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Utility of indium-111 platelet scintigraphy for understanding the mechanism of thrombocytopenia associated with myelodysplastic syndromes and chronic myelomonocytic leukemia

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Abstract

Background Thrombocytopenia occurs in 60% of patients with myelodysplastic syndromes (MDS), increasing the risk of life-threatening haemorrhage in this population of mainly old patients with comorbidities. However, data are scare regarding immune thrombocytopenia (ITP) secondary to MDS.

Aim We analyzed the utility of indium-111 platelet scintigraphy (IPS) to better characterize the mechanisms of thrombocytopenia in 21 adult patients with MDS.

Methods Adult patients with a definite diagnosis of MDS according to the international criteria who underwent IPS between 2009 and 2018 because of an increased bleeding risk were retrospectively selected. Autologous 111Indium platelet labelling was performed with a technique similar to that described previously using a standardized method.

Results Platelet lifespan ≤ 6 days identified patients with peripheral platelet destruction. Taking into account the response to ITP-directed therapies after IPS, the sensitivity, specificity, and positive and negative predictive values of IPS were 100%, 84.6%, 80%, and 100%, respectively.

Conclusion We show that IPS can be a useful tool to identify the mechanism and guide treatment of a chronic thrombocytopenia increasing the bleeding risk in patients with MDS.

Keywords Myelodysplastic syndrome, Immune thrombocytopenia, Indium-111 platelet scintigraphy

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To the Editor,

Myelodysplastic syndromes (MDSs) and chronic myelomonocytic leukemia (CMML) are clonal haematological diseases, and thrombocytopenia with multiple underlying mechanisms occurs in up to two thirds of patients with such disorders [1, 2]. Platelet count can be very low, resulting in increased risk for bleeding and even life-threatening haemorrhage in 10–20% patients [1, 2]. Treatments to increase the platelet count have shown variable efficacy, sometimes leading to therapeutic dead-ends with repeated or clustered platelet transfusions [1, 3]. Indium-111 (111In) platelet scintigraphy (IPS) may be a useful diagnostic tool to search for increased platelet destruction in the specific setting of potentially impaired platelet production due to MDS or CMML. No platelet kinetics studies have been specifically performed in these diseases. Here, we assessed how IPS could be useful for treating patients with both MDS or CMML and refractory thrombocytopenia by better characterizing the underlying mechanisms leading to the low platelet count. Methods are explained in Additional file 1. Briefly, response was defined as recommended in immune thrombocytopenia (ITP) [4]: complete response (CR, platelets > 100 × 109/L and no bleeding); partial response (R, platelets between 30 and 100 × 109/L with a minimal doubling of initial platelet count and no bleeding); and non-response (NR, platelets < 30 × 109/L or less than twice the initial platelet count, or presence of bleeding).

Among 389 cases of IPS registered at our centre, 21 patients with MDS or CMML underwent IPS (Table 1). None had overt clinical features of autoimmune or inflammatory associated disease. Median age of patients was 72 years (57–86). Median platelet count was 45 × 109/L (10–118). The Revised International Prognostic Scoring System (R-IPSS) was assessed in all patients, with a majority of low or intermediate-1 risk. Before IPS, the unexplained mechanism of thrombocytopenia was investigated in all patients by testing their response to ITP-directed treatments: 7 patients received steroids, 7 intravenous immunoglobulin (IVIG), 2 rituximab, 2 thrombopoietin receptor agonists (TPO-RA), and 3 received dapsone: none of these treatments increased the platelet count.

IPS was therefore performed in all patients after a median interval of 22 months (4–41) after the first exploration of thrombocytopenia. A cut-off value of 6 days was used to distinguish patients with possible peripheral destruction of platelets (platelet lifespan ≤ 6 days, positive IPS) from patients with insufficient platelet production (platelet lifespan > 6 days, negative IPS), as suggested in previous studies [5, 6]. IPS was thus considered positive in 10 patients (positive IPS group) and negative in 11 patients (negative IPS group). Notably, most patients in the positive IPS group had splenic sequestration, but none had a platelet life span < 5 days, therefore reinforcing the hypothesis that these patients may have mixed features of ITP and MDS (Table 1), and no patient in the negative-IPS group responded to previous ITP-directed therapies. After IPS, 8 patients from the positive IPS group were re-challenged with ITP-directed treatments, i.e., steroids (n = 3), rituximab (n = 2), IVIG (n = 1), dapsone (n = 1), or TPO-RA (n = 1), which led to an increase in platelet count in 3 patients (37.5%, Table 2): partial response to successive courses of IVIG for the first, sustained partial response with steroids for the two others. Among the 10 patients with positive IPS (none in the negative IPS group), a diagnosis of ITP was finally retained in 8, because the course of the thrombocytopenia was not suggestive in 2 patients. Finally, in this small cohort, sensitivity and specificity of IPS were 100% and 84.6%, respectively. The positive predictive value of IPS in the diagnostic work-up of secondary ITP in patients with MDS/CMML was 80%, while the negative predictive value was 100%.

