# Bleeding in hemato-oncology patients: beyond the platelet paradigm

Cornelissen, L.L.

# Chapter 1

## General introduction and outline of the thesis

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*'…Admitted to the hematology ward last night, was Ms. X, a thirty-year-old woman, presenting with petechia, hematomas, and fever, which are caused by a newly diagnosed acute myeloid leukemia. She received antibiotics and needs to be prepared for intensive chemotherapy. This morning, a blood cell count showed a platelet count of $30x10^9$/L and a Hb of 4.5mmol/L. Last night, transfusion thresholds have not been discussed yet, they need to be decided…'*
*'… Hereby we write to inform you about Mr. Y, a 46-year-old patient, who was admitted to our hospital for an allogeneic stem cell transplantation with myeloablative conditioning, to treat his acute lymphatic leukemia. The stem cell transplantation was complicated by prolonged neutropenia and fever, for which broad spectrum antibiotics were prescribed. Currently, there is an ongoing BK-virus associated hemorrhagic cystitis for which multiple transfusions, saline bladder irrigation, and pain medication have been given. Mr. Y was released home with a urinary tract catheter and has a follow up appointment at the urologist. For hemostatic support, which has been troublesome, follow up at the outpatient clinic is planned…'*
*'…I would like to ask a question about Mr. Z. He is 72 years old and is admitted to our hematology ward to treat his relapsed follicular lymphoma. Two hours ago, his nose started oozing blood a bit, not that much, but it has been quite long now. It is bothering the patient. He already had a platelet transfusion today because he had a platelet count of $8x10^9$/L. My colleague said that two days ago, he did not respond that well to his platelet transfusion. Do I need to do something else right now…?'*

## Introduction

At the morning medical rounds, in discharge letters, in calls about admitted patients during the night shifts: bleeding is often encountered as a complication of hemato-oncological disease or treatment. Indeed, although these patients routinely receive prophylactic platelet transfusions, still bleeding is frequent. Many factors like patient characteristics, disease status, and treatment factors have been proposed to influence the occurrence of bleeding. In this introduction, the rationale behind the currently applied bleeding prevention strategy is described, as well as the evidence on which it is based.

**Prophylactic platelet transfusions in hemato-oncology patients**

To prevent clinically relevant bleeding, hemato-oncological patients who have a transient bone marrow failure receive prophylactic platelet transfusions during episodes of deep thrombocytopenia.

Already in the 1960's, it was clear that platelet transfusions reduced the number of severe bleedings. A study reporting causes of death in acute leukemia, including patients from 1954 to 1963, showed that the number of patients who had a bleeding when they died from acute leukemia declined from 67% to 37% when platelet transfusions became available to treat active bleeding. The number of bleedings that were registered to be the cause of death dropped from 20% to 14%.(1) Furthermore, small randomized trials showed the effect of prophylactic platelet transfusions,(2-4) which eventually lead to platelet prophylaxis (i.e. in the absence of bleeding) to become the standard of care in hemato-oncology patients since the nineteen seventies.(5) Based on larger studies, investigating platelet doses and platelet count triggers,(6, 7) transfusion guidelines advise to prescribe prophylactic platelet transfusions to patients with a transient, deep thrombocytopenia at a threshold of $10x10^9$/L.(8-12)

Despite the shown benefits of this prophylactic transfusion policy, bleeding still occurs. However, the incidence reported in different studies varies dramatically, from 19% to 89%.(13-21) This variability is at least partly due to the different subpopulations of hemato-oncology patients that were included in the studies, different monitoring methods to detect and register bleeding, different follow-up periods, and the different bleeding scores that were applied. Even between studies that use comparable bleeding scores, such as alterations of the World Health Organization (WHO) bleeding score,(22) incidences still vary. For WHO bleeding score with grades 2, 3, and 4 bleedings, incidences have been reported to range between 19% and 70%.(14, 16)

Besides the fact that clearly not all bleeding is prevented by the current prophylactic platelet transfusion strategy, there is also a strong indication that some patients have a very low risk of bleeding. In such patients, platelet transfusions are likely not useful and lead to unnecessary health care costs and labor, while being a potential cause of side effects.

