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RESEARCH

Deciphering clinical features and treatment patterns of thrombocytopenic myelodysplastic syndromes

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Abstract

Here we studied 260 patients with myelodysplastic neoplasms (MDS) focusing on thrombocytopenic patients with PLT < 50×10^9/L. Clinical and laboratory features, bone marrow data, therapies and outcomes were compared with MDS without thrombocytopenia. Thirty-five subjects (13.5%) had moderate to severe thrombocytopenia (median PLT 38×10^9/L, range: 9-50×10^9/L) and 20% displayed signs of bleeding, mostly grade 1–2. At diagnosis, thrombocytopenic MDS were mostly low- or very low- risk IPSS-R, a higher frequency of 40% belonged to intermediate IPSS-R group. Bone marrow evaluation showed hypocellularity (26% vs. 8.4%) and abnormal karyotype (46% vs. 27%), with trisomy 8 and complex karyotype as the most frequent alterations. Eighteen patients (51%) underwent NGS for genes commonly mutated in myeloid neoplasms, detecting at least a mutation in 11 (61%), with *TP53* and *STAG2* as most frequent. In a subgroup analysis immune-histochemistry on bone marrow biopsies highlighted deposits of IgG, IgM, and complement fractions C3 and C4d in most cases. AML transformation and mortality rates were superior in thrombocytopenic versus non-thrombocytopenic patients. Two distinct phenotypes of thrombocytopenic MDS could be hypothesized, one closer to immune thrombocytopenia marked by trisomy 8 and *STAG2* mutation, responsive to immunosuppressive treatment and the other more similar to higher-risk MDS with complex karyotypes and *TP53* mutations showing a worsen outcome.

Key Points

1.Thirty-five MDS subjects (13.5%) had thrombocytopenia < 50 × 10^9/L, had more frequent anti-PLT antibodies, bone marrow hypocellularity, karyotype aberrations, and deposits of IgG, IgM, and complement fractions.
2.Trisomy 8 and STAG2 mutations associated with a better response to immunosuppressive therapy, while complex karyotype and TP53 predicted higher AML transformation.

Keywords Myelodysplastic syndromes · Thrombocytopenia · NGS · Trephine biopsy · Autoimmunity

Introduction

Myelodysplastic syndromes (MDS) are characterized by ineffective haematopoiesis, peripheral cytopenias and potential transformation into acute leukaemia [1]. Thrombocytopenia may be present in about half of patients, being severe in a minority of subjects only. It has been associated with higher-risk international prognostic scoring system (IPSS) subsets, increased risk of leukemic evolution and worse overall survival.

Clinically, thrombocytopenia increases the risk of haemorrhagic complications, from minor to life-threatening ones [2, 3, 4].

The pathophysiologic mechanisms of thrombocytopenia in MDS include a defective megakaryocytic differentiation of the dysplastic clones, the inhibition of megakaryopoiesis by inhibitory cytokines [5, 6], the increase of apoptosis via Fas/FasL pathway [7, 8], and an abnormal thrombopoietin signalling transduction [9]. Additionally, the role of an autoimmune attack against platelets and bone marrow precursors has been reported [10, 11].

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There is no consensus on a specific treatment approach for thrombocytopenic MDS representing an unmet need in clinical practice. Suggested options range from supportive care with platelet transfusions, to medical treatment with immunosuppressive agents such as cyclosporine and anti-thymocyte globulin (ATG) [12], or thrombopoietin receptor agonists [13, 14], to intensive chemotherapy and allogeneic bone marrow transplantation [15, 16].

In this study we aimed at defining the clinical and haematological features of thrombocytopenic MDS, with a focus on their treatment patterns and outcome.

Patients and methods

We retrospectively evaluated patients diagnosed with MDS at single institution in Milan, Italy, from January 2001 until the time of writing. We systematically collected clinical and laboratory features, including positivity of anti-platelet autoantibodies, bone marrow and molecular data, pharmacological therapies and outcome of patients. The study was conducted according to the Declaration of Helsinki, within the observational study CYTOPAN approved by the local Ethical Committee Milano Area 2, and patients gave informed consent. All patients with a diagnosis of MDS according to most recent recommendations [17] were included. Patients were stratified according to platelet levels into non-thrombocytopenic (i.e. PLT > 100 × 10^9/L), with mild thrombocytopenia (PLT < 100 and > 50 × 10^9/L), and those with moderate to severe thrombocytopenia (i.e. PLT < 50×10^9/L). Exclusion criteria were presence of another active hematologic malignancy or immunological disorders, and patients with suspected secondary causes of dysplasia (e.g. nutritional deficiencies, medications, alcohol and infections).

