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Clinical spectrum, outcome and management of immune thrombocytopenia associated with myelodysplastic syndromes and chronic myelomonocytic leukemia

Vincent Jachiet[1], Guillaume Moulis[2], Jérome Hadjadj[3], Julie Seguier[4], Kamel Laribi[5], Nicolas Schleinitz[6], Norbert Vey[7], Karim Sacre[8], Bertrand Godeau[9], Odile Beyne-Rauzy[10], Romain Bouvet[11], Jonathan Broner[12], Natacha Brun[13], Thibault Comont[14], Clément Gaudin[15], Olivier Lambotte[16], Lenaïg Le Clech[17], Pierre Peterlin[18], Frédérique Roy-Peaud[19], Clémentine Salvado[20], Mathilde Versini[21], Françoise Isnard[22], Jean Emmanuel Kahn[23], Delphine Gobert[1], Lionel Adès[24], Pierre Fenaux[24], Olivier Fain[1], Arsène Mekinian[1], on behalf of MINHEMON (French Network of dysimmune disorders associated with hemopathies), GFM, CERECAI and CARMEN investigators group

[1] Sorbonne Université, AP-HP, Hôpital Saint-Antoine, Service de Médecine Interne and Inflammation-Immunopathology-Biotherapy Department (DMU 3iD), F-75012, Paris, France

[2] Service de médecine interne, CHU de Toulouse, France; CIC 1436, CHU de Toulouse, France; UMR 1027 Inserm-Université de Toulouse, France

[3] Imagine institute, laboratory of Immunogenetics of Pediatric Autoimmune Diseases, INSERM UMR 1163, Université de Paris, F-75015, Paris ; Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP), Université de Paris, F-75014, Paris

[4] Département de médecine interne, Hôpital de la Timone, AP-HM, Aix Marseille Université, Marseille, France.

[5] Department of Hematology, Centre hospitalier Le Mans, Le Mans, France

[6] Département de médecine interne, Hôpital de la Timone, AP-HM, Aix Marseille Université, Marseille, France.

[7] Haematology Department, Institut Paoli-Calmettes, Aix-Marseille Université, Marseille, France

[8] Departement de Médecine Interne, Hôpital Bichat, APHP, Université de Paris, INSERM U1149, Paris, France.

[9] Hôpitaux de Paris, Hôpital Henri Mondor, Médecine Interne, Centre de Référence des Cytopénies Auto-immunes de L'Adulte, Université Paris-Est Créteil, F-94010, Créteil, France.

[10] Department of internal medicine, Toulouse University Hospital, Institut universitaire du cancer de Toulouse, and University of Toulouse, F-31059, Toulouse, France

[11] Médecine interne et maladies systémiques, CHU Dijon Bourgogne, 21000 Dijon, France.

[12] Internal Médicine Department, Nîmes University Hospital, University of Montpellier, Nîmes, France

[13] Service de Médecine Interne, Centre Hospitalier de Rodez, Rodez, France.

[14] Department of internal medicine, Toulouse University Hospital, Institut universitaire du cancer de Toulouse, and University of Toulouse, F-31059, Toulouse, France

[15] Department of oncogeriatric medicine, University Hospital Purpan, Toulouse, France.

[16] Hôpitaux de Paris, Hôpital Bicêtre, Médecine Interne et Immunologie Clinique, F-94275, Le Kremlin-Bicêtre, France; INSERM U1184, Immunology of Viral Infections and Autoimmune Diseases, F-94276, Le Kremlin-Bicêtre, France; Université Paris Sud, UMR 1184, F-94276, Le Kremlin-Bicêtre, France; CEA, DSV/iMETI, IDMIT, F-92265, Fontenay-aux-Roses, France.

[17] Department of Internal Medicine, Infectious Diseases and Haematology, Cornouaille Hospital Quimper, France

[18] Service d'hématologie clinique, CHU de Nantes

[19] Service de médecine interne, maladies infectieuses et tropicales, CHU de Poitiers, Poitiers, France.

[20] CH de Dax, Service de Maladies Infectieuses, Dax, France

[21] Institut Arnault Tzanck, Saint Laurent du Var, France

[22] Department of Clinical Hematology, Saint-Antoine Hospital, AP-HP, Paris, France.

[23] AP-HP, Hôpital Ambroise Paré, Service de Médecine Interne, Paris, France

[24] Hopital Saint-Louis (APHP) and Paris University and INSERM U944, Paris, France

Collaborators: CARMEN investigators group: Daniel ADOUE, Laurent ALRIC, Sophie ARISTA, Laurent BALARDY, Sarah BETRIAN, Cécile BOREL, Delphine BONNET, Delphine BRECHEMIER, Miguel CARREIRO, Brice CASTEL, Thibault COMONT, Pierre COUGOUL, Alina DANU, Claire DINGREMONT, Francis GACHES, Marie-Hélène GASPARD, Aurélie GODEL-LABOURET, Patrick GIRAUD, Sondess HADJ-KHELIFA, Benjamin HEBRAUD, Sarah KHATIBI, Lorraine LEPLAY, Yann LEVENEUR, Sylvie OLLIER, Serge MADAULE, Clothilde MARTEL, Guillaume MARTIN-BLONDEL, Martin MICHAUD, Julia MOEGLIN, Philippe MONTANÉ de la ROQUE, Fanny NUCCIO, Maire-Léa PIEL-JULIAN, Laurent

PRUDHOMME, Grégory PUGNET, Christian RECHER, Véronique REMY, Laurent SAILLER, Stéphane SIRE, Agnès SOMMET, Suzanne TAVITIAN, Willy VAILLANT.

Running title: ITP associated with MDS and CMML

Correspondance to : Pr Arsène Mekinian, Service de médecine interne, hôpital Saint Antoine, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France. Tel: +33 (0) 149282392 / Fax: +33 (0) 149282885 E-mail: arsene.mekinian@aphp.fr

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Conflict of interest

GM received research grants form CSL Behring and Novartis for the CARMEN registry in 2016 and 2017-2018. These sponsors have no role in data collection and have not the property of data; they have no role in the conception, the methodology, the analyses, the interpretation of the studies conducted in the registry; the manuscript has not been submitted

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Authors' contributions

VJ, GM, PF, OF and AM designed the research and analyzed data and then wrote the paper. JH, JS, KL, NS, NV, KS, BG, ODR, RB, JB, NB, TC, CG, OL, LLC, PT, FRP, CS, MV, FI, CS, MV, DG JEK, participated to the patient's data, analyse and relecture of the manuscript.

Key message

MDS/CMML-associated ITP have a particular outcome with more severe bleeding and multirefractory profile than primary ITP

MDS/CMML-associated ITP have less progression toward acute myeloid leukemia than MDS/CMML without ITP, with similar overall survival

ABSTRACT

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are associated with systemic inflammatory or autoimmune diseases in 10-20 % of cases. Among them, immune thrombocytopenia (ITP) has been reported but large studies assessing this association are missing. Whether such patients have a particular phenotype and require particular management is unclear.

This study analyzes the clinical spectrum, outcome and therapeutic management of patients with ITP associated with MDS or CMML, in comparison (i) to patients with primary ITP without MDS/CMML and (ii) to patients with MDS/CMML without ITP.

Forty-one MDS/CMML-associated ITP patients were included, with chronic ITP in 26 (63%) patients, low-risk myelodysplasia in 30 (73%) patients and CMML in 24 (59%) patients. An associated autoimmune disease was noted in 10 (24%) patients. In comparison to primary ITP patients, MDS/CMML-associated ITP patients had a higher occurrence of severe bleeding despite similar platelet counts at diagnosis. First-line treatment consisted of glucocorticoids (98%) and intravenous immunoglobulin (IVIg) (56%). Response achievement with IVIg was more frequent in primary ITP than in MDS/CMML-associated ITP patients. Response rates to second-line therapies were not statistically different between primary ITP and MDS/CMML-associated ITP patients. Ten percent (n=4) of patients with MDS/CMML-associated ITP had multirefractory ITP versus none in primary ITP controls. After a median follow-up of 60 months, there was no difference in overall survival between MDS/CMML-associated ITP and primary ITP patients. Leukemia-free-survival was significantly better in MDS/CMML-associated ITP patients than in MDS/CMML without ITP

MDS/CMML-associated ITP have a particular outcome with more severe bleeding and multirefractory profile than primary ITP, similar response profile to primary ITP therapy except for IVIg, and less progression toward acute myeloid leukemia than MDS/CMML without ITP.

