Measuring bleeding as an outcome in clinical trials of prophylactic platelet transfusions

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A 12-year-old girl with acute myeloid leukemia has completed her third cycle of chemotherapy and is in the hospital awaiting count recovery. Her platelet count today is 15 000 and, based on your institution's protocol, she should receive a prophylactic platelet transfusion. She has a history of allergic reactions to platelet transfusions and currently has no bleeding symptoms. The patient's mother questions the necessity of today's transfusion and asks what her daughter's risk of bleeding would be if the count is allowed to decrease lower before transfusing. You perform a literature search regarding the risk of bleeding with differing regimens for prophylactic platelet transfusions.

Introduction

Until the 1960s, hemorrhage was a leading cause of death in newly diagnosed leukemia patients.[1] Prophylactic platelet transfusions were shown to decrease bleeding-related mortality.[2] In the half-century since this discovery, clinicians and researchers have been trying to determine the optimal platelet transfusion regimen that minimizes both bleeding

Table 1. Examples of published scales used to measure bleeding in patients with thrombocytopenia or platelet dysfunction

Scale	Purpose	grades
WHO scale (Miller et al, 1981[14])	Grade toxicity in cancer treatment trials	0 = No bleeding 1 = Petechiae 2 = Mild blood loss 3 = Gross blood loss 4 = Debilitating blood loss
Ajani et al, 1990[8]	Grade toxicity in cancer treatment trials	0 = No bleeding 1 = Petechiae, minimum bleeding 2 = Blood loss requiring 1-2 units of blood 3 = Blood loss requiring 3-4 units of blood 4 = Blood loss requiring > 4 units of blood 5 = Death
GIMEMA scale (Rebulla et al, 1997[5])	Expanded from WHO scale to measure bleeding in patients with chemotherapy-induced thrombocytopenia	0 = No bleeding 1 = Petechiae, mucosal or retinal bleeding not requiring transfusion 2 = Melena, hematemesis, hematuria, hemoptysis 3 = Bleeding requiring RBC transfusion 4 = Retinal bleeding with vision loss 5 = Nonfatal cerebral bleeding 6 = Fatal cerebral bleeding 7 = Fatal noncerebral bleeding
National Cancer Institute Common Terminology Criteria for Adverse Events Version 4, 2009[18]	Grade toxicity in cancer treatment trials (note: "hemorrhage" is not a single category, but rather is divided among all possible organ systems: eg, epistaxis, rectal hemorrhage, vitreal hemorrhage, and intracranial hemorrhage represent 4 different toxicity categories); toxicities have been summarized	1 = Mild symptoms, no intervention required 2 = Moderate symptoms, nonoperative intervention (but not transfusion) required 3 = Transfusion or operative intervention required 4 = Life-threatening consequences, urgent intervention required 5 = Death

Webert et al, 2012[12]	Assess bleeding in patients with chemotherapy-induced thrombocytopenia	0 = No bleeding
		1 = Clinically insignificant bleeding
		  1a = Trace bleeding
		  1b = Mild bleeding
		2 = Clinically significant bleeding
		  2a = Serious bleeding
		  2b = Serious bleeding causing significant morbidity
		  2c = Fatal bleeding

Table 2. Summary of studies of platelet transfusion regimens that report bleeding incidence and/or severity as a primary or secondary outcome