Due to the prophylactic policy currently in practice, the hematology patients now consume approximately two-thirds of all platelet transfusions.(23) Of these, around 75% are described to be transfused prophylactically.(23, 24) In a country like the Netherlands, which produces approximately 52,000 units of platelets per year, it can be estimated that 35,000 will be transfused to hematology patients, and around 27,000 of those will be given prophylactically.(25) Consequently, because of the high transfusion rates, hemato-oncology patients are at high risk of being exposed to platelet mediated transfusion reactions, like transfusion mediated infections (occurring in approximately 0.001% of platelet transfusions), or allergic reactions (occurring in approximately 0.3% of platelet transfusions).(26, 27) Also, anti-HLA antibodies are frequently encountered in up to 43% of hemato-oncology patients. These antibodies can lead to platelet transfusion refractoriness, which has been described in 5-15% of patients who are on chronic platelet transfusion support.(28)

**Prophylactic platelet transfusions versus therapeutic platelet transfusions**

To better assess the amount of overtreatment by prophylactic platelet transfusion strategies, it is important to compare this with the situation in which platelet transfusions are only administered in case of active bleeding events; the so-called therapeutic strategy. Two randomized controlled trials (RCT's) compared these two strategies in adult hemato-oncology patients who were admitted for chemotherapy or stem cell transplantations.(13, 14) Both studies showed a benefit for the prophylactic platelet transfusion strategy to prevent combined WHO grades 2, 3, and 4 bleeding outcomes in 30 days. Stanworth et al. reported an incidence of WHO grades 2, 3, and 4 bleeding of 43% in patients in the prophylactic transfusion arm, versus 50% of these bleedings in the therapeutic-transfusions-only arm.(13) In this study, the reported incidence of serious bleedings (of WHO grade 3 and 4) was below 2%; with no discernable difference between the treatment groups. The observed benefit of prophylactic platelet transfusions was clear in patients receiving intensive chemotherapy or allogeneic stem cell transplantation (SCT). In contrast, patients who were admitted for autologous SCT hardly benefitted from prophylactic platelet transfusions.(29) As a result, and provided that close monitoring of bleeding is feasible, some guidelines now recommend a therapeutic transfusion strategy for patients undergoing autologous SCT. (9, 10)

The RCT of Wandt et al. showed that 19% of the patients with prophylactic platelet transfusions suffered from WHO grades 2, 3, and 4 bleeding, while with therapeutic transfusions this incidence increased to 42%.(14) In this study, a difference was also observed for WHO grade 3 and 4 bleedings. However, many grades 3 and 4 bleedings were intracerebral. Since the study used different diagnostic policies towards intracranial bleedings for the different randomization arms, this difference could be caused or aggravated by detection bias.

**Clinically relevant bleeding**

Currently, most studies use the WHO bleeding score, with grade 2, 3 and 4 bleedings as the primary outcome.(22) Over the years, several research groups have modified these grades, to reduce variation in assessment.(30) Important to realize in this respect, is that the majority of reported bleedings are WHO grade 2 bleedings. Not all of these are of direct importance for clinical care or for the patients' well-being. Other bleeding scores with more emphasis on the clinically relevance of bleeding are available (figure 1). The International Society on Thrombosis and Haemostasis (ISTH) bleeding scale, for example, distinguishes clinically relevant non-major and major bleedings from not-clinically-relevant bleeding.(31, 32) Likewise, the Bleeding Severity Measurement Scale (BSMS), which is especially designed for patients with thrombocytopenia induced by chemotherapy, separates bleeding which is clinically relevant (named clinically significant) from non-significant bleeding, i.e. that are expected not to have a real impact on the patient or the required intensity of patient care.(33) Prophylactic platelet transfusions should aim specifically at the prevention of bleeding that has a relevant impact on patients or patient care. Ideally, this strategy should therefore also be validated using only clinically relevant bleeding as the primary outcome. Unfortunately, due to the much higher number of patients that would be required in such a study, no RCT's have used this outcome yet.

