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

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The observation of bleeding complications in haemato-oncological patients: stringent watching, relevant reporting

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Abstract

The reported percentage of haemato-oncological patients experiencing bleeding complications is highly variable, ranging from 5 to 70%, posing a major problem for comparison of clinical platelet transfusion trials using bleeding complications as a primary endpoint. In a pilot study we assessed the impact of the design of scoring of bleeding on the percentage of patients with World Health Organisation (WHO) grade 2 or higher bleeding grades.

We performed a prospective, observational study using a rigorous bleeding observation system in thrombocytopenic patients with haemato-oncological disorders. Endpoints of the study were the percentage of patients and days with bleeding WHO grade ≥ 2, comparing designs in which days with skin bleeding represent a continuation of a previous bleed or a new bleed.

In four participating hospitals 64 patients suffering 870 evaluable thrombocytopenic days (platelet count < 80 x 10^9/L) were included. At least one episode of bleeding grade ≥ 2 occurred in 36 patients (56%). Most grade 2 bleeding complications occurred mucocutaneously. The percentage of days with bleeding grade ≥ 2 was 16% but decreased to 8% when only newly developed skin bleedings were included.

Rigorous daily observation results in a bleeding incidence that is comparable to recent reportings applying the same method. The results of this study show that censoring for stable skin bleeding has a profound effect on bleeding incidence per day. The clinical relevance of rigorous or clinically judged bleeding scores as an endpoint remains to be defined.

Introduction

Patients with haemato-oncological diseases receiving myelosuppressive chemotherapy or undergoing haematopoietic stem cell transplantation are supported with platelet transfusions to prevent or treat bleeding complications. Despite few policy-driven trials the prophylactic platelet transfusion strategy is maintained, albeit with some changes in transfusion triggers, for almost four decades. Meanwhile, safety as well as economical concerns has led to several changes in platelet production. Although several parameters have been used as an endpoint for platelet transfusion trials, the Guidance for Industry For Platelet Testing and Evaluation of Platelet Substitute Products, published by the FDA in 1999 prescribes the recording of bleeding outcomes as a necessary activity.[1]

However, as a consequence of the several different methods for the observation and grading of bleeding complications, passive versus active reporting, frequency of measuring bleeding complications and differences in patient populations, the reported percentage of patients and of days experiencing bleeding complications turned out to be highly variable, between 12 and 48%, in a review of platelet trigger studies.[2] We observed in studies conducted between 1994 and 2010, including recent platelet dosage studies that the reported incidence of major bleeding (WHO grade ≥ 2) varies from 5 to 70% (Figure 1).[3-27]

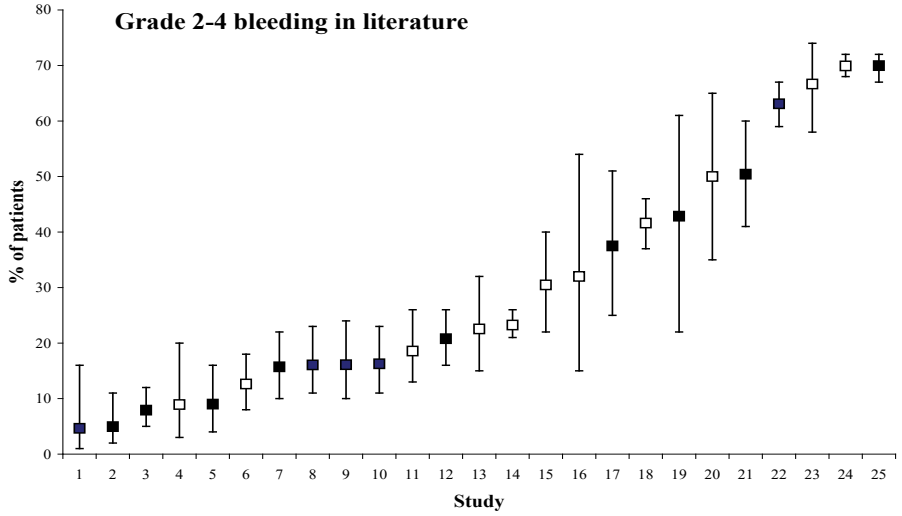

Figure 1. Reported percentages of patients with grades 2 – 4 bleeding complications.

