Because hematologic malignancies are rare disorders, the casual coexistence of a lymphoid and a myeloid neoplasm is expected to be a very rare event. Several studies, however, have previously shown that the risk of developing a lymphoid neoplasm is higher in MPN patients compared with the general population.[9] In the current work, Porpaczy et al have defined a new paradigm, that is, an association between JAK inhibition and lymphoma development in MPN patients.[1] In the Vienna cohort of 626 MPN patients, 4 out of 69 (5.8%) patients developed an aggressive B-cell lymphoma upon JAK1/2 inhibitor treatment, whereas only 2 of the remaining 557 patients without JAK inhibition did so.[1] All 4 patients were treated with ruxolitinib, although 1 had initially been treated with fedratinib, a selective JAK2 inhibitor. Based on the above relative frequencies, MPN patients under JAK inhibition would have a 16-fold higher risk of developing an aggressive B-cell lymphoma.

The above 4 patients developed an aggressive B-cell lymphoma with extranodal involvement, high *MYC* expression, and presence of lymphoma cells in both bone marrow and peripheral blood in 3 cases. Of note, prior to the current work, development of a leukemic B-cell lymphoma was observed in 2 patients with myelofibrosis treated with ruxolitinib.[1] Although there was no evidence of mutations in MPN-driver genes in lymphoma samples in the 4 patients of the current study, clonal immunoglobulin gene rearrangements were found in the bone marrow during the myelofibrosis phase in nearly 16% of patients studied (see figure), and this preexisting B-cell clone was related to aggressive lymphomas in all 3 patients tested.[1] The effects of JAK inhibition were mirrored in a mouse model of abnormal myeloproliferation with the concomitant presence of aberrant B cells. Although these observations are interesting, the mechanism or mechanisms by which JAK inhibition may cause progression from an indolent clonal B-cell proliferation to a leukemic B-cell lymphoma need to be elucidated.

The study by Porpaczy et al further underlines the importance of real-world evidence studies for assessing the long-term risks of new treatments in hematologic malignancies.[10] Studies aimed to define the risk of malignant lymphomas following JAK inhibition in real-world MPN patients are now mandatory. However, the crucial question that practicing hematologists are now facing is how to treat the next patient with myelofibrosis in whom ruxolitinib treatment would be indicated. Clearly, the patient should be informed adequately so that he or she can understand the benefit-risk balance of a JAK inhibitory treatment. According to Porpaczy et al, patients at risk are essentially those with a preexisting B-cell clone in their bone marrow. A clonal B-cell population can be identified using a polymerase chain reaction technique for detection of immunoglobulin gene rearrangements; flow cytometry immunophenotyping might also be employed provided that bone marrow aspiration yields an adequate sample. If there is no evidence of a clonal B-cell population, one may reasonably assume that ruxolitinib treatment is relatively safe and may start treatment, closely monitoring the patient. However, if there is evidence of clonal B cells, therapeutic decision making is really problematic at present. That is why there is an urgent need of ad hoc studies.

Conflict-of-interest disclosure: L.A. and M.C. have participated in clinical trials sponsored by Incyte or Novartis on the use of ruxolitinib in patients with MPNs. ■

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DOI 10.1182/blood-2018-07-858720

CLINICAL TRIALS AND OBSERVATIONS

Comment on LeBlanc et al, page 717

Non-zero-sum game of transfusions: EOL in leukemia

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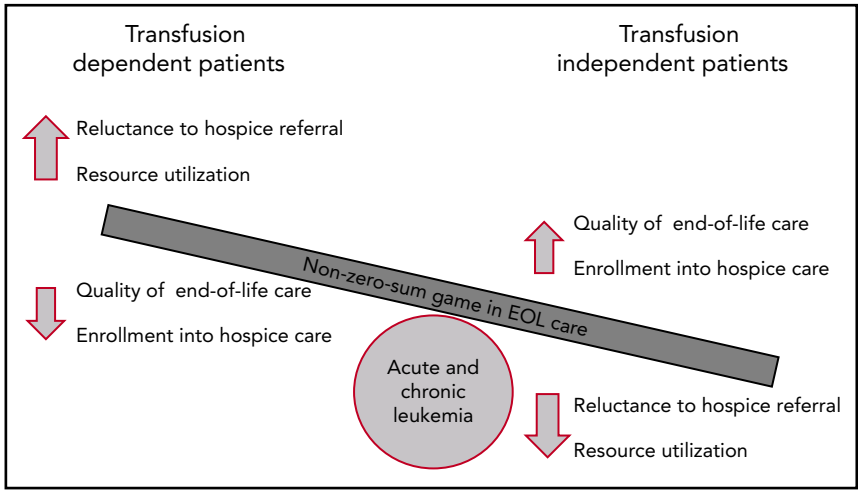
Inability to provide transfusion support to patients with leukemia is a major cause of delays in hospice enrollment for end-of-life (EOL) care. In this issue of *Blood*, LeBlanc et al explore the relationship between transfusion dependence (TD), time to hospice enrollment, and quality of EOL care in patients with leukemia.[1]