IPS may be helpful for characterizing the cause of thrombocytopenia in the specific context of MDS/CMML and low platelet count or bleeding. Platelet lifespan is informative as patients with a platelet lifespan less than 6 days could benefit from ITP-directed therapies. This is important because there is currently no definitive diagnostic test for immune thrombocytopenia associated with MDS/CMML. Quantification of reticulated platelets (i.e., immature platelet fractions) has been attempted in ITP with inconclusive results [7], but did not provide insight into the mechanism of thrombocytopenia in MDS/CMML [8]. Notably, CMML was the main disease associated with peripheral destruction of platelets in our study population, as suggested previously [2, 9]. Furthermore, we showed that a bone marrow smear is probably not useful for diagnosis of the mechanism of thrombocytopenia under these conditions [10]. This study had several limitations due to its retrospective nature and the small number of patients. However, to the best of our knowledge, this is the first study to suggest the usefulness of IPS for understanding the mechanism of clinically significant thrombocytopenia in MDS/CMML according to the later clinical course. IPS could be helpful for tailoring specific treatments for MDS/CMML patients with refractory thrombocytopenia and/or bleeding signs.

Table 1 Characteristics of MDS/CMML patients with positive or negative IPS

	Positive IPS (*n* = 10)	Negative IPS (*n* = 11)
Sex ratio (M/W)	5/5 (1)	5/6 (0.83)
Initial platelet count (*n*, min–max)	49 (40–83)	75 (41–91)
Bleeding symptoms	1 (10%)	3 (27%)
Isolated thrombocytopenia prior to MDS/CMML	8 (80%)	6 (54%)
Interval between first thrombocytopenia and MDS/CMML in months (*n*, min–max)	16 (1–77)	20 (8–59)
Age at diagnosis of MDS/CMML (*n*, min–max)	68 (61–75)	70 (70–77)
Platelet count at diagnosis of MDS/CMML ($\times 10^9$/L; *n*, min–max)	42 (32–56)	59 (44–75)
Disease (MDS/CMML)		
CMML	5 (50%)	3 (27%)
RAEB	1 (10%)	4 (37%)
MDS-MLD	2 (20%)	1 (9%)
MDS-U	1 (10%)	2 (18%)
MDS-SLD	1 (10%)	1 (9%)
Bone marrow cellularity		
Decreased	0 (0%)	2 (18%)
Normal	6 (60%)	5 (45%)
Increased	4 (40%)	4 (36%)
Megakaryocytes in bone marrow		
Decreased	1 (10%)	5 (45%)
Normal or increased	9 (90%)	6 (55%)
Dysplastic megakaryocytes[a]		
Yes	7 (70%)	2 (18%)
No	3 (30%)	9 (82%)
R-IPSS		
Low	5 (20%)	4 (37%)
Intermediate 1	4 (40%)	6 (54%)
Intermediate 2	1 (10%)	1 (9%)
High	0 (0%)	0 (0%)
Presence of ANA		
No	6 (60%)	6 (54%)
Yes	4 (40%)	4 (37%)
Not performed	0 (0%)	1 (9%)
MAIPA		
Positive	1 (10%)	1 (9%)
Negative	6 (60%)	4 (37%)
Not performed	3 (30%)	6 (54%)
Platelet kinetic study		
Interval between first thrombocytopenia and IPS, months (*n*, min–max)	22 (7–37)	22 (4–41)
Sequestration pattern		
None	1 (10%)	7 (64%)
Splenic	7 (70%)	2 (18%)
Hepatic	2 (20%)	2 (18%)
Platelet lifespan (*n*, min–max)	5.5 (5–6)	7 (6.5–7)

ANA, anti-nuclear antibody; CMML, chronic myelomonocytic leukemia; F, female; M, male; MAIPA, monoclonal antibody immobilization of platelet antigens; MDS, myelodysplastic syndrome; MDS-MLD, MDS with multilineage dysplasia; MDS-SLD, MDS with single-lineage dysplasia; MDS-U, MDS unclassified; RAEB, refractory anaemia with excess blasts; R-IPSS, Revised International Prognostic Scoring System

[a] Megakaryocytes with hypolobated nuclei, or with separated nucleus, or micro-megakaryocytes

Table 2 Treatment response rate in MDS/CMML patients after IPS

Treatment	Positive IPS ($n=10$)	Negative IPS ($n=11$)
Platelet transfusion	3/6 (50%)	6/6 (100%)
Steroids	2/6 (33%)	0/4 (0%)
IVIG	1/4 (25%)	0/4 (0%)
Dapsone	0/2 (0%)	0/2 (0%)
Rituximab	0/2 (0%)	0/2 (0%)
TPO-RAs	0/1 (0%)	0/2 (0%)
Danatrol	1/1 (100%)	0/2 (0%)
Azacitidine	1/4 (25%)	1/2 (50%)

IPS, Indium-111 platelet scintigraphy; IVIG, intravenous immunoglobulin; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; TPO-RAs, thrombopoietin receptor agonists

Abbreviations

ANA	Anti-nuclear antibody
CMML	Chronic myelomonocytic leukaemia
F	Female
IPS	Indium-111 platelet scintigraphy
ITP	Immune thrombocytopenia
IVIG	Intravenous immunoglobulin
M	Male
MAIPA	Monoclonal antibody immobilization of platelet antigens
MDS	Myelodysplastic syndrome
MDS-MLD	MDS with multilineage dysplasia
MDS-SLD	MDS with single-lineage dysplasia
MDS-U	MDS unclassified
RAEB	Refractory anaemia with excess blasts
R-IPSS	Revised International Prognostic Scoring System
TPO-RAs	Thrombopoietin receptor agonists

Supplementary Information

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Additional file 1. Supplemental details on the methodology

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PD, VP, JFV and ER designed the research, performed research, analyzed data and wrote the manuscript; CM, EL and FD performed research, analyzed data, and critically reviewed the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
All patients gave informed consent and study was approved by our local IRB.

Consent for publication
All patients gave consent for publication (non-opposition).

Competing interests
The authors have no competing interests to disclose.

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