The error bars reflect the 95% confidence interval. The filled markers represent randomised controlled trials, whereas the open markers represent observational studies. 1 = Blumberg et al., (2004)[3]; 2 = Sensebe et al.(2005)[4]; 3 = Kerkhoffs et al.(2010)[5]; 4 = Oka et al.(2007)[6]; 5 = Tinmouth et al.(2004)[7]; 6 = Gil-Fernandez et al.(1996)[8]; 7 = Zumberg et al.(2002)[9]; 8 = Kerkhoffs et al.(2006)[10]; 9 = The Mirasol Clinical Evaluation Study Group(2010)[11]; 10 = Diedrich et al.(2005)[12]; 11 = Wandt et al.(2006)[13]; 12 = Rebulla et al.(1997)[14]; 13 = Gmur et al.(1991)[15]; 14 = Nevo et al.(1998)[16]; 15 = Wandt et al.(1998)[17]; 16 = Sagmeister et al.(1999)[18]; 17 = Murphy et al.(1982)[19]; 18 = Pihush et al.(2002)[20]; 19 = Higby et al.(1974)[21]; 20 = Navarro et al.(1998)[22]; 21 = Heddle et al.(2009)[23]; 22 = McCullough et al.(2004)[24]; 23 = Lawrence et al.(2001)[25]; 24 = Friedmann et al.(2002)[26]; 25 = Slichter et al.(2010).[27]

Note: the Study numbers in figure 1 do not correspond with the reference numbers in the reference list.

This variability poses a major problem for designing and comparison of clinical platelet transfusion trials using bleeding complications as a primary endpoint. In studies using a rigorous bleeding observation and adjudication process to assess bleeding, at least one episode of major bleeding (WHO ≥ grade 2) is reported in up to 70% of patients and on 17% of thrombocytopenic days, defined by a morning platelet count between 6 and 80 x 10^9/L.[26,27] In contrast, studies that relied on physician's bedside assessment of bleeding complications reported much lower incidences of major bleeding.[3,4] Recently, we initiated a platelet transfusion trial studying the haemostatic efficacy of transfused platelets treated with a pathogen-reduction technique (PREPAReS; Pathogen Reduction Evaluation & Predictive Analytical Rating Score). As bleeding complications are the primary outcome of this study, our aim was to perform a pilot study (BOP, Bleeding Observation Pilot study) to investigate the percentage of patients with major bleeding complications using a rigorous bleeding observation system and two designs for adjudication. Secondary endpoints are the percentage of patients experiencing any bleeding complication (WHO grade 1-4) and the percentage of days with WHO grade ≥ 2 bleeding complications. We

compared the data from this pilot study with the bleeding data as reported by clinicians from a previous study.[5]

Methods

A prospective observational study was performed, including patients ≥ 18 years, admitted to the hospital for receiving high dose chemotherapy or stem cell transplantation for haemato-oncological disease expected to need platelet transfusions during their admittance. Exclusion criteria were suspicion of microangiopathic thrombocytopenia, the use of anticoagulant drugs or active bleeding (grade ≥ 2) at the time of inclusion. The study protocol and consent forms were approved both by a central ethics committee and local institutional review boards. Four haematological centres participated in the study, two academic medical centres and two large general hospitals (HIC, Haematological Intensive Care centres). Hospital discharge, death or patients' refusal to continue were reasons to go off protocol, i.e., to stop the observation of bleeding. Daily assessment of bleeding symptoms for 8 World Health Organisation (WHO) defined sites (oral/nasal; skin/soft tissue/ musculoskeletal; gastrointestinal; genitourinary; pulmonary; body cavity; central nervous system; invasive sites) was performed by trained physicians, nurses or research staff members in each of the four hospitals including physical examination and a patient's interview. Training of members of the study-group was ensured by sharing practical and theoretical instructions. Strict daily examination and documentation of bleeding complications per patient was applied, comparable to the method used in a recent large trial comparing platelet dosages.[27] Adjudication of grades of bleeding according to the WHO criteria was performed by two clinicians, independently (JLK, PY) as proposed by Miller *et al.*[28] For example, a grade 1 mucocutaneous bleeding consists of oropharyngeal bleeding or nose bleed with a duration < 30 min or haematomas smaller than 1 inch. Skin bleeding grade 2 consists of haematomas larger than 1 inch.[27] In the case record form it was noted whether the mucocutaneous bleeding was old or new or getting larger. Platelet transfusions were administered prophylactically, generally based on the morning platelet count, to maintain a platelet count above 10 x 10^9/L or at the treating physicians' initiative if the patient experienced bleeding or using a higher trigger in certain clinical circumstances. The period at risk was defined as from inclusion in the study (hospital admittance and expected to need platelet transfusions during admittance) until discharge from the hospital. Platelet transfusions consisted of a mean of 350 x 10^9 buffy-coat derived pre-storage leukocyte-reduced platelets. Red cell transfusions were administered below an age-dependent trigger. Besides bleeding, each day a blood cell count and transfusion requirements were recorded. For the comparison with a recent study of which case records were available, we extracted all bleeding data from the case report forms of that study.[5] Primary endpoint of the study was the percentage of patients experiencing at least one episode with bleeding WHO grade ≥ 2. Secondary outcome measures were the percentage of patients experiencing bleeding of

