PATIENT BLOOD MANAGEMENT IN HEMATOLOGY AND ONCOLOGY

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Patients undergoing treatment in hematology and oncology (hem/onc) departments are often some of the most challenging for transfusion medicine specialists. These patients are some of the highest users of blood products both in the inpatient and outpatient settings. At the same time, there is a dearth of scientific literature regarding transfusion medicine in this patient population, which has been a hinderance in developing best practice guidelines.

For patients with cancer, anemia is frequently induced via direct (e.g., nutritional [iron and vitamin B12] deficiency, marrow infiltration, and coagulopathy-related bleeding) and indirect (e.g., anemia of chronic disease related to inflammation and autoimmune hemolytic anemia) effects.[1] In addition, anemia and thrombocytopenia are two common side effects of cancer treatment (chemotherapy and radiation therapy). Nevertheless, strategies to minimize exposure to blood products should be considered in light of the risks and complications of blood transfusion. Long-term risks of alloimmunization, iron overload and transfusion-related immunomodulation (TRIM) are of special concern in patients receiving chronic transfusions. Patient blood management (PBM) strategies that may be employed to reduce transfusions in cancer patients in both the inpatient and outpatient settings are the focus of this column.

There are PBM strategies common to all patients that can be applied to hem/onc patients. Adherence to stricter transfusion guidelines, including the use of a hemoglobin level closer to 7.0 g/dL as the transfusion trigger for stable patients with anemia, as well as transfusion of single rather than multiple RBC units in nonbleeding patients, is recommended. A computer-physician-order-entry (CPOE) system with clinical-decision support (CDS) is a useful tool to guide appropriate transfusion therapy. Several studies have demonstrated the value of CPOE/CDS in reducing transfusions, while not necessarily eliminating all non-evidence-based transfusions.[2,3] Zuckerberg et al. found that a significant benefit of CPOE/CDS was in maintaining reductions in RBC utilization achieved through compliance with implementation of evidence-based transfusion guidelines along with preliminary educational programs.[4] Identification of “PBM champions” to serve as role models is also highly useful when implementing strategies necessary to achieve a successful PBM program.[5] Finally, one cannot overstate the important role of data collection and analysis in the development of a PBM program.[6]

In a study conducted in Germany, Keding at al. used well-defined PBM strategies with dedicated project management support to accomplish the provision of PBM education to stakeholders,

implementation of preoperative anemia diagnosis and treatment, utilization of focused management on coagulopathy, emphasis on reduced diagnostic blood sampling and surgery-associated blood loss and defined outcome measures. They demonstrated a reduction of RBC transfusion requirements with improved overall two-year survival post PBM-implementation in abdominal oncologic surgical patients.[7] Not surprisingly, they found that implementation of the aforementioned measures achieved higher preoperative hemoglobin levels that reduced RBC transfusions.

Beyond these more general PBM strategies recommended for all patients, there are several strategies specific to hem/onc patients. Erythropoiesis-stimulating agents (ESAs) are useful for reducing transfusions secondary to chemotherapy-related anemias. The guidelines for ESA use, published by the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), were updated in 2019.[8] The guidelines recommend use of ESAs for treatment of chemotherapy-related anemia below hemoglobin 10 g/dL when the cancer treatment is not curative in intent. They do not recommend use of ESAs for most nonchemotherapy-induced anemias, though it may be offered to selected patients with myelodysplastic syndromes (MDS). Iron replacement may also be used in conjunction with ESAs, with or without iron-deficiency, to improve hemoglobin response and to reduce transfusions. Nevertheless, the guidelines recognize risks associated with the use of ESAs, especially thromboembolism. They recommend use of an ESA dose that will raise the hemoglobin level to the lowest concentration necessary to reduce RBC transfusions and to discontinue ESAs if no response is seen in 6-8 weeks. Li et al. conducted a meta-analysis of eight studies published between January 1990 and March 2013 that examined ESA use vs. placebo in patients with solid and hematological cancers, albeit including higher baseline hemoglobin levels (<11.0 g/dL) and higher targets (13.0 g/dL) than current guideline recommendations. The results demonstrated that ESAs significantly increased the hemoglobin concentration and reduced RBC transfusions.[9] The researchers further concluded that ESAs are not associated with increased severe adverse events, including venous thromboembolism, in anemic patients with cancer, though rates of anticoagulation prophylaxis were not reported in the meta-analysis. Gross et al., applying PBM principles to inpatients and outpatients with cancer, found that increased use of intravenous iron (mean dose changed from 447 to 588 mg) resulted in decreased use of ESAs and reduced RBC transfusions.[10] They reported that the proportion of inpatient single-unit RBC transfusions increased while the mean pre-transfusion hemoglobin and overall RBC transfusion rate decreased. The in-hospital mortality and length of stay (LOS) did not change in their study population.

