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Short Communication

Blood Transfusion and Oncology-A Blessing in Disguise? A Commentary

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Introduction

Blood transfusion has been in the mind of people since ages as a substance that carries all the blessings of life, despite the serious events that happened during the époques where little or no knowledge existed on the characteristics of blood and its composition. The start of breakthroughs happened in the 19th Century, with a tremendous acceleration in the science of transfusion medicine during the 20th Century, which resulted in 23 Nobel laureates up till today [1]. With the socio-economic developments life expectancy has been improved in a growing number of populations spread over this globe [2]. With that we are now able to initiate long term observative studies to understand the slow developing effects of interventions leading to morbidities that become noticeable after years and years. Blood transfusion, be it whole blood or separated cellular components, when selected and prepared with caution and professionalism, seems time after time to generate blessings, supporting a lifesaving balance to occur in otherwise seriously life-threatening situations. That has opened numerous treatment doors for a manifold of disease entities all over the world, including the wide range of malignancies.

Patients with a malignancy might need blood transfusions because of the disease itself:

a) Some cancers, especially gastrointestinal and digestive system malignancies cause internal bleeding, which can lead to anaemia from too few red blood cells

b) Blood cells are produced in the bone marrow (haematopoiesis), the spongy centre of certain bones. Malignancies that start in the bone marrow (like leukaemia's and myelopathies like Kahler's and Waldenström's disease) or cancers that spread into the bones from other places (like prostate and breast cancer) may crowd out normal haematopoietic cells, leading to low blood cell counts (pancytopenia).

c) Patients who have had cancer for some time may develop anaemia of chronic disease. This anaemia is caused by certain long-term medical conditions that affect the production and lifespan of red blood cells (e.g., low dose chemotherapy).

d) Cancer can also lower blood cell counts by affecting organs such as the kidneys and spleen, which help keep enough red cells in the blood.

Treatment of malignancies may also lead to the need for blood transfusions:

a) Surgery to treat cancer may lead to blood loss and a need for red blood cell and/or platelet transfusions.

b) Most chemotherapy drugs affect haematopoiesis in the bone marrow. This commonly leads to low blood cell counts, and can sometimes put a person at risk for life-threatening infections due to low white cell counts, bleeding due to thrombocytopenia or threatening organ failure due to red cell shortages.

c) When radiation is used to treat a large area of the body including the bones, it can affect the bone marrow and lead to low blood cell counts.

d) Bone marrow transplant (BMT), cord blood or peripheral blood stem cell transplant (PBSCT) patients are treated with large doses of chemotherapy (ablative chemotherapy) and/or radiation therapy (total body). This destroys the existing haematopoietic or pluripotent stem cells in the bone marrow.

These patients often have very low blood cell counts after the myeloablative procedure and need supportive transfusions to bridge the period of depletion due to myeloablation.

Supportive Haemotherapy

Blood transfusion or haemotherapy is exclusively supportive, supporting curative or palliative interventions [3]. In that respect it may contribute to tipping the balance to curation or improving comfort of life. The major functions to support are oxygen delivery to the tissues, primary and secondary haemostasis and cellular immune capacity, especially the lymphocyte family. So far the scientific attention and interest has been focused on short term effects and outcomes, both adverse and beneficial, with limited data of medium and long-term follow up of transfused patients, irrespective the indication for supportive haemotherapy [4]. The major cellular immune effects so far studied are stimulation and modulation, tolerance and suppression. Clinically these cellular immune effects hardly ever occur isolated [3]. In cancer patients there is already a disturbance of the internal immune balance, which raises the question to what extend blood and blood components do have an effect or impact on this disturbed immune balance. Will it bring the balance back to (sub)normal, will it aggravate, or will it support cancer treatment and elimination? The other side of this coin is the fact that certain transfusion transmissible viruses like hepatitis B (HBV) and C (HCV) and biologic agents may cause cancer in recipients, e.g., of the liver [5]. Additionally, the immunomodulatory effect of transfused lymphocytes and various congenital and acquired immune system dysfunctions have been associated with increased risk of several neoplasms [3]. In relation to these questions the following could be hypothesised based on recent published studies on large cohorts of patients.

a) Could transfusion of blood or blood components lead to cancer in transfusion recipients?

b) Could blood or blood components of blood donors with subclinical neoplasms cause a malignancy in recipients.

c) To what extend might blood or blood component transfusion have an impact on recurrence of existing cancer?

Impact of Haemotherapy on the Development of Malignancies.

