Bleeding in hemato-oncology patients: beyond the platelet paradigm

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Chapter 7

General discussion and future perspectives

General discussion

Bleeding is a commonly encountered problem in hemato-oncology patients. Despite widely applied prophylactic platelet transfusions that aim to prevent episodes of hemorrhage, bleeding still occurs. It is estimated that between 1.2% and 7.8% of the patients experience severe bleeding during treatment.[1-5] Here, severe bleeding is defined as a bleeding with a World Health Organization (WHO) bleeding score of grade 3 or 4.[6] Bleeding of WHO grade 2 or higher may occur in up to 71% of patients within 30 days of admission for intensive chemotherapy,[3] while up to 89% of all patients experience a bleeding of any grade during their hospital admission.[5]

For more effective prevention, and thus a further reduction in clinically relevant bleeding episodes, more knowledge on bleeding in hemato-oncology patients is needed. First, it is important to understand which factors are contributing to the development of bleeding. This can help to establish targeted prophylactic interventions in the future. Second, adequate prediction of bleeding is essential, to identify patients who might benefit from specific preventive interventions.

The main goal of this thesis was to contribute to these knowledge gaps. We described a part of the current clinical practice in patients with persistent deep thrombocytopenia, a subpopulation that has had little attention in research so far. Furthermore, we identified conditions that are associated with (intracranial) bleeding. Also, we aimed to predict the effect of the most widely applied bleeding prophylaxis, namely prophylactic platelet transfusions, for individual patients.

Current clinical practice

With the ultimate ambition to be able to prevent clinically relevant bleeding more efficiently in the future, a first step is to identify potential points of improvement by describing current clinical practice. For this, a summary of the general recommendations and considerations for prophylactic platelet transfusions for hemato-oncology patients from established transfusion guidelines is provided in table 1.[7-12]

Platelet prophylaxis in patients with transient thrombocytopenia

For hospitalized patients, who receive intensive therapies such as high dose chemotherapy or stem cell transplantations (SCT), and for whom the thrombocytopenia is expected to be transient, all guidelines recommend giving prophylactic platelet transfusions at platelet counts of < $10x10^9$/L. However, for specific subgroups or clinical conditions, recommendations in the different guidelines are inconsistent.[13] Stable patients receiving an autologous SCT form a specific group for whom prophylactic platelet transfusions could be withheld, according to two guidelines.[8, 9] This advice is based on secondary analysis of one randomized controlled trial (RCT), which suggest

Table 1. Guideline recommendations on prophylactic platelet transfusion in adult hemato-oncology patients

Country	Publication year	Organization	Transient thrombocytopenia	Altered thresholds	Persistent deep thrombocytopenia
The Netherlands	2020	Federation of Medical Specialists	- Give one standard dose of prophylactic platelet transfusion to patients receiving intensive chemotherapy of allogeneic SCT at a platelet count of > $10x10^9$/L	- Altered thresholds for several invasive procedures are advised - Altered thresholds for patients with a need for platelet aggregation inhibitors or anticoagulant medication are recommended	- Given a lack of evidence no advices on prophylactic transfusions, or alternative bleeding prevention, are given
United Kingdom	2017	British Committee for Standards in Haematology	- Give one standard dose of prophylactic platelet transfusion to patients receiving intensive chemotherapy of allogeneic SCT at a platelet count of ≥ $10x10^9$/L - Consider not giving prophylaxis to well patients receiving an autologous SCT	- Consider increasing the threshold up to $20x10^9$/L in patients judged to have additional risk factors for bleeding, individual review based - Altered thresholds for several invasive procedures are advised	- Use a no-prophylaxis strategy in asymptomatic patients without or on low intensive therapy - Give prophylaxis to patients who do receive intensive treatment
United States	2015	AABB	- Give one standard dose of prophylactic platelet transfusion to hospitalized patients with therapy induced thrombocytopenia at a platelet count of ≥ $10x10^9$/L	- Altered thresholds for lumbar puncture and central venous catheter placement are advised - Altered thresholds for non-hospitalized patients can be considered	- Not specifically mentioned; altered thresholds for non-hospitalized patients can be considered
United States	2018	ASCO	- Give one standard dose of prophylactic platelet transfusion to patients who receive therapy, including allogeneic SCT, at a platelet count of ≥ $10x10^9$/L - A therapeutic only transfusion strategy may be used in experienced centers for patients receiving an autologous SCT	- Higher thresholds may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count or coagulation abnormalities - Altered thresholds for several invasive procedures are advised	- In absence of active treatment, patients can be observed without prophylactic transfusions, and transfused if bleeding occurs
International	2015	International Collaboration for Transfusion Medicine Guidelines	- Prophylactic platelet transfusion (low or standard dose) should be given at a platelet count of ≥ $10x10^9$/L (NB this is not specifically mentioned for only transient, but for all patients with hypoproliferative thrombocytopenia)	- Not specifically mentioned	- Not specifically mentioned
United Kingdom	2015	NICE	- Give one standard dose of prophylactic platelet transfusion	- Altered thresholds for several invasive procedures are considered	- Do not routinely offer prophylactic platelet transfusions to patients with chronic bone marrow failure