Bone marrow evaluation

Histologic parameters were first assessed on H/E, Giemsa and Gomori stains and supplemented, in a subgroup of patients, with a panel of antibodies for the following antigens: CD8 (clone C8, Dako Agilent), C3 (polyclonal, Merck), C4d (polyclonal, Cell Marque), IgM (polyclonal, Dako Agilent), IgG (polyclonal, Dako Agilent), and cleaved-Caspase_3 (Asp175 clone, Cell Signaling). Cellularity was considered as reduced if below the normal range according to recent literature (up to 20 years old: range 45–85%; 20–40 years-old: 40–70%; 40–60 years old: 35–65%; ≥ 60 years old: 30–60%) [18]. C3 and C4d were assessed as surrogates of complement activation at the tissue level, while IgM and IgG as indicators of humoral immune activation. A 4-tiered, semi-quantitative scoring was provided (0, lack of staining; 1, faint, mostly focal staining; 2, moderate intensity, mostly diffuse; 3, intense staining, diffuse). The involved compartments were recorded, as observed in a serous pattern (i.e. finely granular / diffuse staining present on the non-cellular component of the vascular lumina and sinusoids) or staining red blood cells and nucleated cells of the hematopoietic tissue.

Next generation sequencing

Next generation sequencing assay (Ion Torrents5), Ion Reporter software 5.2, was used to evaluate the mutational status of the following genes on peripheral blood leukocytes, as by the Oncomine Myeloid Research Assay: hotspot genes (*ABL1*, *BRAF*, *CBL*, *CSFR3*, *DNMT3A*, *FLT3*, *GATA2*, *HRAS*, *IDH1*, *IDH2*, *JAK2*, *KIT*, *KRAS*, *MOL*, *MYD88*, *NPM1*, *NRAS*, *PTPN11*, *SETPB1*, *SF3B1*, *SRSF2*, *U2AF1*, *WT1)*, full genes *(ASXL1*, *BCOR*, *CALR*, *CEBPA*, *ETV6*, *EZH2*, *IKZF1*, *NF1*, *PHF6*, *PRPF8*, *RB1*, *RUNX1*, *SH2B3*, *STAG2*, *TET2*, *TP53*, *ZRSR2)*, fusion genes *(ABL1*, *ALK*, *BCL2*, *BRAF*, *CCDN1*, *CREBBP*, *EGFR*, *ETV6*, *FGFR1*, *FGFR2*, *FUS*, *HMGA2*, *JAK2*, *KMT2A*, *MECOM*, *MET*, *MLLT10*, *MLLT3*, *MYBL1*, *MYH11*, *NTRK3*, *NUP214*, *PDGFRA*, *PDGFRB*, *RARA*, *RBM15*, *RUNX1*, *TCF3*, *TFE3).*

Statistical analysis

Numerical variables were summarized by median and range; categorical variables were described with count and relative frequency (%) of subjects in each category. Continuous variables were compared by Student's t-test and categorical ones by chi-square or Fisher test as appropriate. Statistical significance in all tests was concluded for values of $p < 0.05$.

Results

Clinical features

Within the entire cohort of 260 MDS patients, 35 subjects (13.5%) presented with moderate to severe thrombocytopenia (median PLT at diagnosis 38×10^9/L, range $9–50 \times 10^9$/L). Only 13/35 thrombocytopenic patients had isolated thrombocytopenia, while the others had Hb < 11 g/dL and/or neutrophils < 1.5×10^9/L. Main clinical and hematologic features are shown in Table 1. Median age at diagnosis was 77 years (IQR 52–92) with a male predominance (63%). Median Hb at diagnosis was higher in patients with thrombocytopenia versus non-thrombocytopenic ones [10.7 (7-16.4) vs. 9.9 (5.5–15.5), $p = 0.01$], as did LDH levels [227 (151–472) vs. 193 (85–703), $p = 0.006$], while other

Table 1 Main features of the 260 patients with MDS included in the study. Hb: haemoglobin, PLT: platelets, N: neutrophil, LDH: lactate dehydrogenase, NGS: next generation sequencing, NS: not significant, AML: acute myeloid leukaemia; *$p<0.05$

