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Prognostic relevance of anemia and transfusion dependency in myelodysplastic syndromes and primary myelofibrosis

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Anemia is a cardinal manifestation of myelodysplastic syndromes (MDS) and primary myelofibrosis (PMF). Over half (54%) of the patients with *de novo* untreated myelodysplastic syndromes, in the International Prognostic Scoring System (IPSS) cohort, presented with hemoglobin levels of less than 10 g/dL.[1] In another independent cohort with IPSS low or intermediate-1 risk myelodysplastic syndromes, an almost identical proportion (55%) of patients presented with a similar degree of anemia.[2] Similarly, most patients with primary myelofibrosis are anemic at presentation and the hemoglobin level was less than 10 g/dL in 35% to 54% of patients in some studies.[3,4]

The pathogenesis of anemia in both myelodysplastic syndromes and primary myelofibrosis is poorly understood and is attributed to "ineffective erythropoiesis" for convenience. Because both disorders are markedly heterogeneous in their molecular and biological features, it is reasonable to assume that multiple factors contribute to the associated erythropoietic defect. In myelodysplastic syndromes, these include haploinsufficiency of genes and microRNAs in commonly deleted chromosomal regions, mitochondrial dysfunction, acquired abnormalities of hemoglobin synthesis, and abnormal expression of proinflammatory cytokines and other growth factors.[5] The latter has also been implicated in PMF-associated ineffective hematopoiesis;[6] additional contributing factors to MF-associated anemia include mutation profile (presence of *JAK2*V617F[7] might be favorable and *MPL*[8] and *TET2*[9] mutations unfavorable in this regard),[10] bone marrow stromal changes, hypersplenism and chronic low grade hemolysis.[11]

Anemia has long been recognized as an adverse prognostic factor for overall survival in myelodysplastic syndromes.[1,12,13] With the introduction of the World Health Organization (WHO) classification system there has been a re-examination of prognostic factors in myelodysplastic syndromes.[14,15] In a study of 467 *de novo* MDS patients, the development of red blood cell transfusion need was associated with significantly shorter overall and leukemia-free survival in myelodysplastic syndromes without excess blasts.[16] Subsequently, a dynamic prognostic model that

takes red blood cell transfusion need into account was developed and further validated in an independent cohort of 739 *de novo* myelodysplastic syndrome patients.[17] Similarly, red blood cell transfusion need was identified as a strong and independent risk factor for survival in 'myelodysplastic syndrome with isolated del(5q)'[18] and refractory anemia with ring sideroblasts (RARS).[19] Anemia sustained its independent prognostic value even in low and intermediate-1 risk patients with myelodysplastic syndromes[2] and red blood cell transfusion need was shown to be an IPSS-independent risk factor in a more recent practical prognostic model that included 1,915 patients with primary and secondary myelodysplastic syndromes and chronic myelomonocytic leukemia.[20]

Anemia is a powerful risk factor also in primary myelofibrosis. The International Prognostic Scoring System (IPSS) for PMF was recently developed to assess survival from the time of diagnosis.[3] The IPSS-derived dynamic IPSS (DIPSS) is used to predict survival from any time point in the disease course.[21] Both IPSS and DIPSS utilize hemoglobin less than 10 g/dL as one of five risk factors (the others being age >65 years, leukocyte count $>25\times10^9$/L, circulating blasts ≥ 1% and constitutional symptoms) in order to classify patients into four risk groups: low, intermediate-1, intermediate-2 and high. Considering the stronger prognostic effect of anemia, the DIPSS prognostic model assigns two adverse points for hemoglobin less than 10 g/d whereas the other four risk factors are each assigned one adverse point.[21]

More recently, red blood cell transfusion need was identified as an IPSS[22,23] and DIPSS[23] independent risk factor in primary meylofibrosis. Accordingly, a new prognostic model (DIPSS-plus) has been established and includes red blood cell transfusion need as one of eight risk factors; the other seven were age over 65 years, hemoglobin less than 10 g/dL, leukocyte count greater than 25×10^9/L, circulating blasts 1% or over, constitutional symptoms, platelet count less than 100×10^9/L and unfavorable karyotype.[4] The 8 DIPSS-plus risk factors were used to define low (no risk factors), intermediate-1 (one risk factor), intermediate-2 (two or three risk factors) and high (four or more risk factors) risk primary myelofibrosis with respective median survivals of 15.4, 6.5, 2.9 and 1.3 years.[4] In the DIPSS-plus prognostic model, red blood cell transfusion need was not independently associated with inferior leukemia-free survival whereas earlier studies suggested such an association.[4,24]