**Hemato-oncology patients with a persistent severe thrombocytopenia**

While most research attention goes to those hemato-oncological patients who, due to the effects of acute disease or intensive chemotherapy, have the deepest cytopenias and associated morbidities, these conditions are usually transient. There is also a hemato-oncological population with chronic bone marrow failure and hence persistent severe thrombocytopenia. High intensity chemotherapy and other conditions that are associated with bleeding, like inflammation and infections, will be present less frequently in such patients. Thus, these factors can not readily be used to predict bleeding in this population. Whereas in the short term a lower bleeding risk is expected in this group, the chronic thrombocytopenia is eventually likely to induce a high cumulative incidence of bleeding. So far, there are no published RCT's investigating the effect of prophylactic platelet transfusions in this subpopulation with long-lasting thrombocytopenia. Moreover, even observationally registered incidences of bleeding are hardly described in the literature. Interestingly, an observational study in patients with myelodysplastic syndromes reported high cumulative incidences of overall and WHO grade 3 and 4 bleeding of respectively 83% and 14%, in a median time of 27 weeks.(34) In this study, prophylactic platelet transfusions, tranexamic acid, or both did not seem to lower the incidences of WHO grade 3 and 4 bleedings. This study however was small, with non-randomized treatments, making the results likely liable to confounding by indication.(34)