any grade, the percentage of days with bleeding WHO grade ≥ 2 including all days with a bleeding observation as well as the percentage of days with bleeding on observed days with a platelet count < 80 x 10^9/L, calculated per patient.[29]

Statistical Analysis

Categorical patient characteristics and bleeding complications are reported as percentages. Continuous data are presented as the mean with standard deviation (SD) for normally distributed variables and the median with interquartile range (IQR) for other continuous variables not normally distributed. An univariate comparison of patients with and without WHO grade ≥ 2 bleeding was performed. A multivariate logistic regression analysis was performed including parameters associated with bleeding (*P*-value < 0.1) in the univariate analysis (treatment centre, diagnosis, treatment, median platelet count, platelet nadir). Variables considered as possible consequences of bleeding rather than causes (number of platelet and red cell transfusions), were not considered for multivariate analyses. All statistical analyses were performed using SSPS (version 15.0, Chicago, IL). *P*-values < 0.05 were considered statistically significant.

Results

Patients

A total of 68 patients were enrolled at four sites (centre A, B, C and D). Four patients did not receive a platelet transfusion and were excluded for analysis. In total 1295 bleeding observation days were available, of which there were 870 days with a platelet count < 80 x 10^9/L. The patients were not equally divided: centre A enrolled 10 patients, centre B 11 patients, centre C 26 patients and centre D 17 patients. The median follow-up period per patient was 19 days. Patient characteristics are summarized in Table 1. More men than women were included and almost half of the patients suffered from acute leukaemia. The composition of the included patients (age, gender, haematological disease and treatment) does not differ substantially from the patients included in the previous recent studies that reported on bleeding incidence.[5,23,27]

Table 1. Patient characteristics.

	N = 64
Male / female, *n*	43 / 21
Age, mean (SD), y	56 (±12)
Diagnosis, *n* (%)	
Acute leukaemia	30 (47)
Multiple myeloma	12 (19)
Lymphoma	12 (19)
Other	10 (16)

Table 1. Continued.

	N = 64
Therapy, *n* (%)	
Chemotherapy	29 (45)
Stem cell transplantation	32 (50)
Allogeneic transplant	5 (8)
Autologous transplant	27 (42)
Other	3 (5)
Follow-up, median (range), days	19 (7 – 41)
Haemoglobin, median (range), mmol/L	5.9 (5.2 – 8.4)
Platelet count, median (range), 10^9/L	44 (4 – 148)
Platelet nadir, median (range), 10^9/L	7 (0 – 22)
Red blood cell transfusion, median (range), *n*	4.0 (0 - 17)
Platelet transfusion, median (range), *n*[1]	2.5 (1 – 18)

n, numbers of patients or units of red blood cells/platelet transfusions

[1] *Prepared from 5 Buffy-coats, pooled and pre-storage filtered*

Primary Endpoint

One or more episodes of grade ≥ 2 bleeding were experienced by 36 patients (56%). Five patients (7.8%) suffered from a grade 3 or 4 bleeding and 1 patient died from a bleeding complication.