INTRODUCTION

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are clonal hematopoietic stem cell disorders characterized by ineffective and dysplastic hematopoiesis in the bone marrow leading to cytopenias and a risk of developing acute myeloid leukemia (AML) (1). In 10 to 28% of cases, various systemic inflammatory or autoimmune diseases (SIADs) can be associated with MDS or CMML (2). Their impact on MDS/CMML patient survival and acute leukemia progression remains controversial, but they can make therapy challenging. In addition to the most frequently reported SIADs (vasculitis, neutrophilic dermatoses, and polyarthritis), immune cytopenias have been documented in 1 to 16% of cases (3–5). Immune thrombocytopenia (ITP) is an immune-mediated acquired disorder defined by a transient or persistent decrease in the peripheral blood platelet count $<100 \times 10^9$/L after exclusion of other causes of isolated thrombocytopenia (6). ITP is characterized by autoimmune-mediated platelet destruction and impaired platelet production, which can lead to an increased risk of bleeding. Large studies analyzing the specific features, outcome and treatment of ITP in MDS/CMML are lacking. The aim of this study from the "French Network of Dysimmune Disorders Associated with Hemopathies" (MINHEMON) was to describe the clinical spectrum, therapeutic management and outcome of patients with ITP in the context of MDS/CMML in comparison (i) to patients with primary ITP without MDS/CMML and (ii) to patients with MDS/CMML without ITP.

METHODS

Patient selection

We retrospectively collected data on patients with ITP associated with MDS/CMML diagnosed beginning in January 1999 at 16 French departments of internal medicine and hematology. Physicians were asked by the French Network of Dysimmune Disorders Associated with Hemopathies (MINHEMON), the Reference Centre for Autoimmune Cytopenia in Adults (*Centre de Référence des Cytopénies Auto-Immunes de l'adulte*, CeReCAI) and the French Society of Internal Medicine (*Société Nationale Française de Médecine Interne*, SNFMI) to report cases of ITP associated with MDS or CMML. Some patients with ITP and CMML (n=5) presented in this case series have been described in a previous work (7). Clinical, laboratory and immunological data at MDS/CMML and ITP diagnoses and during the follow-up were collected using a standardized form.

Patients were included if they fulfilled the following criteria: (i) age over 18 years, (ii) ITP diagnosis according to the international criteria (6): platelet count < 100 x 10^9/L on at least two separate occasions and the exclusion of other causes of thrombocytopenia, (iii) steroids-responsive thrombocytopenia (response is defined as any platelet count of at least 30 × 10^9/L and at least doubling of the baseline count response, according to Rodeghiero et al (6)), (iv) MDS or CMML diagnosis, based on blood and bone marrow examinations, according to the 2016 World Health Organization classification (8), and (v) a maximum period of 10 years between ITP and MDS/CMML diagnoses.

The exclusion criteria were as follows: (i) patients with secondary ITP not linked to MDS (malignancy, chronic viral infection, primary immune deficiency or drugs) and (ii) lack of response to steroids.

Patients were classified using the Revised International Prognostic Scoring System (IPSS-R) (9) and separated into two subgroups, low- and high-risk MDS, based on the IPSS-R at a cut-off of 3.5 points (10). Secondary MDS refers to therapy-related MDS (occurring after chemotherapy or radiation therapy) or to MDS associated with another primary or acquired bone marrow disorder.

Bleeding was graded according to the bleeding score previously reported by Khellaf et al (9). Severe bleeding was defined as intracranial hemorrhage, overt gastrointestinal bleeding, severe menstrual bleeding, and macroscopic hematuria (10).

Multirefractory ITP was defined as severe chronic ITP not responding to rituximab, splenectomy or thrombopoietin receptor agonist (TPO-RA) use (11).

This study was conducted in compliance with the Helsinki Declaration, upon a database of patients treated according to standard care under the MR04 methodology; therefore, no ethics approval was necessary according to French law (https://www.legifrance.gouv.fr/eli/decret/2017/5/9/AFSP1706303D/jo/texte). The database was declared with registration number 2218061 v 0 to the *Commission Nationale de l'Informatique et des Libertés* (CNIL).

Criteria for the ITP response

Assessment of the response to ITP treatments was timed specific to each treatment according to Rodeghiero et al (6). Complete response (CR) was defined as any platelet count of at least 100 x 10^9/L. Partial response (PR) was defined as any platelet count between 30 and 100 x 10^9/L and at least doubling of the baseline count. No response (NR) was defined as any platelet count lower than 30 x 10^9/L or less than doubling of the baseline count. The definition of PR and CR required concurrent resolution of bleeding symptoms.

Comparison with two prospective cohorts of ITP patients and MDS/CMML patients

Patients with MDS/CMML-associated ITP were matched for age (± 5 years) and sex to patients with primary ITP included between 2013 and 2019 in the multicenter *Cytopénies Auto-immunes: Registre Midi-PyrénéEN* (CARMEN) registry at a 1:2 ratio. CARMEN is a registry that follows prospectively incident ITP adult patients (≥ 18 years) in the Midi-Pyrénées region (southern France, 3 million inhabitants) that began in June 2013 (12,13). The absence of myelodysplasia was confirmed by a bone marrow examination for all primary ITP controls in this study.

Patients with MDS/CMML-associated ITP were also matched for age (± 5 years), sex, type of disorder (MDS or CMML) and IPSS-R (≤ or >3.5 (14)) to patients with MDS/CMML without ITP beginning in 2003 in the multicenter *Groupe Francophone des Myélodysplasies* (GFM) registry of MDS/CMML at a 1:4 ratio.

Statistical analysis

Continuous variables are presented as the mean ± SD or as the median (range) as appropriate. Qualitative variables are presented as the number (%). The Mann-Whitney test and t-test were used to compare continuous variables, and chi-square and Fisher exact tests were used to compare qualitative variables. Overall survival (OS) was calculated from the date of MDS/CMML diagnosis to death or the last date of follow-up. Leukemia-free survival (LFS) was calculated from the date of MDS/CMML diagnosis to the date of AML transformation. OS and LFS were analyzed with the log-rank test, and the results are expressed using Kaplan-Meier methods. A p-value <0.05 was considered statistically significant. Statistical analyses involved the use of GraphPad Prism 5.0 for Mac (GraphPad Software™, La Jolla, CA, USA).

RESULTS

Characteristics of MDS/CMML-associated ITP patients

Between January 1999 and July 2019, we screened 77 patients with MDS/CMML and ITP and ultimately included 41 patients from 16 French hospitals **(Figure 1)**. The median age at diagnosis was 77 years (range: 35-92) in the MDS/CMML group with ITP, and 41% of the patients were women (**Table 1**). The median IPSS-R score was 3 (range: 1-5), and 30 (73%) patients had low-risk MDS. ITP was diagnosed concomitantly with MDS/CMML [± 3 months] in 17 (41%) patients. The diagnosis of ITP preceded that of MDS/CMML [-116 to -6 months] in 16 (39%) patients and occurred after MDS/CMML diagnosis [+4 to +111 months] in 8 (20%) patients (**Supplementary Figure 1**). The median platelet count was 15 x 10^9/L (range: 1-90) at ITP diagnosis, and the nadir platelet count was 8 x 10^9/L. Twenty-nine percent (11/38) of the patients had a high bleeding score (Khellaf's score >8) (9). Platelet transfusion therapy was ineffective in 78% (14/18) of patients. An isotopic measurement of the platelet lifespan carried out in 4 patients revealed for all patients a major reduction in the average platelet lifespan with a median of 2.75 (1-4) days, and the assessment of the site of platelet destruction revealed a purely or predominantly splenic pattern for 2 patients and a mixed (hepatic and splenic) pattern for 2 patients. Antiplatelet antibodies detected by the MAIPA (monoclonal antibody immobilization of platelet antigens) assay were found in 7/16 (44%) patients (4 patients with positive direct MAIPA only, and 3 patients with both direct and indirect positive MAIPA), and autoimmune hemolytic anemia was observed in 5 patients.

