Introduction to a review series on the treatment of thrombocytopenic disorders: something old, something new

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Thrombocytopenia may be a major component of several disorders, exposing patients to an increased risk of bleeding and/or heralding more complex, but often underestimated, clinical scenarios. In a series of reviews in *Haematologica*, leading authors comprehensively discuss the management of thrombocytopenia in three distinct clinical areas generally neglected and still lacking specific treatments.[1-3] Inherited thrombocytopenias,[1] drug-induced immune thrombocytopenia[2] and chemotherapy-induced thrombocytopenia[3] were chosen as illustrative epitomes. In the review on drug-induced immune thrombocytopenia, three subsections expand beyond classical cases of drug-associated thrombocytopenia to include, in addition to the well-known heparin-induced thrombocytopenia, two rare complications recently reported in association with vaccination against coronavirus disease 2019 (COVID-19) – vaccine-induced thrombotic thrombocytopenia[4] and vaccine-associated immune thrombocytopenia.[5]

The readers will learn how to best suspect, diagnose and improve the outcome of these disorders. At the same time, they will gain some insight into the fascinating world of platelets, sometimes considered a Cinderella of hematology, and envisage the long but promising way toward new scientific discoveries for a better understanding and treatment of platelet disorders.

Phylogenetic reconstruction, together with morphological and functional studies in avian and mammalian species, suggest that the small anucleated cells named platelets (Plättchen in German) by the Italian scientist Giulio Bizzozero[6] back in 1881, represent the evolutionary vestige of the more primitive "nucleated thrombocyte". Nucleated thrombocytes of our birds evolved from these ancestors and, reminiscent of their primitive function, remain mostly committed to innate defense mechanisms and wound healing. With the appearance of mammals, some 150 million of years ago, evolutionary forces, driven by the need to ensure more efficient protection from blood loss induced by parturition and trauma, led to the development of anucleated platelets endowed with augmented hemostatic responses.[7] As an undesirable consequence, this hemostatic advantage turned out to be a primary cause of the high rate of thrombotic disorders that plague our times.

The importance of the more primitive hemostatic mechanism stands out in the natural experiments represented by those clinical disorders in which thrombocytopenia is a sufficient cause of bleeding, despite an intact coagulation system. Quite surprisingly, contrary to what is expected, there are clinical situations accompanied by a reduced number of platelets in which thrombosis is also a major factor of morbidity or mortality, posing dramatic management dilemmas (see, for example, heparin-induced thrombocytopenia and vaccine-induced thrombotic thrombocytopenia). Conversely, thrombocytosis may be accompanied by a hemorrhagic tendency as in essential thrombocythemia, whose first denomination was 'hemorrhagic thrombocythemia'.[8] Finally, as detailed in Balduini's review,[1] in a significant proportion of cases with inherited thrombocytopenias an associated impaired platelet function may further aggravate the bleeding tendency. Even worse, in rarer cases, the genetic lesions have impacts beyond thrombopoiesis and thrombocytopenia is just one component of more complex syndromic forms or may herald the future development of hematologic malignancies or bone marrow aplasia or fibrosis, raising ethical dilemmas on how to best inform patients on their condition.

Figure 1 depicts the many inherited and acquired causes that can lead to thrombocytopenia and the main pathogenic mechanisms involved. It is quite evident that a precise diagnosis is essential not only for directing prognosis and treatment, but also for excluding any underlying or associated disorder requiring prompt identification.

