HOW LOW SHOULD WE GO: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EFFICACY AND SAFETY OF A RESTRICTIVE VERSUS LIBERAL TRANSFUSION STRATEGY IN ONCOLOGY

LAUREN PRESCOTT, MD

Introduction
Anemia in cancer patients is common and its etiology multifactorial.[1] Animal and human studies have shown that anemia is a poor prognostic indicator of clinical outcomes including perioperative morbidity, mortality and cancer-specific outcomes such as progression-free and overall survival.[2] A combination of clinical studies revealing the adverse impact of anemia and animal models demonstrating optimal oxygen transport at hemoglobin levels greater than 10g/dl has resulted in the historical trend towards liberal use of blood products to correct anemia in oncology patients.[3-5] Despite the liberal use of transfusion in many oncology studies, there are minimal data to support the efficacy of correcting anemia with transfusion. In fact, there is evidence from other subspecialty fields that a liberal blood transfusion strategy does not improve clinical outcomes over a restrictive strategy.[6-8] As such, many subspecialty societies have developed specific clinical practice guidelines that recommend restrictive red cell transfusion.[9-11] Institutional quality improvement initiatives have demonstrated that restrictive strategies have similar clinical outcomes while utilizing less blood.[12-15] Although blood transfusions are both costly and clinically important, there is lack of consensus regarding the best transfusion strategy in oncology. This has significant implications for synthesis of evidence based medicine guidelines, hospital and public policy. There is a paucity of contemporary systematic review and meta-analysis of transfusion triggers in oncology. The purpose of this review is to compare clinical outcomes of liberal versus restrictive transfusion strategies in oncology patients. Specifically we will aim to find, evaluate and summarize the data from clinical trials that evaluated the impact of utilizing different transfusion thresholds in adult oncology patients with cancer.

Objective
To compare the efficacy and safety of restrictive versus liberal transfusion strategy in patients with cancer.

Methods
We will follow The Cochrane Collaboration methodology and the PRISMA statement will be used to report the results of our systematic review and meta-analysis.[16]

Eligibility criteria

Types of Trials
Given the expected low number of randomized trials, we will include non-randomized trials consistent with the Cochrane Effective Practice and Organization of Care Group Standards.[17] Only published trials will be included.

- Randomized controlled trials (RCTs)
- Non-Controlled clinical trials (CCTs)
• Controlled before and after studies (CBAs)
• Interrupted time series analyses (ITSs)
• Controlled prospective trials (CPTs)

Types of Participants:

Inclusion criteria:
Patients at least 18 years of age diagnosed with cancer as described by the authors receiving treatment with curative or palliative intent. Curative intent may involve surgical or medical treatment including chemotherapy or radiotherapy.

Intervention
• Studies should compare a liberal allogenic packed red blood cell transfusion strategy to a restrictive allogenic packed red blood cell transfusion strategy. The exact trigger or strategy may vary between studies.

Primary Outcome
• All-cause mortality

Secondary Outcomes
• Cancer-related mortality
• Adverse events including total adverse events, serious adverse events, transfusion-related adverse events, and peri-operative morbidity (infection, venous thromboembolism, pneumonia, unintended intubation, renal failure, stroke, cardiac arrest, myocardial infarction, flap failure, prolonged ventilator)[18]
• Transfusion rate

Information Sources
• A literature search will be performed with the guidance from an experienced public health research librarian. The online databases that will be searched include: Medline (Ovid), PubMed (National Library of Medicine), and EMBASE (Ovid). Additionally, highly relevant citations will be searched in Scopus (Elsevier) to determine if any unique studies were missed by the database searches. Bibliographies of highly relevant articles will be examined for potential relevant citations otherwise not found. Authors of key studies will be contacted as needed.

Search strategy
Concepts that will make up the search include “transfusion” “cancer” and “anemia.” Our search will be restricted to adult patients, studies published in English language and controlled studies. No other restrictions will be applied. Our MEDLINE search strategy is provided in Appendix A.

Study selection
Two reviewers (LP and JT) will independently screen a random sample of titles and abstracts in which they will be blinded to authors and journal titles. If at least a moderate level of agreement is reached using an Excel workbook designed specifically for this
purpose,[19] then the two reviewers will independently screen all titles and abstracts. If disagreement, the authors will reach consensus through discussion.

**Data Collection**

Two reviewers (LP and JT) will independently abstract study characteristics and outcomes using a data extraction form. If disagreement, the authors will reach consensus through discussion.

This form will include:

- Reference data: First author’s last name, publication year, citation.
- Study design data: study type (RCT, CRT, CCT, CBA, ITS, CPS).
- Study and participants characteristics: number of patients in intervention and control arms, study aim, definitions of control and intervention arms, hemoglobin threshold or trigger used, methodology descriptions, age of blood, leukocyte reduction, clinical setting (medical, surgical), population, cancer diagnosis, type of surgery (open, minimally invasive), estimated blood loss if surgery, concomitant treatment, etc.
- Outcomes measures: primary and secondary outcomes, number of transfusions, number of units of blood in each arm, length of stay, etc.

Study data will be collected and managed using EXCEL.

**Assessment of quality risk of bias**

Two reviewers will independently appraise the quality of the included studies. The Cochrane risk of bias tool will be used to assess the randomized studies. The tool judges the risk of 5 type of bias (i.e., selection, detection, performance, attrition, reporting) and other potentials to validity threats (e.g., funding, imbalanced use of co-intervention, etc.). Each potential source of bias will be graded as low, unclear (either lack of information or uncertainty over the potential for bias, or high risk of bias. Non-randomized studies will also be independently appraised with A Cochrane Risk of Bias Assessment Tool: for Non- Randomized Studies of Interventions (ACROBAT-NRSI). Studies will be judged for the potential for bias due to confounding, selection of participants, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Each potential source of bias will be graded low, moderate, serious, or critical risk of bias or no information.

**Statistical Analysis**

We will analyze data using intention to treat model when possible. We will pool continuous data as mean difference and dichotomous as risk ratios. Intervention effects (i.e., odds ratio, risk ration, rate ration and hazard ratio) will be combined with a natural log transformation. Data will be synthetized using fixed-effect models except when heterogeneity exists we will use random-effects model. We will used the Cochran Q test and the I² statistic to examine heterogeneity among the studies.[20] In the presence of significant heterogeneity (P<0.05), we will fit a random-effects model based on the method of DerSimonian and Laird.[21] Missing data will be handled following the

Subgroup analyses will be performed to indirectly compare the effects of covariates, such as clinical setting, cancer diagnosis, and type of surgery on the effects of restrictive transfusion. Depending on the numbers of studies, a sensitivity analysis will be performed to explore the influence of study quality and design on the magnitude and direction of the effects. We will also examine the probability of publication bias or small study effects using funnel plots and Egger’s test.[22-26] Analyses will be conducted on RevMan, version 5.3, statistical software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

**Human Subjects, Animal Subjects, or Safety Considerations**

Only published available articles will be utilized for this systematic review. Therefore, no human subjects will be involved in this project and it is exempt from IRB approval.
References:


