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

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# Chapter 8

Summary
Samenvatting

## Summary

In the hemato-oncological population bleeding events are frequently seen, despite widely applied prophylactic platelet transfusions. Part of these bleedings are clinically relevant, leading to for example extended care, invasive procedures, additional medication or transfusions. They may even lead to serious morbidity or mortality. Therefore, to more effectively prevent especially these relevant bleedings, it is important to understand which factors contribute to their development, and to be able to predict which patients are more likely to develop bleeding, or not. In this thesis, we focused on current clinical practice of bleeding prevention in hemato-oncology patients with persistent deep thrombocytopenia, on risk factors for bleeding, and prediction of bleeding.

In **chapter 2**, we evaluated the current clinical practice of bleeding prevention in a subgroup of hemato-oncology patients, namely outpatient patients with persistent deep thrombocytopenia. Also for this subgroup, prophylactic platelet transfusions are commonly provided in the Netherlands, and conform to the guidelines for patients with transient thrombocytopenia applied mostly beneath a platelet count of $10x10^9$/L. We also showed that when patients are not actively treated for their underlying hematological disease, prophylactic transfusions are far less prescribed. Furthermore, we found many different clinical conditions that determine the decision making on platelet prophylaxis. In this regard, previous bleeding events and the use of platelet aggregation inhibitors or anti-coagulant medication were considered most important. For patients with clinical conditions that likely increase bleeding risk, the chosen platelet transfusion thresholds differed substantially. In addition, we surveyed tranexamic acid usage. We showed that this antifibrinolytic agent is mostly prescribed to patients with active or recent bleeding, but hardly ever as prophylaxis in the absence of bleeding. Our results reflect the lack of knowledge on risk factors for bleeding in this particular patient population, and underline the need for more research of bleeding preventive strategies.

**Chapter 3** and **chapter 4** focus on acute leukemia patients with intracranial hemorrhage. In **chapter 3**, we described how absolute platelet counts and the percentage of time with low platelet counts (exploring time-frames up to seven days) were associated with intracranial hemorrhage. We found that longer periods of thrombocytopenia coincide with a higher risk of intracranial hemorrhage. However, due to a small number of patients with intracranial hemorrhage, we could not substantiate a true effect size, nor correct for confounding factors that influence the association between thrombocytopenia and intracranial hemorrhage. We additionally

showed that patients who need a higher numbers of platelet transfusions also seem to have a higher risk. This was especially the case for more than two platelet transfusions in a five to seven day period preceding the intracranial hemorrhage. This association likely reflects conditions that lead to the greater need for transfusions, and thus no direct causal relation.

In **chapter 4** we investigated the predictive association of pre-existent cardiovascular risk factors with intracranial hemorrhage in leukemia patients. Cardiovascular risk factors are described as risk factors and/or predictors of intracranial, mostly intracerebral, hemorrhage in the general population. However, it was not known if these associations are also equally important for leukemia patients. We showed that especially pre-existent hypertension or a history of ischemic heart disease are strong predictors of intracranial hemorrhage in leukemia patients. Moreover, the predictive power seems higher than is expected in the general population. The possible causality of course needs more research, but we hypothesize that the combination of chronic vascular damage (of which hypertension and ischemic heart disease are surrogates) and the acute endothelial damage and low platelet counts during treatment of acute leukemia, synergize and explain the even stronger association. If confirmed, it is of interest to see of patients with pre-existing cardiovascular risk factors benefit from altered or additional interventions to prevent bleeding.

To prevent bleeding more effectively on one hand, while also avoiding unnecessary platelet transfusions, one should be able to predict who is likely to bleed or not, and hence who will likely benefit from prophylactic platelet transfusions. In **chapter 5** we therefore studied the effect of platelet prophylaxis in groups of patients with different baseline characteristics as possible bleeding predictors. To do so, we first designed a prediction model from several baseline characteristics that in previous studies seemed to associate with bleeding. Yet, this prediction model of combined baseline risk factors, had low predictive power and could not really differentiate between high and low bleeding risk groups. Within the small range of predicted risks, via a heterogeneity of treatment effect analysis, we could conclude that patients with different risk factor distributions all seem to benefit more or less equally from the prophylactic platelet transfusions. However, from clinical practice, and other studies, we know that present practice does prevent bleeding in some patients but not in all. On the other hand, other patients could likely do without prophylactic transfusions and not have any relevant hemorrhage. From our findings, we hypothesize that a model including time varying variables should lead to a more accurate prediction of bleeding. This could potentially also better discriminate which patients do or do not benefit from the platelet prophylaxis. Such a dynamic prediction tool in our opinion is an important step in

improving bleeding prevention for hemato-oncology patients and additionally averting unnecessary use of platelet transfusions.

In **chapter 6** we describe the BITE study protocol, an ongoing case control study by which we eventually aim to describe and quantify potential risk factors of bleeding in hemato-oncology patients, as well as the combined effects of risk factors. The way the data is collected namely allows for dynamic prediction as well; by this a personalized and time-specific bleeding risk can be predicted. Hopefully, this will eventually allow more effective and personalized strategies to prevent bleeding in future, and to avoid those strategies if likely unnecessary.