Chapter 10

General discussion

Blood transfusions are one of the most common procedures in hospitals and an essential part of supportive care in the treatment of hematological malignancies.[1] For the research presented in this thesis we used routinely collected health care data to investigate the safety and effectiveness of platelet transfusions in hematological patients.

Routinely collected health care data

Routinely collected health care data constituted the cornerstone of several studies described in this thesis. In general, big data, including routinely collected health care data, are increasingly used in research.[2,3] By using routinely collected health care data, observational studies can reach sample sizes which are 100- to 1000-fold bigger while minimizing costs and effort. This gives the opportunity to study subgroups which are often overlooked in randomized controlled trials or to investigate rare events. Moreover, trials are not always feasible or ethical and patients in trials are selected using stringent in- and exclusion criteria resulting in limited generalizability, whereas patients in this kind of observational studies reflect daily clinical practice.[4,5] However, the use of routinely collected health care data is criticized as these data are not collected with research as the prime motive, but healthcare driven. This could imply that the data is not complete, the level of detail is less than desired, or the information is not uniformly coded.[6-8] Therefore, the investigator has to ensure the completeness, validity, and applicability of the data for the question of interest.

Incompleteness due to underreporting is one potential source of bias which could arise by using this kind of data. For the research presented in **chapter 9**, we used the national register of transfusion reactions as main data source. Reporting of severe transfusion reactions, like transfusion transmitted bacterial infections, is compulsory under European law, which ensures completeness of this register regarding these reactions.[9,10] In **chapter 8**, we used databases of Denmark, to what, for a reason, is referred as 'not a country, but a cohort'.[8] The Danish government underlines the importance of epidemiological research and facilitates the required infrastructure. As a consequence, the entire country is covered and registers can be individually linked via the personal registration number, ensuring complete follow-up.[11,12]

The validity of the data determines the reliability of research. In contrast to laboratory measurements, diagnostic and procedural codes, like DBC codes and ICD codes, are prone to interpretation.[13] Coding is especially inaccurate for poorly defined diseases with a high prevalence, like asthma or diabetes.[14] For the research

presented in this thesis, we used DBC codes to identify hematological patients. Chart review, used as golden standard for the development of the model described in **chapter 4**, revealed that this coding was correct for all patients in the sample. Besides via chart review, validity of the data could also be assessed by comparing the data with other data sources. The validity of ICD codes is, for example, evaluated by linking these data to data of the West of Scotland Coronary Prevention Study (WOSCOPS) trial. The WOSCOPS trial aimed to evaluate the effect of pravastatin on cardiovascular endpoints.[15] Eighty percent of the non-fatal cardiovascular endpoints and even 99% of fatal events could be linked with routinely recorded ICD codes.[16] Thus, although ICD and DBC codes are prone to differences in use and changes in definitions, the validity of the data, with respect to these outcomes, seemed to be good.

The applicability of the data depends upon the depth of the information. The depth may be insufficient when not all information a researcher needs for a specific study is accurately recorded in the registry or database.[8] Proxies could be used to overcome this lack of detailed information. In **chapter 7 and 8**, we used positive blood cultures as a proxy for clinically relevant infections. This automatically implicates a certain degree of misclassification, as not all positive blood cultures are accompanied by clinical symptoms. However, this misclassification is not related to the exposure of interest, in this case storage time of the transfused product, neither to other variables nor to errors in these variables. Therefore, it is most likely that this non differential misclassification will have resulted in bias towards the null and thereby an underestimation of the true effect.[17] The alternative of using a single variable as a proxy, is to combine several variables into a model to predict or identify certain outcomes. In **chapter 4** we described such a model to identify leukemic patients with major hemorrhage based on information regarding CT scan of the brain, drop in hemoglobin level, and need of transfusions.

When the completeness, validity and applicability of the data is ensured, practical hurdles have to be taken before the data can be actually used. The key problem in retrieving the data is that a large amount of data is recorded as a by-product of health care and leverage of the information therein is not straightforward. At first glance, laboratory measurements and transfusion data are the most easily accessible data, as these are not prone to different interpretations. However, hospitals use different computer systems, like GLIMS, LABOSYS, MOLIS, or Labtrain, and even within the same program each hospital could set up its own feature. As a consequence, queries to obtain the data are not interchangeable between hospitals.