Abbreviations: SCT = stem cell transplantation, AABB = Association for the Advancement of Blood & Biotherapies, ASCO = American Society of Clinical Oncology, NICE = National Institute for Health and Care Excellence

that these patients do not benefit from the transfusions, while patients with intensive chemotherapy or allogeneic SCT do benefit.[14] A meta-analysis of the results of this RCT with the results of one other RCT did not provide conclusive results regarding the lack of benefit in patients with autologous SCT. Accordingly, some of the guidelines do not give specific guidance for patients with autologous SCT.[7, 10-12] It would be of great interest to study the non-benefit in these patients once more. If confirmed, we would infer that the advice to withheld platelet transfusions from patients receiving an autologous SCT should be wider applied in guidelines, and clinical practice.

Likewise, for conditions in which bleeding risk is considered high, different guidelines give conflicting advises, or are unspecific. This reflects the lack of evidence on which risk factors, or combination of risk factors, are most important. Moreover, the effectivity of prophylactic platelet transfusions, let alone altered prophylactic strategies, in patients with various risk factor profiles are unknown. Examples of clinical conditions or circumstances that potentially increase bleeding risk are infections or sepsis, graft versus host disease, and the need for anticoagulant therapy.[15-18] For clinically admitted patients who undergo intensive therapy, there is substantial heterogeneity in transfusion practice, especially in the presence of such expected risk factors.[19]

Platelet prophylaxis in patients with persistent severe thrombocytopenia

Next to the intensively treated population with transient thrombocytopenia, a significant number of patients suffer from persistent severe thrombocytopenia. These patients have chronic bone marrow failure and are not eligible for, or are refractory to, curative treatments. Most often, they are outpatients. For this specific, and far less studied, population, incidences of bleeding have only scarcely been described. These outpatients are generally more 'stable', with a relatively low bleeding risk profile in the absence of inflammation and other risk factors that complicate intensive treatments. Hence the momentary incidence of bleeding among these clinically stable, outpatients with persistent severe thrombocytopenia is expected to be relatively low. However, due to the long period of thrombocytopenia, the cumulative bleeding incidence increases with time, likely leading to substantial long term bleeding incidences.

For patients with persistent severe thrombocytopenia, evidence on how best to prevent bleedings is lacking. Based on expert opinion, some international guidelines suggest to consider to withhold part of the prophylactic transfusions in this population (table 1).[8, 9, 11] However, these recommendations are, again, not consistent between the different guidelines.

The clinical practice of bleeding prevention in these outpatients with persistent severe thrombocytopenia in the Netherlands has not been described before, and was explored in **chapter 2.** Platelet prophylaxis appeared widely applied in these patients, especially when recently receiving intensive chemotherapy, or when treated with

hypomethylating agents as anti-cancer therapy. The most applied platelet transfusion threshold is 10x10^9/L, conform the guidelines in intensively treated patients. A minority of physicians choose higher thresholds, like a trigger of 20x10^9/L, up to sporadically even 80x10^9/L. For some subpopulations a therapeutic only transfusion policy is considered by others.

Another group of patients do not receive any disease modifying therapies, like low-dose chemotherapy. These patients are transfused with prophylactic platelet transfusion far less. Mostly, they are frailer and/or have a shorter life expectancy compared to patients who do receive treatment.[20-22] Our survey did not provide insight in the reasoning behind withholding prophylactic platelet transfusions. However, we presume the benefit of prophylaxis is probably weighed smaller as compared to the burden a patient may experience by visiting the hospital frequently. Another reason for less platelet support may be that, in the absence of disease modifying treatment, the bleeding risk is often estimated as low.

