Secondary Myeloid Malignancies after Autologous Stem Cell Transplantation for Multiple Myeloma Are Associated with a Distinct Mutational Profile

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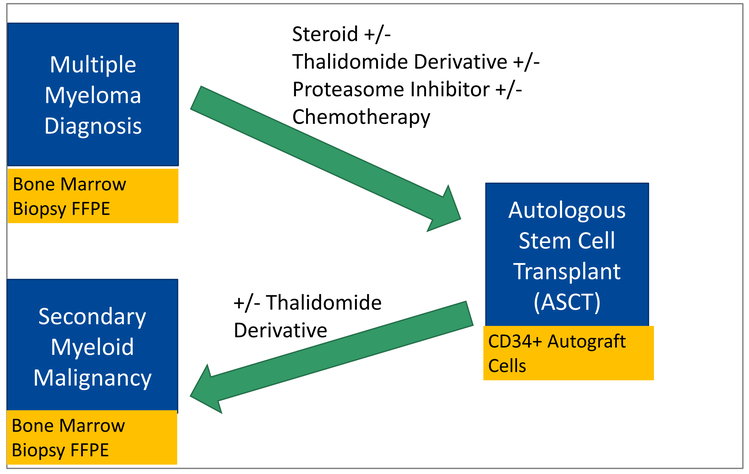
Background

- Given improvement in Multiple Myeloma survival, patients are living longer with a 5 year relative survival of 53.9%
- Patients with Multiple Myeloma are at risk (~5-11.6%) for developing secondary primary malignancies, including secondary myeloid malignancies (SMM)
- Etiology and timing of SMM associated genetic alterations is unclear

Hypothesis

- Genetic alterations present in Myeloma-associated-SMM have a distinct profile compared to de novo or other therapy related myeloid malignancies

Multiple Myeloma Treatment Paradigm



Objectives

For a sample of Multiple Myeloma patients who develop SMM:

- Compare genetic alterations at initial diagnosis, Autologous Stem Cell Transplant (ASCT) and at diagnosis of SMM
- Assess for presence of previously reported deleterious myeloid genetic alterations

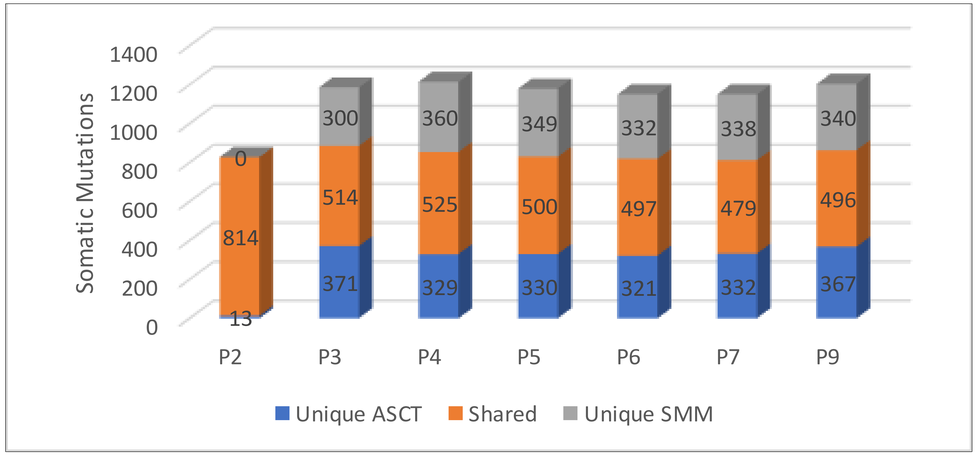
Methods

- Retrospectively identified 8 patients with Multiple Myeloma who developed SMM post-ASCT
- Charts abstracted for clinical data
- Whole exome sequencing performed on all three samples (Multiple Myeloma diagnosis bone marrow, ASCT CD34+ autograft cells (auto), and SMM bone marrow biopsy)
- From literature review identified 89 reported GAs in myeloid malignancies
- Performed targeted deep sequencing for these mutations and obtained variant allele frequencies
- GAs with known clinical significance, variant allele frequency (VAF) ≥0.05 or ≤0.9, and high or moderate impact on the gene-encoded protein were used for analysis

Results

Patient	Age at MM Dx	Pre-ASCT Lenalidomide	SMM	Post-ASCT Lenalidomide
P1	66	N/A	AML	Yes
P2	64	Yes	MDS	Yes
P3	56	Yes	AML	N/A
P4	61	No	MDS	Yes
P5	62	No	AML	Yes
P6	69	Yes	AML	No
P7	71	No	MDS	Yes
P9	61	Yes	MDS	Yes

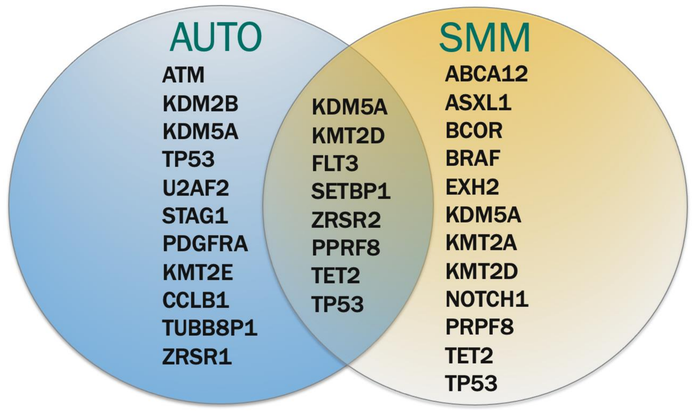
Somatic Mutations



Significant Genetic Alterations

- 118,614 total gene alterations identified
- 2,074 Gene Alterations included for analysis
- Average mutational burden similar between the auto and SMM samples
- *TP53* represented the most frequent mutation with the highest amount of variants. Seen in 6 patients in both auto and SMM samples. Harbored 6 high impact and 3 moderate impact variants with alterations of structural interaction variants, missense variants, and frameshift variants.
- Other frequent mutations were *KMT2A* in 3 pts, *KMT2D* in 3 pts, *PRPF8* in 2 pts, and *TET2* in 2 pts

Frequent Genetic Alterations



Conclusions

- These results suggest that the mutational profile for SMM after ASCT in MM is distinct from de-novo myeloid malignancies
- The average mutational burden did not change from pre-ASCT to the development of SMM
- Targeted sequencing suggests that SMM was not caused by clonal evolution from auto sample
- Frequent mutations in this population include TP53, KMT2A, KMT2D, PPRF8, and GATA2
- Studies with a larger patient population are needed to confirm genetic alteration trends in this SMM population