Comparison of ITP with and without MDS/CMML

MDS/CMML-associated ITP patients were matched to 75 primary ITP controls without MDS/CMML (median age: 76 years [range: 35-92]; 39% women) from the CARMEN registry (**Table 1**). The platelet count at the time of ITP diagnosis was not significantly

different between the MDS/CMML-associated ITP group (15 x 10^9/L [range: 1-90]) and the primary ITP group (11 x 10^9/L [1-91]); p = 0.39), with similar rates of a high hemorrhagic score (Khellaf's score > 8) (29% vs. 28%, p=0.92). However, MDS/CMML-associated ITP patients had a higher occurrence of severe bleeding (26% vs. 4%, p=0.0009) touching the central nervous system (n=3), gastrointestinal tract (n=2) and other sites (n=3). Polyclonal hypergammaglobulinemia (gamma globulin level >14 g/L) tended to be more frequent in the MDS/CMML-associated ITP group (35%) than in the primary ITP group (18%) (p = 0.07).

Comparison of MDS/CMML with and without ITP

MDS/CMML-associated ITP patients were matched to 200 MDS/CMML controls without ITP (median age: 78 years [range: 28-92]; 38% women) from the GFM registry (**Table 1**). The distribution of MDS and CMML subtypes was similar between the two groups (MDS/CMML with and without ITP) (**Supplementary Figure 2**). The most frequent MDS subtypes were MDS with multilineage dysplasia (53% of MDS/CMML-associated ITP patients and 39% of MDS/CMML patients without ITP, respectively), MDS with single lineage dysplasia (29% and 17%, respectively) and MDS with excess blasts (12% and 15%, respectively). The proportion of secondary MDS was not different between groups: 10% of MDS/CMML patients with ITP (chemotherapy (n = 3), exposure to solvents (n = 1) or radioactivity (n = 1)) and 14% of MDS/CMML patients without ITP.

MDS/CMML patients with ITP had a lower platelet count than MDS/CMML patients without ITP (median 15 x 10^9/L vs. 137 x 10^9/L, p <0.0001), without significant differences concerning hemoglobin levels, neutrophil and monocyte counts, the number of bone marrow blasts and the median IPSS-R score. The karyotypic abnormality rates were similar between groups (29% versus 32%, p = 0.73), and the most frequent were 20q (n = 4) and Y (n = 4) deletions. The frequency of 20q deletion in the MDS/CMML with ITP group was higher than

that in the MDS/CMML without ITP group (40% vs. 6%, respectively, p = 0.002). Approximately 20% of patients in each group (22% of the MDS/CMML with ITP group and 23% of the MDS/CMML without ITP group) received a specific hematological treatment for myelodysplasia: hydroxyurea (n=5/41 in the MDS/CMML with ITP group and n=25/200 in the MDS/CMML without ITP group), azacytidine (n=4/41 and none, respectively), allogeneic bone marrow transplant (n=1/41 and n=4/200, respectively) or other therapies (n=2/41 and n=11/200, respectively).

Therapeutic management of ITP in MDS/CMML-associated ITP patients

All patients received a specific treatment for ITP, either for a platelet count <30 x 10^9/L without hemorrhagic syndrome (44%), hemorrhagic syndrome (41%), concomitant antithrombotic medication or invasive procedure (10%) and associated autoimmune hemolytic anemia (5%). The response rates for each therapeutic strategy are indicated in **Table 2**. First-line treatment consisted of glucocorticoids and intravenous immunoglobulin (IVIg) (56%), with higher response rates with IVIg in primary ITP patients than in MDS/CMML-associated ITP patients (90% vs. 61%, respectively, p = 0.0003). ITP relapse rates after first-line therapy were significantly higher in the MDS/CMML-associated ITP group (69% after glucocorticoids and 77% after IVIg) than in the primary ITP group (42% after glucocorticoids and 43% after IVIg) (p = 0.009). Second-line treatment consisted of TPO-RA (68%), danazol (44%), rituximab (40%), dapsone (20%) and splenectomy (13%). The mean number of immunosuppressive treatments used in second-line therapy was similar between the two groups (2.1 ± 1.5 in MDS/CMML-associated ITP patients vs. 1.6 ± 0.8 in primary ITP patients; p=0.42), and approximately 40% of patients in each group received at least two different second-line treatments. The efficacy of each second-line treatment was comparable between the two groups, as illustrated in **Figure 2**. In the MDS/CMML-associated ITP group,

the median duration of exposure was 18 months (range: 6-29) after rituximab, 14 months (range: 1-46) with TPO-RA, 6 months (range: 4-28) with danazol and 6 months (range: 5-6) with dapsone, with no significant difference between the different therapies.

Among the 3 patients with concomitant ITP and MDS/CMML treated with azacytidine (for MDS/CMML indications and 2 for refractory ITP), a complete hematological response concomitant to ITP CR was noted in 1 patient (15).

Unlike patients with primary ITP, 4 (10%) patients with MDS/CMML-associated ITP presented with multirefractory ITP without simultaneous progression of the underlying myelodysplasia (confirmed by bone marrow aspiration and karyotype analysis in all 4 refractory cases).

Outcome

The median follow-up was 66 months (range 1-176) in the MDS/CMML-associated ITP group, 23 months (range 0-106) in the MDS/CMML without ITP group and 10 months (range 0-53) in the primary ITP group. There was no difference in OS between MDS/CMML-associated ITP and primary ITP patients (log-rank test p=0.15, median OS not reached in any group) (**Figure 3A)**. LFS was better in MDS/CMML-associated ITP patients than in MDS/CMML without ITP patients (log-rank test p=0.05, median LFS not reached in any group) (**Figure 3B)**. The four ITP patients who developed AML had CMML.

DISCUSSION

From this multicenter study, we obtained the following results: (i) MDS/CMML-associated ITP patients had a higher occurrence of severe bleeding despite similar platelet levels than primary ITP patients, which is probably explained by associated dysmegakaryopoiesis and platelet dysfunction, (ii) ITP was observed mostly in low-risk MDS patients according to the IPSS-R classification, (iii) the presence of 20q deletion was more frequent among MDS/CMML patients with ITP than those without ITP, (iv) MDS/CMML-associated ITP was characterized by a lower response rate to IVIg, more frequent relapses after first-line therapy and a multirefractory profile than primary ITP, and (v) there was no unfavorable impact on OS and a low risk of AML progression.

Up to 20% of patients with MDS or CMML experience a systemic inflammatory or autoimmune disease (3). These manifestations are part of a large and heterogeneous group of disorders. Among the various autoimmune or inflammatory disorders related to MDS/CMML, ITP is a rare condition. Among the 61 MDS/CMML patients with thrombocytopenia <70 x 10^9/L in this study, 15% (n=9) presented a reduced platelet lifespan, and 6 were treated with splenectomy, allowing a platelet response in 3 patients (16). In another series, 3.3% (n=46) of 1408 MDS patients developed ITP (4). Among 2882 French ITP patients, 2.3% (n=67) were associated with MDS, suggesting a role for MDS in the peak ITP incidence in the elderly (17). Conversely, another French series of 565 ITP patients found that 1.4% (n=8) were associated with CMML (7). Among 62 MDS patients, Braun et al reported that an isolated 20q deletion, which is associated with a good prognosis, was associated with a lower platelet count than among MDS patients without a 20q deletion (18).