In the ATTACH study, we assembled data regarding transfusions, laboratory measurements, microbiology, and DBC codes in nine hospitals. As an ongoing study, most of the gathered data is incorporated into the Dutch Transfusion Datawarehouse, which will be updated regularly.[18] Other examples of such large transfusion databases are the Scandinavian Donation And Transfusion Database 2 (SCANDAT2) which we used in the study described in **chapter 8**, registers in Finland and Canada, or the REDS-III program in the United States.[19-22] In England, the National Health Service Blood and Transplant (NHSBT) planned to develop a transfusion dataset that can be downloaded from the hospitals into a datawarehouse.[23]

So, many efforts have been made to obtain transfusion databases and these will constitute a key element in future transfusion research. In the research described in this thesis, we applied the aforementioned methods to obtain and analyze data from various resources to assess safety and effectiveness of platelet transfusions.

The platelet concentrate: storage medium

As illustrated by the research presented in **chapter 7, 8, and 9**, transfusions are not without side effects and could even deteriorate the clinical situation of a patient. The thrombocytopenia for which hematological patients require platelet transfusions is often accompanied by neutropenia, leading to an increased risk of infections. The storage conditions of platelet concentrates facilitate ideal circumstances for bacterial growth once a product is contaminated.[24] These growth characteristics vary among storage media. Compared to plasma, bacteria initiate the log-phase faster in PAS and after 24 hours the concentration of bacteria is higher although the maximum bacterial concentration is similar in both storage media. In addition, there is less biofilm formation in PAS and this could potentially result in a larger amount of bacteria available for sampling and thereby a lower risk of false negative screening results.[25-27]

The incidence of transfusion transmitted bacterial infections is very low, approximately 22 per million platelet transfusions in the Netherlands. This corresponds to one case each year. Despite the fact that our database encompassed more than a decade, we could include only fourteen cases in the study described in **chapter 9**. Although comparing incidences between countries would result in more cases, this estimate would be confounded by differences in definitions, vigilance, transfusion indications and patient characteristics, which are hard to quantify. The distribution of storage media in the Netherlands provides the unique opportunity to

perform such a study within one country. In the additional analyses we have demonstrated that hemovigilance and patient characteristics were similar over the regions. The risk of transfusion transmitted bacterial infections was a fourfold increased after transfusion of PAS-stored platelet concentrates, although the aforementioned differences in growth characteristics did not result in an increased incidence of confirmed positive screening results. Apparently, the differences in growth characteristics do not result in differences at the moment of screening, but do make a clinical difference after storage. Whether the presence of proteins like complement in plasma contribute to this phenomenon requires further research.
Many attempts are made to further reduce the risk of transfusion associated infections with pathogen reduction technologies. These have the major advantage that it eliminates all kind of pathogens, including bacteria, viruses, and unknown pathogens. However, it could be questioned whether this is cost effective compared to current screening policies.[28] Based on the results of our study, it could be advised to use plasma as storage medium for platelet concentrates to reduce the risk of transfusion transmitted bacterial infections. However, PAS has several other advantages such as a lower risk of other transfusion reactions, like allergic reactions.[29-31]

Besides differences in safety profile, PAS and plasma stored platelet concentrates may also differ in effectiveness. Platelet concentrates stored in PAS-C had lower 1 and 24 hour corrected count increments compared to plasma stored platelet concentrates.[32,33] Newer generations of PAS showed similar *in vitro* quality characteristics as plasma.[29] More important from a clinical and patient's perspective are differences in bleeding rates. The aforementioned studies were not powered sufficiently to assess this outcome. The model described in **chapter 4** could be used to compare effectiveness of platelet concentrates between regions which use PAS or plasma stored platelet concentrates, similar as the approach used in **chapter 9**. However, the endpoint in the latter study, transfusion transmitted bacterial infections, was directly related to a single transfusion. Such a direct association cannot be assumed between transfusion and major hemorrhage. In addition, we described the large variation in clinical practice among hematologists in **chapter 2**. Whereas in one hospital a patient will receive a transfusion before removal of a central venous catheter when the platelet count is below $40x10^9$/L, this patient will receive this transfusion not before the platelet count drops below $10x10^9$/L in another hospital. This variation in daily practice challenges a direct comparison of the effectiveness of platelet concentrates stored in PAS or plasma, but with adequate adjustments for variation in clinical practice, studies based on routinely

collected health care data can be a valid guide in deciding which storage medium should be used and whether newer generations of PAS should be implemented. Nowadays, such decisions are based on the results of *in vitro* studies or trials that were powered on laboratory measurements, which are at most proxies for clinically relevant outcomes. Moreover, before a decision can be made which storage medium should be used, a cost effectiveness analyses should be made to take the stock of all clinical relevant differences in safety and effectiveness.

