Platelets—to transfuse or not to transfuse

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In *The Lancet,* Hannes Wandt and colleagues[1] report findings from a large, randomised, multicentre trial comparing the traditional prophylactic platelet transfusion strategy with a therapeutic transfusion strategy in low-risk adult patients with haematological cancers. Patients undergoing either intensive chemotherapy for acute myeloid leukaemia or autologous stem-cell transplantation for haematological cancer received routine platelet transfusion when morning platelet counts were 10 000 per µl or lower (prophylactic use, n=197) or when clinically evident bleeding occurred (therapeutic use, n=199). Number of platelet transfusions was significantly reduced by 33·5% (95% CI 22·2–43·1) in the therapeutic group compared with the prophylactic group. In the therapeutic group, 28% (19–37) of the transplant patients had bleeding of grade 2 or higher versus 8% (3–14) in the prophylactic group. About 93% of bleeds in the therapeutic group were not severe (ie, of grade 2, with severe bleeds defined as WHO grade 3 or 4). The investigators noted no significant increase in severe bleeding with the therapeutic strategy in transplant patients; however, in those with acute myeloid leukaemia, a significant increase in clinically serious, severe bleeding was reported.

For patients with leukaemia, 51% (95% CI 43–59) of patients transfused therapeutically had bleeds of grade 2 or higher (7% had grade 4 bleeds) versus 24% (18–30) of those transfused prophylactically (2% had grade 4 bleeds). Two patients died from cerebral haemorrhages in the therapeutic group compared with none in the prophylactic group. Clinicians frequently ordered prophylactic platelet transfusions (22% of total transfusions) for patients in the therapeutic group, which suggests that they regarded these patients as having a high risk of bleeding. This finding is unsurprising because patients being treated for acute myeloid leukaemia are generally more acutely ill than are those undergoing autologous transplantation. These data support continuation of routine prophylactic transfusion in patients with acute myeloid leukaemia.

Findings from this and smaller studies show that risk of fatal haemorrhage in patients undergoing myeloablative chemotherapy for haematological diseases is very low (<1%), as is the risk of severe, disabling bleeds (<1%). However, bleeding is an event that is deeply distressing for patients, families, and their physicians, and often needs interventions that have risks and discomforts of their own—eg, nasal packing or assessments of gastrointestinal bleeding. Thus, if platelet transfusions were largely benign, they could be given prophylactically, before any bleeding occurs. Unfortunately, such transfusions are associated with many serious complications.[2] Some morbid events caused by transfusion are fever; rigors; platelet transfusion refractoriness; acute lung injury; cardiac failure due to volume overload; haemolysis when platelets contain ABO-incompatible plasma; bacterial contamination; and, rarely, viral transmission. Other complications have been proposed and causality is controversial, such as increased multiorgan failure and mortality in surgical patients,[3] increased bleeding after ABO mismatched transfusion,[4] increased mortality due to transfusion immunomodulation and early tumour recurrence,[5] and increased thrombosis.[6]

Platelets are often in short supply because they can only be stored for 5–7 days. Apheresis platelets—the most widely used product in the USA and commonly used in Europe—are more expensive to collect and process and are a greater risk and inconvenience to the donor than is whole-blood platelet production as a by-product of red-cell collection. There are clinical, donor safety, and economic reasons for minimising use of platelet transfusions, even as our understanding of platelet transfusion biology is growing.

The concepts underlying platelet biology have been revolutionised in the past 15 years. The platelet is now

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recognised as a cell that not only has haemostatic function, but is also involved in host defence, inflammation, and immunity.[7,8] Transfused stored platelets release many biologically active mediators, such as VEGF, soluble CD40 ligand, and interleukin 8. Platelets and their released mediators are clearly associated with alterations in the recipient's immune, haemostatic, and vascular functions.[9] Many platelet-derived molecules have proangiogenic and antiapoptotic properties that could be relevant and deleterious in patients with malignant disease or impaired host defences against infection.[10] Understanding of the balance between benefit and risk of platelet transfusions is evolving. The emerging hypothesis, with preliminary supportive clinical and laboratory data, is that transfused platelets might be promoters of arterial and venous thrombosis,[6] tumour growth, and metastasis.[11] These possibilities provide additional reasons to favour a restrictive policy for platelet transfusion in view of the moderate benefits of transfusion shown in autologous transplant patients.[1]

For now, clinical judgment as to which patients are at high risk for life-threatening or disabling bleeding will continue to have a key role in who receives platelet transfusions, regardless of the precise platelet count. Platelet count is less crucial in deciding whether transfusion is warranted than is a history of bleeding after injury or invasive procedures, the presence of widespread petechia or purpura, and the condition of the skin and mucous membranes of the mouth as indicators of the degree of haemostatic impairment.