Table 2 summarizes the bleeding complications by different bleeding sites as defined by the WHO criteria. Some patients suffered from more than one episode of grade ≥ 2 bleeding. The vast majority of bleeding complications occurred on mucocutaneous sites as expected.

Table 2. Bleeding complications by site.

Bleeding site	Grade 1 bleeding, *n*	Grade ≥ 2 bleeding, *n*
Oral cavity and nose	39	2
Skin, soft tissue and musculoskeletal	25	19
Digestive tract	-	14
Urogenital tract	-	-
Respiratory tract	-	6
Body cavity	-	3
Central nervous system / retina	-	4
Invasive site	-	3

n, number of patients. Patients could suffer from bleeding complications at one or more sites and different grades during the observation period. Seven patients did not suffer from any bleeding complication.

Figure 2 shows the comparison for the several bleeding sites as reported in a recent study, the HOVON 82-study, in which clinically judged bleeds had been reported.[5] The striking difference in grade ≥ 2 bleeding complications is almost completely on account of the difference in mucocutaneous bleeding complications. The proportion of patients with grade 3 or 4 bleeding did not differ between the current pilot study (BOP) and the HOVON 82 study (7,8% vs. 5.8%; P = 0.5).[5]

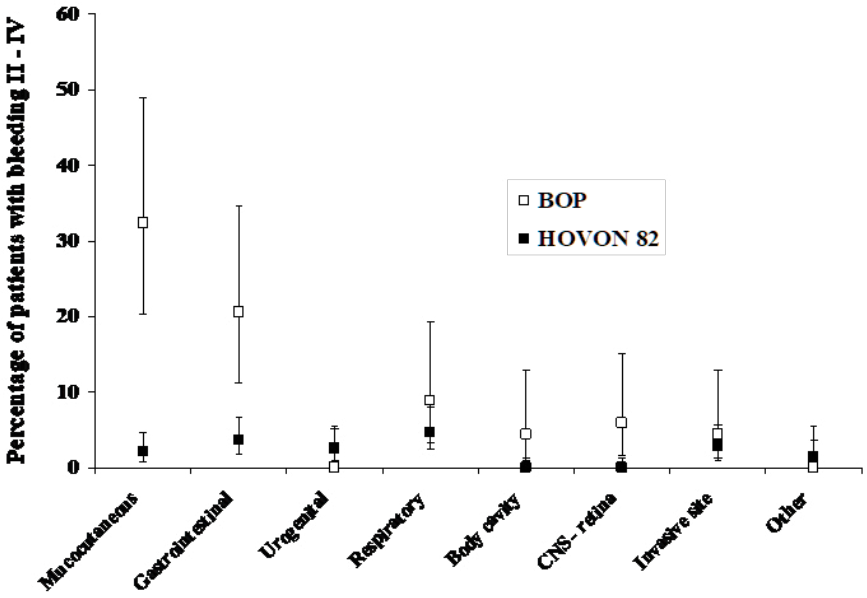

Figure 2. The comparison between the current study (BOP) and the HOVON 82 trial of patients with bleeding WHO grade ≥ 2 grouped by the anatomical sites.[5]
The bars reflect 95% confidence intervals.

Secondary Endpoints

Fifty-seven (89%) patients experienced one or more bleeding episodes of any grade. The percentage of days with bleeding of any grade during the whole observation period was 42%. The percentage of bleeding on days with a platelet count < 80 x 10^9/L was 49% and the percentage of days with grade 2 or higher bleeding was 19%.

Most of the grade ≥ 2 bleeds occurred on the skin. Including only newly perceived haematomas, the percentage of days with bleeding of grade ≥ 2 was 8.1%. Figure 3 shows the relation between morning platelet counts and percentage of days with grade 2-4 bleeding with or without excluding persisting haematomas, again illustrating the effect of mucocutaneous bleeding on the total incidence of bleeding.