The platelet concentrate: storage time

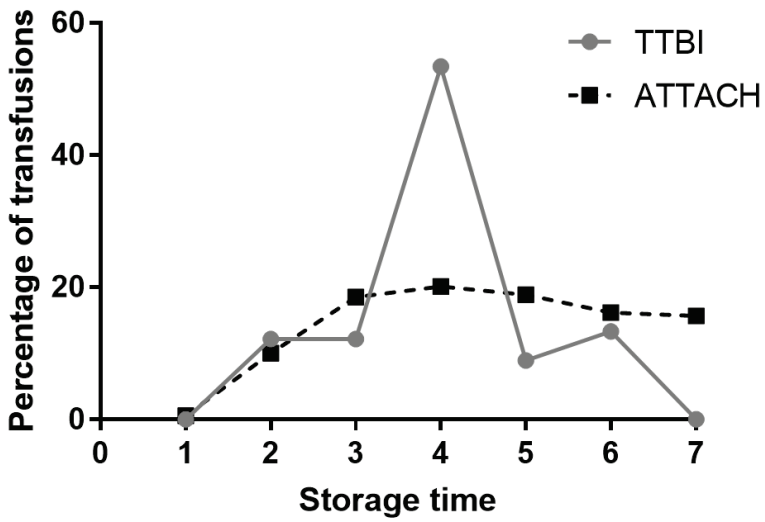
Besides storage medium, also storage time influences safety and effectiveness of platelet transfusions. As shown in **chapter 5 and 6** fresh platelets have better increments and showed superior survival and recovery. In addition, less transfusion reactions occurred after transfusion of fresh, non-leukoreduced platelets. The detrimental effect of storage time on risk of transfusion reactions was not seen when the platelet concentrates were leukoreduced. Hematological patients need more platelet transfusions when older products are transfused as the interval between transfusions is shortened and the risk of bleeding may increase with increasing storage time.

Although fresh platelets seems superior regarding several measures of effectiveness, safety concerns, especially bacterial infections, remain the main reason to restrict maximal storage time. This highly varies between countries, ranging from 3.5 days without bacterial screening to 5 or 7 days with the implementation of universal bacterial screening.[34] In March 2016, the FDA published a draft guideline in which they announced extension of maximum storage time up to seven days, provided that all products are screened prior to transfusion. However, up to date, no screening method has been certified as an adequate safety measure.[35]

The assumed increased risk of transfusion transmitted bacterial infections is based on several case reports of severe septic reactions after transfusion of platelet concentrates stored for four days or more.[36-39] In **chapter 9**, we specifically studied these adverse transfusion reactions. Storage time is recorded for eleven of the fourteen cases with transfusion transmitted bacterial infections. The median storage time of the products involved in these reactions was 4 days (IQR 4 to 5.5), compared to 5 days (IQR 3 to 6) for all products in the ATTACH study. However, storage time for products stored in PAS-B, which was used up to 2012, was restricted to 5 days and whereas 56.3% of the products involved in a TTBI was stored in PAS,

only 26.7% of the products in the ATTACH study were stored in PAS. Figure 1 shows the directly standardized storage time of products involved in TTBIs, compared to the storage time of all transfused products between 2005 and 2014 in the ATTACH study. This indicates that restriction of storage time to 5 days does not reduce the risk of TTBI and that safety concerns seems no valid reason to limit storage time to 5 days, under the condition that all products are screened by the BacT/Alert.

Figure 1. Storage time of transfused products involved in TTBI and the ATTACH study



In contrast to this assumed increased risk during storage, we showed in **chapter 7 and 8** that storage time was not associated with an increased risk of all-cause bacteremia. If anything, the risk even decreased with increasing storage time. In both studies, we used a positive blood culture of the recipients as a proxy for bacterial infections. Inherent to such a strategy is that we grouped transfusion transmitted bacterial infections with bacterial infections of all other causes. Rationale for this approach was that bacterial infections could be caused directly by the transfusion, but also indirectly via modulation of the immune system.