For platelets, the thrombopoiesis-stimulating agents (TSAs) eltrombopag and romoplostim have been studied in patients with cancer to mitigate thrombocytopenia, though they are not currently approved for such use. In one recent phase II randomized trial of romoplostim treatment for patients with solid tumors, the agent was found to be effective in correcting chemotherapy-induced thrombocytopenia.[11] On the other hand, the results of initial studies investigating use of TSAs for thrombocytopenia in patients with intermediate- to high-risk MDS do not indicate a role for such agents. In fact, TSAs carry a warning of the risk of MDS progression to acute myeloid leukemia.[12-14] Like ESAs, TSAs are associated with thromboembolic risks.

Atallah et al., in their AABB eCast presentation on PBM in patients with cancer, described implementation of a system in which disease-specific trained nurses were utilized in outpatient treatment centers to determine appropriate transfusion needs of individual patients undergoing chemotherapy, based on laboratory values as well as clinical assessment.[15] This strategy was part of a PBM plan to improve overall blood utilization, in both inpatients and outpatients, as well as management of patients with hematological malignancies requiring frequent transfusions and was used in conjunction with other PBM strategies noted above (e.g., data collection, provider education, single-unit transfusions, CPOE/CDS, etc.). As a result, they reported success in decreasing annual blood product transfusions by 9-12% during a three-year period despite significant increases in inpatient and outpatient volumes. The cost savings based on direct blood product acquisition was more than $120,000. They reduced two-unit RBC transfusions (single unit inpatient transfusions increased from <50% to 78%), decreased mean pre-transfusion hemoglobin from 7.7 to 7.1 g/dL, and decreased mean inpatient LOS. In addition, use of the disease-specific trained nurses improved consistency of transfusion practices across providers and improved patient quality of life by reducing outpatient visits for transfusions.

In summary, although patients with cancer often require transfusions of blood products as part of their treatment, there are defined measures that may be implemented to reduce the frequency of transfusions in this patient population. Newer treatment regimens, including immunotherapy (e.g., monoclonal antibodies, CAR-T therapy, etc.), may offer more targeted therapy with less bone marrow suppression, resulting in milder cytopenias and the need for fewer transfusions.

1. Girnius S. "Patient blood management from an oncology/hematologist point of view." AABB eCast #20EL-538. May 28, 2020.
2. Fernández Pérez ER, Winters JL, Gajic O. The addition of decision support into computerized physician order entry reduces red blood cell transfusion resource utilization in the intensive care unit. *Am J Hematol*. 2007;82(7):631-3.
3. McWilliams B, Triulzi DJ, Waters JH, Alarcon LH, Reddy V, Yazer MH. Trends in RBC ordering and use after implementing adaptive alerts in the electronic computerized physician order entry system. *Am J Clin Pathol*. 2014;141(4):534–41.
4. Zuckerberg GS, Scott AV, Wasey JO, Wick EC, Pawlik TM, Ness PM, et al. Efficacy of education followed by computerized provider order entry with clinician decision support to reduce red blood cell utilization. *Transfusion*. 2015;55(7):1628-36.
5. AABB White Paper – Building a Better Patient Blood Management Program. AABB, Bethesda, MD. April 2015. Available at: *http://www.aabb.org/pbm/Documents/AABB-PBM-Whitepaper.pdf*
6. Cohn CS, Welbig J, Bowman R, Kammann S, Frey K, Zantek N. A data-driven approach to patient blood management. *Transfusion*. 2014;54(2):316-22.
7. Keding V, Zacharowski K, Bechstein WO, Meybohm P, Schnitzbauer AA. Patient blood management improves outcome in oncologic surgery. *World Journal of Surgical Oncology*. 2018;*16*(1):159.
8. Bohlius J, Bohke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *Blood Adv*. 2019;3(8):1197-1210.
9. Li X, Yan Z, Kong D, Zou W, Wang J, Sun D, et al. Erythropoiesis-stimulating agents in the management of cancer patients with anemia: a meta-analysis. *Chin J Cancer Res*. 2014;26(3): 268–276.
10. Gross I, Trentino KM, Andreescu A, Pierson R, Maietta RA, Farmer S. Impact of a patient blood management program and an outpatient anemia management protocol on red cell transfusions in oncology inpatients and outpatients. *Oncologist*. 2016;21(3):327-32.
11. Soff GA, Miao Y, Bendheim G, Batista J, Mones JV, Parameswaran R, et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. *Journal of Clinical Oncology*. 2019;37(31):2892-8.
12. Dickinson M, Cherif H, Fenaux P, Mittelman M, Verma A, Portella MSO, et al. Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia. *Blood*. 2018;132(25):2629-38.
13. NPLATE® (Romoplostim) Prescribing Information. Amgen, Inc. Thousand Oaks, CA. October 2019. Available at: *https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/nplate/nplate_pi_hcp_english.pdf* Accessed: March 4, 2020.
14. PROMACTA® (Eltrombopag) Prescribing Information. Novartis Pharmaceuticals Corp. East Hanover, NJ. April 2019. Available at: *https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf* Accessed: March 4, 2010.
15. Attallah E, Fournogerakis M, Curtis T. "Patient blood management in oncology patients". AABB eCast #18EL-378. November 8, 2018.