Acute leukemias (acute myeloid leukemia [AML] and acute lymphoblastic leukemia [ALL]) are devastating and often fatal malignancies characterized by an acquired and progressive bone marrow failure. Without treatment, the median overall survival of patients with AML or ALL ranges between 6 and 8 weeks, independent of patient age.[2,3] In addition, most adult patients with acute leukemia



The zero-sum game of transfusion support during EOL care in patients with acute and chronic leukemia. For patients who are not dependent on transfusion, providers are more willing to refer patients to hospice, which increases hospice enrollment with improvements in quality of EOL care and decreases use of resources for patients with leukemia. Conversely, for patients who are dependent on transfusion of blood products, increased provider reluctance leads to decreased enrollment in hospice for EOL care, worse quality of care, and an increase in use of resources during the EOL care.

will succumb from their disease or complications. Data from the Surveillance, Epidemiology, and End Results (SEER) Program demonstrate that the 5-year survival for patients with AML remains less than 30%. The 5-year survival for ALL patients older than age 50 years is equally disappointing (<35%).[4] For these reasons, EOL care remains an integral component of the care provided to most patients with acute leukemia, independently of the intent of initial treatment. Fortunately, 5-year survival rates for patients with chronic leukemia have improved significantly over the past decade.

Given that bone marrow failure in patients with leukemia often presents with clinically significant cytopenias, TD is common in patients with acute and chronic leukemia. In these patients, up to 40% may be dependent on transfusions of packed red blood cells (PRBCs), platelets, or both at the time of diagnosis.[5] In addition, prior studies have demonstrated that the presence of TD at diagnosis and the intensity of TD during treatment are prognostic in patients with leukemia.[5,6] Although the observed rate of TD in patients with acute leukemia enrolled in hospice remains mostly underrecognized, limited data suggest that progressive cytopenias are common in these patients, with up to one-third of them being dependent on PRBC transfusion and nearly half being dependent on platelet transfusion.[7]

The report by LeBlanc et al on the correlation between blood TD, the use of hospice services after exhaustion of treatment options, and the quality of EOL care in patients with leukemia is the first to assess the impact of TD on the use of hospice services in patients with acute and chronic leukemia. The current cancer registry cohort, extracted from the SEER-Medicare data set, establishes the real-world incidence of TD for patients with acute and chronic leukemia who are enrolled into hospice and the independent impact of TD on median duration of EOL hospice care (6 days for transfusion-dependent patients vs 11 days for transfusion-independent patients; $P < .001$). Although the proportion of transfusion-dependent patients enrolled into hospice for their EOL care was lower than that for transfusion-independent patients, the study also demonstrated that greater transfusion support needs were associated with lower rates of enrollment into hospice. This is important information, because enrollment into hospice care, independent of dependency on transfusion of blood products, was associated with improvements in EOL quality measures, such as lower rates of admissions to the intensive care unit, inpatient death, or treatment with chemotherapy within 30 days of death. In addition, these data contrast significantly with those for patients with different solid tumors, in whom the optimal duration of hospice care associated with improved quality of dying and death exceeds 20 days.[8]