Study	Type	Objectives	Measurement of bleeding incidence/severity
Heckman et al, 1997[13]	RCT comparing 10 000/μL vs 20 000/μL in adult leukemia patients	Primary: bleeding episodes and platelet utilization	Severity (minor vs major bleeding) determined by patient's physician in a subjective manner with a formal scale[7] mentioned in methods section
Rebulla et al, 1997[5]	RCT comparing 10 000/μL vs 20 000/μL in adult AML patients	Primary: frequency and severity of hemorrhage; secondary: number of platelet and RBC transfusions, remission rates, mortality	Original GIMEMA scale
Zumberg et al, 2002[9]	RCT comparing 10 000/μL vs 20 000/μL in HSCT patients > 2 y of age	Primary: number of platelet transfusions; secondary: bleeding incidence and severity	Modified GIMEMA scale[3] 0 = None 1 = Petechial, mucosal, microscopic 2a = Melena or hematemesis not requiring RBC transfusion 2b = Gross hematuria 3 = Bleeding requiring RBC transfusion 4 = Retinal bleeding with visual impairment 5 = Nonfatal cerebral bleeding 6 = Fatal cerebral bleeding 7 = Fatal non-cerebral bleeding
Diedrich et al, 2005[15]	RCT comparing 10 000/μL vs 30 000/μL in HSCT patients > 2 y of age	Primary: number of platelet transfusions; secondary: number of RBC transfusions, incidence of hemorrhage and GVHD, survival	WHO scale[14]
Sensebé et al, 2005[16]	Crossover RCT to compare single dose (0.5×10^{11}/10 kg) vs a double dose (1×10^{11}/10 kg) in adult acute leukemia and HSCT patients	Primary: time to subsequent transfusion; secondary: corrected count index, number of transfusions, bleeding complications	WHO scale[14]
Tinmouth et al, 2004[10]	RCT to compare low-dose and standard-dose platelets in adult acute leukemia and HSCT patients	Primary: bleeding complications and platelet utilization	Modified GIMEMA scale[3] 1 = Petechiae, mucosal, or vaginal bleeding not causing a decrease in hemoglobin to not greater than 2 g /dL within past 24 h 2 = Melena, hematemesis, hematuria, hemoptysis 3 = Any bleeding with a fall in hemoglobin level to $\geq$ 2 g/L within the past 24 h 4 = Retinal bleeding 5 = Nonfatal cerebral bleeding 6 = Fatal cerebral bleeding 7 = Fatal non-cerebral bleeding
Murphy et al, 2006[11]	RCT to compare efficacy of pathogen-inactivated platelets vs standard apheresis platelets in adults with acute leukemia and HSCT patients	Primary: incidence of $\geq$ grade 2 bleeding	Modified WHO scale[14,17] 1 = Epistaxis/oral bleeding < 1 hour duration, occult blood in stool, vaginal spotting, petechiae, microscopic hematuria 2 = Epistaxis/oral bleeding $\geq$ 1-h duration, melena, hemoptysis, purpura $\geq$ 1-inch diameter 3 = Requires RBC transfusion, grossly bloody bodily fluids, asymptomatic CNS bleeding evident on imaging only 4 = Bleeding resulting in joint damage, retinal bleeding with visual impairment, symptomatic CNS bleeding, and/or hemodynamic instability

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Table 2. Summary of studies of platelet transfusion regimens that report bleeding incidence and/or severity as a primary or secondary outcome (continued)

Study	Type	Objectives	Measurement of bleeding incidence/severity
Heddle et al, 2009[6]	RCT to compare low-dose platelets (1.5-3.0 $\times$ 10^{11} platelets/unit vs 3.0-6.0 $\times$ 10^{11} platelets/unit)	Primary: incidence of $\geq$ grade 2 bleeding; secondary: frequency of individual grades of bleeding, time to first bleed, mean number of bleeding days, duration of thrombocytopenia, platelet and RBC transfusion requirements	Modified WHO scale[15] 1 = Epistaxis/oral bleeding $<$ 1 h, occult blood in stool, vaginal spotting, petechiae, microscopic hematuria 2 = Epistaxis/oral bleeding $\geq$ 1 h or packing required, hematoma, melena, hemoptysis, purpura $\geq$ 1-inch diameter, retinal hemorrhage without visual impairment, bleeding from invasive sites 3 = Requires RBC transfusion, grossly bloody bodily fluids, asymptomatic CNS bleeding evident on imaging only 4 = Bleeding resulting in joint damage, retinal bleeding with visual impairment, symptomatic CNS bleeding, and/or hemodynamic instability, fatal bleeding
Slichter et al, 2010[7]	RCT to compare low-, medium-, and high-dose platelets (1.1 $\times$ 10^{11}, 2.2 $\times$ 10^{11}, 4.4 $\times$ 10^{11}/m^2, respectively)	Primary: clinical signs of bleeding; secondary: RBC and platelet transfusions, changes in recipient's posttransfusion platelet count, days to next transfusion, and adverse events	Modified WHO scale[15] 1 = Epistaxis/oral bleeding $<$ 30 min (total duration in prior 24 h), occult blood in stool, vaginal spotting, petechiae, microscopic hematuria 2 = Epistaxis/oral bleeding $\geq$ 30 min (total duration in prior 24 h), hematoma, melena, hemoptysis, purpura $\geq$ 1-inch diameter, retinal hemorrhage without visual impairment, blood in cerebrospinal fluid after nontraumatic lumbar puncture 3 = Requires RBC transfusion, grossly bloody bodily fluids, bleeding with moderate hemodynamic instability 4 = Bleeding resulting in joint damage, retinal bleeding with visual impairment, bleeding with severe hemodynamic instability, symptomatic CNS bleeding, asymptomatic CNS bleeding evident on imaging only, fatal bleeding