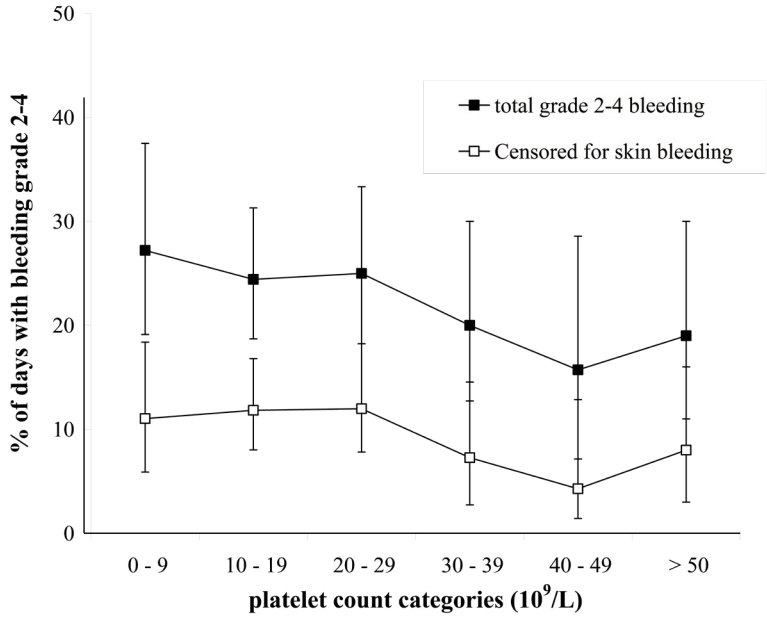

Figure 3. The percentage of days with bleeding grade ≥ 2 with the 95% confidence interval according to the platelet count categories based on the days with a platelet count < 80 x 109/L (n = 870 days).

The closed symbols represent the percentage of days with bleeding if all the events are included. The open symbols show the censored percentage after exclusion of successive days with stable skin bleeds.

Univariate analysis indicated that patients in academic centres experienced fewer bleeding episodes as compared to patients in general hospitals ($P = 0.05$). Acute leukaemia as indication for treatment (compared to other haematological disorders) and the administration of chemotherapy (as opposed to transplantation therapy) resulted in significantly higher bleeding frequencies. A multivariate analysis showed that stem cell transplantation therapy was associated with a decreased risk of grade ≥ 2 bleeding in patients with haemato-oncological diseases (Table 3).♦ Although maintained as a factor in the model of the backward multivariate analysis, a low mean platelet count only showed a trend towards association with bleeding (p = 0.08).

♦*this sentence has been modified from the original publication because the manner of reporting was not consistent with the representation in Table 3*

Table 3. Comparison of patients with no bleeding or grade 1 bleeding versus grade ≥ 2 bleeding.

	No or grade 1 bleeding	Grade ≥ 2 bleeding
	n = 28	*n* = 36
Male / female, *n*	21 / 7	22 / 14
Age, median (range), y	59 (19-70)	59 (23-77)
Acute Leukaemia, *n* (%)	8 (29)	23 (64)#
Stem cell transplant, *n* (%)	20 (71)	12 (33) # **
Academic centre, *n* (%)	16 (57)	12 (33) #
Haemoglobin, median (range), mmol/L	6.0 (5.4-7.5)	5.8 (5.2-8.4)
Platelet count, median (range), 10^9/L	65 (14-139)	38 (4-148) #
Platelet nadir, median (range), 10^9/L	8 (2-15)	6.5 (0-22)
Red blood cell transfusion, median (range), *n*	2 (0-16)	5 (0-17) #
Platelet transfusion, median (range), *n*	1 (1-16)	5 (1-18) #

n, number of patients or units of red blood cells/platelet transfusions

 # P < 0.05 (univariate)

*** In the multivariate analysis only stem cell transplantation was independently associated with a decreased bleeding incidence (P < 0.01).*

Discussion

This study was performed to explore the effect of the design of a rigorous bleeding observation and adjudication strategy in preparation of a multicentre platelet transfusion trial. As bleeding prevention is the primary focus of platelet transfusions, we compared the effect of two bleeding observation strategies with a clinical spontaneous reporting strategy. We observed an incidence of WHO grade ≥ 2 bleeding of 56% in our patient population and in 19% of the days with platelet counts < 80 x 10^9/L , which was in the range of other studies applying a rigorous bleeding assessment.[23,27]

Comparison with a recent previous study (HOVON 82) using a "passive" reporting of bleeding shows that the main difference in bleeding incidence is explained by the difference in mucocutaneous bleeding.[5] Many formal grade 2 mucocutaneous bleeds are apparently not perceived by clinicians as relevant bleeds and this seems to explain the high variation in the reporting of grade ≥ 2 bleeding.