There is very limited data bases on cancer risks associated with blood transfusion. Since the late 1990s blood collected for transfusion of patients is all over the world tested by nucleic acid amplification, ruling out almost completely the risk for transmission of viruses causative for e.g., liver cancer like HBV and HCV. However, there may be other unknown viruses that could be transmitted and trigger neoplastic derangement of normal human organ cells when time of life allows [6]. The spectrum of transfusion transmissible biologic agents continuously grows where so far, neither the underlying mechanisms and biochemical pathways nor the clinical implications of transfusion related cellular immune effects such as modulation or suppression have been fully clarified. However, scientists speculate that transfusion of blood or blood components could increase the risk of cancer, be it medium or long-term in its expression e.g., non-Hodgkin lymphoma and liver cell cancer [7,8]. A prospective cohort of 37,337 older cancer free US women 55 to 69 years age with self-reported histories of blood transfusion (questionnaire) were followed over a period of 5 years [9], which disclosed 440 malignancies (4.6%), corresponding to a relative risk (RR) of 2.20 for non-Hodgkin lymphoma and 2.53 for kidney cancer. The RR for these malignancies were greater with decreasing time from first transfusion. No risk occurred for neoplasms of the breast, lung, uterus corpus, ovary, pancreas, colon and rectum, skin (melanoma), or for all malignancies considered together. The authors concluded that blood transfusion may be a risk factor for developing non-Hodgkin lymphoma and kidney cancer. Several other studies with substantially smaller cohorts varying from 621 (Sweden) [10] to 12,600 (Britain) [11] showed overall RRs of 1.04 to 1.12. However, in 2007 a proportionally large study from Scandinavia analysing a cohort of 888.843 cancer-free recipient of blood and blood components followed over a period of 34 years [7] reported that the marked increase in cancer risk shortly after a blood transfusion may reflect the presence of undiagnosed occult cancers with symptoms that necessitated the blood transfusions. The continued increase of tobacco and alcohol-related malignancies suggests that lifestyle and other risk factors contributing to conditions indicated blood transfusion rather than transfusion-related exposures *per se* are important to the observed cancer occurrence in the recipients with an overall initial standardised incidence rate (SIR) of 5.36 during the first six months, which decreased over a period of 2 years follow-up down to 1.10. This study showed that the initial 6 months SIR for malignancies of tongue, mouth, pharynx, oesophagus, liver, respiratory and urinary tract, and squamous cell skin neoplasms remained elevated for more than 10 years after the transfusion. The study covered a period before the routine nucleic acid testing for HCV and other mandatory transmissible agents of donated blood. The largest cohort studied so far is a British study published in 2016 [8] which included 1,299,246 women aged 52-60 recruited in 1998 and followed for an average of 12.7 years; 11,274 cancer-free women (0.86%) received a first blood transfusion in 2000 or later. In the years 2000-2013 (5 or more years after the first transfusion) a total of 160,041 malignancies occurred in the entire cohort (12.31%) of which 1,648 were in the 11,274 women (14.61%) who were first transfused in 2000 or later. Among the malignancies observed in the non-transfused and transfused group breast cancer occurred in 4.2% and 2.3% respectively, where colorectal cancer showed an incidence of 1.3% and 2.5%, and non-Hodgkin lymphoma 0.4% and 1.0% respectively indicating for these last two malignancies a transfusion association. Liver carcinoma showed an incidence of 0.009% and 0.22% respectively without correction for chronic alcohol consumption. The absolute risk for liver carcinoma calculated was 0.16 per 1000 patient years and for non-Hodgkin lymphoma 0.40 per 1000 patient years compared to 0.07 and 0.28

respectively for the non-transfused group, an outcome with high significance. Emerging evidence also suggest a possible association between some non-Hodgkin lymphomas and Epstein-Barr [12] and hepatitis G virus [13,14], which are not routinely screened for in donated blood.