Transfusions could have an immunosuppressive effect, which is beneficial in transplantations and autoimmune diseases, but could be detrimental in oncological diseases and infections. Most research regarding transfusion related

immunomodulation focuses on red blood cell transfusions.[40-42] It has been speculated that the immunomodulatory effect of red blood cell transfusions could be attributed to the remaining platelets or plasma in the product.[40,43] In critically ill patients, neither red blood cell transfusions, nor plasma transfusions were associated with an increased risk of nosocomial infections, whereas platelet transfusions were identified as an independent risk factor.[44] It has been hypothesized that platelets not only play a role in hemostasis, but also have immunological capacity.[45,46] This theory is supported by the expression of HLA class I molecules and the ability to secrete mediators.[43,47] During storage, platelets lose the expression of HLA class I molecules and thereby the ability to stimulate antibody production. Moreover, only fresh platelets were able to modulate skin graft rejection in mice.[47] The potential immunomodulatory effect of fresh platelet may explain our findings of a lower risk of all-cause bacteremia after transfusions of older platelet concentrates. However, this remains speculation and the pathogenic mechanism explaining our findings has to be entangled.

The patient

Besides all aspects of the products, transfusing at the moment the patients benefit the most from it, remains the fundamental key of good practice. For hematological patients, the moment when to transfuse platelets seems clearly specified in the guidelines: prophylactically when the platelet count drops below $10x10^9$/L or therapeutically in case of bleeding.[48-50] However, recommendations are lacking for patients who may face an increased risk of bleeding or need an invasive procedure. The results of the survey described in **chapter 2** indicated a large variation in clinical practice, suggesting over-, as well as under-treatment of certain patients. In order to improve supportive care, risk factors of bleeding need to be identified and we need to know to which extent platelet transfusions are able to reduce this risk to enable the development of a personalized transfusion threshold for each situation.

As demonstrated in **chapter 3**, transfusions are not effective in all patients. Patients who have developed multiple HLA-alloantibodies require platelet concentrates from HLA matched donors. However, HLA highly varies among ethnicities and blood banks face the major challenge to find suitable donors for all immunized patients in the current multicultural society with mixing of cultures. Lack of an acceptable donor could even force physicians to refrain from treatment, as no adequate support can be supplied. Selective HLA typing of donors from all required ethnic backgrounds would increase the variation in HLA phenotypes in the current HLA-typed donor

population and enhance the availability of HLA matched platelet products for non-Caucasian, immunized patients.

The future

With the studies presented in this thesis we assessed the safety and effectiveness of platelet transfusions by using routinely collected health care data. Transfusion thresholds in specific situations and identification of risk factors for bleeding have not received much attention so far. Several challenges have to conquered to ensure the use of routinely collected health care data in the future to study these topics. The first issues which have to be addressed are the privacy of the patient, informed consent, confidentiality, security, and ownership of the data.[51-53] These are subject of an ongoing discussion and National and European laws and guidelines are changing. Obtaining informed consent from a large amount of participants can pose a financial and bureaucratic burden for research and when informed consent is routinely asked from all patients in a hospital, the 'informed' part of the consent may be violated. Not all possible studies are known at the moment the data is collected, which makes it impossible to fully inform patients about all future uses of the data. When historical data are used, asking informed consent can be a disproportional burden and invasion of personal life. It has been argued that explicit informed consent is not required for database research when data can be anonymized or analyzed at a group level. So, it remains a delicate balance between ethical ideals of data protection and informed consent on one hand and the use of gathered data for medical research on the other hand.

Within databases of routinely collected health care data, detailed information about signs and symptoms of the patient and considerations of the threating physician is lacking. This constitutes probably the most valuable part of information, but also the most challenging part to unravel. Manual review of medical charts is labor intensive and hampers the ability to examine large numbers of patients in an efficient manner. Natural language processing can automatically interpret this information and makes it available for analyses. It has been used for example for the identification of postoperative complications, but many investments are still needed to make it suitable for the analysis of all unstructured medical notes.[54,55] This wouldn't be necessary if registration is in such a way that data are also applicable for research purposes. A good initiative to promote this, is 'Registratie aan de bron', a program from the Nederlandse Federatie van Universitaire Medische Centra (NFU) and Nictiz to stimulate unambiguous registration and facilitate transmission of data between hospitals for research, bench marking, and quality control.[56,57]

To conclude, a close collaboration of researchers, clinicians, and ICT is needed to develop a digital system which does not interfere, but supports daily practice, improves efficiency, and enables optimal use of all recorded data. In addition, clinical knowledge and a strong epidemiological foundation are indispensable to convert the immense potential of big data into valuable, clinically relevant, research results.[12,58,59] When these requirements are met, studies regarding safety and efficacy of blood transfusion can focus on clinically relevant outcomes, reflect daily practice which will amplify generalizability, and in the end improve and personalize supportive care for all future patients.

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