involvement	147	Midostaurine, 2CDA, allogeneic transplant	Symptoms control, normalization of bone marrow function	Alive	
#13	64	F	ASM	Itching, blistering, flushing, bone pain, osteoporosis, anorexia, gastric involvement	39	TKI, midostaurine, 2CDA, avapritinib	Improvement of symptoms	Alive	
#14	48	F	ASM	Itching, blistering, bone involvement	77	Midostaurine	Symptoms control	Alive	
#15	54	F	ISM	Bone fracture	36	IFN	Stable disease	Alive	
				Diarrhea, intestinal			Symptoms remission,		

Figure 1

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