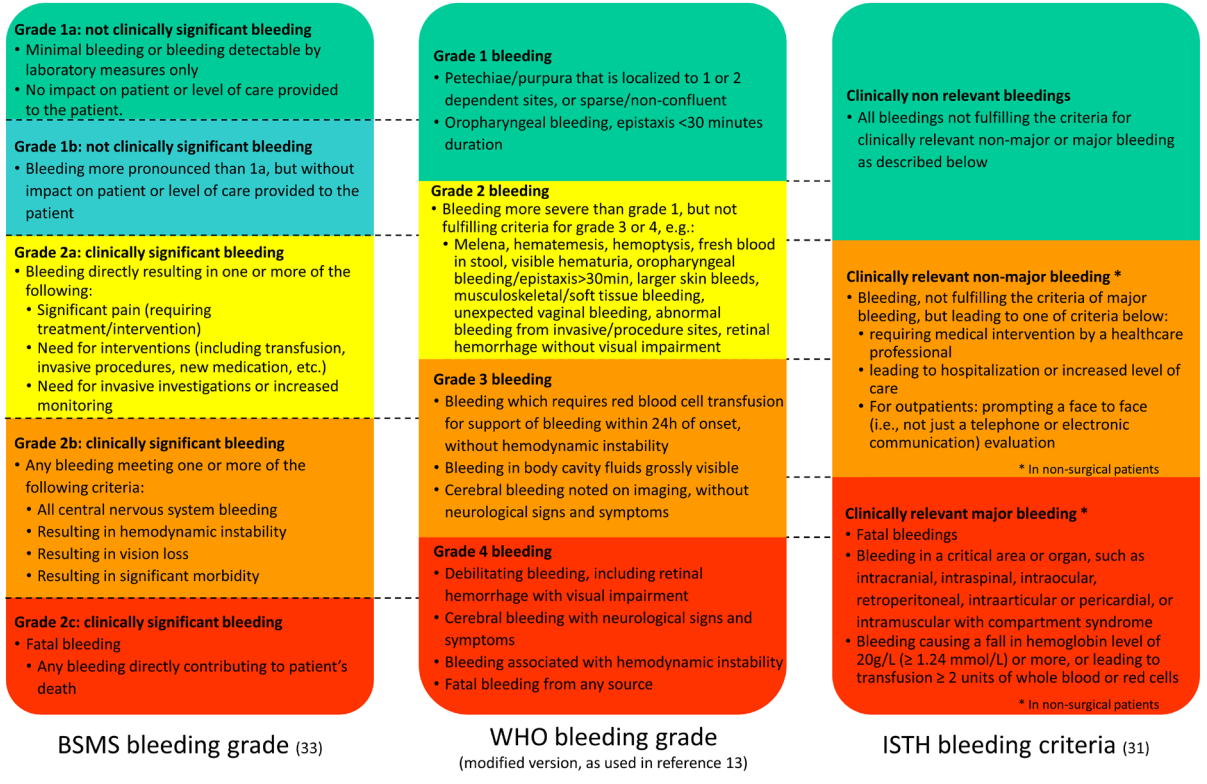


**Figure 1. Comparison of bleeding scores**
The WHO bleeding grade, which has been mostly used in research so far, does not provide a clear difference between clinically significant/relevant bleeding and non-significant/relevant bleedings, as do the BSMS and ISTH criteria. WHO grade 2 bleedings are only partly classified as clinically relevant, namely if there is a clear impact on the patient or medical care. The size of the boxes are not representative of the incidence of bleedings, but illustrate the overlap in BSMS and ISTH criteria with the WHO grading system. Abbreviations: BSMS = Bleeding Severity Measurement Scale, WHO = World Health Organisation, ISTH = International Society on Thrombosis and Haemostasis.

While some guidelines indicate that more liberal transfusion thresholds, or even a therapeutic platelet transfusion strategy, might be applied in these patients, evidence for such advice is insufficient. Overall, there is no consensus on the best strategy for bleeding prevention in patients with persistent severe thrombocytopenia. (9-12)

**Risk factors for bleeding**

In conclusion, there seems to be a general benefit of prophylactic platelet transfusions to prevent bleeding in transient severe thrombocytopenia. However, both even better bleeding prevention than currently achieved, and a reduction in unnecessary use of platelet transfusions clearly require the personalization of supportive transfusion strategies. Understanding of risk factors is indispensable to identify patients with a high, low, or virtually absent risk of bleeding and might enable adapting the platelet transfusion strategy accordingly.

So far, platelet counts are used to guide platelet transfusions. Platelet counts, however, correlate poorly with bleeding. Only at platelet counts of $5x10^9$/L or lower, a substantial increase in bleeding events is seen, where remarkably at counts from $6x10^9$/L to $80x10^9$/L bleeding frequencies remain more or less stable.(16, 35) Indeed, in trials that investigated platelet transfusion triggers, no benefit was observed in raising thresholds from $10x10^9$/L, to $20x10^9$/L, or $30x10^9$/L.(7) Moreover, increasing the platelet dose per transfusion also failed to lower the remaining bleeding incidence.(6) This suggests that, additionally to platelet count, other factors modulate the bleeding risk in hemato-oncology patients. Meanwhile, platelet transfusions are unable to overcome all mechanisms leading to bleeding.

Several clinical factors have been reported to be associated with an increased risk of bleeding in hemato-oncology patients, like sex (with a higher risk for women),(36) and diseases with a poor prognosis.(20) Furthermore, associations were shown between fever, infection, or sepsis and the occurrence of bleeding.(36-38) Results from animal studies also support the association between bleeding and infection which is more evident in case of thrombocytopenia.(39, 40) Furthermore, conditions known for their effect on hemostasis (like uremia or use of anticoagulants), are also associated with bleeding in hemato-oncological patients.(41, 42) Other conditions associated with bleeding, like usage of penicillin or medication against invasive mold infections, graft versus host disease, splenomegaly and bleeding in the preceding days are mechanistically less clear.(9) Moreover, the clinical relevance of most of these associations is uncertain because they are derived from (small) observational datasets or post-hoc analyses, or were absent in other datasets.

