Bleeding in haemato-oncological diseases: how to score, treat, predict

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The comparison of the WHO bleeding scale and post hoc alternative bleeding scales in a randomized controlled platelet transfusion trial in haemato-oncological patients

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Abstract

In platelet transfusion trials, measurement of bleeding symptoms is challenging. The most used WHO (World Health Organization) bleeding scale insufficiently discriminates between clinically relevant and non-relevant bleeds. In this study, we report the readjudication of bleeding data from a randomized controlled platelet transfusion trial (PREPAReS) according to the BSMS (Bleeding Severity Measurement Scale) and the ISTH (International Society on Thrombosis and Haemostasis) definition of clinically relevant non-major bleeding and major bleeding.

Readjudication of all bleeding days of the PREPAReS trial was performed by three adjudicators. Descriptive analyses were reported as bleeding days according to WHO, BSMS and ISTH scales and comparisons were made between the three. Readjudicated bleeding days were compared to active reporting of bleeding in the medical files. A recalculation of the PREPAReS study results was done by comparing proportions of transfusion treatment episodes with clinically relevant bleeding according to the BSMS and ISTH scales.

In total, 9,107 bleeding days were re-evaluated in 556 transfusion treatment periods. Only 1.3-1.7% of WHO grade 1 and 2 bleeding days were redirected into clinically relevant bleeding grades according to BSMS and ISTH. ISTH showed the best correlation with active reporting of bleeding in medical records. Re-analysis of the PREPAReS showed a comparable outcome irrespective of bleeding scale used.

Applying BSMS or ISTH bleeding scales in clinical platelet trials could improve the clinical relevance aspect of bleeding reporting. More data needs to be collected for further validation of both the BSMS and ISTH bleeding scales.

Introduction

The structural monitoring and scoring of hemorrhagic symptoms is an essential part of platelet transfusion trials, but remains ambitious, and is common ground for discussions, with outcome discrepancies between several reported platelet transfusion trials as a result.[1] The measurement of bleeding symptoms in patients is challenging at several stages, such as the monitoring and documentation of bleeding, assessment of the severity, and the grading in several available bleeding scales, trying to capture various aspects of bleeding in an objective and clinically meaningful way.[2,3] Moreover, some bleeding scale systems are only validated for specific patient populations, such as the skin (S), visible mucosae (M), and organs (O), with gradation of severity (SMOG)-system to describe bleeding in immune thrombocytopenia, and the International Society on Thrombosis and Haemostasis (ISTH) grading of clinically relevant bleeding in patients using anticoagulant medication.[4,5] For hematological patients, although not specifically validated for the purpose, the WHO bleeding scale or variants of this scale are commonly used.[6] The PREPAReS study, comparing pathogen reduced platelet transfusions to a standard platelet product, reported a WHO grade 2 or higher bleeding in 51% of patients with active daily monitoring, whereas another randomized controlled trial studying pathogen reduced platelet products with mostly the same hospitals participating (HOVON 82 trial), only documented 5% of patients with such a bleeding.[7,8] This difference was largely explained by the underreporting of mucocutaneous bleeds as well as the method by which bleeding was recorded in the latter trial, where clinicians were asked to report "relevant bleeds".[7] Besides inconsistent recording of bleeding, this discrepancy reflects one of the inherent problems of the WHO bleeding scale; there is paucity of standardization with respect to the descriptive terms used in the WHO scale.[9] Several years ago, a novel Bleeding Severity Measurement Scale (BSMS) was introduced to assess bleeding severity in thrombocytopenic haemato-oncological patients.[9] Although intended to improve validity and reliability as opposed to the WHO bleeding scale, the BSMS has not been used widely in platelet trials. The reason for this is that many platelet transfusion trials take several years to complete, and traditionally used the WHO bleeding scale for their endpoints, also with the intent to be able to compare results with respect to bleeding to outcomes of previous studies.[10] However, as stated before, the bleeding incidences in several platelet transfusion studies with the clinical endpoint bleeding using this bleeding scale vary unequivocally, urging the need for better grading. The case report form (CRF) of the PREPAReS trial had a detailed design, with documentation of bleeding per organ system, also including information on the documentation of bleeding in the medical files. Since all this information on bleeding was comprehensively captured, it allowed adjudication of bleeding symptoms not only in the prespecified WHO scale, but also according to the BSMS and the ISTH bleeding scales.[5,9] The congruency of "everyday medical reporting" with actual bleeding data reported on the trial report forms reflect a notion of clinical relevance. The purpose of the current study is to compare bleeding frequencies obtained according to the different scales, to

compare the bleeding rates with frequencies of active reported bleeds in the patient files, and to evaluate the primary PREPAReS study outcome applying the alternative (BSMS and ISTH) bleeding scales.