Alternative anti-bleeding strategies

Besides bleeding prevention via prophylactic platelet transfusions, alternative strategies to avoid (clinically relevant) bleeding are also of interest. Hemostasis is an interplay between platelets, the endothelium, and coagulation and fibrinolysis. Therefore, agents optimizing any of these factors can potentially help in the prevention of bleeding.[23] Agents that have been studied in the hemato-oncological population include thrombopoietin mimetics, platelet poor plasma and desmopressin. Although the data is scarce, so far, no benefits of these measures have been described. [24, 25]

Another potentially effective anti-bleeding strategy is to inhibit fibrinolysis. In this context, tranexamic acid is the most frequently used anti-fibrinolytic agent. It is a synthetic drug, which binds plasminogen and thereby reduces the conversion to plasmin, and consequently decreases fibrin degradation. In several non-hemato-oncological populations, tranexamic acid provides adequate protection against bleeding.[26, 27] Moreover, tranexamic acid has the advantages of being easily administered orally and having relatively little adverse effects. Therefore, it is sometimes used as an alternative or adjunct to transfusions to prevent bleeding in patients with (persistent) thrombocytopenia.[28, 29]

Since there is little known on the extend of usage of tranexamic acid, as well as on the clinical reasoning for prescription, we surveyed the clinical use of tranexamic acid in hematological outpatients. The results were presented in **chapter 2**. In the Netherlands, clinicians hardly ever prescribe tranexamic acid to patients without recent or active clinically non-relevant bleeding. The fact that tranexamic acid is not often given for pure prophylactic purposes in the Netherlands, may not reflect its usage elsewhere. A Canadian observational study of 99 patients with myelodysplastic

syndrome, described the incidence of bleeding for different antibleeding strategies.[28] It was found that 28% of patients received solely prophylactic tranexamic acid, and 39% had both platelet transfusions and tranexamic acid as bleeding prophylaxis. Only 19% received solely platelet prophylaxis and 13% did not receive any prophylaxis. So, in contrary to our results, in this study the majority of patients received tranexamic acid. Intriguingly, this study reported no significantly different number of WHO grade 3 or 4 bleedings between the four patient groups.[28] Yet the efficacy of tranexamic acid remained uncertain, because the study was small and potentially the result of confounding. In other small studies, tranexamic acid has not been shown to be effective to prevent bleeding in the hemato-oncological population.[30] Preliminary results of a large RCT suggest that prophylactic tranexamic acid in adjunct to regular platelet prophylaxis in patients with intensive chemotherapy or SCT does not positively affect the clinical outcomes of patients[31] Similarly it is not clear whether tranexamic acid, as adjunct or substitute, positively affects the prognosis of outpatients with persistent deep thrombocytopenia,. Thus, there remains an important medical need in identifying effective alternative interventions to prevent bleeding.

Prediction of the effect of prophylactic platelet transfusions on bleeding

The beneficial effect of prophylactic platelet transfusions at a threshold of $10x10^9$/L on reducing the occurrence bleedings in intensively treated hemato-oncology patients is clearly established.[32] However, bleeding is by far eradicated. Thus, although this strategy is effective for part of the patients, many still bleed. Additionally, other patients would never bleed even in absence of prophylaxis.[1, 2] Therefore, to establish a more efficient use of transfusions, it is important to identify patients that do benefit from prophylactic transfusions, those that might need additional measures, and patients that do not need transfusions at all.

In the literature, by far most attention has gone to the effect of platelet count, and platelet count driven transfusion strategies, on the occurrence of bleeding. However, besides platelet counts, several other patient characteristics and clinical conditions associated with the bleeding risk have been described.[8, 15-17, 33-36] These expected risk factors are also potentially important to identify patients who could benefit more from transfusions. However, a risk prediction model that includes risk factors to predict the effect of prophylactic transfusions is lacking so far.

In **chapter 5**, we present a prediction model based on baseline characteristics of clinical intensively treated patients with hemato-oncological diseases. We included baseline risk factors that have been described to be associated with bleeding before. When combined, their predictive power was low. Furthermore, based on these baseline bleeding risks, no patient subgroups could be identified that clearly benefitted more or less from prophylactic transfusion strategies. Several reasons, all argued in the

discussion of chapter 5, can explain why the selected baseline risk factors together could not predict bleeding more accurately. In our opinion the lack of information on, mostly short term, time-varying clinical conditions, plays a pivotal role. These time-varying conditions, like platelet count, inflammation, or other processes that temporarily impact the hemostatic integrity, are however not available for data analysis in most studies. One would need large numbers of both patients and relevant variables and take timing of the separate conditions and the eventual (absence of) bleeding events into account.