One puzzling aspect of this trial[1] and PLADO, a randomised trial of platelet dose,[12] is the great divergence in rate of bleeding. In PLADO, 890 (70%) of 1272 patients receiving three different doses of prophylactic platelet transfusions had bleeding compared with only 19% (65 bleeds in 194 patients undergoing 343 treatment cycles) in the prophylactic group in Wandt and colleagues' study. In the *Lancet* study, even with no prophylactic platelet transfusions, the bleeding rate was only 42% (95% CI 36–48), perhaps because of interobserver variability or different approaches to how bleeds were classified. However, a probable contributing factor for bleeding in transfused patients could be that repeated prophylactic transfusions of ABO-mismatched platelets, a common practice, might impair haemostasis. Both clinical and laboratory evidence suggest this possibility.[2,4] A randomised trial to compare transfusions that are only ABO identical with standard practice would address this question.

A controversial subject not addressed by Wandt and colleagues is whether patients with thrombocytopenia who are going to have invasive procedures (eg, placement of intravascular access catheters, liver biopsies, or lumbar puncture) need prophylactic platelet transfusions, and, if so, at what level of thrombocytopenia. No data from randomised trials are available, but observational studies show that patients without evidence of poor haemostatic or platelet function by history and physical examination can tolerate most invasive procedures at platelet counts of 10 000–25 000 per μl or greater.[13]

The main lessons from this important study[1] are that prophylactic platelet transfusion can be much less aggressive than at present, and history and clinical signs and symptoms should drive decisions about platelet transfusion more than any arbitrary platelet-count threshold. Should therapeutic platelet transfusion become the standard of care, particularly for patients undergoing routine autologous stem-cell transplantation, and perhaps low-risk patients with acute myeloid leukaemia? Wandt and colleagues' and previous findings support the advancement of practice at centres where patients are frequently and carefully monitored by nursing staff for clinical evidence of early bleeding by examination of skin and mucous membranes and questioning about new symptoms. For decades, haematologists have relied on platelet transfusions to protect patients from bleeding, and the decision to implement this approach will be dependent on the judgment of clinicians at each hospital, and development of personal experience with a parsimonious approach to platelet transfusion.

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Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study

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Summary

Background **Routine prophylactic platelet transfusion is the standard of care for patients with severe thrombocytopenia. We assessed the effect of a new strategy of therapeutic platelet transfusion on the number of transfusions and safety in patients with hypoproliferative thrombocytopenia.**

Methods **We did a multicentre, open-label, randomised parallel-group trial at eight haematology centres in Germany. Patients aged 16–80 years, who were undergoing intensive chemotherapy for acute myeloid leukaemia or autologous haemopoietic stem-cell transplantation for haematological cancers, were randomly assigned via a computer-generated randomisation sequence to receive either platelet transfusion when bleeding occurred (therapeutic strategy) or when morning platelet counts were 10×10^9 per L or lower (prophylactic strategy). Investigators undertaking interventions were not masked to group assignment. The primary endpoint was the number of platelet transfusions. Analysis was by intention to treat. This trial is registered, NCT00521664.**

Findings **197 patients were assigned the prophylactic strategy and 199 the therapeutic strategy. Of 391 patients analysed, the therapeutic strategy reduced the mean number of platelet transfusions by 33·5% (95% CI 22·2–43·1; p<0·0001) in all patients (2·44 [2·22–2·67] in prophylactic group *vs* 1·63 [1·42–1·83] in therapeutic group), 31·6% (18·6–42·6; p<0·0001) in those with acute myeloid leukaemia (2·68 [2·35–3·01] *vs* 1·83 [1·58–2·10]), and 34·2% (6·6–53·7; p=0·0193) in those who had had autologous transplantation (1·80 [1·45–2·15] *vs* 1·18 [0·82–1·55]. We noted no increased risk of major haemorrhage in patients who had undergone autologous transplantation. In those with acute myeloid leukaemia, risk of non-fatal grade 4 (mostly CNS) bleeding was increased. We recorded 15 cases of non-fatal haemorrhage: four retinal in each transfusion group, and one vaginal and six cerebral in the therapeutic group. 12 patients died in the study: two from fatal cerebral haemorrhages in the therapeutic group, and ten (five in each treatment group) unrelated to major bleeding.**

Interpretation **The therapeutic strategy could become a new standard of care after autologous stem-cell transplantation; however, prophylactic platelet transfusion should remain the standard for patients with acute myeloid leukaemia. The new strategy should be used by some haematology centres only if the staff are well educated and experienced in the new approach and can react in a timely way to first signs of CNS bleeding.**

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Introduction

In patients with hypoproliferative thrombocytopenia, prophylactic platelet transfusions at a morning platelet trigger of 10×10^9 per L or lower are regarded as the standard.[1,2] However, whether such transfusions are necessary in patients who are clinically stable with no bleeding, or whether a therapeutic transfusion strategy could be sufficient and safe, has long been debated.[2–5] 30 years ago, a few small studies[6–8] showed favourable results for the therapeutic strategy, but these results cannot be applied to clinical practice now because the chemotherapy dose-intensity, and supportive care have changed greatly. Furthermore, quality of the studies was too low and the number of patients treated too small for any conclusion for routine care to be reached.