The long-term excess risks for especially liver cancer and non-Hodgkin lymphoma following transfusion of blood or blood components seems evident. However, there is no information available on the immune capacities of transfused lymphocytes to support unravelling the underlying pathophysiology. Another interesting question to be answered is about the risk of cancer following transfusion with blood from donors who appear to have an undiagnosed subclinical malignancy. Sofar, there is little research done on transfusion complication with a delayed onset, such as the transmission of chronic disease agents and malignancies. Several investigators have explored the hypothesis of transmission of neoplasm triggering bio-agents causing on the long-term development of a malignancy in recipients of blood or blood components [9,11,15-21]. Pathophysiological mechanisms suggested include cellular immune function like modulation, factors causally related to neoplasm development, and engraftment of undetected tumor cells present in donor blood when transfused. However, repeatedly hypothetic associations of transfused oncogenic viruses like herpes viruses and Epstein-Barr virus that might trigger development of both solid and non-solid malignancies, e.g., Kaposi sarcoma and non-Hodgkin lymphoma, have been published [22-25]. Despite all the efforts there is still no clear conclusion to be drawn. In 2007 a joint Scandinavian and NIH Cancer Institute, Bethesda research was published in The Lancet [26], reporting on a retrospective study on the risk of cancer following transfusion of blood or blood components from blood donors with undiagnosed subclinical cancer at the time of blood donation. The focus was on potential transmission of viable neoplastic cells. Of a cohort of 354,094 eligible patients, 12,012 (3%) were exposed to blood components from regular blood donors with an undiagnosed subclinical malignancy diagnosed during follow up. Evidently there is no evidence that premalignant or malignant cells were present in the blood components transfused at the time of the index blood donation. However, evidence does suggest that the process leading to the development of cancer is lengthy and that circulating tumour cells do exist at an early stage of neoplasm development and might be captured during blood collection and subsequently transfused. Recipients were followed starting 6 months after the index transfusion to avoid misinterpretation of manifesting already existing malignancies in the recipient that might have triggered the transfusion indication. Additionally, the probability that transfusion-induced malignancies would become clinically evident within 6 months is extremely low, based on clinical experience with transplantation-transmitted malignancies. The report concludes: There is no evidence that transfusion of blood or blood components from undiagnosed precancerous otherwise healthy blood donors is associated with an increased risk of malignancies developed among recipients, compared with transfusion from cancer-free blood donors.

Impact of Haemotherapy on Recurrence and Mortality in Colorectal Cancer patients

Many hypotheses on reactivation or recurrence of cancer through allogeneic perioperative blood transfusion have been published. However, such exacerbation after surgical intervention in humans with e.g., colorectal cancer resection remains inconclusive. A relatively recently published (2018) study of a cohort of 4,030 colorectal cancer resection patients (stages I – III) who did (1,010) or did not (3,020) receive blood transfusion during the surgical intervention, were included in the study for a propensity score analysis [27]. After the propensity score matching each remaining group consisted of 486 patients (total 972) for analysis; no more unbalanced variables were found between the groups. The study compared disease-free survival and overall survival to evaluate the putative impact of perioperative blood transfusion.

Disease-free survival

The 3- and 5-years disease-free survival rates for the transfused and non-transfused group were respectively 71.4% and 66.7%, and 66.7 and 83.5%, and 83.3% and 80.3%. The transfused group showed a significantly higher cancer. recurrence risk of 1.41 ($p<0.001$) and the association was independent of pre-surgery anaemia.

Overall Survival

The overall 3- and 5-years survival for the transfused group was respectively 83.4% and 74.4%, where these were respectively 95.2% and 91.5% for the non-transfused group. After the propensity score matching, perioperative blood transfusion remained a significant risk factor of mortality with a HR 2.00. It is hypothesised that the detrimental effect of allogeneic blood transfusion on surgical outcomes in colorectal cancer patients are initiated by cellular immunological derangements caused by transfused lymphocytes. However, data on the composition and shelf life of the transfused units of blood or blood components were not available. A recent study showed that limiting transfusion dosages did not impact disease free intervention survival in colorectal cancer patients [28]. The authors conclude that perioperative blood transfusion was significantly associated with increased cancer recurrence and overall mortality in patients after curative colorectal cancer resection, independently of preoperative anaemia status. The blessing of the study is in the scientific provision of better insight into elucidating the association among transfusion of blood and blood components, anaemia, and postoperative oncologic outcomes in colorectal cancer surgery.

Epilogue

Blood transfusion has shown to be a most valuable supportive treatment contributing strongly to survival and comfort of life

A propensity score is the probability of a unit (e.g., person, classroom, school) being assigned to a particular treatment given a set of observed covariates. Propensity scores are used to reduce selection bias by equating groups based on these covariates

of millions of people. However, despite all the blessings daily experienced all over the world, there also situations in which the expected blessings seem to profile blood transfusion in a disguise, which particularly show up as a long-term effect. Clinicians and transfusion medicine specialists are urged to include the medium- and long-term evaluations of transfusion practices in their considerations, indication settings and decision taking when prescribing supportive haemotherapy as an important contribution to patient safety [28,29].

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