As Balduini mentions in his review,[1] the prevalence of in-

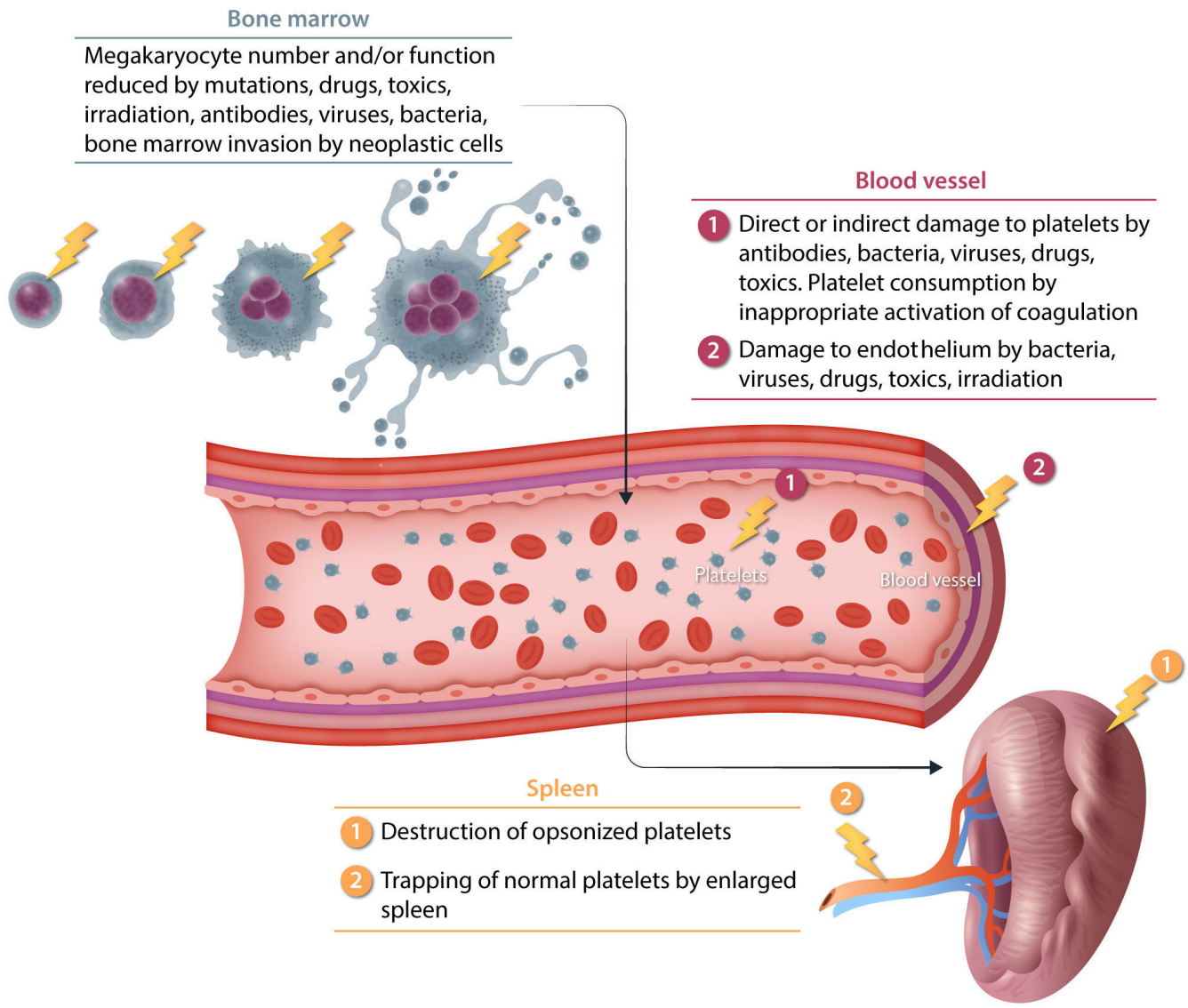

Figure 1. Pathogenic mechanisms of congenital and acquired thrombocytopenia. The pathogenic mechanisms responsible for thrombocytopenia can be grouped into three categories: reduced production of platelets, increased consumption/destruction in the bloodstream, and increased destruction/entrapment in the spleen. The causes of thrombocytopenia are shown in the figure and many of them act through more than one pathogenic mechanism. Increased awareness of the many distinct forms of thrombocytopenia is a prerequisite for appropriate prevention, as in drug-associated thrombocytopenia, or for making a precise prognosis or planning comprehensive treatment exploiting as best possible the limited options available for the various different types of congenital and acquired thrombocytopenia.

