COMMENTARY

blood advances

TO THE EDITOR:

Positivity rate of systematic bone marrow smear in patients over 60 years old with newly diagnosed immune thrombocytopenia

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Recently, *Blood Advances* published an updated international consensus report (ICR) by Provan et al[1] and American guidelines (supported by the American Society of Hematology [ASH]) by Neunert et al[2] on managing immune thrombocytopenia (ITP). The 2019 ICR is an update of the first report published in 2010.[3] By using the same methodology as that used in the first report, Provan et al selected those who have recognized clinical and research expertise in ITP (international adult and pediatric hematologists, experts in methodology, and a patient representative) to help with their review and report. The ICR consists of a literature search with a final review by the authors. Evidence levels for the articles were assigned recommendation grades (A, B, or C), which were determined at the end of the review and were assigned and reviewed by the authors following the same scoring system as that used in the first report.

The 2019 ASH guidelines were built from the last practice guidelines published in 2011.[4] For this work, Neunert et al selected adult and pediatric hematologists, experts in methodology, and a patient representative for their expertise in systematic reviews and guideline development. Most of them were from the United States, and they did not have any direct connection with pharmaceutical companies. There are important differences between the ICR and ASH guidelines. The ASH guidelines are based on a systematic literature review, and the recommendations are focused on clinical questions that describe management issues, with a detailed level of evidence (Grading of Recommendations, Assessment, Development and Evaluations [GRADE] approach). The ICR contains different therapeutic options listed in strict alphabetical order to avoid showing a preference for a particular treatment.

These updated guidelines do not recommend systematic bone marrow smear at ITP diagnosis in adults for those with typical ITP. This is a new statement for international consensus guidelines because systematic bone marrow smear was recommended in all patients older than age 60 years in the 2010 version.[3] Indeed, this recommendation is not consensual: although the ASH guidelines are in line with the new international consensus recommendations, the French and German guidelines still recommend systematic bone marrow smear in all patients older than age 60 years with typical ITP to detect associated hematologic disease,[5,6] particularly myelodysplastic syndrome (MDS), which accounts for 2.3% of incident ITP in adult patients.[7]

All of these guidelines are driven by expert consensus only and the usefulness of bone marrow examination in ITP is still being discussed[8]; data are lacking about the positivity rate of this examination in older patients with typical ITP. The aim of this study was to assess the positivity rate of bone marrow smear at ITP diagnosis in patients older than age 60 years with no other clinical or biological signs of hematologic malignancy.

Ethical approval was obtained from the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés) for the Cytopénies Auto-Immunes: Registre Midi-Pyréneen (CARMEN) registry (authorization number 2012-438). The CARMEN registry includes patients with ITP who were registered from June 2013 to December 2018. CARMEN is a multicenter registry that is used for prospective follow-up of all newly diagnosed adult patients with ITP in the Midi-Pyrénées region in southern France (~3 million inhabitants). Patients with either primary or secondary ITPs are included.[9,10] ITP was defined by including a platelet count of $<100 \times 10^9$/L and excluding other causes of thrombocytopenia.[11] Patients included in this study were older

than age 60 years, had no clinical signs of hematologic malignancy, had isolated thrombocytopenia (platelets $<100 \times 10^9$/L) on blood count, and had a bone marrow smear performed at ITP diagnosis. We assessed the frequency of pathological bone marrow smears and described the evolution of these patients.

Among 421 incident patients included in the CARMEN registry during the study period, 197 patients were older than age 60 years without clinical signs of hematologic malignancy with isolated thrombocytopenia (platelets $<100 \times 10^9$/L) on blood count. Among them, 114 patients (66 men and 48 women) had a bone marrow smear performed at diagnosis. Mean platelet count at diagnosis was 32.7×10^9/L (standard deviation, 27.7×10^9/L), and 58 patients (50.9%) presented with bleeding: cutaneous bleeding only (n = 33), oral bleeding (n = 17), epistaxis (n = 10), and hematuria (n = 3).

Only 1 patient (0.8%) had an abnormal bone marrow smear corresponding to a characterized hematologic disease: MDS with multilineage dysplasia (MDS-MLD). He was a 62-year-old man without a medical history who presented in 2014 with extensive skin bleeding and isolated thrombocytopenia (platelets 6×10^9/L). A bone marrow smear revealed normal cellularity. The megakaryocytic lineage was present with a significant number of megakaryocytes having multiple separated nuclei. Significant dysgranulopoiesis was also observed with pseudo-Pelger-Huët anomaly and cytoplasmic hypogranulation. Some erythroblasts had defective hemoglobination, and cytoplasmic vacuolation was present. Karyotype was normal.

During a 5-year follow-up, the patient was treated for ITP with steroids, immunoglobulins, danazol, eltrombopag, romiplostim, and rituximab, and he achieved a partial or complete response with each treatment. A second bone marrow smear was performed 4 years after ITP diagnosis, and the findings were similar to those of the first smear.

Our study using the prospective CARMEN registry confirms that abnormal bone marrow smear is very rare in typical ITP patients older than age 60 years. Only 1 instance of MDS was found that did not impact the management of ITP and did not progress to other cytopenias or to myeloid leukemia with a 5-year follow-up. However, our patient with MDS-MLD needed several lines of treatments for ITP. Whether he had a particular phenotype of myelodysplasia-related ITP is not known. Of note, this real-life study describes the detection of full-blown MDS based on cytologic definition. Indeed, molecular assessment is not performed routinely in France, except in the case of characterized MDS. Consequently, it is still not known whether the presence of molecular abnormalities has an impact on the course of ITP.

Considering all of the above observations, we believe that bone marrow smear should be performed only for patients who present with signs of bone marrow disease other than isolated thrombocytopenia (eg, deterioration of general condition, adenomegaly, splenomegaly, anemia, leukopenia, monocytosis, macrocytosis). Cytogenetics, molecular analyses, and trephine biopsy should be considered systematically as part of our hypothesis. However, our strategy needs to be evaluated. In conclusion, this study sustains the guidelines that do not recommend systematic testing for bone marrow examination in patients with typical ITP who are older than age 60 years.

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Contribution: G.M. and T.C. designed the study, performed analyses, analyzed the results, and wrote the manuscript; and J.G., O.B.-R., and D.A. contributed to patient recruitment, informed consent, and data collection and have reviewed and approved the final version of the manuscript for submission.

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A list of the collaborators of the CARMEN investigators group appears in "Appendix."

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Appendix

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