Notwithstanding the low level of evidence, some guidelines advise to consider increasing the platelet transfusion threshold in patients with additional risk factors. (9, 10) In clinical practice, the absence of high quality evidence often leads to heterogeneity

in the adherence to such guidelines and thus in the use of different thresholds.(43) As discussed, studies investigating different transfusion triggers, did not show a reduction in the number of bleedings with the use of a higher threshold.(7) However, in those studies patients with additional potential risk factors for bleeding were never studied separately. Therefore, it remains unclear if high-risk patients may benefit from the use of higher platelet triggers.

Invasive procedures like lumbar punctures or insertion of central venous catheters are evidently risk factors for bleeding. Yet, even for these procedures there is no strong evidence for the benefit of higher platelet transfusion thresholds.(44, 45) Still awaiting the results of an ongoing RCT study on this topic,(46) the Dutch 2019 transfusion guidelines, advises to prescribe prophylactic platelet transfusions at higher triggers in case of invasive procedures, as do other international guidelines.(8-12) Similarly, without strong evidence, but based on expert opinion, increased thresholds are also advised for patients with a transient thrombocytopenia who use therapeutic anticoagulation or platelet aggregation inhibitors, who cannot stop such medication.(8)

Overall, although there are many risk factors described that are likely to influence bleeding risk, the precise quantification of this increased risk is still lacking. Further, the effects of applying alternative bleeding preventive strategies, if such risk factors are present, are not well understood either.

**Biomarkers**

Clinical conditions that modulate the bleeding risk will only lead to bleeding if they negatively affect hemostasis. Therefore, next to platelet counts, additional biomarkers for hemostasis (e.g. biomarkers that reflect platelet function, coagulation, fibrinolysis or endothelial function) can also be of importance to predict the bleeding risk.

In this respect, a decreased platelet function or activation state has been suggested to have predictive value.(18, 47, 48) A reduced p-selectin expression and a diminished (*ex vivo*) platelet response to standard platelet stimulation have both been observed in patients who developed bleeding. These results, however, could equally well imply that either circulating platelets have diminished functionality, or that they have a reduced 're-activation' in vitro because of high functional *in vivo* platelet activation.

Also, some endothelial markers have been described to be associated with bleeding. For example, in leukemia patients an association between bleeding and high values of syndecan-1, which as part of the glycocalyx is indicative of endothelial damage, is described.(49) Likewise, urine albumin excretion, known to be a biomarker of renal vascular wall damage, was found to be associated with bleeding in hemato-oncology patients.(50)

Associations between coagulation-markers and coagulation assays and bleeding are not consistent.(35, 51) However, studies investigating these (and other) potentially

important biomarkers are often small, and a direct comparison between studies is complicated by sampling at different stages of treatment of the patient. Therefore, no biomarkers have consistently been established to predict the bleeding risk in hemato-oncology patients.

**Alternatives for prophylactic platelet transfusions**

To further reduce the amount of bleeding events in hemato-oncology patients, alternatives for or additions to prophylactic platelet transfusions such as TPO-mimetics or antifibrinolytic agents, like tranexamic acid, have been studied.(52) However, again, studies are insufficient to conclude if the bleeding incidence can be relevantly influenced by these strategies.(53, 54) Recently, a trial was completed investigating tranexamic acid, as an adjunctive anti-bleeding therapy. Although the complete trial results are awaited, first results did not report a benefit in intensively treated hemato-oncological patients.(55) Autologous SCT patients have been reported to have less benefit of prophylactic platelet transfusions.(29) An ongoing RCT in this patient group will determine if tranexamic acid can be used as an alternative strategy to prevent bleeding, instead of platelet transfusions. (56)

## Aim and outline of the thesis

With the current prophylactic platelet transfusions, bleeding is still a commonly occurring problem in hemato-oncology patients, and information on risk factors that can guide prediction of bleeding is insufficient. The aim of this thesis is to provide more insight into bleeding in hemato-oncology patients, by investigating risk factors that are needed for prediction, and by describing current clinical practice of preventive strategies.

