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ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Characterization of Clonal Hematopoietic of Indeterminate Potential (CHIP) Mutations in an Imid-Naïve Multiple Myeloma (MM) Autologous Stem Cell Transplant (ASCT) Population: First Results from a Pre-Transplant Time Point in a Prospective, Longitudinal Study

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Background:
Clonal Hematopoiesis of Indeterminate Potential (CHIP) is defined by the acquisition of ≥ 1 somatic mutations in the blood of healthy adults, but can also be detected at higher prevalence in patients with malignancies, particularly after DNA damaging therapy. The presence of CHIP mutations in MM confers a reduced overall survival (Mouhieddine, JCO 2020) but high quality, prospective evaluation of CHIP mutation evolution over the transplant sequence, including the impact of high-dose melphalan and immunomodulatory (IMiD)-based therapy, is largely under-studied. Serial assessment of CHIP over the transplant course has been reported from the coMMpass dataset, demonstrating a 4-fold increase in mutation prevalence from 5.8% at diagnosis to 25% after 3.1 years (Mouhieddine, Blood, 2021). In this data set, most patients were exposed to prior IMiD-containing at some point during therapy. Whether the survival benefit reported with IMiD-based maintenance therapy post-transplant is associated with CHIP mutation modulation is unclear. We are therefore investigating the longitudinal evolution of CHIP in a cohort of transplant-eligible, largely IMiD-naïve patients (pts) over the pre- and post-ASCT course in an ongoing study. Here, we present preliminary findings from the pre-transplant time-point after non-IMiD-containing induction but before high-dose melphalan and ASCT.
Methods:
The ongoing Princess Margaret Cancer Center ARCH 001 trial is a prospective, longitudinal study evaluating evolution of CHIP in a transplant-eligible MM population. Mutation testing is performed using the highly sensitive single-molecule molecular inversion probe (SmMIP) next-generation sequencing (NGS) technique (Abelson, Bioinformatics, 2022). After sequencing with a minimum sequencing depth of 4000x, the list of mutation calls produced by smMIP-tools is subject to various filters to reduce the likelihood of false positives. Synonymous mutations, as well as any variants falling within introns or splice regions are removed. The minor allele frequency of the variant (if available) is required to be above 0.1% so as to exclude mutations that are common SNPs. VAF frequency threshold of 1-30 % is set for calling somatic mutations, with a view to minimize false positives and germ-line mutations.
Multiple time points for testing pertinent to therapy include: within 1 month pre-transplant (after induction and stem cell collection), 3 months post-transplant, and two subsequent samples 12 and 24 months post-sample 2. Here we report preliminary results of CHIP mutation testing in the first 66 pts at the pre-transplant time point.
Results:
Patient, disease and treatment characteristics for all pts and their stratification by the presence of CHIP mutations are outlined in Table 1. The total cohort is typical for a transplant-eligible population with median age 65 years, male predominance (M

59%/F 41%), 60% IgG subtype, 23% high-risk FISH cytogenetics. Most (90%) received a non-IMiD containing induction regimen CyBorD; only 6% received an IMiD pre-ASCT. CHIP mutations were identified in 28/66 pts, for a mutation prevalence rate of 43%; 6 patients (9%) carried ≥ 1 mutation. The median age at transplant as well as other baseline demographics did not differ between those with and without mutations (Table 1).

Mutation profiles are shown in Figure 1, and are consistent with those described in the literature with the most commonly mutated genes being DNMT3a, TET2, ASXL1 and PPM1D, and the mutation prevalence rate highest for DNMT3a at 21%. 6 pts (9%) had ≥ 1 mutation (range 2-3) identified, with 3 of 6 involving the DNMT3a gene. Other genes involved in patients with multiple mutations were TET2 (n=3), ASXL1 (n=2), PPM1D (n=2), SRSF2 (n=1), SF3B1 (n=1). Mean allele frequency was 4%, ranging from 1-19.

Conclusion:

Our results using deep SmMIP sequencing show a mutation prevalence rate of 43% in a cohort of transplant-eligible, largely IMiD-naive MM pts studied after induction. These rates are higher than those generally described in the literature, which may relate to the high sensitivity of the assay used, variation in filtering between institutions, and the deliberate use of a relatively low VAF threshold with the intent to capture clinically significant variants for longitudinal tracking during the course of this ongoing study. Further studies during lenalidomide maintenance will be forthcoming.

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Table 1

		Total		Unmutated		Mutated		p-value
		n	(%) of total	n	% of mutated	n	% of unmutated	
Sex	Male	39	59	24	63.2	15	53.6	0.29
	Female	27	41	14	36.8	13	46.4	
Ig HC	IgG	40	60	25	65.8	15	53.6	0.36
	IgA	14	21	8	21.1	6	21.4	
	IgD	1	1.5	2	2.6	0	0	
	LC	11	17	4	10.5	7	25	
LC sub-type	Kappa	45	68	27	71	18	64	0.4
	Lambda	21	32	11	29	10	35	
High risk TP53, t(4;14), t(14;16)	Yes	15	23	7	18	8	29	0.38
	No	51	77	31	82	20	71	
ISS stage	1	21	40	10	33	11	50	0.33
	2	16	46	9	30	7	32	
	3	15	14	11	37	4	18	
Revised ISS stage	1	15	33	9	33	6	33	0.28
	2	20	44	10	37	10	56	
	3	10	22	8	30	2	11	
Induction chemothera	CyBORD	58	89	34	89	24	89	0.66
	RVD-based	4	6	2	5.3	2	5.3	
	Other	3	5	2	5.3	1	3.7	
Continuous variables				Unmutated		Mutated		
Age, years (median)		65 (57 – 73)		65 (57 – 73)		67 (62 – 73)		0.14
Pre-clearance blood counts								
Hb (mean),		115 (91 – 137)		115 (85 – 134)		115 (95 – 130)		0.98
WBC		6.3 (2.5 – 39.6)		6.9 (2.5 – 39.6)		5.8 (2.2 – 9.6)		0.26
Plat		166 (2 – 363)		156 (2 – 363)		174 (49 – 287)		0.33

Fig 1

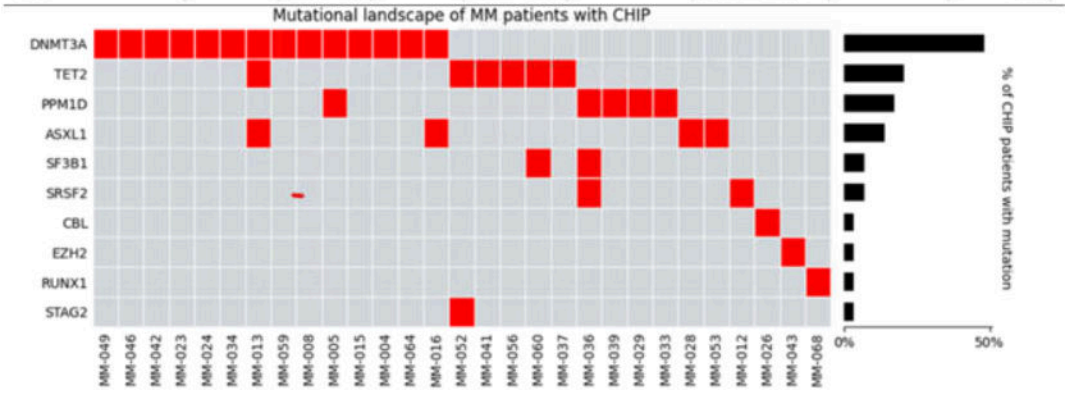

Figure 1

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