According to a recent survey by health care providers, the inability of most hospices to provide blood transfusions is a major contributor to the underuse of hospice care for patients with acute and chronic leukemia. The survey also showed that most practitioners strongly agree that they would refer more patients to hospice if red cell and/or platelet transfusions were allowed.[9] In addition, approximately half of responding practitioners answered that limiting PRBC and/or platelet transfusions within the last days of life was not an acceptable quality metric for patients with hematologic malignancies.[9] This creates a clinical dilemma for EOL care in patients with leukemia, especially those with AML and ALL, whereas other supportive measures and transition to hospice play an integral role in the management of these patients. As shown by LeBlanc et al, for these patients, hospice enrollment is clearly associated with several positive EOL quality end points, such as lower rate of inpatient deaths, decreased hospitalization time, and use of resources. LeBlanc et al and others have also shown that enrollment into hospice improves quality of EOL care and, in certain situations, overall survival (not addressed by LeBlanc et al). Unfortunately, the limited availability of transfusion support for patients enrolled in hospice limits the benefits of hospice to leukemia patients and is a major roadblock for health care providers who may otherwise refer these patients to hospice care. In game theory, non-zero-sum games are those where 1 player's gain does not necessarily translate into bad news for the other players. Indeed, in highly non-zero-sum games, the players' interests overlap entirely. On the basis of the results from LeBlanc et al and others, it is time for hospice agencies to reconsider their transfusion support guidelines so that patients with hematologic malignancies can readily benefit from hospice enrollment earlier in the course of their EOL care (see figure). These guidelines would be akin to services allowed by hospice programs for pediatric oncology patients for whom transfusion support is permitted by ~70% of agencies. More flexible hospice services lead to increased referral to hospice and more patients dying at home.[10]

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood-2018-06-856336

THROMBOSIS AND HEMOSTASIS

Comment on Dai et al, page 727

Moving target PF4 directs HIT responses

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In this issue of *Blood*, Dai et al demonstrate a dynamic interchange of cell surface–bound platelet factor 4 (PF4) among hematopoietic and vascular cells that may limit the thrombocytopenia and promote prothrombotic processes in heparin-induced thrombocytopenia (HIT).[1]

HIT is an immune complication of therapy with heparin characterized by thrombocytopenia and increased risk of thrombosis, the most dreaded complication of HIT responsible for the majority of the morbidity and mortality.[2] HIT is triggered by antibodies that recognize complexes of PF4 and heparin.[3] The cellular target for the HIT antibodies is platelets, resulting in antibody-mediated platelet destruction leading to thrombocytopenia. Furthermore, HIT antibodies may also target platelet FcγRIIA,[4] causing platelet activation and the release of procoagulant microparticles that may contribute to thrombosis.[5] Moreover, cellular activation via monocyte FcγRIIA has been shown to be a trigger for intense thrombin generation and thrombosis in HIT.[6] HIT immune complexes not only form on the surface of monocytes but also form on endothelial cells expressing glycosaminoglycans, further contributing to prothrombotic processes.[7] Using a murine passive immunization model of HIT, it was previously shown that monocyte depletion attenuated thrombosis but surprisingly worsened the degree of thrombocytopenia in the mice.[8] In the current study, the authors test this mechanism in HIT, focusing on cellular PF4 binding. They report that the redistribution of PF4 from platelets to monocytes (and perhaps endothelium) lessens the severity of the thrombocytopenia in HIT, leaving an increased number of platelets in the circulation that may possibly contribute to development of thrombosis. Monocytes bind PF4 with a greater affinity than other cell types, including platelets as was shown in vitro as well as in vivo using the murine passive immunization model of HIT. In vivo, HIT induction caused a transient monocytopenia, which normalized followed by an increase in the platelet count. Interestingly, it was also observed that the red blood cell (RBC) pool contained the most bound PF4; however, the surface-bound PF4 level per cell was low. This suggests a potential role for the RBC pool as a low-affinity reservoir for PF4 in the circulation. To further assess the dynamic nature of PF4, white blood cell (WBC) to platelet ratios were altered, and it was shown that the amount of PF4 bound per platelet varied inversely with the WBC:platelet ratio. When monocytes were depleted, platelets bound more PF4. Subsequently, the redistribution of PF4 between hematopoietic and vascular endothelial cells was investigated. Using microfluidic channels coated with endothelial cells, it was demonstrated that PF4 translocated more effectively from platelets than from WBCs to the endothelium. The severity of trauma, which includes both vascular and inflammatory components, has been shown to correlate with the immune response in HIT patients.[9] The authors therefore investigated the effect of endothelial injury using microfluidic channels and observed increased binding of HIT antibodies with injured endothelial cells compared with resting endothelial cells. Thus, PF4 distribution on the endothelial cell surface is dependent on the vascular lining and endothelial activation.

Dai and colleagues have convincingly demonstrated that shuttling of PF4 occurs between diverse hematopoietic and vascular endothelial cell surfaces and that these dynamics are strongly dependent on monocytes, which have a high binding affinity for PF4, on alterations in cell counts, and on endothelial cell injury/inflammation. Their findings suggest that redistribution of PF4 away from platelets may mitigate the severity of thrombocytopenia, which may paradoxically allow those platelets to be involved in thrombosis (see figure). However, how PF4 redistribution among different