SF3B1 and *DNMT3A* mutations might play a role in poor prognosis and AML progression in patients with isolated del(5q) MDS

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Background

Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal disorders of hematopoietic stem cells. MDS with isolated del(5q) represent a subtype defined by the World Health Organization (WHO) in 2016 with very good prognosis. However, several studies have shown that the presence of somatic mutation, such as TP53, might have an impact on prognosis. In addition, recent publications suggest a role for SF3B1 in the poor outcome of some del(5q) MDS patients[1,2].

Aims

Our aim was to validate the poor prognosis of SF3B1 mutations, present in patients with del(5q) MDS and to identify mutational profiles that could promote AML progression of patients del(5q) MDS.

Materials & Methods

We performed a retrospective study including MDS patients with both isolated del(5q) and del(5q) with another alteration different from chromosome 7. We included 50 patients and a control group of 123 low risk MDS patients with normal karyotype. Next-generation sequencing (NGS) data from bone marrow samples were analyzed using an in-house custom panel (>100 myeloid genes).

Results

Table 1. Patient data and variables studied

Variable	p	Median CTG normal	Median 5q
Age at diagnosis	0.244	71,8	72,9
%BM Blasts	0.131	3,56	4,2
% RS	**0.032***	**17,9**	**2,75**
N. Dysplasias	0.985	2,3	2,25
Hemoglobin	0.373	9,98	9,62
Platelets	**0.003***	**183,4**	**257,7**
Neutrophils	0.326	4,46	2,33
N. Cytopenias	0.454	1,24	1,11
N. Mutations	**<0.0001*****	**3,16**	**1,7**

CTG: cytogenetics; BM: bone marrow; RS: ring sideroblasts; N: number

Figure 1. Incidence of mutations

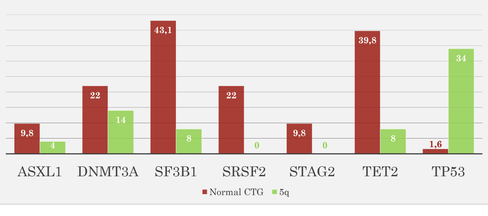


Figure 2. Overall survival (OS) in the del(5q) and normal cytogenetics (CTG) patients

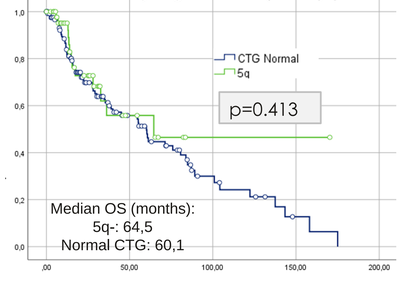
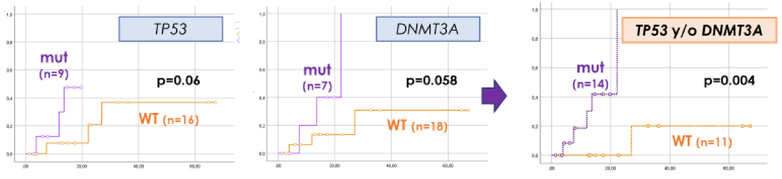


Figure 4. Progression to AML (Acute Myeloid Leukemia) with TP53 and/or DNMT3A mutations in del(5q) patients

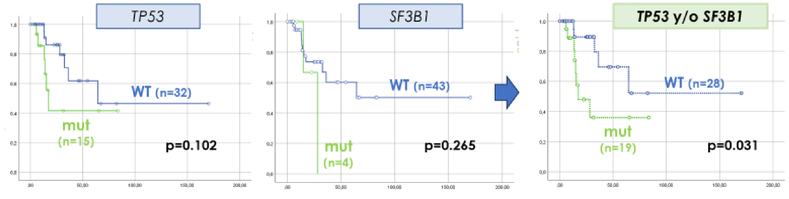


Median progression to AML (months): *TP53*mut-: 13,6 No mut: 26,97

Median progression to AML (months): *DNMT3A*mut-: 13,6 No mut: 22,17

Median progression to AML (months): *TP53/DNMT3A*mut-: 13,6 No mut: 26,97

Figure 3. OS with TP53 and/or SNMT3A mutations in del(5q) patients



Median OS (months): *TP53*mut-: 17,3 No mut: 64,5

Median OS (months): *SF3B1*mut-: 28 No mut: 64,53

Median OS (months): *TP53/SF3B1*mut-: 28,0 No mut: 64,53

When analyzing del(5q) patients individually, OS was significantly lower in those patients with either TP53 or SF3B1 mutation (64.5 vs. 28 months median) (p=0.031). Regarding progression to AML, patients with TP53 and/or DNMT3A mutations (n=14) had a shorter time to progression compared to patients without mutations in these genes, with a median of 13.6 months vs. 26.97 months (p=0.004).
Median follow-up for these patients was 14.93 (0-170.30) months.

Summary

MDS patients with del(5q) have a good prognosis and a higher time to progression to AML compared to other MDS subgroups. However, the mutational profile may modify this evolution. In our study, mutations in SF3B1 and DNMT3A may be involved in OS and transformation to AML (respectively), but a larger cohort of patients is needed to confirm that.

References

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