herited thrombocytopenias is reported to be as high as more than two cases per 100.000 persons, an order of magnitude similar to that of immune thrombocytopenic purpura (ITP). Nevertheless, only a very tiny proportion of patients is diagnosed with inherited thrombocytopenias at major hematology centers, thus highlighting the underdiagnosis of this pathology. No prevalence data are available for drug-induced immune thrombocytopenia, but its diagnosis is very difficult without a high index of suspicion and underdiagnosis is anticipated also for this condition. Indeed, even in expert centers, several cases of isolated thrombocytopenia are initially misdiagnosed as ITP with potentially dangerous consequences.[9]

For most of the disorders reviewed in the series, reducing or aborting bleeding – the enemy platelets were evolved to fight against - is the primary goal that should dictate management. Whereas many agents can negatively interfere with the thrombotic potential of platelets, thus reducing platelet-dependent thrombotic risk at the cost of slightly increasing the hemorrhagic risk, there are no drugs that can augment platelet hemostatic activities without increasing thrombotic risk. Some “hemostatic” agents act in an indirect way by reducing fibrinolysis or by potentiating the clotting mechanism. These include desmopressin, which releases high molecular weight multimers of von Willebrand factor and factor VIII into the circulation, and recombinant activated factor VII, which can directly activate the extrinsic pathway of coagulation. Unfortunately, there are no robust data to support the use of these agents in thrombocytopenic patients and recombinant activated factor VII may lead to an increased risk of thrombosis. Educating patients to avoid risky situations and drugs that may interfere with platelet function remains a principal duty of treating physicians, but ultimately the only practical way to reduce the hemorrhagic risk is to increase platelet concentration in the circulation by platelet transfusions or by stimulating platelet production by megakaryocytes with thrombopoietin-receptor agonists (TPO-RA) or with human recombinant thrombopoietin, currently available only in China.

It is still debatable what is an optimal platelet count sufficient to avoid spontaneous bleeding or to prevent

hemorrhages associated with menstruation or parturition or in preparation for surgery or dental extraction. We have to admit that despite intensive research we still do not understand why patients with the same platelet count manifest bleeding at different frequencies and with different severity. The seminal research by Harker and Slichter[10] proved that the bleeding time (a surrogate measurement *in vivo* of the bleeding tendency) is differently correlated to the actual platelet count in different disorders. Indeed, at parity of platelet count, the bleeding time was most prolonged in Wiskott-Aldrich syndrome, followed by aplastic anemia and only moderately increased in ITP. A correlation was found with the platelet volume, in keeping with the increased volume of the more active and young, regenerating platelets. Experience with ITP also suggests that platelet count and platelet activity are not the only determinants of bleeding severity.

To escape from vessels, blood must go through the endothelium and basal membrane before a platelet plug is formed. Below a critical number of platelets, the steady-state trophic effects on the endothelium are impaired and the multimolecular vascular endothelium cadherin complex breaks down, with subsequent loss of the intercellular barrier, permitting extravasation of red cells into the surrounding tissues.[11] Furthermore, basal membrane breakage may be favored by a second hit such as inflammation. Remarkably, in both humans and rabbits, glucocorticoid treatment corrects endothelium abnormalities together with the bleeding manifestations associated with severe thrombocytopenia,[12] in accordance with the pioneering clinical observation of the early 1950s that corticosteroids rapidly improved bleeding manifestations of ITP within the first 2 days of treatment and before an increase in platelet count could be observed. Unfortunately, this beneficial effect is not found in the clinical situations described in this review, once again reinforcing the concept that different pathogenic mechanisms and different clinical circumstances require distinct therapeutic approaches. Once again, ITP provides illustrative examples. In this autoimmune disorder, corticosteroids, intravenous immunoglobulins, immunosuppressive agents, splenectomy and TPO-RA are all variably effective. However, none of them is indicated in classical drug-induced immune thrombocytopenia in which the only treatment is to stop the incriminated drug. In the case of heparin-induced thrombocytopenia or vaccine-induced thrombotic thrombocytopenia, it is not sufficient to stop heparin or its congeners and anticoagulation with non-heparin agents remains the mainstay of treatment. Unless there is bleeding, no attempt to increase platelet count is recommended, but intravenous administration of immunoglobulins is felt useful by some investigators. For inherited thrombocytopenias, splenectomy and administration of TPO-RA (still an experimental therapy) may be appropriate in very selected cases but, unfortunately, platelet transfusion is still of fundamental importance in cases of severe bleeding.

