Is anemia a harbinger of poorer outcomes after allogeneic hematopoietic cell transplant?

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In the article by Konuma et al., the authors suggested that the number of red blood cell units transfused by day 30 after a single-unit umbilical cord blood transplant in adults with hematologic malignancies may be associated with poorer outcomes. Those patients who had received 18 or more transfusions by day 30 had increased non-relapse mortality and decreased survival [1]. According to Xenocostas et. al., during the first two months after allogeneic hematopoietic cell transplant, red blood cell transfusion rates are at the highest than any other time after transplant. Transfusion needs during allogeneic transplant are associated with the degree of pre-transplant anemia, advanced disease, older age, ABO mismatch of the donor-recipient pair and use of an unrelated donor [2]. Recipients receiving single-unit umbilical cord blood transplants may have had additional risk factors for anemia and increased pre-transplant red blood cell transfusion requirements contributing to the increased mortality seen, confounding the results of the study [1, 2]. Is anemia a harbinger of poorer outcomes after allogeneic hematopoietic cell transplant?

Pre-transplant anemia is a common presenting symptom for patients with hematologic malignancies, many of whom will have advanced disease and ultimately need an allogeneic transplant. Furthermore, chemotherapy regimens used to treat hematologic malignancies can cause significant anemia as an adverse side effect. Many of these patients are heavily transfused prior to proceeding to allogeneic transplant. In a study of myelodysplastic syndrome patients undergoing myeloablative conditioning followed by allogeneic transplant, advanced disease and the number of pre-transplant transfusions had negative impacts on overall survival, increased non-relapse mortality and increased

relapse [3]. Pre-transplant red blood cell transfusion requirement was associated with the number of units transfused by day 30 and day 100 by multilinear regression analysis in the study presented, suggesting that pre-transplant red blood cell transfusion requirements may increase non-relapse mortality and decrease survival [1]. Thus, pre-transplant anemia and transfusion requirements may be an indication of sicker patients who have other comorbidities such as iron overload and red cell alloimmunization which may impact post-transplant outcomes.

Clinically significant anemia requiring red blood transfusion support is an expected adverse event during an allogeneic transplant. Inadequate erythropoietin production during transplant [4] in combination with the myelosuppression of the conditioning regimen contributes to anemia. Donor graft characteristics can increase red blood cell and platelet transfusion requirements as seen with a blood group O recipient transplanted with an A, B or AB donor [5]. In the multivariate linear regression analysis, ABO incompatibility between the single-unit umbilical cord blood graft and the recipient was associated with an increase in number of red blood cell transfusions by day 30 [1].

Red blood cell transfusions are not without risks; there are risks of transfusion-related acute lung injury [6], transfusion-associated circulatory overload [6], transfusion reactions [6], infectious disease risk [6], iron overload [7], idiopathic pneumonia syndrome [8], increased graft versus host disease [9], and economic burdens [10]. Several of the transfusion risks, transfusion-associated acute lung injury, transfusion-associated circulatory overload, transfusion reactions, and infection risk are not unique to transplant, but are associated with transfusions in general [6]. Elevated pre-transplant ferritin, a marker of iron overload, has a negative impact on 3 year overall survival for allogeneic transplant recipients [11]. Additionally, red blood cell transfusions may be associated with an increased risk of idiopathic pneumonia syndrome after allogeneic hematopoietic cell transplant [8]. Increased numbers of blood transfusions are associated with increased risk of severe acute graft versus

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host disease and decreased overall survival after allogeneic hematopoietic cell transplant [9]. In contrast to the findings of Hosoba and colleagues [9], the authors did not find an association between number of red blood cell units transfused and acute or chronic graft versus host disease in a single-unit umbilical cord blood transplant [1]. This difference in outcomes could be related to decreased graft versus host disease seen in cord blood transplant recipients.

Delayed engraftment during umbilical cord blood transplant remains an important consideration in the selection of this graft source. Median time to red blood cell engraftment in the study presented was 32 days after umbilical cord blood transplant [1]. University of Minnesota compared blood product transfusions for a hemoglobin < 8.0 g/dL in 229 adult allogeneic hematopoietic cell transplant recipients, 131 of the patients received umbilical cord blood grafts. In this study, the median time to red blood cell transfusion independence was 44.5 days with umbilical cord blood compared to 44 days in patients who had a sibling donor. In the leukemia cohort, patients with umbilical cord blood transplants required more red blood cell transfusions in the first 3 months after transplant compared to patients who had received matched related donor hematopoietic cell grafts [12]. Umbilical cord blood transplant recipients have delayed engraftment compared to traditional donors, resulting in higher number of red blood cell units transfused and may take a longer time to achieve red blood cell transfusion independence [1, 12].

When the number of red blood cell units transfused are reduced, there is a reduction in transfusion-related risks [6–9] and a significant cost savings [10]. Two potential strategies may reduce the usage of red blood cell transfusions in allogeneic hematopoietic cell transplants, reduce the number of transfusions using a restrictive transfusion policy [13] or prevent the hemoglobin from dropping below a defined level using erythropoietic stimulating agents [14]. The transfusion policy for patients in the single-unit umbilical cord blood transplant study was to transfuse two units of red blood cells for a goal hemoglobin > 8 g/dL [1]. Gastecki et al. found that when one unit of red blood cells is transfused instead of two units per transfusion event for a hemoglobin ≤ 8.0 g/dL in allogeneic hematopoietic cell transplant recipients, there is a small reduction in the red blood cell utilization. Moreover, a longer hospital stay is associated with a higher number of red blood cell units transfused [13]. The delay in engraftment with umbilical cord blood may lengthen the hospital stay and increase the number of transfusions these patients receive compared to using adult donors [1].

Erythropoietic stimulating agents have a role in treating chemotherapy related anemia in many different cancers. If anemia is a risk factor for poor outcomes after allogeneic transplant, theoretically erythropoietic stimulating agents

may overcome the inadequate erythropoietin production [4], shorten red blood cell recovery and reduce the need for blood transfusions [14]. Their role in the treatment of anemia between hematopoietic cell infusion and red cell engraftment is less clear [14, 15]. In the small trial by F. Baron, et. al., seven patients were treated with erythropoietin from day +1 after transplant until hemoglobin recovery to 10 g/dL. Unfortunately, the number of red blood cell transfusions required for these patients did not decrease [15]. Additional studies are needed to determine the appropriate timing and duration of erythropoietin therapy in allogeneic hematopoietic cell transplant [14].

In conclusion, patients with pre-transplant anemia who are candidates for allogeneic transplant may be sicker and have other underlying comorbidities that may impact outcomes after transplant. These transplant recipients may have advanced disease, iron overload and be heavily transfused all of which negatively impact outcomes after transplant. Determining management strategies for anemia before and during transplant including drawing blood in pediatric tubes, limiting blood draws, identifying whether restrictive compared to liberal transfusion policies impact post-transplant outcomes, and evaluating the use of erythropoietin stimulating agents in the transplant setting are important next steps in mitigating the risks of anemia and transfusions on allogeneic transplant outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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