We believe that the presence and severity of anemia in both myelodysplastic syndromes and primary myelofibrosis signify a clonally advanced and biologically more aggressive disease. This, in our opinion, is the primary reason for the negative prognostic impact of anemia in these diseases. Based on strictly retrospective data analysis and using surrogate markers of questionable value, some investigators have considered the possibility that iron overload contributes to the association between poor survival and red blood cell transfusion need in myelodysplastic syndromes. This unsubstantiated claim has further been propagated by additional and equally misinterpreted retrospective studies in the context of allogeneic stem cell transplantation. In a series of studies from the Mayo Clinic, iron overload, measured by both transfusion burden and serum ferritin level, did not carry an independent prognostic value in RARS,[19] myelodysplastic syndromes associated with isolated del(5q)[19] or primary myelofibrosis.[25] Furthermore, the value of serum ferritin as a surrogate for iron overload is confounded by its nature as an acute phase reactant; it might influence survival for reasons that have nothing to do with iron overload. Therefore, it would be much more rewarding to focus interest and research on the mechanisms of impaired hematopoiesis and its effect on prognosis rather than continuing to rework the possibly non-existing role of iron overload in such matters. In this regard, we continue to be amazed by the power of Pharma to turn the attention of the MDS community from scientifically-relevant to industry-relevant issues.

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Determinants of platelet count in humans

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An adequate supply of circulating platelets is essential to maintain vascular integrity and to facilitate thrombus formation at sites of vascular injury. The normal platelet count in humans ranges from 150×10^9/L to 400×10^9/L. Given that platelets have a circulating lifespan of around 10 days, and that about one third of platelets are sequestered in the spleen at any time, approximately 100×10^9 of these small anucleate cells must be released from mature megakaryocytes into the circulation each day in order to maintain a normal platelet count. A constant balance is, therefore, required between thrombopoiesis, and platelet consumption and senescence. Thrombopoietin is the primary humoral regulator of megakaryocyte differentiation and platelet number under steady state conditions.[1] It is synthesized in the liver and kidney and mediates its effects through its receptor c-Mpl which is present on megakaryocyte and platelet membranes.[1] Levels of thrombopoietin are controlled via binding to, and internalization into, cells expressing the receptor. When platelets and megakaryocytes are decreased in number, less thrombopoietin is removed from plasma, and the thrombopoietin level rises, while when platelet numbers increase, more thrombopoietin is cleared from the plasma and the thrombopoietin level falls again.[2] In addition to the thrombopoietin (*THPO*) and c-Mpl (*MPL*) genes, a large number of genes encoding membrane glycoproteins, cytoskeletal components and proteins involved in transcription, cell cycle regulation and signaling have been demonstrated to participate in the differentiation of pluripotent stem cells to mature platelet-shedding megakaryocytes.[3]

Defined as a platelet count less than 150×10^9/L, thrombocytopenia is usually an acquired disorder. Causes include increased platelet consumption, splenomegaly, drugs or infection-mediated bone marrow suppression, and bone marrow failure. Increasingly, however, inherited forms of thrombocytopenia, caused by mutations in genes encoding proteins involved in the differentiation of megakaryocytes and platelet production, which can result in autosomal dominant, autosomal recessive, and X-linked recessive forms of inherited thrombocytopenia, are being recognized.[3]

Thrombocytosis, defined as a platelet count exceeding the upper limit of the normal range ($>400\times10^9$/L), is associated with an increased risk of thrombosis.[4] Primary thrombocytosis can be either inherited or acquired and is caused by alterations targeting hematopoietic cells (e.g. *MPL*, *THPO* or *JAK2* mutations) while secondary thrombocytosis is due to external factors such as chronic inflammation or cancer.[4]

While much has been done to elucidate the molecular mechanisms controlling megakaryocyte differentiation and platelet production and to identify defects in the genes encoding the relevant proteins in patients with inherited thrombocytopenia, the factors that determine platelet count in the normal population are less well characterized. In a study published in this issue of the journal, Biino *et al.* addressed this issue by carrying out a cross-sectional investigation of platelet counts among 12,517 inhabitants of ten villages in the Ogliastra region of