Chapter 1

General introduction and outline of this thesis

A healthy individual has approximately 150-400x10^9 platelets per liter in the circulation. In patients with a hematological malignancy this can drop to unmeasurable low amounts as a consequence of the treatment or the disease itself, leading to an increased risk of hemorrhage. These patients need platelet transfusions to prevent or treat these hemorrhages. Yearly, approximately 59,000 platelet concentrates are transfused in the Netherlands, 2.9 million in Europe and 1.5 million in the USA, of which the majority, up to 67%, are given to hematological patients.[1-5]

History

The history of platelet transfusions goes back to the beginning of the twentieth century. In 1910, William Duke demonstrated the role of platelets in stopping hemorrhages and the beneficial effect of transfusions on platelet count, bleeding time and bleeding tendency. Duke described three patients with spontaneous hemorrhages in whom the bleeding time normalized after a transfusion of whole blood and in two of these patients the bleeding even stopped. This resulted in the suggestion that a low platelet count could be a cause of hemorrhages instead of only an accompanying symptom.[6] Nowadays, Duke's paper is known as a landmark paper and one of the outstanding contributions to medicine in the first half of the twentieth century.[7]

It took until 1962 before Gaydos et al. quantified the relationship between platelet count and the occurrence and severity of hemorrhages. Hardly any patient bled at a platelet count above 20x10^9 platelets/L.[8] Although Gaydos et al. did not define a transfusion threshold, this study and two small trials laid the groundwork for prophylactic platelet transfusions at a trigger of 20x10^9 platelets/L.[9,10] This became an essential part of supportive care for thrombocytopenic patients and was considered to be the leading reason for the major decline of fatal hemorrhages among leukemia patients from 67% to 37% in the sixties.[11,12] The increased demand for platelet concentrates and the concerns about the risks and costs of transfusions resulted in several studies comparing the efficacy of different thresholds for platelet transfusions.[13-19]

Transfusion practice

Nowadays, a prophylactic transfusion policy with a trigger of 10x10^9 platelets/L is recommended for clinically stable patients.[20-23] The safety of this threshold is supported by the suggestion that a platelet count of 7.1x10^9 per liter per day is sufficient to maintain vascular integrity.[24]

The alternative to maintaining the platelet count above certain threshold with a prophylactic transfusion policy is a therapeutic policy in which patients only receive platelets in case of a symptomatic bleeding. Although such a policy results in a reduction of the total number of transfused products compared to a prophylactic policy, the risk of bleeding increases and the bleeding free survival shortens, according to a recent Cochrane analysis.[25] Only for patients receiving autologous stem cell transplantation a therapeutic transfusion strategy could be safe.[26,27]

A prophylactic transfusion policy with a trigger of $10x10^9$ platelets/L is probably not sufficient in non-stable patients who face an increased risk of bleeding. Reported risk factors for bleeding are previous bleedings, active infection (predominately fungal infections), fever, allogenic transplantation, graft versus host disease, severe mucositis, and, in older studies, also leukocytosis.[28,29] It is debated which trigger should be adhered by these patients and recommendations in guidelines are based on consensus and differ between countries. The same uncertainty applies to patients undergoing an intervention which potentially increases the bleeding risk. The variation in recommendations results in variation in clinical practice.[30] Although it is unknown whether increasing the threshold truly reduces the bleeding risk, many clinicians increase the transfusion threshold to counterbalance the assumed increased risk of bleeding.