The potential utility of TPO-RA in chemotherapy-induced thrombocytopenia is an ongoing subject of intensive investigation, and is a major focus of Kuter's review on the treatment of chemotherapy-induced thrombocytopenia in non-hematologic malignancies.[3] Chemotherapy regimens for cancer treatment are designed to deliver the maximum tolerable dose intensity, an objective often limited by organ toxicity or by myelotoxicity, forcing reductions in the dosage with the risk of decreasing response rate and survival. Blood transfusion and growth factors may help to reduce anemia and neutropenia, but until the advent of TPO-RA (romiplostim and eltrombopag and, more recently, avatrombopag) no treatment was available to increase platelet production. There is no doubt that the occurrence of thrombocytopenia during chemotherapy for solid tumors (but similar considerations also apply to chemotherapy for malignant hematologic diseases) has several negative effects such as forcing the delivery of less than optimal chemotherapy, in terms of dosage and timing, thus leading to a reduction of relative dose intensity, and causing an increased risk of bleeding, with a negative impact on quality of life. Moreover, platelet transfusion may become necessary even in the absence of hemorrhage when the platelet count falls below a minimal threshold considered sufficiently safe (usually set at $10x10^9$/L or $20x10^9$/L in febrile patients) with related risks of infection and refractoriness due to alloimmunization and the additional burden of hospitalization.

Many studies have been and are being conducted with traditional TPO-RA (romiplostim and eltrombopag) or with more recently introduced ones, such as avatrombopag, lusutrombopag and hetrombopag, in efforts to fully exploit the potential of TPO-RA to eliminate thrombocytopenia as an additional limiting factor to giving the desired dose intensity of chemotherapy.[13] However, although chemotherapy-induced thrombocytopenia may affect a sizable proportion of patients with solid tumors, grade 3-4 thrombocytopenia occurs in less than 10% and appears to be isolated in less than 1%.[14] Thus, considering that other cytopenias or toxicities may lead to a reduction of dose intensity, it is difficult to envisage how much the additional reduction or elimination of chemotherapy-induced thrombocytopenia will contribute to improving relative dose intensity. One can only concur with Kuter's conclusion that the beneficial effect of TPO-RA on relative dose intensity, tumor response, transfusion, bleeding and survival have not yet been adequately demonstrated and that we still do not have sufficient evidence for a widespread adoption of TPO-RA use.[3] On the other hand, several studies have shown that platelet count is, on average, higher when TPO-RA are administered although these studies differ as to de-

sign, patient selection, type of chemotherapy, timing of TPO-RA administration and with regard to single or composite endpoints. It is to be hoped that building on the partial success of these studies might give impetus to sounder investigational protocols.

We are confident that increased awareness of the relevance of the disorders discussed in this review series may stimulate further basic and clinical research. Cutting-edge technologies and bioinformatics applied to genomics will contribute to the identification of an increasing number of inherited thrombocytopenias and to make their diagnosis easier and more precise. Perhaps, more importantly, we need a reinvigorated international collaboration to produce large cohorts of patients with long-term follow-up to better capture the most relevant outcomes of these disorders. As to drug-induced immune thrombocytopenia, the recent unexpected emergence of thrombocytopenic disorders after COVID-19 vaccination or after an increasing list of innovative drugs, such as immune checkpoint inhibitors, calls for supranational pharmacovigilance systems and creation of easily accessible, updated repertories of drugs identified or suspected to cause immune or non-immune thrombocytopenias. Waiting for artificial platelets to become available in clinical settings and possibly make platelet transfusion an obsolete practice, the potential benefit of increasing natural thrombopoiesis in chemotherapy-induced thrombocytopenia and other thrombocytopenias needs to be further exploited by well-designed prospective studies investigating old and new TPO-RA.

Disclosures

No conflicts of interest to disclose.

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