Methods

Description of the data source

The data source for the current study was the PREPAReS trial, a randomized multicenter trial for the evaluation of platelet products in haemato-oncological patients who were platelet transfusion dependent due to myelosuppressive therapy.[8,11] In this non-inferiority trial, patients received trigger-based prophylactic and therapeutic platelet transfusions (standard plasma stored platelets or pathogen-inactivated platelets) during a transfusion treatment period. The primary outcome parameter of the PREPAReS study was the proportion of transfusion treatment periods where patients had a WHO grade ≥ 2 bleeding complication. This endpoint occurred in 51% of the transfusion treatment periods in the control arm versus 54% of for those receiving pathogen-reduced platelets (difference 3 percent points; 95% confidence interval [CI], −6 to 11; p = 0.012 for non-inferiority). All patients underwent daily assessment of their bleeding symptoms, and the grades of severity according to the WHO bleeding scale were adjudicated by independent adjudicators as well as with a computer algorithm.[11,12] Data of the intention to treat population of PREPAReS were used.[8]

Re-adjudication of bleeding

For this study we defined a bleeding as clinically relevant when the bleed had been noted in the patient files. Re-adjudication based on the trial CRFs according to the BSMS and the ISTH scale was performed by the same three adjudicators as the PREPAReS trial, but without automated adjudication. In case of discrepancies in bleeding grade among the adjudicators, the final bleeding grade was decided during a consensus meeting. Discrepancies were defined either as "clerical error" (for example, accidentally selecting the wrong category from a drop-down menu or forgetting to select a category) or actual "disagreements". For the latter cases, agreement was sought by detailed consideration of the bleeding episode. Figure 1 schematically shows the three bleeding scales. For the WHO bleeding scale, grades 0-4 reflect no bleeding (0), minor bleeding (1), mild bleeding (2), considerable blood loss (3) and (very) serious bleeding with debilitating or fatal sequelae (4). The BSMS defines, besides grade 0 (no bleeding), two grades of bleeding, not clinically significant bleeding (1) and clinically significant bleeding (2), which in turn are subdivided in different grades of seriousness (a-b and a-c, respectively).[9] The ISTH defines clinically relevant non-major bleeding (CRNMB) and major bleeding.[5] ISTH definitions serve the purpose to classify clinically relevant bleeding very precisely and do not define less serious bleeding. The ISTH definitions in turn are composed in alignment with the Bleeding Academic Research Consortium's (BARC) recommendations to

define bleeding in general in cardiovascular trials.[13] Type 0 and 1 bleeding according to BARC recommendations are, respectively, no bleeding (type 0) and bleeding that is not actionable (non-relevant bleeding, type1).[13] In our study we grouped these accordingly as grades 0 and 1 under the ISTH bleeding scale (figure 1).

Statistical analyses

For this report, re-adjudicated bleeding scores were tabulated using the number of observation days as denominator. For each grade, the number and percentage of days with active reporting in the medical file was tabulated. The recalculation of the PREPAReS study results was done by comparing the percentage of transfusion treatment periods with at least bleeding grade 2 (WHO), at least grade 1b (BSMS), at least grade 2 (BSMS), or at least CRNMB and major bleeding (ISTH) between the two treatment arms. Because patients could be randomized multiple times in the PREPAReS trial, we applied a generalized estimating equation approach using a generalized linear model with as dependent variable the presence or absence of a bleeding complication (WHO, BSMS and ISTH) during a transfusion treatment period, with treatment arm and treatment period number as covariates. All statistical analyses were performed using SPSS Statistics (version 23, IBM Corp., Armonk, NY, USA).