Efficacy of platelet transfusions

The main reason to transfuse platelets is to prevent or treat hemorrhages. Of all platelet transfusions issued to hematological patients, 69% is given for prophylactic purposes to patients with a platelet count $<10x10^9$ platelets/L.[3] The clinically most relevant outcome to evaluate the efficacy of these transfusions is the incidence of bleeding. Severity of bleeding can be categorized according to the WHO grading scale.[31] The original scale has been adapted to make it less prone to subjective interpretation and suitable to use in several trials. Table 1 shows the scale with the definitions as has been used in the PlaDo and PREPAReS trials.[32,33] The TOPPS trial used a slightly different scale with as main difference the classification of 'CNS bleeding noted on CT scan without symptoms' as grade 3 instead of grade 4 hemorrhage.[27]

Table 1. WHO bleeding severity score[32,33]

Grade	Symptoms
Grade 1: Minor	Petechiae, oropharyngeal bleeding Epistaxis <30 minutes Purpura <1 inch Occult blood stool (1+) Urine hemoglobin (1+) Vaginal bleeding, spotting
Grade 2: Mild blood loss	Melena, hematemesis, hemoptysis, hematuria, hematochezia, abnormal vaginal bleeding, not requiring RBC transfusion Epistaxis, oropharyngeal bleeding > 30 minutes Retinal hemorrhage without visual impairment Occult blood stool (≥2+) Urine hemoglobin (≥2+) Abnormal vaginal bleeding, more than spotting
Grade 3: Gross blood loss	Any bleeding requiring RBC transfusion over routine transfusion needs Bleeding from invasive sites
Grade 4: Debilitating blood loss	Debilitating bleeding including retinal bleeding with visual impairment CNS bleeding Bleeding associated with hemodynamic instability Fatal bleeding

The use of bleeding as main outcome measure in studies regarding the efficacy of platelet transfusions is challenging. Documentation of signs and symptoms of bleeding is labor intensive and it is difficult to translate these into a single score.[34] Differences in observation methods and grading systems resulted in large variation in reported incidences.[35] Moreover, the clinically most relevant bleedings, grade 3 and 4, have a low incidence and therefore large sample sizes would be required to obtain sufficient power.[36]

An alternative measure of efficacy of platelet transfusions is a platelet count increment, which can be measured after each transfusion. The absolute count increment expresses the absolute increase in platelet count after transfusion. The corrected count increment (CCI) takes the platelet dose and the body surface area of the patient into account, by using the following formula:

$$CCI = \frac{(post\ transfusion\ platelet\ count(10^9) - pretransfusion\ platelet\ count(10^9))x\ body\ surface\ area\ (m^2)}{platelets\ transfused\ (10^{11})}$$

A standard platelet concentrate in the Netherlands contains on average 380±55x10^9 platelets.[33] The CCI is usually calculated 1 or 18-24 hours after transfusion. The 1 hour CCI is predominantly determined by quality of the product, spleen size, and alloimmunization, whereas the 24 hours CCI expresses the survival of platelets and is mainly influenced by the clinical condition of the patient.[20,37] A patient is refractory to platelet transfusions when two subsequent fresh ABO identical transfusions are unsuccessful. According to the Dutch CBO guideline, a transfusion is unsuccessful when the 1 hour CCI is <7.5 dm^{-1} or the 24 hours CCI <4.5 dm^{-1}.[20]

Transfusion side-effects

As applies to everything in medicine, also transfusions are not without side effects. A quote attributed to Karl Landsteiner (1868-1943), who described the AB0 blood group system as first, stated "A blood transfusion should never be ordered or given unless it is worth the risk".[38,39] This quote is still valid, although many improvements have been made since.

Nowadays, the risk of dying as a direct consequence of a transfusion has been estimated to be around 1 in 322,580 and the risk of major morbidity around 1 in 21,413 transfused components.[40] Transfusion reactions vary from mild urticaria to severe transfusion reactions or even death. Compared to plasma or red blood cell transfusions, platelet transfusions carry the highest risk of transfusion reactions.[41,42] In the Netherlands, the incidence of severe reactions was 0.18 per 1000 red blood cell transfusions in 2015 compared to 0.38 per 1000 platelet transfusions. Including all severities, these incidences ranged from 4.28/1000 till 5.22/1000 transfusions.[41] One of the most feared adverse reactions is transfusion associated sepsis. If this is directly related to the transfusion of a contaminated product, this is called a transfusion transmitted bacterial infection (TTBI).[41] The incidence of TTBI ranges from 7 up to 26 per million transfused platelet components.[43,44] This variation could be partly explained by differences in vigilance of reporting, but also differences in products could play a role.