The main difficulty in the setting of MDS/CMML is to distinguish immune-related peripheral thrombocytopenia from that of central origin (i.e., due to bone marrow failure). Arguments for

the peripheral immune origin of thrombocytopenia in MDS could be supported by the existence of common immune-mediated pathophysiological mechanisms, in particular humoral and cellular immune activation directed against both peripheral blood cells and bone marrow precursors, or impaired megakaryopoiesis attributed to autoantibodies cross-reacting against platelet glycoproteins or cytokine dysregulation (19–22). Barcellini et al hypothesized a shift from autoimmunity against circulating blood cells to bone marrow precursors, leading to an insufficient marrow compensatory response, a progressive/variable degree of bone marrow dysplasia, and ultimately overt bone marrow failure (19). Even if none of these features were pathognomonic of ITP, the probable peripheral origin of thrombocytopenia in MDS/CMML was based, in our study, on the following: (i) a clear-cut response, either partial or complete, to glucocorticoids, (ii) a discrepancy between an increased megakaryocyte count and deep thrombocytopenia, (iii) prominent dysimmune features in most cases, including positive antiplatelet antibodies, polyclonal hypergammaglobulinemia and other dysimmune diseases and/or autoantibodies, (iv) the absence of platelet transfusion efficiency and (v) mainly low-risk underlying MDS. An isotopic measurement of the platelet lifespan and assessment of the site of platelet destruction might help to predict the efficacy of splenectomy in ITP patients (24–26) but it is usually not routinely performed in France. Mahevas et al. recently showed that platelet kinetic studies could be used in ITP patients treated with TPO□RAs to discuss splenectomy (27). Furthermore, Bourgeois et al showed that 15% of low risk MDS patients had peripheral platelet destruction, attested by isotopic autologous platelet kinetic study (16). However, the low rate of patients having benefited from platelet scintigraphy does not allow the results to be generalized in this population of MDS/CMML-associated ITP patients.

Finally, the most striking conclusion from our study is that immune thrombocytopenia in the setting of MDS/CMML could be raised in some cases, and the benefit of immunomodulation could be tested in patients who do not need a specific MDS treatment.

The most challenging question is the management of presumed immune peripheral cytopenias in the MDS/CMML setting **(Figure 4)**. Few studies have assessed the outcome and management of MDS/CMML-associated ITP, and the previous French case series of 8 patients showed better response rates under IVIg in primary ITP than in MDS/CMML-associated ITP patients (15). In this population of elderly patients, TPO-RA seem to be an interesting therapy because of their efficacy in our series and an acceptable safety profile. In a meta-analysis, Dodillet et al found that treatment with TPO-RA resulted in a lower number of MDS patients suffering from bleeding events. Although some studies have highlighted the potential risk of TPO-RA in accelerating leukemic progression or blast increase in MDS patients (28–30), more recent data from randomized controlled trials (31–33) or meta-analysis (34,35) did not seem to confirm this assumption. Moreover, preclinical studies founded that eltrombopag could inhibit leukemic cell growth in tissue culture and in animal models of leukemia (23,36–39). While waiting for further clinical studies, close monitoring of peripheral blood counts and bone marrow and cytogenetic evaluations should be performed while on TPO-RA. Beyond their effect of megakaryopoiesis stimulation, additional mechanisms of action of TPO-RA include immunomodulating activity, such as the modulation of T-regulatory cells (21) and restoration of the Fc-g receptor balance in phagocytes (40). Finally, the efficacy of TPO-RA in MDS/CMML-associated ITP patients is probably due to the fact these drugs are efficient in both ITP and MDS. The efficacy of azacytidine for immune ITP must be interpreted with caution due to the small number of patients treated, and an ongoing phase II French trial is currently assessing the efficacy and safety of azacytidine in various steroid-dependent/refractory MDS/CMML-associated SIADs (NCT02985190).

The prognostic significance of MDS-associated SIADs remains controversial (3,4,41–44). In our study, we found no difference in OS between MDS/CMML patients with ITP and MDS/CMML patients without ITP. However, LFS was significantly better in MDS/CMML patients with ITP than in MDS/CMML patients without ITP.

Our study has inherent limitations considering its retrospective design, but the main limitation is the difficulty in ascertaining the immune origin of thrombocytopenia in MDS/CMML. We believe that our very strict definition of ITP in MDS/CMML patients limits the patients with a predominant central, non-immunological, origin of thrombocytopenia.

In conclusion, MDS/CMML-associated ITP is associated with a particular outcome: more severe bleeding than primary ITP and a multirefractory profile, but a lower progression rate toward AML.

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TABLES

Table 1. Baseline characteristics and outcome of patients with MDS/CMML-associated ITP, MDS/CMML without ITP and primary ITP.

	MDS/CMML -ITP	Primary ITP	MDS/CMML without ITP	*p*
	n=41	**n=75**	**n=200**	
Age at diagnosis, years	77 [35-92]	76 [35-92]	78 [28-92]	0.33
Female sex (n; %)	17 (41)	29 (39)	75 (38)	0.89
ITP features				
Platelet count at ITP diagnosis, x 10^9/L	15 [1-90]	11 [1-91]	137 [8-1488]	**<0.01** ‡
Khellaf bleeding score > 8 (n; %)	11/38 (29)	21/75 (28)	-	0.92
Severe bleeding (n; %)	8/31 (26)	3/75 (4)	-	**0.01** *
Antiplatelet antibodies (n; %)	7/16 (44)	-	-	-
Direct antiglobulin test (n; %)	12/22 (55)	-	-	-
Antinuclear antibodies (n; %)	12/29 (41)	26/57 (46)	-	0.71
Polyclonal hypergammaglobulinemia (n; %)	12/34 (35)	9/51 (18)	-	0.07
MDS/CMML features at inclusion				
MDS (n; %)	17 (41%)		84 (42%)	0.95
CMML (n; %)	24 (59%)		116 (58%)	
Platelet count, x 10^9/L	15 [1-90]	11 [1-91]	137 [8-1488]	**<0.01** ‡
Hemoglobin, g/dL	11.8 [5-15]	-	10.9 [6-16]	0.14
Neutrophils, x 10^9/L	3.9 [1.2-23]	-	3.9 [0.3-68]	0.72
Bone marrow blasts (%)	3 [0-13]	-	3 [0-29]	0.26
Abnormal karyotype (n; %)	10/34 (29)	-	63/197 (32)	0.73
Low-risk MDS/CMML (n; %)	30/41 (73)	-	155/200 (78)	0.55
IPSS, median (range)	0.5 [0-2]	-	0.5 [0-3.5]	0.66
IPSS-R, median (range)	3 [1-5]	-	2.5 [0-8]	0.39
Secondary MDS (n; %)	4/40 (10)	-	14/97 (14)	0.14
MDS treatment (except EPO and transfusion)	9/41 (22)	-	45/200 (23)	0.94
Number of treatment lines for MDS	1 [1-2]	-	1 [1-3]	0.91
Outcome				
Median follow-up, months	66 [1-176]	-	23 [0-106]	**<0.01** †
AML transformation (n; %)	4/41 (10)	-	15/200 (8)	0.63
Deaths (n; %)	17/41 (41)	-	43/200 (22)	**0.01** †
Deaths related to MDS/CMML or a specific therapy	13/17 (76)	-	18/43 (42)	**0.02** †

ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; IPSS: International Prognostic Scoring System; IPSS-R: Revised International Prognostic Scoring System; EPO: erythropoietin; AML: acute myeloid leukemia.

*: p<0.05: MDS/CMML-associated ITP versus primary ITP
†: p<0.05: MDS/CMML-associated ITP versus MDS/CMML without ITP
‡: p<0.05: MDS/CMML-associated ITP versus primary ITP versus MDS/CMML without ITP

Table 2. ITP treatments and response rates in MDS/CMML-associated ITP and primary ITP patients.