A

WHO 0	No bleeding
WHO 1	Minor bleeding: petechiae, oropharyngeal bleeding and/or epistaxis ≤30 min., purpura ≤ 1 inch, microscopic haematuria, abnormal vaginal bleeding with spotting
WHO 2	Mild blood loss, never requiring red cell transfusion over routine needs: oropharyngeal bleeding or epistaxis > 30 min, purpura > 1inch, spontaneous haematoma deeper tissue, joint bleeding visible haematuria, abnormal vaginal bleeding more than spotting, haemoptysis, blood in broncho-alveolar lavage of body cavity fluid, haematochezia, melanotic stool, haematemesis, bleeding at invasive site > 1 hour, retinal bleeding without visual impairment, lumbar puncture with blood
WHO 3	Haemorrhage requiring red blood cell transfusion over routine needs and specifically related to treatment of bleeding (<24 hours) or any bleeding associated with moderate hemodynamic instability
WHO 4	Bleeding associated with severe hemodynamic instability and requiring red blood cell transfusion, fatal bleeding, any CNS bleeding (except for traumatic lumbar puncture with blood), retinal bleeding with visual impairment

Figure 1, continued on next page

B

BSMS 0	No bleeding
BSMS 1a	Minimal bleeding or bleeding detectable by laboratory measures only. (No impact on patient/no impact on the level of care provided)
BSMS 1b	Mild bleeding (non–clinically significant bleeding). (No impact on patient/no impact on level of care provided)
BSMS 2	**2a:** Serious bleeding, resulting in: significant pain, need for interventions, invasive investigation or increased monitoring **2b**: Serious bleeding causing significant morbidity (all CNS bleeding, vision loss, hemodynamic instability, other sign morbidity) **2c:** Fatal bleeding

C

No bleeding	
Non relevant bleeding	
ISTH CRNMB	Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: 1.requiring medical intervention by a healthcare professional, 2. leading to hospitalization / increased level of care, 3. prompting a face to face evaluation
ISTH major bleeding	Fatal bleeding, and/or bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20 g/ L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

Figure 1. Bleeding scales: (A) WHO bleeding scale (criteria used in PREPAReS) 6,11 (B) Bleeding Severity Measurement Scale9 and (C) ISTH definition of clinically relevant non-major bleeding and major bleeding.5

Results

A total number of 9,107 observation days were re-evaluated in 556 transfusion treatment periods. The number of days with any bleeding scored using the WHO, the BSMS and

the ISTH bleeding scales was 5,273 (58%), 2,383 (26%) and 5,274 (58%) respectively. Table 1 shows the re-adjudication results in relation to the WHO bleeding score. When using the BSMS scale, the largest shift occurred in the WHO grade 1 and 2 bleeding category; 58 % of bleeding days WHO grade 1 and 54% of bleeding days WHO grade 2 were in BSMS designated to the "no bleeding" category (grade 0). For the ISTH scale, 97% of days with WHO grade 2 and 30% of days with grade 3 bleeding complications were categorized in the "non- relevant bleeding" category. The most serious bleedings, fatal as well as for example symptomatic CNS bleeds, were categorized consistently between all three bleeding scales.

Table 1. BSMS- and ISTH bleeding scales in relation to the WHO-bleeding scale (shown as days (%)).

BSMS				
WHO	**BSMS Grade 0**	**BSMS Grade 1a**	**BSMS Grade 1b**	**BSMS Grade 2 (2a-2c)**
Grade 0	3832 (99.9)	0 (0)	2 (0.1)	0 (0)
Grade 1	1420 (57.9)	459 (18.7)	565 (23.1)	7 (0.3)
Grade 2	1472 (53.7)	133 (4.9)	1073 (39.2)	60 (2.2)
Grade 3	0 (0.0)	4 (17.4)	4 (17.4)	15 (65.2)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	61 (100)
ISTH				
WHO	**No bleeding**	**Non relevant bleeding**	**CRNMB**	**Major bleeding**
Grade 0	3832 (99.9)	2 (0.1)	0 (0)	0 (0.0)
Grade 1	1 (0.0)	2442 (99.7)	8 (0.3)	0 (0.0)
Grade 2	0 (0.0)	2658 (97.1)	80 (2.9)	0 (0.0)
Grade 3	0 (0.0)	7 (30.4)	3 (13)	13 (56.5)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	61 (100)

Information on the CRFs whether a bleed was noted in the medical files was available for 8,962 days. For all bleeding scores, the percentage of registration increased in line with bleeding severity, although in approximately 30% of days on which bleeding of the highest severity occurred, a registration in the medical records was missing, irrespective of the bleeding scale (Table 2). WHO grade 2 bleeding complications, that were part of the primary endpoint of the PREPAReS trial, were only registered in the clinical notes in 22% of days. For the BSMS, grade 1b (mild bleeding) was reported in 28% of days in the medical files. In contrast, CRNMB in the ISTH grading was reported in the medical notes in the majority of days (69%) (Table 2). For both the WHO and the ISTH scales, in 1% of days the trial CRF reported no bleeding in contrast to the medical file. For the BSMS this was the case in 5% of days with bleeding (Table 2).