First, we aimed to investigate the current clinical practice of bleeding prevention. For patients who are intensively treated, and for whom the deep thrombocytopenia is expected to be transient, guidelines provide clear advises for general transfusion thresholds, and sometimes suggestions for patients with (suspected) additional bleeding risks. However, the absence of clear evidence of altered thresholds in patients with additional risk factors leads to variability in care. While this variability was reported before for patients with deep, transient thrombocytopenia, for patients who suffer from persistent deep thrombocytopenia, due to chronic bone marrow failure, optimal bleeding prevention has not been investigated, leading to a lack of clear advice in guidelines. In **chapter 2**, we report on a Dutch survey which assessed both usage of prophylactic platelet transfusions and tranexamic acid to prevent bleeding in hematological outpatients who suffer from persistent severe thrombocytopenia. Besides the current clinical practice, we describe which clinical conditions guide clinical decision

making for the preventive therapy.

Of all bleeding events, intracranial hemorrhage is one of the most feared. As with other bleeding complications, the association with platelet counts and intracranial hemorrhage has already been studied. However, besides platelet counts at the time of hemorrhage, the course of the preceding platelet counts, including the lowest 'through' counts in preceding days and the percentages of time exposed to such low platelet counts have not been investigated for intracranial hemorrhage. These platelet count parameters were hence studied as possible risk factors for intracranial hemorrhage in a case-control study which is reported in **chapter 3**. Furthermore, in this chapter, the number of platelet transfusions needed to maintain the target platelet thresholds was studied for its association with intracranial hemorrhage.

Since the etiology of bleeding is multifactorial, there are many other clinical factors that may predict the occurrence of intracranial hemorrhage in acute leukemia patients. In **chapter 4**, in the same case-control population as described in chapter 3, we focus on the predictive power of one likely risk factor, namely the presence of cardiovascular risk factors, which likely lead to chronic vascular damage. The association of such factors with intracranial hemorrhage might be of importance, because of the concurrent risk factors for diminished vascular integrity in this patient population, for example thrombocytopenia and inflammation.

Improving bleeding prevention in hemato-oncology patients, can likely be improved by validation of risk factors that can be used in a prediction model to identify patients who indeed have a very high bleeding risk. For the purpose of identifying such risk factors, we performed a post-hoc analysis in the dataset of the randomized controlled TOPPS trial, and investigated if baseline parameters – suggested to be associated with bleeding risk – indeed could be used to predict the actual occurrence or absence of bleeding that was observed in the study cohort. Furthermore, we performed a heterogeneity of treatment effects analysis, with the goal to explore if patients with different bleeding risks at baseline benefitted differently from a prophylactic platelet transfusion strategy. Results of this study are described in **chapter 5**.

Although bleeding in hemato-oncological patients has been studied quite often, there is still much unknown about contributing risk factors. Consequently, well-functioning and validated models to predict bleeding are lacking. Both for etiologic research into risk factors for bleeding in hemato-oncology patients, as for adequate risk prediction, large datasets of sufficient variables to enable extensive adjusting and/or modeling will be necessary. Ideally, these datasets will include time varying clinical variables. Additionally, biomarkers for hemostasis or endothelial function might add to adequate prediction. In **chapter 6**, we present the study design for the ongoing BITE (Bleeding In Thrombocytopenia Explained) study. This study will not only assess the overall incidence of bleeding in hemato-oncology patients, but also in subgroups.

Furthermore, a case control study nested within the study population will enable us to further investigate risk factors for bleeding. Sampling of biomarkers will be performed in the last phase of the BITE study. After identification of clinical and laboratory risk factors, both baseline and time-varying data of this study can contribute to the adequate prediction of bleeding risk of hemato-oncology patients.

In **chapter 7** we discuss the main findings of this thesis, as well as our view on the implications for future research.

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