The platelet concentrate

Internationally, large variation exists in methods to collect, produce and store platelets. In the Netherlands, 90 to 95% of platelet concentrates are prepared from buffy coats and the remaining 5 to 10% of issued platelet concentrates are derived via apheresis. These are only used for specific indications like neonates, or refractory

patients who need HLA or HPA-matched platelets. For the buffy coat method, whole blood is held overnight at room temperature and split by hard spin centrifugation into a red cell layer, plasma, and the buffy coat, consisting of platelets and leukocytes. Buffy coats of five donors with the same AB0 and rhesus D blood group are pooled, leukocytes are removed via a soft-spin procedure and filtration, and the platelets are resuspended in plasma or platelet additive solution (PAS), with 25ml of plasma left per donor.[20]

Storage medium

PAS is a generic term for a solution with a standardized composition of electrolytes. It was developed in the 1980s to remove plasma from the platelet concentrate, as it was thought that plasma had a deleterious effect on platelet quality during storage. Other supposed advantages of PAS were a reduced risk of allergic reactions, a lowered anti-AB0-titer and the conservation of plasma for fractionation.[2,45]
PAS gave the opportunity to control the storage environment. Most important is to maintain a pH above 6.0 to maintain platelet viability. The main energy source of platelets is oxidation of glucose into ATP and lactic acid, resulting in lowering of the pH, which in turn leads to more activation of platelets and thereby more glucose consumption and accompanying lactic acid production, a vicious circle. Most PASs contain acetate as nutrient for platelets to hamper the oxidation of glucose into lactic acid. Metabolism of acetate results in the formation of bicarbonate, which forms an extra buffer to stabilize the pH. All PASs still contain 20-35% of plasma as main source of glucose and to maintain platelet membrane integrity.[2,46,47]

In the Netherlands, both plasma and PAS are used as storage medium. The geographic location of the hospital determines the choice of storage medium. In hospitals in the South-West of the Netherlands PAS is used, whereas in the other regions plasma is used as main storage medium.[2] PAS-B (T-sol, Baxter) was used up to 2012, and PAS-C (Intersol, Fenwal, Inc) since January 2013. The difference between PAS-B and PAS-C is the addition of phosphate as extra buffer in PAS-C. From January 2018 PAS-E will be used as additive solution.

Storage time

Within the circulation, platelets can survive up to ten days. This shortens to as low as 3.4 days when the platelet count drops below $20x10^9$/L.[24] Once donated, platelets can be stored for up to seven days at room temperature under constant agitation. As these are ideal conditions for bacterial proliferation, all products are screened for bacterial contamination. In the Netherlands, the BacT/Alert system (bioMérieux, Nürtingen, Germany) is used, consisting of an aerobic and an anaerobic bottle, each inoculated with 7.5 ml of the platelet product. Products are released according to a 'negative to date' system, which means that products can be transfused as long as the BacT/Alert stays negative.[48] Internationally, large variation exists in the maximal allowed storage time of platelet concentrates. Besides in the Netherlands, storage up to seven days is also allowed in Spain and Denmark, whereas this is limited to 5 days in Canada, Austria and the United States. Without bacterial screening, storage is limited to 3.5 days in Japan, 4 days in Germany and to 5 days in France.[49] As outdating is the main reason for discarding of platelet concentrates, prolonged storage could have logistic benefits.[50] However, *in vitro* studies showed a gradual loss of platelet function during storage.[51] These 'platelet storage lesions' could also implicate a loss of hemostatic functions *in vivo*.[52]

Transfusion research

In general, transfusions are safe, effective, and integrated in daily practice. Despite the high quality of supportive care, major hemorrhages do still complicate the treatment of patients with a hematological malignancy. Moreover, adverse events related to the transfusion still occur. This illustrates the importance of studies to improve the safety and effectiveness of blood transfusions.