	ALL ($N=260$)	PLT < 50 × 10^9/L ($N=35$)	PLT > 50 × 10^9/L ($N=225$)	*p value
Median Age, years (range)	76 (41–101)	77 (52–92)	76 (41–101)	NS
M/F	150/110	22/13	128/97	NS
IPSS-R VL/L/I/H/VR	90/119/42/6/3	5/11/14*/4/1	85/108/28*/2/2	0.0001
Hb, gr/dl, median (range)	10 (5.5–16.4)	10.7 (7.0-16.4)*	9.9 (5.5–15.5)*	0.01
PLT, 10^9/L, median (range)	145 (9-1.024)	38 (9–50)	167 (54-1.024)	NS
N, 10^9/L, median (range)	2.15 (0.21–12.12)	2.08 (0.63–12.12)	2.16 (0.21–11.65)	NS
LDH, UI/L, median (range)	197 (85–703)	227 (151–472)*	193 (85–703)*	0.006
Reticulocytes, 10^9/L, median (range)	51 (6-1020)	56 (24–220)	50 (6-1020)	NS
Indirect Bilirubin, mg/dl, median (range)	0.6 (0.1–3.3)	0.6 (0.2-1.0)	0.6 (0.1–3.3)	NS
Erythropoietin, mg/dl, median (range)	49 (6.1–4368)	61.2 (6.1–566)	48.9 (7,9–4368)	NS
Creatinine, mg/dl, median (range)	0.97 (0.23–4.30)	1.0 (0.5–4.3)*	0,96 (0.23–2.46)*	0.01
Antiplatelet antibodies, N (%)	29 (11)	17 (48)*	12 (5)*	< 0.0001
Marrow cellularity, % (range)	40 (10–95)	40 (10–90)	40 (10–95)	NS
Hypocellularity, N (%)	27 (10)	9 (26)*	19 (8.4)*	0.005
Cytogenetic				
Normal (%)	183 (70)	19 (54)	164 (73)	0.04
Del5q (%)	17 (7)	1 (3)	16 (7)	0.55
Del20 (%)	7 (3)	1 (3)	6 (3)	0.61
DelY (%)	14 (5)	3 (9)	11 (5)	0.61
Tris8 (%)	10 (4)	5 (14)*	5 (2)*	0.002
Complex karyotype (%)	7 (3)	5 (14)*	2 (1)*	< 0.0001
Others (%)	22 (8)	1 (3)	21 (9)	0.34
NGS mut./unmut.	89/40	11/7	78/33	NS
1 mutation (%)	41 (32)	7 (39)	34 (31)	
2 mutations (%)	26 (21)	2 (11)	24 (22)	
> or = 3 mutation (%)	22 (17)	2 (11)	20 (18)	
AML transformation, N (%)	8 (3)	4 (11.4)*	6 (2.6)*	0.04
Mortality, N (%)	68 (26)	14 (40)	54 (24)	0.07

hematologic markers were similar between the two groups. Anti-platelet autoantibodies were present in 29 patients, 48% thrombocytopenic versus 5% non-thrombocytopenic ($p<0.0001$). Thrombocytopenic MDS displayed a higher prevalence of intermediate IPSS-R risk group as compared to non-thrombocytopenic ones (40% vs. 12%, $p=0.0001$). Overall, 20% of patients with thrombocytopenia showed signs of bleeding either at diagnosis or during the follow up, mostly grade 1–2 (e.g. petechiae, bruises). Acute myeloid leukemia (AML) transformation rates were superior in thrombocytopenic MDS patients as compared to non-thrombocytopenic ones (11.4% vs. 2.6%, $p=0.04$). Over a median follow up of 40 months (0-256), a difference in mortality rate was also noted between the two groups, although not statistically significant (40% vs. 24%, $p=0.07$); notably, no one of the patients died because of bleeding. The analysis of the dataset by considering a cut-off of 100×10^9/L platelets, didn't reveal significant associations.

Bone marrow studies

At bone marrow trephine, thrombocytopenic patients had a higher prevalence of hypoplasia (26% vs. 8.4%, $p=0.005$) and abnormal karyotypes (46% vs. 27%, $p=0.04$) compared to non-thrombocytopenic subjects. The most common alterations were trisomy 8 (14% vs. 2%, $p=0.002$) and complex karyotype (14% vs. 1%, $p<0.0001$). The other bone marrow features at morphology and flow cytometry were comparable between the two groups.

In a subgroup analysis, with clinical features representative of the two cohorts (i.e. thrombocytopenic and not), we evaluated immunoglobulin and complement deposits by immunohistochemistry. In thrombocytopenic patients, by utilizing a semiquantitative score, significant (score ≥ 3) IgM and IgG deposits were present as serous positivity in 75% and 62% respectively and on megakaryocytes in 55%; C3 and C4 serous deposits were present in 50% and 25% respectively (score > 2) and on megakaryocytes in 50%. In non-thrombocytopenic group, IgM and IgG deposits were identified in a smaller percentage of cases (56% and 43%, respectively), whilst complement deposits were present at

a similar rate (53% and 47%, respectively), but fewer on megakaryocytes. Typical examples of immunoglobulin and complement deposits on megakaryocytes are depicted in Fig. 1.

NGS analysis

Eighteen thrombocytopenic patients (51%) and 111 non-thrombocytopenic patients (49%) underwent NGS for genes commonly mutated in myeloid neoplasms, detecting at least one mutation in 11 (61%) and 78 (70%) respectively, including *STAG2*, *TET2*, *TP53*, *SF3B1*, *RUNX1*, *DNMT3A*, *SRSF2*. The majority of thrombocytopenic patients had only one mutation and the most common were *TP53* and *STAG2* (Fig. 2a). Additionally, all patient with TP53 mutation had complex karyotype (100%) and among patients with STAG2 mutation the majority had trisomy 8 (50%). Whereas among non-thrombocytopenic patients the most frequent mutations found were SF3B1 and TET2 (Fig. 2b).