	MDS/CMML-associated ITP	Primary ITP	p-value
	n=41	**n=75**	
First-line treatment	**41/41 (100)**	**73/75 (97)**	0.30
Glucocorticoids	40/41 (98)	72/73 (99)	0.69
CR (n; %)	18/40 (45)	39/67 (58)	0.19
PR (n; %)	19/40 (48)	25/67 (37)	0.30
NR (n; %)	3/40 (8)	3/67 (5)	0.52
IVIg	23/41 (56)	43/73 (59)	0.77
CR (n; %)	7/23 (30)	21/39 (54)	0.08
PR (n; %)	7/23 (30)	14/39 (36)	0.67
NR (n; %)	9/23 (39)	4/39 (10)	**0.01**
Second-line treatment	**25/41 (61)**	**32/75 (43)**	0.06
TPO-RA	17/25 (68)	16/32 (50)	0.18
CR (n; %)	13/17 (76)	11/15 (73)	0.86
PR (n; %)	3/17 (18)	4/15 (27)	0.56
NR (n; %)	1/17 (6)	0	0.38
Danazol	11/25 (44)	4/32 (13)	**0.01**
CR (n; %)	5/11 (45)	3/4 (75)	0.37
PR (n; %)	1/11 (9)	0	0.65
NR (n; %)	5/11 (45)	1/4 (25)	0.54
Rituximab	10/25 (40)	15/32 (47)	0.61
CR (n; %)	3/9 (33)	6/9 (67)	0.19
PR (n; %)	2/9 (22)	0	0.58
NR (n; %)	4/9 (44)	3/9 (33)	0.14
Dapsone	5/25 (20)	7/32 (22)	0.87
CR (n; %)	2/4 (50)	4/7 (57)	0.9
PR (n; %)	2/4 (50)	2/7 (29)	0.5
NR (n; %)	0	1/7 (14)	0.48
Splenectomy	4/25 (16)	0	**0.02**
CR (n; %)	1/4 (25)	-	-
PR (n; %)	1/4 (25)	-	-
NR (n; %)	2/4 (50)	-	-
Other treatment	5/25 (20)	10/32 (31)	0.35
Number of second-line treatments for ITP	2.1 (1.5)	1.6 (0.8)	0.42
Multirefractory ITP (n; %)	4/41 (10)	0	**0.01**

ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; CR: complete response; PR: partial response; NR: no response; IVIg: intravenous immunoglobulin; TPO-RA: thrombopoietin receptor agonist; Other treatment: among vinca alkaloids, hydroxychloroquine, cyclosporine A, mycophenolate mofetil and azathioprine.

LEGENDS TO THE MAIN FIGURES

Figure 1. Flow chart of ITP and MDS/CMML patients in the study

ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; IVIg: intravenous immunoglobulin.

Figure 2. Response rates to second-line treatment in MDS/CMML and primary ITP

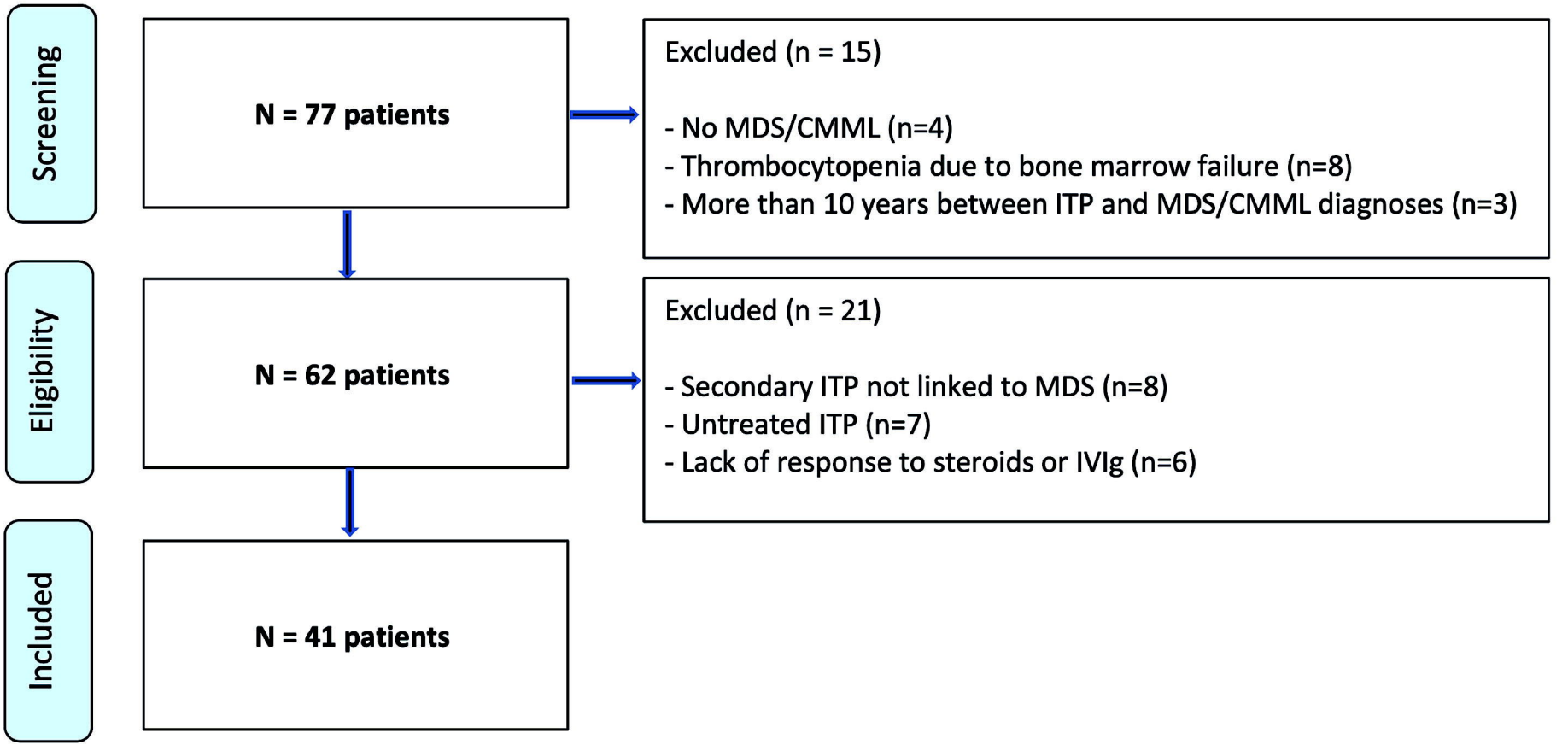
ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; TPO-RA: thrombopoietin receptor agonist; CR: complete response; PR: partial response; NR: no response; ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome.

