Editorial

Blood transfusions in critically ill cancer patients remain an area of uncertainty

Imrana Alam Malik[1], Konrad Reinhart[2]

[1]The University of Texas, Anderson Cancer Center, Houston, TX, USA; [2]Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany

Correspondence to: Imrana Alam Malik. The University of Texas, Anderson Cancer Center, Houston, TX, USA. Email: imalik@mdanderson.org; Konrad Reinhart. Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany. Email: konrad.reinhart@med.uni-jena.de.

Provenance: This is a Guest Editorial commissioned by Section Editor Yanfei Shen, MM (Department of Critical Care Medicine, Dongyang People's Hospital, Dongyang, China).

Comment on: Bergamin FS, Almeida JP, Landoni G, *et al*. Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. Crit Care Med 2017;45:766-73.

Received: 17 June 2017; Accepted: 21 June 2017; Published: 26 July 2017.

doi: 10.21037/jeccm.2017.06.02

View this article at: http://dx.doi.org/10.21037/jeccm.2017.06.02

In a single center, randomized, controlled trial entitled "Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial", the authors conclude that a liberal strategy for blood transfusions (hemoglobin threshold <9 g/dL) may be more favorable in adult cancer patients with septic shock, compared to a restrictive strategy which utilized a hemoglobin threshold of <7 g/dL (1). The transfusions included only leukodepleted units, and hematologic malignancy patients were excluded due to high inherent transfusion requirements.

The study conclusion appears to be discordant with the Surviving Sepsis Campaign (SSC) guidelines for the management of anemia in sepsis and septic shock. From 2004 to 2012, the SSC guidelines recommended a restrictive approach to blood transfusions "once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as significant coronary artery disease, acute hemorrhage, or lactic acidosis" (2-4). Interestingly, in the 2016 SSC guidelines the caveat of "once tissue hypoperfusion has resolved" was omitted and the recommendations emphasized only the "extenuating circumstances" and a hemoglobin threshold of <7 g/dL (5). The rationale for the recommendations in the 2016 guidelines was based on two studies, namely the transfusion requirements in septic shock (TRISS) and the protocol-based care for early septic shock (ProCESS) trials (6,7). Both trials showed similar mortality rates for the two treatments groups with respect to transfusions; however, it is notable that the patients in the ProCESS trial had already received resuscitation at the time of enrollment and thus potentially had less tissue hypoperfusion. Neither of the studies included a significant enough percentage of oncology patients for the results to be valid in that particular population.

Prior studies reviewing the use of blood transfusions in critically ill patients, not limited to sepsis or cancer, showed increased mortality rates for those patients who received transfusions or a liberal transfusion strategy (8,9). In contrast, the 2006 observational SOAP study (10) concluded that blood transfusion was not associated with an increased risk of death when controlled for organ dysfunction scores, such as SAPSII and SOFA. Interestingly, another study incorporating a leukoreduction program demonstrated a decreased mortality in critically ill surgical patients who received blood transfusions (11).

Unfortunately, studies specifically addressing blood transfusions in critically ill cancer patients with sepsis are severely limited, and the current SSC guidelines do not adequately address the question in this particular population. Of the limited data available in cancer patients,

studies have shown that blood transfusions for anemia are associated with increased risk of mortality, and of venous and arterial thrombosis (12).

It is also worthwhile to mention that the adverse effects of blood transfusions may not only be related primarily to leukocytes but rather to the impact of the high amounts of free hemoglobin especially in older blood due to its properties to inactivate NO that may severely impair nutritive blood flow (13,14). This may be especially harmful in sepsis patients (15). A number of studies that evaluated the impact on NO inactivation in septic shock by NO inhibitors demonstrated harmful effects and worse outcomes (16,17). Phase II studies evaluating the safety and efficacy of free hemoglobin solutions were stopped prematurely for safety reasons. What the above studies collectively illustrated is that a liberal transfusion strategy is not superior to a restrictive one.

The study authors agree that their results have limited external generalizability due to the selected cohort of patients studied, i.e., solid tumor cancer patients at a single tertiary care institution which specializes in cancer care. Another potential limitation is the small sample size of the study population, consisting of 300 patients. We would stress this as a major limitation, because it is well-known that small-sized sepsis studies again and again have produced results that could not be confirmed in larger multiple-center trials (18-20).

Based on our review and assessment, this study does not provide conclusive enough evidence that a liberal strategy for blood transfusion should be utilized in cancer patients with sepsis. However, this important clinical question clearly requires further investigation with a larger multiple-center study to help clarify the area of uncertainty.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bergamin FS, Almeida JP, Landoni G, et al. Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. Crit Care Med 2017;45:766-73.
2. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73.
3. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
4. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
5. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017;45:486-552.
6. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
7. ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93.
8. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499-507.
9. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.
10. Vincent JL, Sakr Y, Sprung C, et al. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology 2008;108:31-9.
11. Hébert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 2003;289:1941-9.
12. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med 2008;168:2377-81.
13. Roback JD, Neuman RB, Quyyumi A, et al. Insufficient nitric oxide bioavailability: a hypothesis to explain adverse effects of red blood cell transfusion. Transfusion 2011;51:859-66.
14. Almac E, Bezemer R, Hilarius-Stokman PM, et al. Red blood cell storage increases hypoxia-induced nitric oxide

bioavailability and methemoglobin formation in vitro and in vivo. Transfusion 2014;54:3178-85.
15. Kirkebøen KA, Strand OA. The role of nitric oxide in sepsis--an overview. Acta Anaesthesiol Scand 1999;43:275-88.
16. López A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 2004;32:21-30.
17. Ishikawa K, Bellomo R, May CN. The impact of intrarenal nitric oxide synthase inhibition on renal blood flow and function in mild and severe hyperdynamic sepsis. Crit Care Med 2011;39:770-6.
18. Angstwurm MW, Engelmann L, Zimmermann T, et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med 2007;35:118-26.
19. Bloos F, Trips E, Nierhaus A, et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern Med 2016;176:1266-76.
20. Marshall JC. Why have clinical trials in sepsis failed? Trends Mol Med 2014;20:195-203.

doi: 10.21037/jeccm.2017.06.02
Cite this article as: Malik IA, Reinhart K. Blood transfusions in critically ill cancer patients remain an area of uncertainty. J Emerg Crit Care Med 2017;1:13.