Therapies

Concerning treatment (Table 2), thrombocytopenic MDS patients more frequently received steroids (69% vs. 15%), eltrombopag (20% vs. 0%), danazol (14% vs. 2%), and cyclosporine (9% vs. 1%) as compared to non-thrombocytopenic ones. Thrombocytopenic patients showed at least a partial PLT response ($>50\times10^9$/L) to eltrombopag (4/7), to cyclosporine (2/3), and to steroids (8/24); only one patient responded to danazol. Regarding erythroid responses, thrombocytopenic patients had a lower response rate to erythropoiesis stimulating agents (33% vs. 69%, $p=0.02$) versus non-thrombocytopenic ones.

Finally, thrombocytopenic patients were divided in three groups according to the presence of autoimmune (i.e. positive anti-PLT, trisomy 8, and *STAG2* mutations), higher risk features (i.e. higher IPSS-R score, complex karyotype and *TP53* mutations) or neither (Table 3). The former were treated more frequently with immunosuppressive therapy, like steroids (90% vs. 42%, $p=0.02$), achieving good results in most cases (41%), and the second showed an increased risk of developing AML (43% vs. 5%, $p=0.01$), whilst difference in mortality was not significant.

Discussion

In this study moderate to severe thrombocytopenia was present in 13.5% of MDS patients and was associated with mild bleeding tendency (mainly grade 1–2) in 20% of subjects. Only two patients required platelet transfusions, and none died because of haemorrhagic complications. This prevalence was similar to other reports that however used different platelet cutoffs (i.e. PLT $<100\times10$^9/L) [19, 20]. Thrombocytopenia was also associated with positivity of anti-PLT autoantibodies in about 50% of cases, more frequently than in non-thrombocytopenic MDS, confirming the immune mediated physiopathology in a group of patients. In keeping with this observation, we reported the presence of bone marrow hypocellularity in 26% of cases (namely hypocellular MDS), and of complement and immunoglobulin deposits on megakaryocytes in thrombocytopenic patients, highlighting the contribution of humoral autoimmunity to thrombocytopenia. Furthermore, thrombocytopenic patients had a higher frequency of trisomy 8 at karyotype analysis, and of *STAG2* mutation at NGS, as compared to non-thrombocytopenic ones; these alterations have been previously associated with autoimmune diseases (e.g. Behcet's disease, inflammatory arthritis, vasculitis) [21–23]. The second most frequent cytogenetic aberration in thrombocytopenic patients was complex karyotype, known to be associated with worse prognosis and leukemic evolution. Additionally, *TP53* mutation was prevalent in this cohort as compared to non-thrombocytopenic one.

Overall, thrombocytopenic low-risk MDS patients were more frequently treated with cyclosporine (CyA) and steroids as compared to non-thrombocytopenic ones, with responses in about half of cases, in line with other reports and with data on hypoplastic MDS [24–32].

Interestingly, eltrombopag yielded a response in more than 30% of subjects, and some improvement in bleeding tendency might be observed even in patients lacking an increase in PLT count.

Concerning androgen therapy, danazol has recently been shown promising results in treating thrombocytopenia in MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) [33]. Finally, anemia response to erythropoiesis-stimulating agents (ESA) was worse in thrombocytopenic patients (33% vs. 70%), in line with previous studies [34].

This study carries some limitations, particularly the retrospective nature and the limited number of patients tested by NGS. However, the detailed clinical data collected at a single centre allowed some interesting findings.

All in all, two different phenotypes of thrombocytopenic MDS emerged: one more "autoimmune", including positive anti-PLT, trisomy 8, and *STAG2* mutations, and one with "higher risk features", i.e. higher IPSS-R score, complex karyotype and *TP53* mutations. The former is more responsive to immunosuppressive therapy, the second showed a higher rate of AML transformation.