In a retrospective review[9] of almost 3000 adult patients with thrombocytopenia between 1998 and 1997, Friedmann and colleagues showed no relation between first morning platelet count or lowest platelet count of the day and risk of haemorrhage. Investigators of other studies[5,10] noted similar results. In two single-centre pilot studies,[11,12] we showed that a new strategy of therapeutic platelet transfusion was feasible, with no increase in risk of major bleeding and substantially reduced numbers of platelet transfusions compared with historical controls. Therefore, we assessed the effect of this new strategy compared with routine prophylactic platelet transfusion on the number of transfusions and safety in patients with hypoproliferative thrombocytopenia to investigate prospectively whether these results could be reproduced in a multicentre randomised study.

Methods

Study design and participants

We undertook a multicentre, open-label, randomised parallel-group trial at eight haematology centres in Germany between Feb 1, 2005, and May 31, 2010. Centres had to have a 24 h medical and transfusion service providing platelet transfusions within 4 h. Patients were allocated to two groups: group A for those with all subtypes of acute myeloid leukaemia (patients with promyelocytic leukaemia could be included only after reaching complete remission) and group B for those who had undergone autologous peripheral blood stem-cell transplantation. Eligible participants in group A were aged 16–80 years and receiving induction and consolidation chemotherapy of standard dose intensity. These patients could follow the protocol during induction and consolidation. Eligible participants in group B were aged 16–68 years and receiving the standard intensity of a high-dose chemotherapy regimen. For both groups we excluded patients who were refractory to platelet transfusions or who had previous major bleeding or plasmatic coagulopathy. Additionally, from group B, we excluded patients with pulmonary or cerebral lesions. All participants were hospital inpatients during the study.

The study was done according to the Declaration of Helsinki and approved by the institutional review boards and ethics committees of all participating centres. All patients provided written informed consent. The study was registered by the German authorities before the start, number PEI1224-01.

Randomisation and masking

We used a computer-generated randomisation sequence (SAS version 8.2) with minimisation to randomly assign patients, in a 1:1 ratio, to the therapeutic or prophylactic platelet transfusion protocol. Patients in groups A and B were randomised separately. Randomisation was stratified by centre, sex, and age, and was done at the study centre in Dresden (Germany) and communicated by fax. Investigators undertaking interventions were not masked to group assignment, but assessment of bleeding category according to modified WHO criteria was done in a blinded manner.

Procedures

Transfusion of packed red blood cells was given to maintain haemoglobin concentrations at 80 g/L or higher. For platelet transfusions, we accepted both single-donor apheresis platelets and pooled platelet concentrates. In Germany, apheresis units are standardised to contain $200–400\times10^9$ platelets; pooled concentrates in Germany produced from four to six buffy coats from random donors contain a similar amount (at least 200×10^9, range $240–360\times10^9$). All platelet products were provided leucoreduced to less than 1×10^6 leucocytes per unit. Random AB0-identical (non-HLA-typed) platelet transfusions were given when available. Fever by itself was not an indication for transfusion.

Platelet transfusion according to protocol started at day 1 after the end of induction chemotherapy, or at day 1 of each consolidation cycle in group A and at the day of stem-cell transplantation in group B. Patients in the group assigned the prophylactic platelet transfusion strategy with no signs of clinically relevant bleeding were transfused prophylactically with one platelet unit when the morning platelet count was 10×10^9 per L or lower. Those in a stable clinical state in the therapeutic group were given platelet transfusions only when clinically relevant bleeding occurred, defined as bleeds of grade 2 or higher according to modified WHO criteria (table 1).[13,14] If bleeding continued despite one platelet transfusion, further transfusions were given according to the decision of the treating physician. A prophylactic platelet transfusion at platelet counts of 10×10^9 per L or lower was recommended when sepsis or infections with an increased bleeding risk, such as invasive fungal infection or plasmatic coagulopathy (eg, disseminated intravascular coagulation or hyperfibrinolysis), were present.

Daily morning blood counts were done of EDTA (edetic acid)-anticoagulated blood with an automated haematology analyser. When plasmatic coagulopathy was suspected, tests for partial thromboplastin time, Quick's test, fibrinogen, antithrombin 3, and products of fibrin or fibrinogen degradation were done. We did not register retinal bleeding without visual impairment because fundoscopy was not routinely done. Petechiae and purpura of skin of any size were not regarded as clinically relevant and not registered. New headache and other signs of cerebral symptoms were regarded as first signs of CNS bleeding. These symptoms had to be investigated by CT in the therapeutic group.

A physician or experienced nurse examined patients twice a day for new signs of bleeding. The treating haematologist was responsible for documentation and reporting in each centre. Two investigators masked to treatment strategy transformed the bedside bleeding report into modified WHO categories (table 1). Consensus was needed in cases of disagreement. An independent central monitor of the coordination centre of clinical studies at the Technical University of Dresden, Germany, reviewed and checked all clinical report forms with patients' charts; clinical data were then entered into the central data bank. To decide whether the study should be continued, a data and safety monitoring board reviewed major bleeding events after treatment of the first 100 patients and after any lethal bleeding. A predefined stopping rule would be applied if more than two fatal events happened that were clearly attributable to the new strategy.

We regarded the study as completed when the platelet count was self-sustaining at more than 20×10^9 per L for 2 days or a maximum of 30 days, at hospital discharge, when treatment failure was diagnosed, at death, or at study withdrawal, which ever occurred first.

Statistical analysis

The primary endpoint was the number of platelet transfusions given during a standardised observation time of 14 days per patient. Major grade 4 bleeds could not be the primary endpoint because those events are too rare. The knowledge[11,12] that overall bleeding risk would be roughly doubled due to the stringent transfusion protocol was well accepted by patients. We standardised the observation time to fairly compare the number of platelet transfusions between the two transfusion groups despite a different duration of observation in patients who underwent differing numbers of treatment cycles. The primary analysis was a negative binomial regression with adjustment for the stratification variables age (<50 years and ≥50 years) and sex, and a random effect for repeated measures data of a patient's treatment cycles clustered in centres. We included all patients who underwent randomisation and whose data were available. We analysed patients by intention to treat. For the primary analysis, patients in groups A and B were first pooled then analysed separately.

The secondary endpoint of major interest was clinically relevant bleeding; other endpoints were numbers of red blood cell transfusions, days with platelet counts less than 20×10^9 per L, side-effects of transfusions, duration of hospital stay, and survival. Survival and time to onset of bleeding were estimated by the Kaplan-Meier method. The percentage of days in which patients had bleeds of grade 2 or higher, dependent on morning platelet count, was estimated with a repeated measures Poisson-regression model. Means and SDs were calculated for continuous variables. Comparisons were made with Student's *t* test and linear mixed models when appropriate. We report binary variables as counts and percentages with Agresti-Coull 95% CI. Comparisons were made with χ^2 tests, Cochrane-Mantel-Haenszel tests, or generalised linear mixed models when appropriate. The study was designed to have a minimum power of 90% to detect a clinically meaningful difference of 25% in the primary endpoint in the two subgroups separately for which 180 patients per group were needed. For all analyses we used SPSS (version 18.0.0). This trial is registered, NCT00521664.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 197 patients were assigned the prophylactic strategy and 199 the therapeutic strategy. Seven patients were excluded from analysis (figure 1); thus, we analysed 391 patients for 644 treatment cycles and 11825 days. Baseline characteristics of study patients were similar between the two transfusion groups (table 2).

The number of platelet transfusions was significantly lower in the therapeutic group than in the prophylactic group for all patients and for those with leukaemia or after stem-cell transplantation (table 3). Apheresis platelet units were used in 375 (96%) of 391 patients. In the therapeutic group, 186 (30%) of transfusions were given prophylactically, but according to the transfusion protocol. Clinically relevant bleeds judged by the treating physician, such as extended petechial bleeding or purpura of the skin, were the main reason for patients in the therapeutic group receiving transfusions not in accordance with the

	Grade 2	Grade 3	Grade 4
Oral and nasal	Any bleeding that could not be treated at the bedside by a nurse, or that was unpleasant for the patient	Any bleeding necessitating transfusion of red blood cells over routine needs within 24 h	Any bleeding necessitating transfusion of red blood cells and associated with severe haemodynamic instability necessitating intensive care; any fatal bleeding
Skin, soft tissue, musculoskeletal	Spontaneous haematoma in deep tissues, joint bleeding	Same as for oral and nasal	Same as for oral and nasal
Gastrointestinal	Haematochezia, melanotic stool (proven by faecal blood test), haematemesis	Same as for oral and nasal	Same as for oral and nasal
Genitourinary	Visible haematuria, abnormal vaginal bleeding more than spotting	Same as for oral and nasal	Same as for oral and nasal
Pulmonary	Haemoptysis and bloody sputum with no nasal or oropharyngeal bleeding	Same as for oral and nasal	Same as for oral and nasal
Invasive sites	Bleeding at venepuncture sites, intravenous lines	Same as for oral and nasal	Same as for oral and nasal
Retinal	..	Routine fundoscopy without visual impairment was not done	Bleeding with visual impairment proven by fundoscopy
CNS	..	..	CNS symptoms and sudden headache showing CNS bleeding on CT, any fatal CNS bleeding
Other bleeding	As described in the clinical report form	Any bleeding necessitating transfusion of red blood cells over routine needs within 24 h	Any bleeding necessitating transfusion of red blood cells and associated with severe haemodynamic instability needing intensive care; any fatal bleeding

Table 1: **Modified WHO bleeding scale**

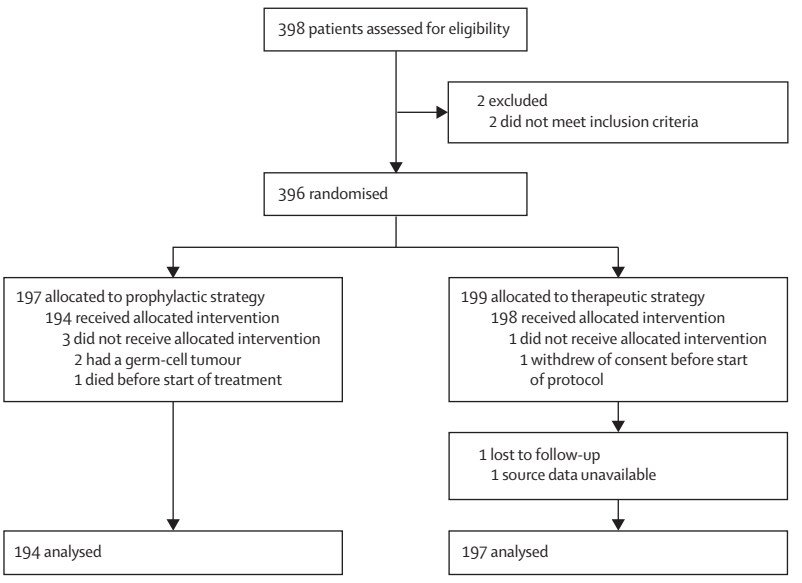

Figure 1: **Trial profile**

protocol (n=140; [22%]). In the prophylactic group, routine prophylactic platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than 10×10^9 per L.

See Online for appendix

The risk of bleeding of grade 2 or higher was greater in the therapeutic group than in the prophylactic group for all patients, and for those with leukaemia and those who had had autologous transplantation (table 3). Overall, 26% (95% CI 20–33) of bleeds in the therapeutic group and 7% (3–12) in the prophylactic group occurred on more than 1 day. Time to onset of first bleeding of grade 2 or higher was similar in both treatment groups, as were days on which first bleeds occurred (figure 2). The ratio of days of bleeding as a measure of the relative bleeding risk between groups was 0·43 for all different platelet counts. An interaction analysis showed that the effect of low platelet counts on bleeding risk did not differ between the strategies (figure 3). We registered only grade 2 bleeds in 99 (93%) of all haemorrhages in the therapeutic group.

In the group of patients who had received autologous stem-cell transplantation, grade 3 bleeds were rare in both strategy groups; we noted no grade 4 bleeding (table 3). In patients with leukaemia the bleeding risk was significantly higher ($p<0\cdot0001$) than in the transplant group (37% [95% CI 32–43%] *vs* 18% [13–24]). In patients with leukaemia, we noted significantly more grade 4 bleeds in the therapeutic group than in the prophylactic group (table 3). All but two of these bleeds could be controlled by timely platelet transfusion or local intervention at the bleeding site. 15 patients had non-fatal haemorrhages: one patient in the therapeutic group had a major vaginal bleed due to myomas at a platelet count of 44×10^9 per L, four patients in each treatment group had retinal bleeds with visual impairment, and six in the therapeutic group had minor cerebral bleeds documented by CT after new-onset of headache (appendix). All 15 non-fatal haemorrhages had no long-term consequences for the patients.

At time of haemorrhage, eight patients had platelet counts above 10×10^9 per L and seven had counts below this value. However, we registered two additional fatal cerebral bleeds in the therapeutic group: one at a

	All patients (n=391)		Acute myeloid leukaemia (n=190)		Autologous transplantation (n=201)	
	Prophylactic group (n=194)	Therapeutic group (n=197)	Prophylactic group (n=96)	Therapeutic group (n=94)	Prophylactic group (n=98)	Therapeutic group (n=103)
Median age (years; range)	55·5 (46–63)	55·0 (46–62)	54·0 (44–65)	54·0 (45–64)	56·5 (48·5–62)	55·0 (47–61)
Sex						
Male	108 (56%)	108 (55%)	46 (48%)	46 (49%)	62 (63%)	62 (60%)
Female	86 (44%)	89 (45%)	50 (52%)	48 (51%)	36 (37%)	41 (40%)
Primary diagnosis						
Acute leukaemia	..	..	96 (100%)	94 (100%)	6 (6%)	7 (7%)
Lymphoma	..	..	..	..	29 (30%)	31 (30%)
Multiple myeloma	..	..	..	..	63 (64%)	65 (63%)
Laboratory values at study entry						
Platelet count ($\times10^9$/L)	66·5 (18·75–146·0)	64·0 (21·0–137·0)	19·5 (10·0–40·0)	21·5 (11·75–52·25)	135·0 (84·75–181·75)	126·0 (65·0–180·25)
Haemoglobin (g/L)	95 (87–106)	94·5 (85–106)	88 (83–95)	88 (82–96)	105 (96–113)	102 (92–110)
Leucocyte count ($\times10^9$/L)	1·5 (0·60–3·83)	1·5 (0·50–3·21)	0·73(0·40–1·30)	0·77 (0·40–1·50)	3·15 (1·78–4·83)	2·80 (1·40–5·02)
Number of treatment courses						
Autologous stem-cell transplantation	..	..	..	..	98	103
Induction chemotherapy	90	85	..	..	..	..
Consolidation chemotherapy	..	..	155	113	..	..

Data are n (%) and median (IQR), unless otherwise indicated.

Table 2: **Characteristics of study patients according to treatment and transfusion group**

	All patients (n=391)			Acute myeloid leukaemia (n=190)			Autologous transplantation (n=201)		
	Prophylactic group (n=194)*	Therapeutic group (n=197)†	Reduction (%)	Prophylactic group (n=96)‡	Therapeutic group (n=94)§	Reduction (%)	Prophylactic group (n=98)¶	Therapeutic group (n=103)‖	Reduction (%)
Primary endpoint									
Platelet transfusions per patient	2·44 (2·22–2·67)	1·63 (1·42–1·83)	..	2·68 (2·35–3·01)	1·83 (1·58–2·10)	..	1·80 (1·45–2·15)	1·18 (0·82–1·55)	..
Therapeutic *vs* prophylactic (95% CI; p value)	..	..	33·5% (22·2–43·1; p<0·0001)	..	..	31·6% (18·6–42·6; p<0·0001	..	..	34·2% (6·6–53·7; p=0·0193)
Secondary endpoints									
Bleeding**									
Grade 2 or higher	65 (19%; 14–23)	127 (42%; 36–48)	<0·0001	57 (24%; 18–30)	98 (51%; 43–59)	<0·0001	8 (8%; 3–14)	29 (28%; 19–37)	0·0005
Grade 3	3 (1%; 0–2)	7 (2%; 0–4)	0·21	3 (1%; 0–4)	6 (3%; 1–7)	0·32	0 (0%; 0–5)	1 (1%; 0–6)	1
Grade 4	4 (1%; 0–2)	14 (5%; 2–7)	0·0159	4 (2%; 0–3)	13 (7%; 3–11)	0·0095	None	None	..
Red blood cell transfusions per patient	2·85 (2·58–3·12)	3·14 (2·81–3·46)	0·18	3·66 (3·29–4·04)	3·90 (3·45–4·35)	0·41	1·61 (1·24–1·99)	2·15 (1·72–2·58)	0·06
Days with thrombocytopenia (<20×10⁹/L)	9·48 (5·81)	10·17 (6·51)	0·38	12·68 (5·13)	12·68 (6·55)	0·98	6·36 (4·62)	7·88 (6·00)	0·0327
Days in hospital	17 (16–19)	18 (17–18)	0·69	19 (18–20)	20 (19–21)	0·16	14 (13–14)	14 (14–15)	0·15
Side-effects of transfusions	25 (13%; 8·9–18·4)	27 (14%; 9·6–19·3)	0·88	22 (23%; 15·6–32·4)	21 (22%; 15·1–31·9)	1	3 (3%; 1·0–9·1)	6 (6%; 2·5–12·5)	0·50
Overall survival from study entry (months, 95% CI)††	16·1 (10·4–21·8)	11·9 (5·73–18·1)	0·84	8·68 (6·47–10·9)	5·88 (3·05–8·70)	0·66	34·0 (15·9–52·0)	35·9 (14·4–57·4)	0·59

Data are mean (95% CI), n (%; 95% CI), or mean (SD), unless otherwise indicated. *343 treatment cycles. †301 treatment cycles. ‡245 treatment cycles. §198 treatment cycles. ¶98 treatment cycles. ‖103 treatment cycles. **Per treatment cycle, by WHO criteria. ††75% quartile, by log-rank test.

Table 3: **Primary and secondary endpoints by treatment and transfusion group**

platelet count at slightly greater than 10×10⁹ per L and one at a platelet count below the cut off. Both bleeds started with headache. The patient with a platelet count of less than 10×10⁹ per L had an invasive pulmonary fungal infection. She did not receive the prophylactic platelet transfusion recommended by the protocol. After sudden onset of headache, CT showed a mass bleed. The patient died 2 h later despite being given platelet transfusions. Autopsy was refused; therefore, we cannot exclude a cerebral fungal lesion as a reason for the mass bleed. The patient with the platelet count above 10×10⁹ per L developed headache 1 day before the fatal event, but CT was done only when complaints increased. The patient's state deteriorated quickly during CT, which showed supratentorial and infratentorial cerebral bleeds with compression of the fourth ventricle. Immediate platelet transfusions increased the platelet count to 122×10⁹ per L, but despite emergency operation, the patient died 2 days later. No specific reason for the bleeding event apart from thrombocytopenia could be identified by operation or autopsy. The data monitoring board recommended an alert letter be sent to ensure that all investigators adhered precisely to the protocol and gave a platelet transfusion to all patients with sudden new headache and a morning platelet count of less than 20×10⁹ per L. We recorded ten further deaths (five in each transfusion group) unrelated to major bleeding. Overall survival of

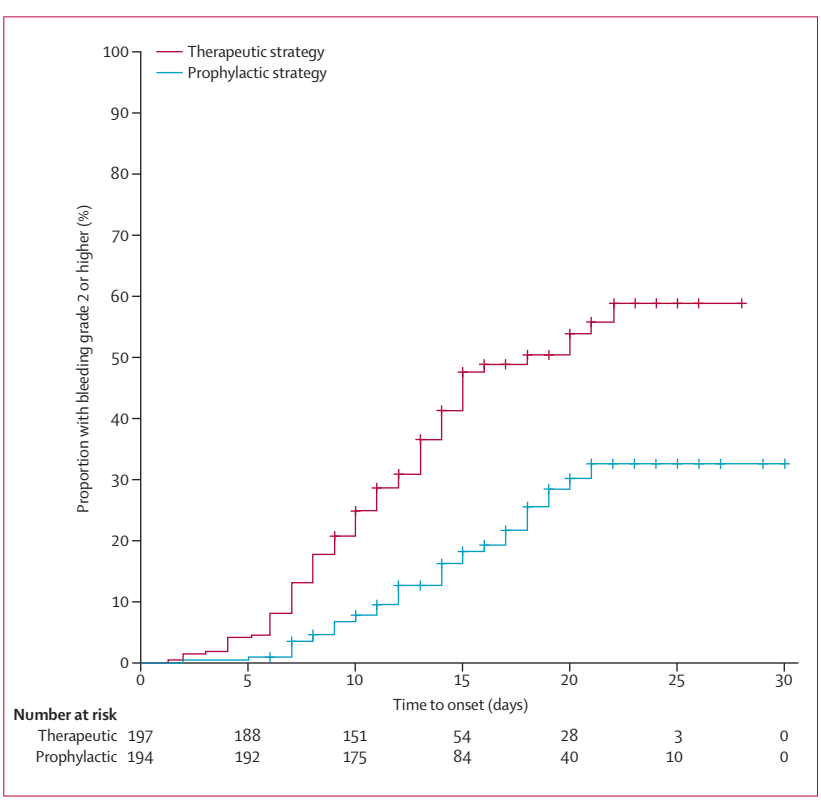

Figure 2: **Time to onset of bleeding of grade 2 or higher in all patients**

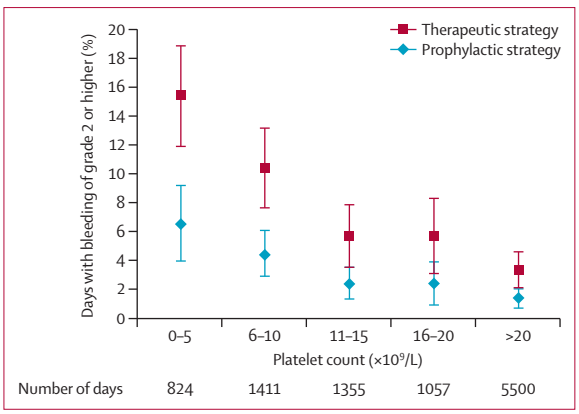

Figure 3: **Days with bleeding of grade 2 or higher in both transfusion groups by categories of morning platelet count**
Error bars show 95% CI. Data are based on the 10 147 days during the study period in which patients had a morning platelet count, and on information about bleeding of grade 2 or higher.

patients in the therapeutic and prophylactic groups was similar for all patients and for those with leukaemia or after stem-cell transplantation (table 3).

For all patients, the number of red blood cell transfusions in the therapeutic and prophylactic groups, the duration of thrombocytopenia less than 20×10⁹ per L, days in hospital per treatment cycle, and number of side-effects did not differ significantly (table 3).

Discussion

This study is the first large randomised multicentre trial comparing the traditional prophylactic platelet transfusion strategy with a therapeutic transfusion strategy in clinically stable adult patients with haematological cancers (panel).[5] Our findings show that the number of platelet transfusions was significantly lower, by roughly a third, in the therapeutic group than in the prophylactic group. However, this clinically meaningful difference must be weighed against the increased bleeding risk. Platelet transfusions have minor and major side-effects. Rare but potentially lethal complications are transfusion-associated acute lung injury and bacterial contamination.[17,18] Although platelet transfusions are undoubtedly beneficial, debate continues about when and how many platelets should be given to maximise transfusion benefits and minimise the risks.[5,14,15] A reduction in the number of platelet transfusions is very important because maintenance of an adequate platelet inventory is a continuing challenge for most blood centres worldwide.

Slichter and colleagues[14] showed that the platelet dose per transfusion can be significantly and safely reduced for routine prophylactic transfusions. Our results suggest that platelet use could be further reduced in patients with hypoproliferative thrombocytopenia. Compliance with the transfusion protocol was better in the prophylactic group than in the therapeutic group, but was well within the range reported in other studies.[14,19] Our results show that the frequency of grade 2 or higher bleeding was roughly two times higher in the therapeutic group than in the prophylactic group because platelet transfusion was used to treat bleeding only once it had occurred. However, this increase was well tolerated by the patients because about 93% of bleeds were only grade 2. Almost all bleeds could be controlled by timely platelet transfusion.

The overall probability of bleeding and especially the frequency of major bleeding were within the same range as those reported previously.[14,17,20,21] Despite the higher absolute bleeding risk in patients in the therapeutic group, the relation to the prophylactic group remained stable, even when decreasing platelet counts are considered. In other words, despite an absolute increase in bleeding days in both groups when platelets fall below 10×10⁹ per L, the relation of bleeding risk remained the same and did not increase further.