One of the challenges within the field of transfusion medicine is to set up a study with sufficient power and a clinically relevant endpoint. The low incidence of adverse reactions and major hemorrhages, the most relevant measure of effectiveness of platelet transfusions, oblige researchers to include large populations. Observational studies, using routinely collected health care data can be an appropriate method to obtain sufficient power.

In order to investigate the safety and effectiveness of platelet transfusions, we set up a nationwide cohort study, the ATTACH study, in which we collected and assembled data of platelet transfusions issued between 2005 and 2015 in nine hospitals spread around the Netherlands. For all transfused patients additional information was requested regarding transfusions of other blood products, laboratory measurements, blood cultures, and diagnoses and procedures.

Information regarding characteristics of the transfused product was obtained from Sanquin, the national blood supply. TRIP (Transfusion and Transplantation Reactions In Patients), the national hemovigilance organization, provided information on all reported transfusion reactions related to a platelet transfusion since 2003.

The final database comprised 29,440 patients, who received in total 133,424 platelet transfusions. Of these, 5,583 patients (73,383 transfusions) had a diagnosis of a hematological malignancy or aplastic anemia. Variation in transfusion practice and transfused products, i.e. storage time and storage medium, offers the opportunity to study various aspects of platelet transfusions as has been described in **chapter 4**, **7 and 9**.

Aim and outline of this thesis

The aim of this thesis was to address several aspects of platelet transfusions in patients with a hematological malignancy in order to improve the safety and effectiveness.

It starts with the decision when to transfuse. For clinically stable patients, a prophylactic transfusion strategy is well accepted and the trigger of $10x10^9$ platelets/L is uniformly implemented in routine care. However, less consensus exists regarding the optimal transfusion threshold for patients with an increased risk of bleeding or those who need to undergo an intervention. In **chapter 2**, we describe the results of a survey among hematologists in which we asked which trigger they adhere in such situations.

Some patients develop anti-HLA or anti-HPA antibodies and as a consequence they become refractory for platelet transfusions. The best option for these patients to prevent or treat hemorrhages is transfusion of HLA and eventually HPA-matched platelet concentrates. In the study described in **chapter 3** we explored the HLA haplotypes of refractory patients in relation to a population of typed Dutch donors.

Ideally, only those patients who face an increased risk of bleeding receive transfusions. In order to study risk factors for bleeding in large populations, we developed a model to identify leukemia patients with major hemorrhage in routinely collected health care data **(chapter 4)**.

Platelets survive for ten days in the normal circulation, so donated platelets are on average five days old. Subsequently, platelet concentrates can be stored for up to seven days. Storage affects safety and efficacy of the transfused products. In **chapter 5**, we systematically reviewed the existing literature about the effect of storage time on measurements, including (corrected) count increment, recovery, survival and half-life of the platelet after transfusion. Subsequently, in **chapter 6**, we reviewed the literature regarding the effect of storage time on clinical outcomes, including transfusion reactions, complications, length of hospital stay, transfusion interval, transfusion need, bleeding and mortality.

The thrombocytopenia in patients with a hematological malignancy is often accompanied by neutropenia which predisposes these patients to an increased risk of infections. With respect to platelet concentrates, it has been suggested that during storage the risk of infections increases. This could be a direct consequence of

contamination and proliferation of bacteria in the product, or indirectly via modulation of the immune response. In **chapter 7** we investigated the association of storage time of platelet concentrates with all-cause bacteremia the day after transfusion. Based on the results of this study, the question remained whether this effect was similar in PAS stored platelets. Therefore, we used Danish transfusion and microbiology databases to examine whether storage of platelet concentrates in PAS –C for up to six or seven days increases the risk of a positive blood culture at different times after transfusion **(chapter 8)**.

In the Netherlands, the geographic location of the hospital determines whether a patient receives a platelet concentrate stored in plasma or in PAS. In **chapter 9** we investigated the effect of storage medium on the risk of transfusion-transmitted bacterial infections.

In **chapter 10** we discuss the main findings and implications for further research and clinical practice, followed by an English and Dutch summary in **chapter 11.**

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