Intracranial hemorrhage – etiology and prediction

Of all bleeding complications in patients with leukemia, intracranial hemorrhage is one of the most feared, since it has a strong impact on quality of life and life expectancy.[37-40] In **chapter 3** we demonstrated it is likely that low platelet counts are associated with intracranial hemorrhage. This result may not come as a surprise, since several studies already described an association.[41-43] Mostly, the platelet count at the day before bleeding, or the bleeding day itself, is studied. However, we show that in time periods up to 7 days preceding the bleeding event, this association becomes stronger than the more generally applied association of platelet count one day before bleeding. Also, the percentage of time with low platelet counts is likely associated with intracranial hemorrhage. Platelet transfusions also seem associated with intracranial hemorrhage. Probably, this is due to general conditions that lead to raised transfusion thresholds and hence more transfusions. Higher thresholds are among others applied when anticoagulant medication or platelet aggregation inhibitors is needed, or when other (non-intracranial) bleeding events occur. In other words, intracranial hemorrhage is more likely to be caused by these threshold-increasing clinical conditions, instead of by the ensuing raise in platelet transfusions.

To prevent intracranial hemorrhage, it would be worthwhile to identify patients who are more likely to develop these events. Bleeding is obviously not only influenced by platelet counts, but also by the condition of the vascular wall.[44, 45] Therefore, we focused on cardiovascular risk factors that are likely to compromise the vascular wall chronically. In **chapter 4,** we demonstrate that pre-existing hypertension and a history of ischemic heart disease both are strongly associated with the occurrence of intracranial hemorrhage in patients with acute leukemia. Such predictors are easily obtainable in clinical care. It needs further investigation to confirm if these predictors, as hypothesized, lead to intracranial hemorrhage via the combination of chronic vascular damage and acute vascular effects of chemotherapy and thrombocytopenia. Also, studies on the clinical consequence of alternative preventive strategies in patients with increased risk might eventually lead to improved clinical outcomes.

Future perspectives

With the studies presented in this thesis, we assessed aspects of bleeding in hemato-oncology patients. First, we described clinical care to prevent bleeding. Second, we investigated clinical risk factors for and predictors of (intracranial) bleeding in hemato-oncology patients. Finally, we studied the effect of risk factors of bleeding on the treatment effect of prophylactic platelet transfusions.

Given the continuing high incidence of bleeding, and the large amounts of prophylactic platelet transfusions administered, it is essential to identify both hematology patients with high, and low bleeding risks. Moreover, for efficient clinical use of transfusions it is important to identify patients who are likely to benefit from platelet prophylaxis. Accordingly, identification of patients who don't need prophylactic transfusions would improve transfusion practice. The harms of platelet transfusions, the burdens, and the considerable costs should be avoided if they serve no benefit. Moreover there is a remaining medical need for more effective bleeding prevention by adjunctive or altered bleeding prevention strategies.

The current standardized and generalized – platelet count threshold based-prophylactic platelet transfusion policy, which is used for a very heterogeneous patient population, is suboptimal. Our studies are steps towards more effective and efficient bleeding prevention, by exploring options beyond platelet counts.

Clinically relevant bleeding and patient perspectives

When striving to have a both effective and efficient policy to prevent bleeding, there are several considerations that need to be addressed. As an important first step, one must wonder what we truly aim to prevent when giving platelet prophylaxis. Not all bleeding events lead to substantial burden or harm for patients. Almost all evidence about prophylactic platelet transfusion medicine is based on bleedings classified by the WHO bleeding grade.[6] This score was originally validated for another purpose, namely to score therapy related toxicity instead of primarily reporting of bleeding. While using slightly different variations of the WHO score, most studies focus on WHO 2, 3 and 4 bleedings as a combined main outcome. However, not all of these bleedings may lead to direct danger, alterations of medical treatment, intensified care, transfusions, or invasive procedures. Instead, there are other bleeding scores, namely the ISTH bleeding score and BSMS bleeding score, that try to divide bleedings into clinically relevant versus non-relevant.[46, 47] These scores have so far not often been used in the hemato-oncological population. A recent study (P.F. Ypma, submitted for publication) reports on readjudication of WHO bleeding scores used in a large platelet transfusion RCT in hemato-oncological patients.[48] They describe that 97.1% of the WHO grade 2 bleedings and even 30.4% of WHO grade 3 bleedings were classified as non-