The bleeding risk was higher in patients with leukaemia than in those who had undergone autologous stem-cell transplantation, as shown in other studies.[13] However, by contrast with our previous experience of patients with acute myeloid leukemia,[11] we noted a significant increase in grade 4 haemorrhages in the therapeutic group. This increase could be explained by the multicentric nature of our study, and perhaps by the more stringent transfusion protocol—ie, we did not regard major petechial bleeding or purpura as a regular trigger for a therapeutic transfusion as we did in our previous protocol.[11,12] However, of 13 grade 4 bleeds in the therapeutic group, seven occurred with platelet counts between 56×10⁹ per L and 11×10⁹ per L. As such, about half of those bleeds could have happened equally in the prophylactic group, and they probably occurred by chance in the therapeutic group.

Grade 4 bleeds, as defined by the commonly used criteria, range widely in severity from retinal to fatal events.[14] 11 of 13 grade 4 bleeds in the therapeutic group were controlled by platelet transfusions with no sequelae. All spontaneous cerebral bleeds in this group were preceded by new headache that prompted CT. We did not regularly do CT in the prophylactic group, which might explain why we recorded no minor cerebral bleeds. The two fatal cerebral haemorrhages in the therapeutic group are notable. These serious bleeds might not have been prevented by a prophylactic approach. Both fatal bleeds occurred in parallel with protocol violations (eg, fungal infection in one patient and new headache at 11×10⁹ per L platelets in the other). This finding emphasises that transfusion decision should be based on the individual clinical situation of a patient, rather than on transfusion trigger. Lethal bleeding in 1–2% of patients has been reported previously, with no clear association between the platelet count and the occurrence of major life-threatening bleeding.[5,9,10,20,21]

Our analysis had some limitations. The study was not powered to prove a significant difference in grade 4

Panel: Research in context

Systematic review

We hand-searched PubMed and our own scientific literature data bank from Jan 1, 2000, to Dec 31, 2011, with search terms "therapeutic and prophylactic platelet transfusion", "randomized study", and "review". We identified three reviews[1,5,15] and one meta-analysis[2] published in the past 12 years about the long-lasting debate over the clinical use of a prophylactic versus a therapeutic platelet transfusion strategy. However, clinical studies of the therapeutic strategy are rare. Our search identified only three very old and small studies[6–8] of this topic, in addition to our two pilot studies[11,12] with the therapeutic platelet transfusion strategy in patients after autologous stem-cell transplantation and in those with acute myeloid leukaemia after intensive chemotherapy. In 1999, one observational study[16] showed favourable results of a mainly therapeutic platelet transfusion approach in patients with chronic thrombocytopenia due to severe aplastic anaemia.

Interpretation

This study is the first large randomised multicentre study comparing the traditional prophylactic platelet transfusion strategy with a therapeutic strategy in clinically stable adult patients with haematological cancers. Although the number of platelet transfusions was reduced significantly with the therapeutic transfusion strategy, and prophylactic transfusions were not absolutely necessary in patients with thrombocytopenia after intensive chemotherapy, the new strategy should not be regarded as a general standard because of the increase in bleeds. The therapeutic strategy is feasible in patients after autologous stem-cell transplantation, but cannot be easily transferred to those with acute myeloid leukaemia for whom special attention to the increased risk of CNS bleeding is needed.

events and even less so for lethal events. For such a design, we would have needed to enrol about 2000 patients; however, this limitation is common to all published platelet trigger studies, even in those cited most frequently.[14,19] This issue can be resolved only with a meta-analysis (as done by the Cochrane Institute[2] for the prophylactic strategy) of comparable studies, such as the Trial of Prophylactic Platelet Study, which is underway in the UK and Australia.[15] The compliance rate of 78% in the therapeutic group is a second limitation. We cannot rule out that the bleeding rate would still be increased with a protocol compliance of 100%. On the basis of our findings, we recommend a therapeutic platelet transfusion in case of major petechial skin bleeding or purpura, as stated in our pilot studies.[11,12]

The new therapeutic strategy could become the standard of care for clinically stable patients who have had autologous peripheral blood stem-cell transplantation. In patients with acute myeloid leukaemia who already have an increased risk of major bleeding, routine prophylactic platelet transfusion at a trigger of 10×10^9 per L or less should remain the standard. Haematology centres that want to use our therapeutic strategy in patients with leukaemia should have well educated and experienced staff who are familiar with the strategy and can react timely to first signs of CNS bleeding. Furthermore, we recommend platelet transfusions in cases of major skin bleeding. Our findings provide evidence for a more restrictive platelet transfusion strategy than is presently used worldwide in non-bleeding and clinically stable patients despite a morning platelet count of less than 10×10^9 per L when platelet transfusions are not easily available on the same day.

Contributors

HW, KS-E, KW, and GE designed the study. HW, KS-E, KW, MW, UM, MS, MKr, RS, GD, and CJ wrote the paper. MKr did the statistical analysis. HW, KS-E, KW, BP, MW, MT, UM, AH, MS, MKa, LL, RS, RC, GD, AK, MH, RH, CJ, and GE gathered and analysed the data. All authors reviewed and edited the paper and have seen and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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