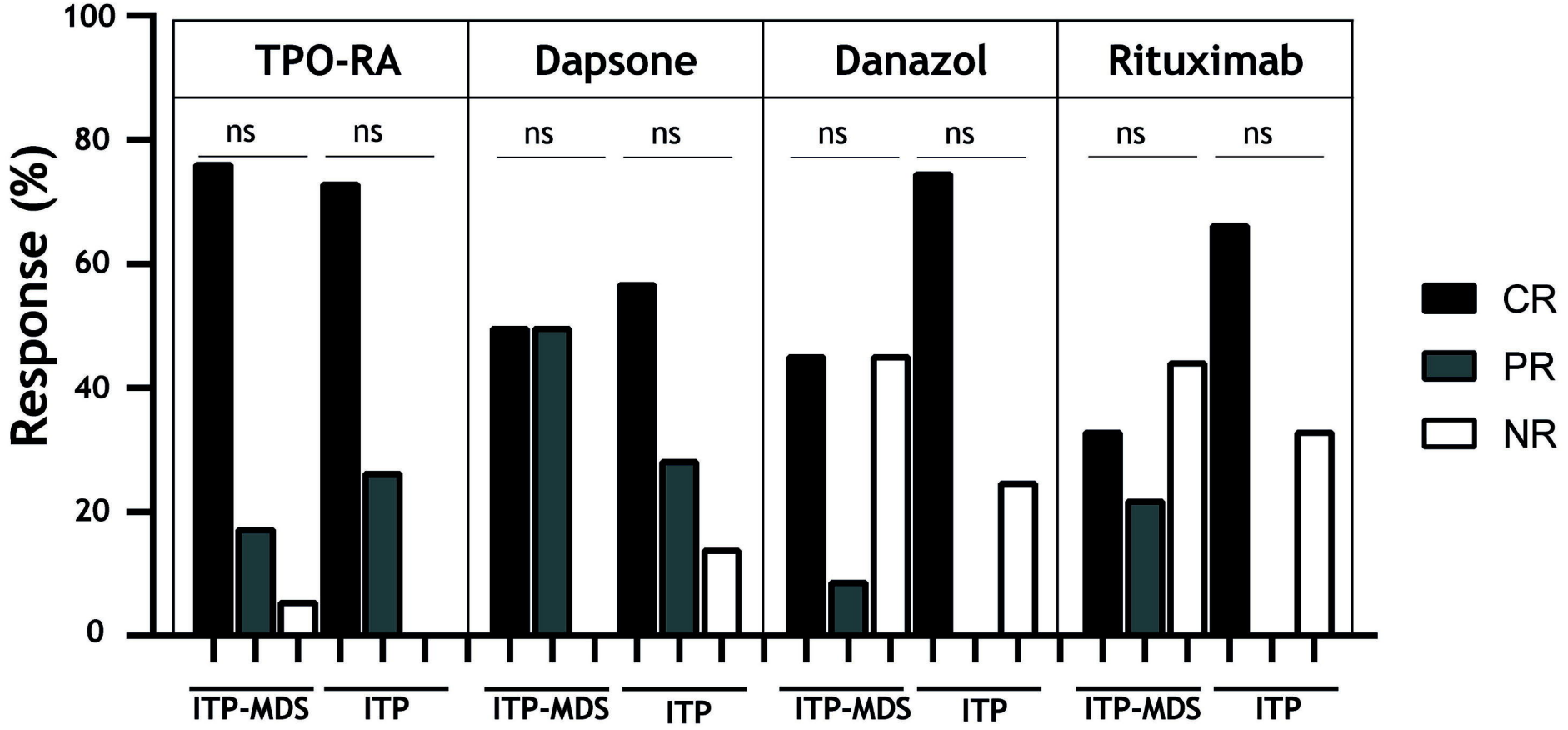
Figure 3. Overall survival (A) and leukemia-free survival (B) in MDS/CMML-associated ITP, MDS/CMML without ITP and primary ITP

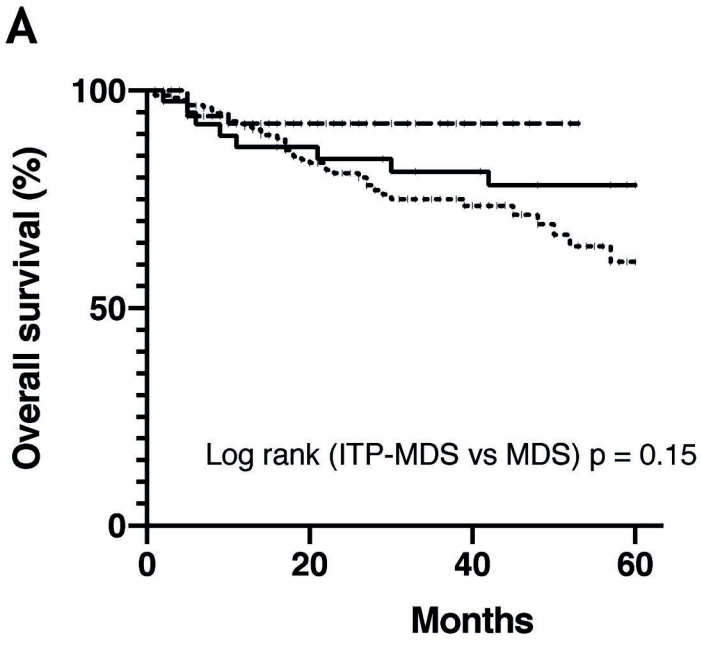
ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia.

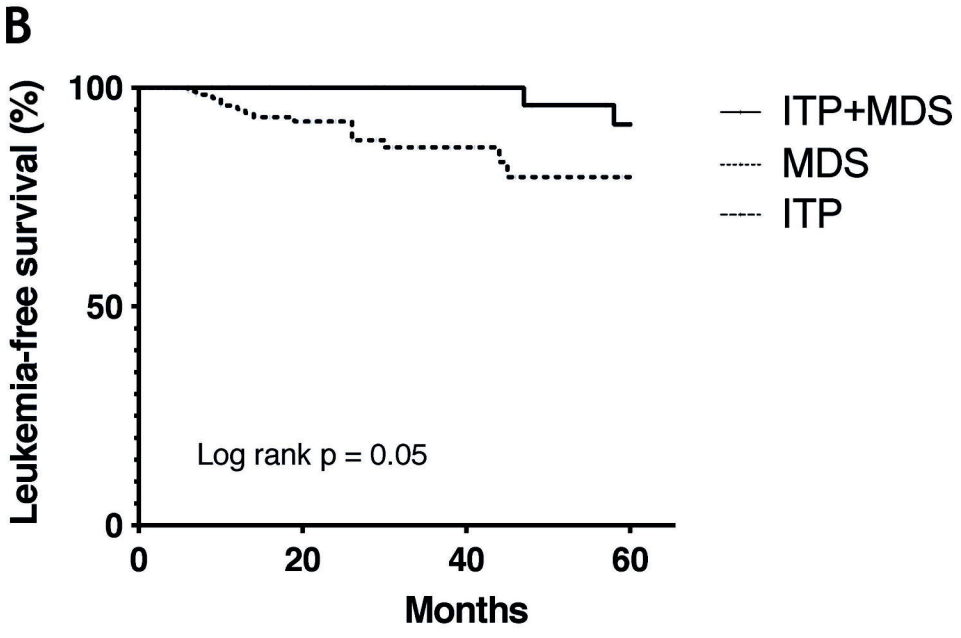
Figure 4. Proposed therapeutic strategy for suspected immune thrombocytopenia associated with MDS or CMML

MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; TPO-RA: thrombopoietin receptor agonist.


Screening
N = 77 patients
Excluded (n = 15)
- No MDS/CMML (n=4)
- Thrombocytopenia due to bone marrow failure (n=8)
- More than 10 years between ITP and MDS/CMML diagnoses (n=3)
Eligibility
N = 62 patients
Excluded (n = 21)
- Secondary ITP not linked to MDS (n=8)
- Untreated ITP (n=7)
- Lack of response to steroids or IVIg (n=6)
Included
N = 41 patients


Response (%)
100
80
60
40
20
0
TPO-RA
Dapsone
Danazol
Rituximab
ns
ns
ns
ns
ns
ns
ns
ns
ITP-MDS
ITP
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ITP
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ITP
CR
PR
NR