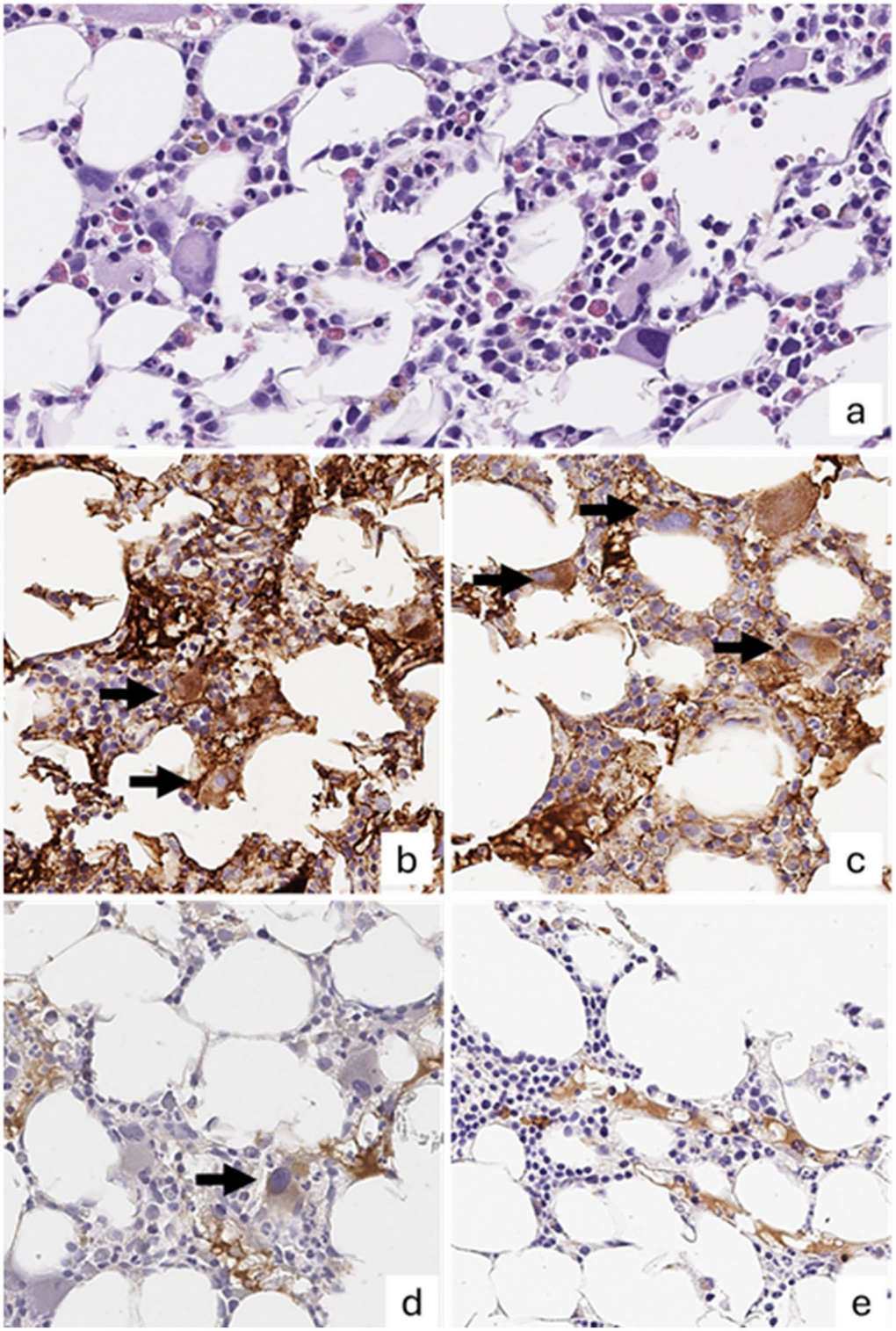

Fig. 1 Immunoglobulin and complement deposits by immunohistochemistry. A prototypic case of MDS displaying mildly hypocellular bone marrow with prominent megakaryocytic atypia (a. H/E, 200x). Anti-IgM (b. 400x) and IgG (c. 400x) highlight abundant immunoglobulin deposits in the serum and in the cytoplasm of scattered megakaryocytes (arrows). Few deposits of complement fractions C3 (d. 400x) and C4d (e. 400x) are also observed on nucleated cells (arrow) and in the serum