Re-analysis of the PREPAReS study essentially showed that the differences between the two study populations remained small and statistically non-significant (Table 3). If we had chosen BSMS grade 2 (clinically significant bleeding) or ISTH CRNMB + major bleeding complications as the primary endpoint, the percentage of patients reaching this endpoint (for both scales 8%) would be only a fraction of the patients reaching the primary endpoint using the WHO bleeding score (Table 3).

Table 2. Bleeding reporting frequencies according to the WHO bleeding scale, the BSMS and the ISTH definition and according to bleeding registration in the medical records.

			Bleeding not registered	**Bleeding registered**
Bleeding category		*n days*	*n days (%)*	*n days (%)*
WHO	**Grade 0**	3753	3704 (98.7)	50 (1.3)
	Grade 1	2399	2119 (88)	280 (12)
	Grade 2	2725	2125 (78)	600 (22)
	Grade 3 and 4	84	27 (32)	57 (68)
BSMS	**No bleeding**	6615	6307 (95)	308 (5)
	Grade 1a	585	457 (78)	128 (22)
	Grade 1b	1620	1168 (72)	452 (28)
	Grade 2	142	43 (30)	99 (70)
ISTH	**No bleeding**	3754	3705 (99)	49 (1)
	Non relevant bleeding	5046	4222 (84)	824 (16)
	CRNMB	88	27 (31)	61 (69)
	Major bleeding	74	21 (28)	53 (72)

Discussion

In this study we showed that with the use of a comprehensive CRF to document bleeding symptoms, bleeding scales other than the most widely used WHO scale can be applied to evaluate trial results. In the current study, 56% of bleeding days recorded as WHO grade 1-2 were classified as BSMS grade 0. In the BSMS, for (oral) petechiae and bruising of the skin, in order to be counted as a grade 1(a) bleeding, the explicit fact that it is new or increased in size is conditional.[9] This means that many days of persisting (that is, not new) bruising or petechiae counted as bleeding days in the WHO scale (grade 1 and 2), are not counted as bleeding days in the BSMS.[9] The mere fact that the BSMS considers new bleeds increases its clinical relevance. Except for the 54% of bleeding days WHO grade 2 redirected to grade 0 of the BSMS, almost 40% of the WHO grade 2 bleeding days are categorized in the BSMS as grade 1b, mild bleeding. The original WHO scale used relatively general terms to describe bleeding, with a more or less continuous increase in severity of the bleeding from grade 0 to 4.[6]

Table 3. PREPAReS trial results for each of the scoring systems**;** comparison of the proportion of transfusion treatment periods in which the patient had a clinically relevant bleeding between the control and intervention arms of the intention to treat population according to the WHO bleeding scale, the BSMS and the ISTH definition of CRNMB + major bleeding.

	Control	Intervention
Transfusion treatment period, n	279	277
WHO		
WHO grade ≥2, n (%)*	143 (51)	150 (54)
Highest grade of bleeding, n (%)		
None or grade 1	136 (49)	127 (50)
grade 2	131 (47)	139 (50)
grade 3	6 (2)	5 (2)
grade 4	6 (2)	6 (2)
BSMS		
BSMS grade 1b + 2, n (%)∞	184 (66)	187 (68)
BSMS grade 2, n (%)♯	22 (8)	17 (6)
Highest grade of bleeding, n (%)		
0	54 (19)	47 (17)
1a	41 (15)	43 (16)
1b	162 (58)	170 (61)
2a-c	22 (8)	17(6)
ISTH		
CRNMB + major bleeding, n (%)§	23 (8)	17 (6)
Highest grade of bleeding, n (%)		
No or non-relevant	256 (92)	260 (94)
CRNMB	14 (5)	7 (3)
Major	9 (3)	10 (4)

556 Transfusion-treatment periods took place in 469 patients

** WHO ≥2: difference 3 percentage points 95% CI (-6 to 11)*

∞ BSMS ≥1b: difference 2 percentage points 95% CI (-6 to 9)

♯ BSMS ≥2: difference -2 percentage points 95% CI (-6 to 2)

§ ISTH CRNMB + major: difference -2 percentage points 95% CI (-6 to 2)