relevant bleeding according to the ISTH bleeding score. This would mean that these bleedings did not lead to increased or altered medical care. For the BSMS scores, even 97.8% of WHO grade 2 bleedings were not judged as clinically significant, for WHO grade 3 bleedings this percentage was 34.8%. These interesting findings emphasize that indeed the combined outcome of WHO bleeding grade 2, 3 and 4 consist of many bleedings that are not of clinical relevance. Although both the ISTH and the BSMS bleeding scores are in need for further evaluation and validation in the particular patients population of thrombocytopenic hemato-oncological patients, these scores might align better with the present medical needs.

An obstacle in studying the outcome of only clinically relevant bleedings is that the incidence is low. One needs large sample sizes in a RCT or cohort study with clinically relevant bleeding as an outcome. For these rare outcomes, case control studies may be preferred as study design to efficiently and realistically study clinically relevant bleeding.[49]

It is increasingly recognized that studies focusing on clinically relevant bleedings, should also include how patients experience the burden of bleeding. At the same time, their opinion on both benefits and inconveniences of preventive strategies needs to be accounted for. Patient centered outcomes are more and more acknowledged as an important end point for clinical studies.[50, 51] Yet all the before mentioned bleeding scores are designed by physicians or expert researchers, and lack patients perspectives. It is the patient who might experience the benefit from transfusions, but also who is at risk of transfusion related complications and burdens. This applies to transfusions given to bridge transient or therapy induced thrombocytopenia, but perhaps even more so for outpatients with persistent thrombocytopenia. For the latter group, the benefits are less known, and the burdens of recurrent and cumulative transfusions are likely higher. In transfusion medicine, so far few studies examined patient perspectives, and none reported on platelet transfusions specifically.[52] Weighing the patients view on prophylactic strategies to prevent bleedings is worthy to receive more clinical and scientific attention.

Persistent deep thrombocytopenia and prevention of bleeding

Another subject that needs attention when aiming to optimize efficient and effective anti-bleeding strategies, is persistent deep thrombocytopenia due to chronic bone marrow failure. For these patients, well registered bleeding incidences as well as the evidence for effectiveness of bleeding preventive strategies are almost completely lacking.

The ultimate step to improve both knowledge and treatment policies in this group would be to perform a RCT, comparing various prophylactic platelet transfusion thresholds. Ideally, as studied in intensively treated patients,[1, 2] a prophylactic platelet

transfusion strategy should be compared with only prescribing transfusions in case of active bleeding. Also, it could be of value to include an arm with an alternative prophylactic strategy. Though, such a study may have practical difficulties, like completeness of bleeding registration in outpatients. For adequate registration a patient likely needs to be seen or contacted regularly. Another complicating factor may be the long follow-up time needed when studying an outcome that is not very frequent. Where WHO grade 2, 3 and 4 bleedings are not very rare, clinically relevant bleedings have lower incidences.[48] Nonetheless, it would lead to the best possible evidence on how to prevent bleeding via transfusions in this vulnerable patient population.

An alternative could be an observational study, for example on retrospective data or a prospective cohort or case control population. In both of these study designs, also quality of bleeding registration can influence the study results significantly. Reporting of bleeding is likely less in patients without prophylactic transfusions, since they are not as frequently seen in the hospital. For mild bleedings without clinical relevance this perhaps is not worrisome, since these are not the bleedings we are trying to avoid by platelet transfusions. However, missing relevant bleeding would confound the results. Another important difficulty of an observational study would be that physicians often do not report extensively why they choose a prophylactic strategy for one patient, and not for the other. Likely there will be confounding by indication that will be hard to correct for. All difficulties can be expected to be more challenging in retrospective data, compared to prospective observational data. Prospective observational research has the advantage that physicians can be asked to be aware on how they score and report important data in the medical chart. If performed diligently, this would lead to less confounding. Additionally, also in observational prospective studies a long follow-up time is needed in when studying an outcome that is not very frequent. Since bleeding incidences are not widely described for patients with chronic bone marrow failure, sample size calculations will likely be largely based on estimations or small studies. Therefore, in my opinion, also in this patient population a case control design would be preferable for the outcome of clinically relevant bleeding.