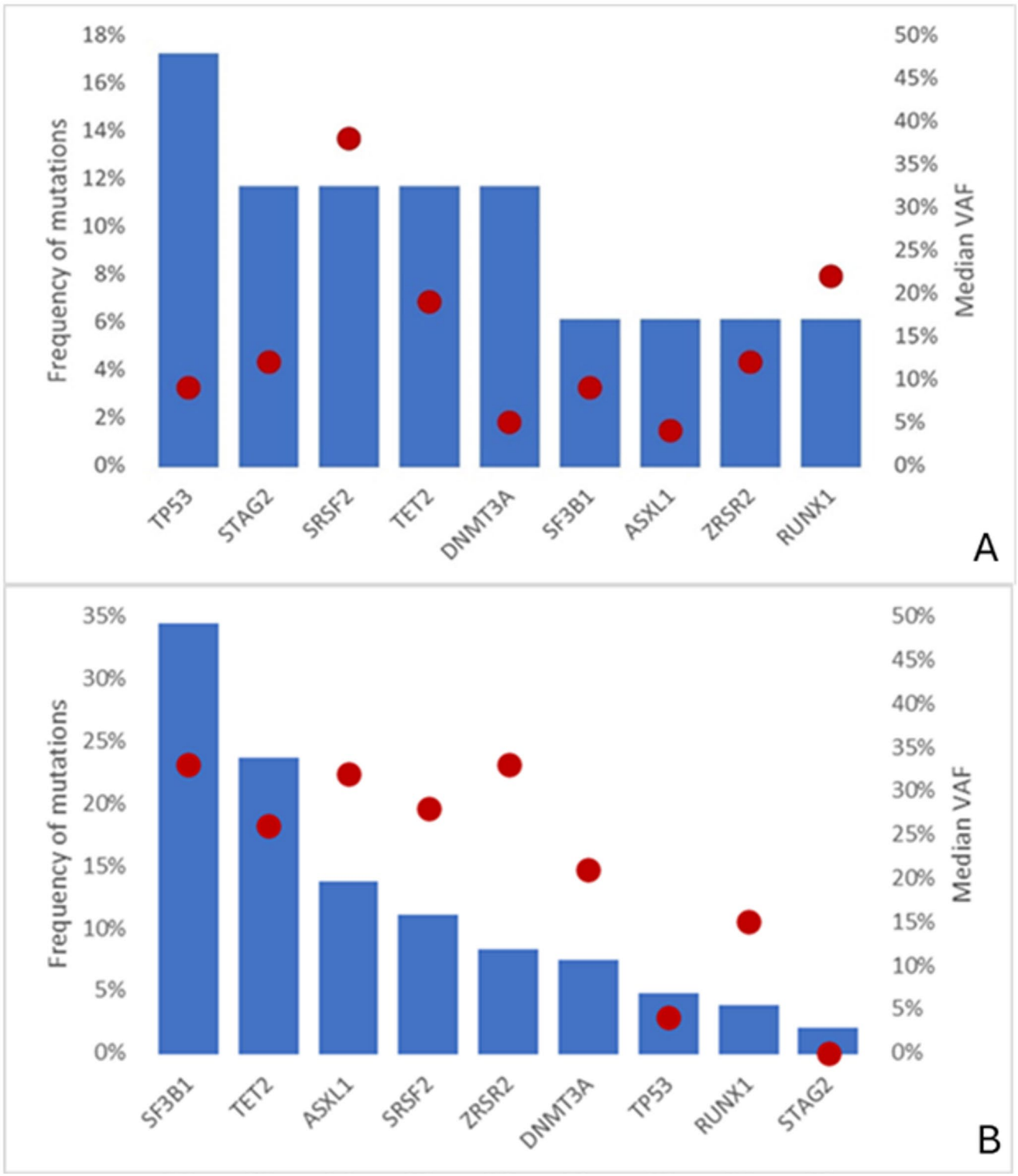

Fig. 2 Molecular studies by next generation sequencing assay. **A**. Results of NGS evaluation on 18 thrombocytopenic patients. **B**. Results of NGS evaluation on 111 non-thrombocytopenic patients. The histogram columns show the frequency of mutations (left vertical axis), while median VAF is reported by red dots (right vertical axis)

Table 2 Therapies of the 260 patients with MDS included in the study. NS: not significant, *$p<0.05$

	ALL ($N=260$)	PLT < 50.000 ($N=35$)	PLT > 50.000 ($N=225$)	*p value
Erythropoietin, N (%)	138 (53,1)	12 (34)*	126 (56)*	*0,02
Response YES (%)	91 (65,9)	4 (33)*	87 (69)*	*0,02
Luspatercept, N (%)	23 (9)	1 (3)	22 (10)	NS
Response YES (%)	11 (55)	0	11 (50)	
Lenalidomide, N (%)	9 (3,5)	0	9 (4)	NS
Response YES (%)	4 (44,5)	0	4 (44)	
Cyclosporine, N (%)	5 (1,9)	3 (9)	2 (1)	NS
Response YES (%)	3 (60)	2 (67)	1 (50)	
Steroids, N (%)	57 (22)	24 (69)*	33 (15)*	*< 0,0001
Response YES (%)	25 (44)	8 (33)	17 (52)	0,27
Danazol, N (%)	8 (3,1)	5 (14)*	3 (2)*	*0,0003
Response YES (%)	2 (25)	1 (20)	1 (33)	0,67
Eltrombopag, N (%)	7 (3)	7 (20)*	0*	*< 0,0001
Response YES (%)	4 (57)	4 (57)	0	*< 0,0001

Table 3 Main features of the 35 thrombocytopenic MDS included in the study. Hb: haemoglobin, PLT: platelets, N: neutrophil, LDH: lactate dehydrogenase, NGS: next generation sequencing, AML: acute myeloid leukaemia. NS: not significant, *$p<0.05$