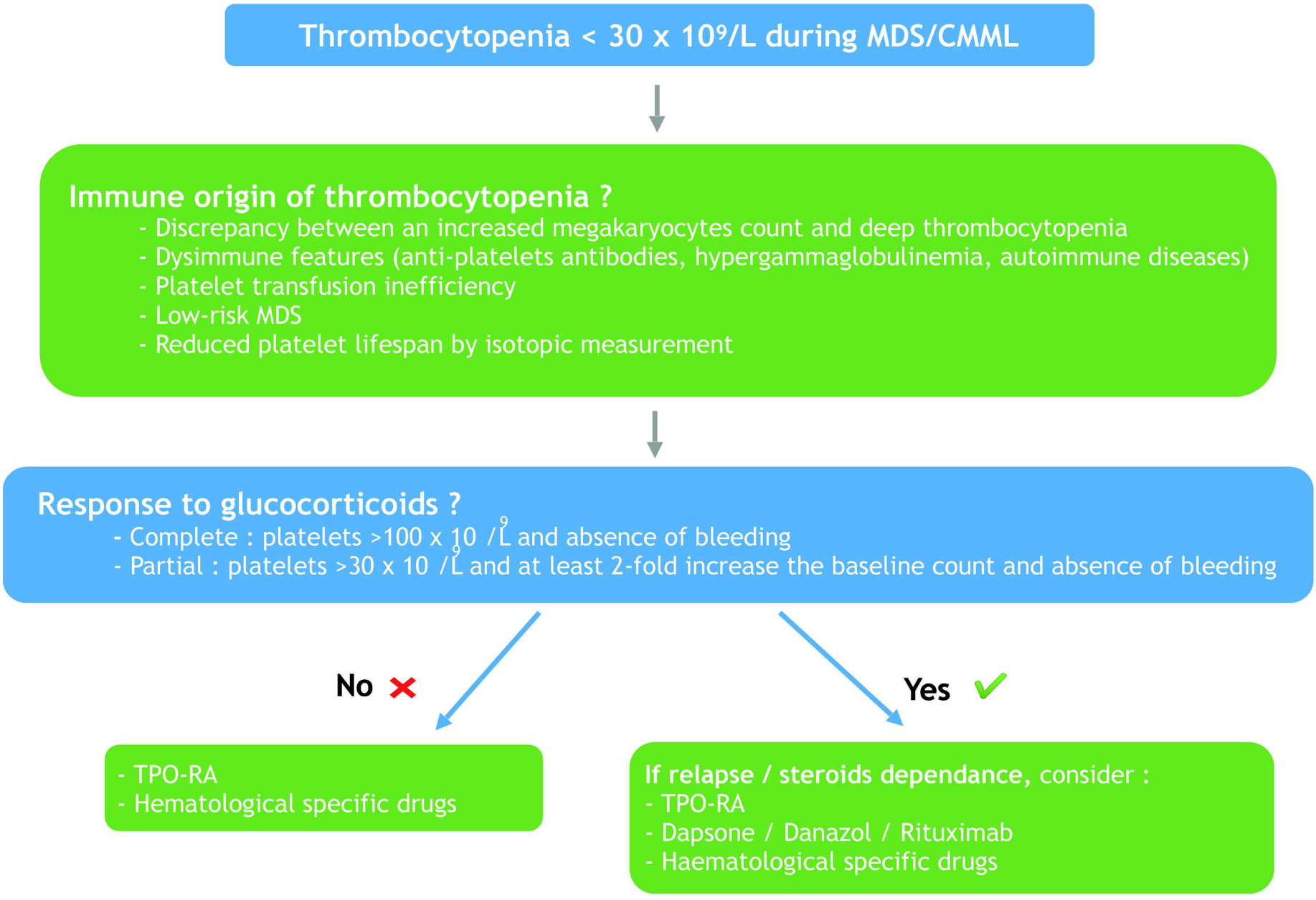


# of subjects at risk

ITP-MDS	41	33	28	22
MDS	185	112	44	12
ITP	88	35	10	0

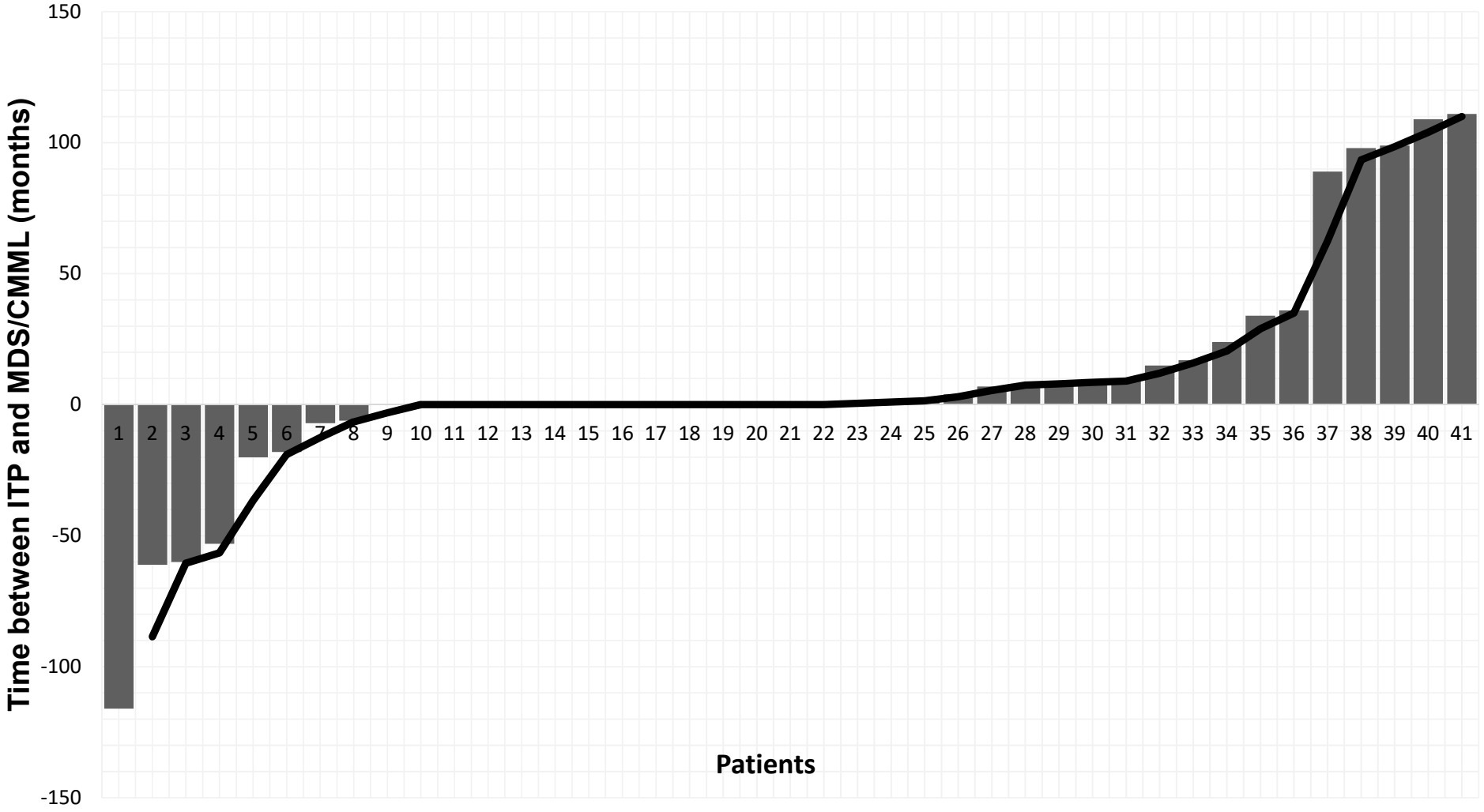
# of subjects at risk

ITP-MDS	41	33	28	20
MDS	141	84	29	7


Thrombocytopenia < 30 x 10⁹/L during MDS/CMML
Immune origin of thrombocytopenia ?
- Discrepancy between an increased megakaryocytes count and deep thrombocytopenia
- Dysimmune features (anti-platelets antibodies, hypergammaglobulinemia, autoimmune diseases)
- Platelet transfusion inefficiency
- Low-risk MDS
- Reduced platelet lifespan by isotopic measurement
Response to glucocorticoids ?
- Complete : platelets >100 x 10⁹ /L and absence of bleeding
- Partial : platelets >30 x 10⁹ /L and at least 2-fold increase the baseline count and absence of bleeding
No
Yes
- TPO-RA
- Hematological specific drugs
If relapse / steroids dependance, consider :
- TPO-RA
- Dapsone / Danazol / Rituximab
- Haematological specific drugs