Close observation thus results in higher WHO grade ≥ 2 mucocutaneous bleeding incidence. The relevance of skin bleeding in a daily observation and scoring system requires special consideration. Although the presence of a grade ≥ 2 bleeding of the skin might be relevant, it seems less appropriate to include every day a skin bleeding is visible as a 'bleeding day' in the scoring system. Bruising of the skin takes several days to weeks to disappear and counting all those days forms a distorted picture of the bleeding

tendency. As shown in Figure 3, excluding successive days with stable haematomas affects only the percentage but does not affect the course of the line. There was no significant difference in the percentage of days with grade ≥ 2 bleeding when platelet counts were 0-9 x 10^9/L or 10-19 x 10^9/L or 20-29 x 10^9/L, although the number of days may be too small to identify a trend in patients with the deepest thrombocytopenia. Even with platelet counts above the transfusion trigger a considerable percentage of days remained to be reported on which patients suffer from grade ≥ 2 bleeding in agreement with the platelet dose trial reported by Slichter *et al*., clearly indicating the existence of additional bleeding risk factors.[27]

The doubt on the clinical relevance of reporting of grade 2 bleeding for platelet transfusion studies has been recognized since a decade.[16] Recently, in a commentary Heddle and colleagues discuss the use of grade 2 bleeding in transfusion studies and conclude that this type of bleeding is likely to neither represent a valid surrogate for an effect of the intervention (bleeding occurs despite adequate prophylactic platelet transfusions), nor a valid composite outcome.[30] According to methodological criteria these bleeding reportings lack reproducibility and accuracy.[30]

Our pilot study underscores the importance of these concerns. We showed that passive reporting by clinicians assessing global bleeding results in considerable differences with independent assessment of specific anatomic sites as previously recognized by Koreth *et al*.[31] Moreover, we illustrate that slight differences in definitions of scoring assessment also have a large impact on the estimation of bleeding. Awaiting consensus on the nature of (surrogate) criteria to evaluate platelet transfusion therapy, we conclude –for the purpose of a multicentre randomised controlled trial- that independent assessment and registration of bleeding sites of sustained as well as new bleeds allowing differentiated adjudication, is the best option. This may contribute to the identification of an effect on any bleeding tendency, albeit not a surrogate for clinical outcome, but it might be informative that certain modifications of the platelet product have an adverse effect on the haemostatic capacity.[32]

At last, with respect to the issue of uniformity of bleeding scores among different haematological departments we investigated differences in interpretation and effort of bleeding score measurements by different responsible persons among hospitals. In the multivariate analyses there were no significant differences between centres. Rather, different patient populations as well as differences in treatment explain the apparent variation between academic and non-academic centres (Table 3). Indeed, patients with a newly diagnosed acute myeloid leukaemia often receive their remission-induction and consolidation therapy in a non-academic centre, while post remission transplant procedures were only performed in the academic setting. We identified patients with acute leukaemia on treatment with chemotherapy as being associated with the highest risk of bleeding (Table 3). Given this fact it might be sensible if not mandatory to stratify for different patient categories within the haemato-oncological population in future platelet transfusion trials.

To summarise, using a rigorous method for the detection and reporting of bleeding results in higher bleeding incidences than passive reporting. Precise reporting of all bleeding days on all sites provides the investigator with the opportunity to determine the relevance of certain bleeding events and to prospectively investigate the predictive value of for example persisting or new grade 2 skin bleeding on more serious bleeds. From a patient's perspective relevance is without a doubt different, but more important is the discrepancy of the "relevance" concept between the clinicians taking care of the patients and blood establishment interest aiming to improve platelet products. The application of a stringent bleeding observation policy in randomised controlled platelet product trials might eventually bring us further at one hand in the search for the optimal acceptable platelet product and at the other hand in choosing the most appropriate indications for platelet transfusions.

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