	MDS with high-risk features ($N=7$)	MDS with autoimmune features ($N=19$)	Others ($N=9$)	*p value
Median Age, years (range)	76 (60–82)	81 (64–92)	76 (52–92)	0.08
M/F	4/3	12/7	6/3	NS
Hb, gr/dl, median (range)	9 (7–14)	11 (9–16)	11 (8–15)	0.08
PLT, 10^9/L, median (range)	38 (11–50)	27 (9–50)	43 (25–50)	NS
N, 10^9/L, median (range)	1.79 (0.63–3.91)	2.28 (0.84–12.12)	2.50 (0.67–5.11)	NS
LDH, UI/L, median (range)	227 (151–456)	213 (166–314)	250 (158–472)	NS
Reticulocytes, 10^9/L, median (range)	53 (32–220)	57 (28–145)	60 (24–168)	NS
Indirect Bilirubin, mg/dl, median (range)	0.6 (0.3–0.9)	0.6 (0.2–0.8)	0.6 (0.2–0.96)	NS
Erythropoietin, mg/dl, median (range)	69.4 (25–85)	62.4 (6.1–566)	61 (8–284)	NS
Creatinine, mg/dl, median (range)	0,9 (0.7–1.07)	1.0 (0.6–4.3)	1.0 (0.5–2.21)	NS
Marrow cellularity, % (range)	70 (15–90)	40 (10–85)	33 (10–60)	0.08
Hypocellularity, N (%)	1 (14)	5 (26)	3 (33)	NS
Cyclosporine, N (%)	0	2 (10)	1 (11)	NS
Response YES (%)		2 (50)	0	
Steroids, N (%)	3 (42)*	17 (90)*	4 (44)	***0.02**
Response YES (%)	0	7 (41)	1 (25)	
Danazol, N (%)	0	3 (16)	2 (22)	NS
Response YES (%)		1 (33)	0	
Eltrombopag, N (%)	2 (29)	5 (26)	0	NS
Response YES (%)	1 (50)	3 (60)		
Erythropoietin, N (%)	2 (29)	7 (37)	3 (33)	NS
Response YES (%)	1 (50)	1 (14)	2 (67)	
Luspatercept, N (%)	0	0	1 (11)	NS
Response YES (%)			0	
Azacitidine, N (%)	4 (57)*	0*	0	***0.001**
Response YES (%)	2 (50)			
AML transformation, N (%)	3 (43)*	1 (5)*	0	***0.01**
Mortality, N (%)	2 (29)	8 (42)	4 (44)	NS

Author contributions NG, LP, MB and BF followed patients and collected data; GC performed immunohistochemical assays; NG, WB, and BF wrote the manuscript; FP revised the manuscript for important intellectual content; All Authors approved the present version of the article.

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Data availability All data were included in the article manuscript and supplementary material. Additional information may be obtained upon reasonable request to the Corresponding Author.

Declarations

Human ethics and consent to participate Patients gave informed consent and the study was conducted according to the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

References

1. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka H-M et al (2022) International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood [Internet] 140(11):1200–1228
2. Sanz GF, Sanz MA, Greenberg PL (1998) Prognostic factors and scoring systems in myelodysplastic syndromes. Haematologica 83(4):358–368
3. Neukirchen J, Blum S, Kuendgen A, Strupp C, Aivado M, Haas R et al (2009) Platelet counts and haemorrhagic diathesis in patients with myelodysplastic syndromes. Eur J Haematol [Internet] 83(5):477–482
4. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F et al (2012) Revised international prognostic scoring system for myelodysplastic syndromes. Blood [Internet] 120(12):2454–2465
5. Will B, Zhou L, Vogler TO, Ben-Neriah S, Schinke C, Tamari R et al (2012) Stem and progenitor cells in myelodysplastic syndromes show aberrant stage-specific expansion and harbor genetic and epigenetic alterations. Blood [Internet] 120(10):2076–2086
6. Hofmann W-K, Kalina U, Koschmieder S, Seipelt G, Hoelzer D, Ottmann OG (2000) Defective megakaryocytic development in myelodysplastic syndromes. Leuk Lymphoma [Internet] 38(1–2):13–19
7. Kitagawa M, Yamaguchi S, Takahashi M, Tanizawa T, Hirokawa K, Kamiyama R (1998) Localization of Fas and Fas ligand in bone marrow cells demonstrating myelodysplasia. Leuk [Internet] 12(4):486–492
8. Navas TA, Mohindru M, Estes M, Ma JY, Sokol L, Pahanish P et al (2006) Inhibition of overactivated p38 MAPK can restore hematopoiesis in myelodysplastic syndrome progenitors. Blood [Internet] 108(13):4170–4177
9. Adams JA, Liu Yin JA, Brereton ML, Briggs M, Burgess R, Hyde K (1997) The in vitro effect of pegylated Recombinant human megakaryocyte growth and development factor (PEG rHuMGDF) on megakaryopoiesis in normal subjects and patients with myelodysplasia and acute myeloid leukaemia. Br J Haematol [Internet] 99(1):139–146
10. Mittelman M, Zeidman A (2000) Platelet function in the myelodysplastic syndromes. Int J Hematol [Internet] 71(2):95–98
11. Barcellini W, Fattizzo B. Immune Phenomena in Myeloid Neoplasms: An "Egg or Chicken" Question. Front Immunol [Internet]. 2021 Sep 29;12.
12. Parikh AR, Olnes MJ, Barrett AJ (2012) Immunomodulatory treatment of myelodysplastic syndromes: antithymocyte Globulin, cyclosporine, and alemtuzumab. Semin Hematol [Internet] 49(4):304–311
13. Oliva EN, Riva M, Niscola P, Santini V, Breccia M, Giai V et al (2023) Eltrombopag for Low-Risk myelodysplastic syndromes with thrombocytopenia: interim results of a phase II, randomized, Placebo-Controlled clinical trial (EQOL-MDS). J Clin Oncol 41(28):4486–4496
14. Giagounidis A, Mufti GJ, Fenaux P, Sekeres MA, Szer J, Platzbecker U et al (2014) Results of a randomized, double-blind study of Romiplostim versus placebo in patients with low/intermediate-1–risk myelodysplastic syndrome and thrombocytopenia. Cancer [Internet] 120(12):1838–1846
15. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R et al (2002) Randomized controlled trial of Azacitidine in patients with the myelodysplastic syndrome: A study of the Cancer and leukemia group B. J Clin Oncol [Internet] 20(10):2429–2440
16. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A et al (2009) Efficacy of Azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol [Internet] 10(3):223–232
17. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF et al (2022) The 5th edition of the world health organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leuk [Internet] 36(7):1703–1719
18. Wong J, Jackson R, Chen L, Song J, Pillai R, Afkhami M et al (2024) Determination of age-dependent bone marrow normocellularity. Am J Clin Pathol [Internet] 161(2):170–176
19. Waisbren J, Dinner S, Altman J, Frankfurt O, Helenowski I, Gao J et al (2017) Disease characteristics and prognosis of myelodysplastic syndrome presenting with isolated thrombocytopenia. Int J Hematol [Internet] 105(1):44–51
20. Gyan E, Andrieu V, Sanna A, Caille A, Schemenau J, Sudaka I et al (2016) Myelodysplastic syndromes with single neutropenia or thrombocytopenia are rarely refractory cytopenias with unilineage dysplasia by world health organization 2008 criteria and have favourable prognosis. Br J Haematol [Internet] 175(5):975–979
21. Lin Y-C, Liang T-H, Chang H-N, Lin J-S, Lin H-Y (2008) Behçet disease associated with myelodysplastic syndrome. JCR J Clin Rheumatol [Internet] 14(3):169–174
22. Wesner N, Drevon L, Guedon A, Fraison JB, Trad S, Kahn JE et al (2019) Inflammatory disorders associated with trisomy 8-myelodysplastic syndromes: French retrospective case-control study. Eur J Haematol [Internet] 102(1):63–69
23. Katamesh B, Nanaa A, He R, Viswanatha D, Nguyen P, Greipp P et al (2022) Autoimmune manifestations in STAG2-mutated myeloid neoplasms. Ann Hematol [Internet] 101(12):2785–2787
24. Fattizzo B, Serpenti F, Barcellini W, Caprioli C (2021) Hypoplastic myelodysplastic syndromes: just an overlap syndrome?? Cancers (Basel). [Internet] 13(1):132
25. Passweg JR, Giagounidis AAN, Simcock M, Aul C, Dobbelstein C, Stadler M et al (2011) Immunosuppressive therapy for patients with myelodysplastic syndrome: A prospective randomized multicenter phase III trial comparing antithymocyte Globulin plus cyclosporine with best supportive Care—SAKK 33/99. J Clin Oncol [Internet] 29(3):303–309