Primary outcomes are those that were explicitly stated as such or were the outcome to which the study was powered.
RCT indicates randomized, controlled trial; AML, acute myeloid leukemia; and HSCT, hematopoietic stem cell transplantation.

risk and transfusion exposures. There are several variables to such a regimen, including prophylactic threshold, platelet dose, and component preparation. Because the primary goal of platelet transfusions is to reduce the risk of hemorrhage, bleeding incidence and severity are often the primary or secondary objectives of these studies.

Currently, there is neither a universally agreed upon definition of clinically significant bleeding nor a consensus on the best method to quantify bleeding. Researchers report bleeding outcomes in a variety of ways, including the proportion of patients with bleeding, the percentage of thrombocytopenic days with bleeding, the highest bleeding grade, and the time to first bleed. Conclusions drawn regarding the relative safety and efficacy of a platelet transfusion regimen will vary depending on the type of analysis chosen by the investigators.[3] Complicating these issues is the variety of scales that can be used to measure bleeding (Table 1). The most commonly used scale was created by the World Health Organization (WHO) in 1979[4] to standardize toxicity reporting in cancer treatment trials. The WHO scale is a broad categorical scale that leaves a significant amount of interpretation up to individual raters. Most researchers consider WHO grade 2 and above to be significant

bleeding because of the relative rarity of WHO grades 3 and 4 bleeding (6%-9% and 1%-2%, respectively). However, grade 2 bleeding does not predict grades 3 and 4 bleeding, nor is there evidence that patients with WHO grade 2 bleeding have increased long-term morbidity or decreased survival compared with patients with grades 0 or 1 bleeding.

To examine the literature regarding the use of bleeding scores in recent platelet transfusion trials, we performed a PubMed search using the terms "platelet transfusion" and "bleeding" and "thrombocytopenia" with limits of "clinical trial" and got 49 hits. References chosen for this review include 9 randomized platelet transfusion trials in leukemia or stem cell transplantation patients in which bleeding was a primary or secondary outcome and that described the bleeding scale used in the methods section (Table 2).

The original Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) scale was an expanded WHO scale described by Rebulla et al in 1997.[5] The use of various scales by investigators makes it impossible to perform cross-study comparisons and meta-analyses. For example, because one trial defined $>$ 60 minutes[6] as a

grade 2 nosebleed and another used > 30 minutes,[7] a patient with a 45-minute nosebleed would have clinically significant bleeding in one trial, but not the other. An asymptomatic CNS bleed could be defined as grade 1 (of 4) in the Heckman trial,[8] grade 5 (of 7) in the studies using the GIMEMA scale,[3,9,10] grade 3 (of 4) in the Murphy[11] and Heddle[6] trials, and grade 4 (of 4) in the Slichter trial.[7]

We identified only one bleeding scale (designed by Webert et al) that has undergone psychometric evaluation to confirm validity and reliability.[12] This scale was designed to separate clinically significant from clinically insignificant bleeding by determining whether medical or surgical intervention and/or increased level of care was needed. This definition of "significant" describes the type of bleeding that prophylactic transfusions are designed to prevent: that which exposes patients to the risks associated with medications, surgical procedures, long-term morbidity, and mortality.

None of the available bleeding scales take into account the impact that bleeding has on the quality of life of patients and families. Although daily nosebleeds lasting 15-20 minutes may not require intervention, they can be upsetting or disruptive to some patients. Therefore, combining the scale developed by Webert et al[12] with quality-of-life measurements may provide the most complete representation of bleeding severity.

We rate the level of evidence for using the WHO scale and/or its variations in clinical research level 2C, because there are no studies comparing bleeding scores with regard to their completeness or accuracy in measuring clinically significant bleeding. There is insufficient evidence to determine which bleeding scale should be selected in the design of a clinical trial. This review highlights the difficulties created in this field of research due to the use of different scales to measure bleeding. As researchers move forward in creating clinical trials to mitigate bleeding incidence and severity, consistency in measuring bleeding across trials will improve the quality and standardization of research in this field by allowing for a common method of communicating and comparing results across studies.

Disclosures

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