Although perhaps not easy, it is important to study the outpatient population with persistent thrombocytopenia specifically, both for their efficiency and for the patient perspectives. While this is important for many treatments and populations, given the expected chronic use of, and time consuming and invasive nature of platelet prophylaxis, especially for these patients this is of crucial importance.

Identification of bleeding risk and expected benefits of transfusions

A crucial step in preventing clinically relevant bleeding is to be able to identify patients with a high bleeding risk, or even patients who are likely to profit from transfusions or not.

Bleeding risk continuously changes. The risk in time likely differs more in intensively treated patients compared to patients with chronic thrombocytopenia. The intensive chemotherapy, or conditions that develop during therapy or admission, like infections, fever and mucositis, influence platelet numbers and function, as well as vascular integrity. So far, although likely, it is neither known how these factors interact, nor how they are influenced by other patient characteristics. Therefore, a model that can incorporate time varying variables with 'fixed' risk factors is needed to accurately predict bleeding risk. Such a model could take along many clinical variables, but biomarkers that represent the pathophysiological effects of the clinical conditions might prove to be most informative.

Biomarkers indeed can serve as predictors, while in the mean time learning us more about the balance between vascular integrity, platelet function, platelet counts, the coagulation system and fibrinolysis. Thereby, biomarker studies can help unravel the complex pathophysiologic pathways of bleeding in this particular patient population. This could be helpful in steps toward alternative, biomarker-based, approaches to prevent bleeding, namely therapies that directly target the pathway mostly involved in the impaired hemostasis.

Although most emphasis so far has been on identifying patients who benefit from bleeding preventive strategies, there are two sides of the medal. We also need tools to identify patients that will not benefit from the transfusions, as is described for patients undergoing autologous SCT.[2, 14] As a biological agent that is being administered, platelet transfusions are not without risk. Acute transfusion reactions are rare, but may lead to substantial burden if they occur.[53, 54] Platelet transfusions furthermore can lead to HLA antibodies, which potentially lead to refractoriness.[55, 56] Therefore, exposure of patients who will likely not benefit of transfusions should be avoided where possible. More evidence, perhaps from observational studies investigating the safety of a non-prophylaxis strategy in low risk patient subgroups, is likely needed before withholding of transfusions will be implemented more consistently in guidelines.

BITE study

As described, previous studies investigated the effect of prophylactic platelet transfusions in intensively treated hemato-oncology patients, as well as some risk factors for bleeding. Yet, there is still a need to identify additional risk factors, and confirm previously suggested risk factors. Also, it is of importance to clarify how the several risk factors interact over time, and even more importantly which (combination of) risk factors can serve as a robust prediction model to identify patients that are likely to bleed, or not.

In **chapter 6**, we described an ongoing case control study, that intends to fill some of the described gaps of knowledge: the BITE study (Bleeding In Thrombocytopenia Explained). We gather the clinical data for such prediction models in cases with clinically relevant bleeding, and in control patients. Importantly, in this case control study, besides baseline characteristics also time depending data will be collected. Time dependent variables will be looked into from a period of time preceding clinically relevant bleeding for cases, and in a matched time for controls. In this way, risk factors are aimed to be both identified and quantified, taking into account potential time dependent effects of intensive treatment. Also, a dynamic prediction model can be realized, which will be an important next step in accurate bleeding prediction, and hopefully more personalized preventive strategies in future. Furthermore, for a part of the included patients also biomarkers will be measured, concentrating on platelet and endothelial function.

Subsequently, new studies will be needed to show the efficacy of prophylaxis in patients with different bleeding risks. For patients at high risk despite prophylactic platelet transfusions, alternative or additional treatment should be studied. In case of alternative or additional treatments, it would be preferable to focus on treatments that encounter the biological bleeding mechanisms shown by biomarkers. For patients with low bleeding risk, larger studies need to identify the populations that will also have low bleeding risks in absence of prophylactic therapy. For these patients, this would mean they do not need to be exposed to transfusions they will likely not benefit from, but that can burden or harm them. Also, identification of the population that can do without transfusions is important to reduce health care costs and blood supply demands.

To conclude, within the field of transfusion medicine and hematology, there remains a medical need for improved bleeding preventive strategies for hemato-oncology patients. Identification of risk factors, and prediction models leading to personalized estimates of risks and expected benefits, are of great importance to prevent bleeding more effectively and thereby improve the care for and outcomes of hemato-oncology patients.

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