26. Selleri C, Maciejewski JP, Catalano L, Ricci P, Andretta C, Luciano L et al (2002) Effects of cyclosporine on hematopoietic and immune functions in patients with hypoplastic myelodysplasia. Cancer [Internet] 95(9):1911–1922
27. Barcellini W, Zaninoni A, Imperiali FG, Boschetti C, Colombi M, Iurlo A et al (2007) Anti-erythroblast autoimmunity in early myelodysplastic syndromes. Haematol [Internet] 92(1):19–26
28. Barcellini W, Giannotta JA, Fattizzo B (2021) Autoimmune complications in hematologic neoplasms. Cancers (Basel) [Internet] 13(7):1532
29. Novaretti MCZ, Sopelete CR, Velloso ERP, Rosa MFC, Dorlhiac-Llacer PE, Chamone DAF (2001) Immunohematological findings in myelodysplastic syndrome. Acta Haematol [Internet] 105(1):1–6
30. Gañán-Gómez I, Wei Y, Starczynowski DT, Colla S, Yang H, Cabrero-Calvo M et al (2015) Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. Leuk [Internet] 29(7):1458–1469
31. Fattizzo B, Levati GV, Giannotta JA, Cassanello G, Cro LM, Zaninoni A, et al. Low-Risk Myelodysplastic Syndrome Revisited: Morphological, Autoimmune, and Molecular Features as Predictors of Outcome in a Single Center Experience. Front Oncol [Internet]. 2022 Mar 22;12.
32. Fattizzo B, Serpenti F, Versino F, Cassanello G, Cro LM, Barbieri M et al (2023) Use of steroids in the management of low-risk myelodysplastic syndromes with autoimmune features. Blood Transfus 21(5):452–460
33. Riva M, Bosi A, Rizzo L, Mazzon F, Ferrari S, Lussana F et al (2023) Danazol treatment for thrombocytopenia in myelodysplastic syndromes: can an old-fashioned. Drug Be Effective? HemaSphere 7(4):E867
34. Santini V, Schemenau J, Levis A, Balleari E, Sapena R, Adès L et al (2013) Can the revised IPSS predict response to erythropoietic-stimulating agents in patients with classical IPSS low or intermediate-1 MDS? Blood [Internet] 122(13):2286–2288