Over the years, platelet transfusion trial methodology required more comprehensive and objective description of the grades. Different trials used adaptations and interpretations of the WHO grades that are not completely similar, which makes comparison of bleeding rates between trials less precise.[14] Unlike the WHO scale, BSMS grades 1a, 1b, and 2 a-c reflect a more equal increase in clinical relevance of the bleeding, and apply accurate instructions to adjudicate bleeding symptoms that are more in line with clinical practice.[9] To our knowledge, no randomized platelet transfusion trials have used the BSMS criteria

yet. There is only one report concerning a pilot randomized study comparing tranexamic acid with platelet transfusion in haemato-oncological patients using the BSMS.[15]
The ISTH definition was not developed nor validated for an in-hospital thrombocytopenic population.[5] Most of the WHO grade 2 bleeds (97%) do not fulfil the criteria for clinically relevant bleeding in the ISTH scale, and even grade 3 (WHO) bleeding is not clinically relevant in 30% of days according to the ISTH scale. In this respect the ISTH definition performs comparable to the BSMS, with 35% of WHO grade 3 bleeding categorized in the BSMS grade 1a and 1b. The ISTH definition is less defined in the minor bleeding category and does not distinguish between bleeds in several locations of organ systems.[5] For all three bleeding scales, in about 70% of days the highest bleeding grade was also captured in the medical notes, suggesting clinical relevance. For the second highest grade of the ISTH scale, still 69% is captured, but for the lower bleeding grade of the BSMS (grade 1b), this is only the case in 28%. For the WHO grade 2 bleeding days, this is even lower, 22%, reflecting a clinician's perception of clinical irrelevance in four out of every five days a bleeding is reported on the trial CRF. Furthermore, it is noticeable that around 30% of the ISTH CRNMB + major bleeds are not mentioned in the files, which also applies for BSMS grade 2 and WHO grades 3 and 4. A possible reason for not recording serious bleeding in a patient report could be that bleeding occurs alongside other serious concurrent complications demanding full attention, and as a consequence, causing omissions in the reporting rather than the bleeding being assessed as non-relevant.
Lastly, the study outcomes of the PREPAReS trial were re-analyzed using the BSMS and ISTH bleeding scales. Of note, for this analysis the highest bleeding score per treatment period was used, instead of the total of bleeding days. Overall, no major shifts in the comparison between study arms could be observed. For the BSMS, the grades 1b and 2 may be combined for the purpose of a study endpoint, to have clinical relevance as well as a high enough bleeding incidence to require a reasonable number of patients for future platelet trials in which comparable relative effect sizes or non-inferiority margins are applied. For a future platelet dosing trial, we will use the BSMS scale, with percent of days with grades 1b+2 bleeding symptoms as primary endpoint. This trial will start in the near future and is registered at the Netherlands Trial Registry under number NL9204. This study will generate more data on the usefulness and clinical relevance of that bleeding scale. The ISTH definition, as mentioned, not developed nor validated before for thrombocytopenic patients with bleeding, is also further investigated for its applicability in this platelet trial.
A limitation of the current study is the relatively low number of days with a relevant bleed using a CRF developed for the WHO bleeding scale, and so more data needs to be collected for further validation of both the BSMS and ISTH bleeding scales. The comprehensive description of the BSMS includes any intervention, and also has significant pain and increased monitoring as criteria for clinical relevance of a bleeding.[9] Those data were neither complete nor consistently captured with the PREPAReS bleeding CRF. It is therefore conceivable that, using the CRF specifically composed to score

according to WHO, omissions have occurred with respect to these aspects, since the prescription of pain medication or tranexamic acid or reports on intensifying blood pressure measurement was not always delineated in conjunction with the bleeding CRF, and therefore, possibly BSMS grade 2 bleeding days may have been underreported in the re-adjudication process.

In conclusion, the ISTH bleeding scale indicates the highest clinical relevance. However, clinically relevant bleeds are rare, and will lead to a low outcome incidence in transfusion trials.[16] The BSMS may be a good alternative if grades 1b+2 are combined, leading to higher bleeding numbers but somewhat at the expense of clinical relevance relative to using only grade 2 of the BSMS. However, this is probably still advantageous over using the even less clinically relevant bleeds now captured in WHO grade 1 and 2. Further optimization of the BSMS is warranted. In the future, using the BSMS and possibly the ISTH bleeding scales, with a CRF fully adjusted to capturing "clinical relevance" aspects of these scales will undoubtedly lead to more meaningful interpretation of bleeding outcomes of platelet transfusion trials.

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