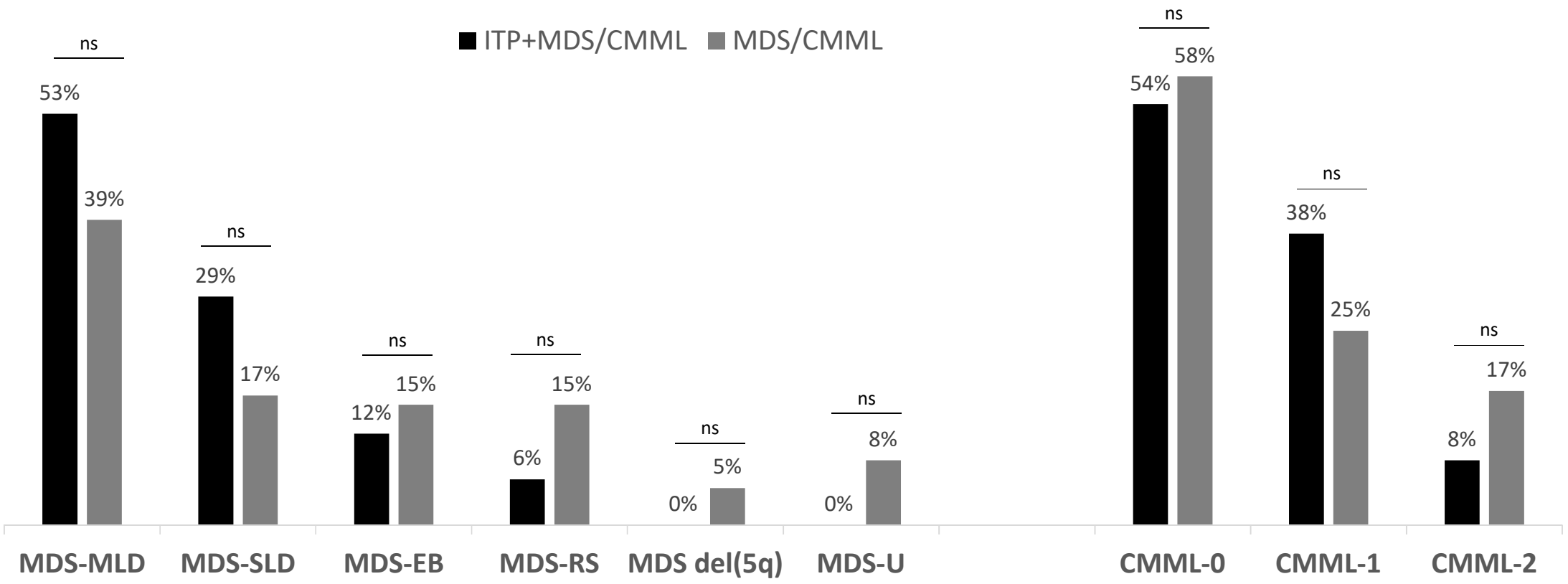
Supplementary Figure 1. Time between ITP and MDS/CMML diagnoses in MDS/CMML-associated ITP

ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia.


Time between ITP and MDS/CMML (months)
150
100
50
0
-50
-100
-150
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Patients

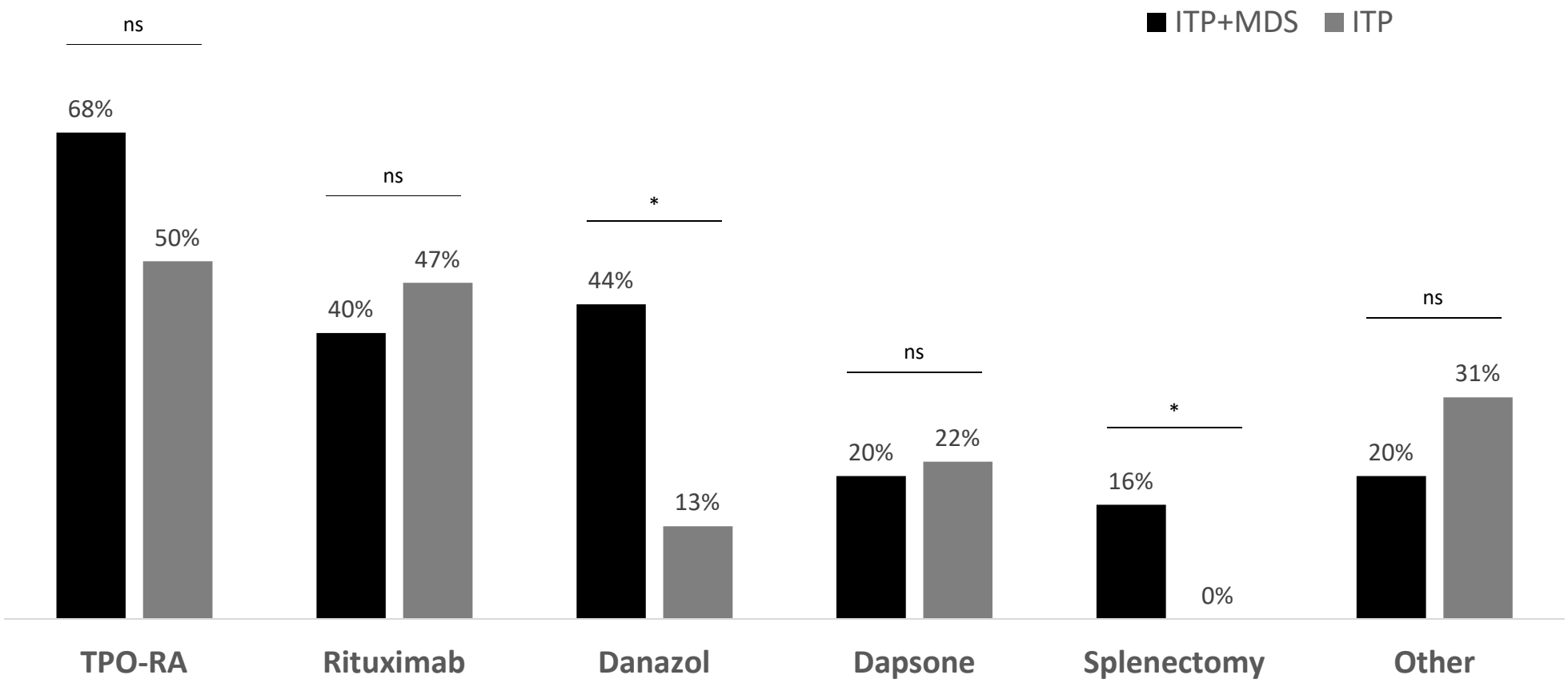
Supplementary Figure 2. Distribution of MDS and CMML subtypes in patients with and without ITP

ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; MDS-MLD: MDS with multilineage dysplasia; MDS-SLD: MDS with single lineage dysplasia; MDS-EB: MDS with excess blasts; MDS-RS: MDS with ring sideroblasts; MDS del(5q): MDS with isolated del(5q); MDS-U: MSD, unclassifiable.


ITP+MDS/CMML
MDS/CMML
ns
53%
39%
ns
29%
17%
ns
12%
15%
ns
6%
15%
ns
0%
5%
ns
0%
8%
ns
54%
58%
ns
38%
25%
ns
8%
17%
MDS-MLD
MDS-SLD
MDS-EB
MDS-RS
MDS del(5q)
MDS-U
CMML-0
CMML-1
CMML-2

Supplementary Figure 3. Second-line therapies in MDS/CMML-associated ITP versus primary ITP

ITP: immune thrombocytopenia; MDS: myelodysplastic syndrome or chronic myelomonocytic leukemia; TPO-RA: thrombopoietin receptor agonist.


ITP+MDS
ITP
ns
68%
50%
ns
40%
47%
*
44%
13%
ns
20%
22%
*
16%
0%
ns
20%
31%
TPO-RA
Rituximab
Danazol
Dapsone
Splenectomy
Other