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Guest Editorial

Transfusion and alternatives therapeutic support for oncology patients with hematological problems: "Are we doing more harm than benefit"?

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1. Commentary on transfusion for oncology patients' theme: The path sustaining a better quality of care

Transfusion support for cancer patients, with hematological or oncological problems, is a multifaceted challenging medical intervention for clinicians. Management strategies must take into account associated complications related to surgery, chemotherapy and radiation, possible hematopoietic stem cell transplantation [HSCT]; and wide spread metastatic disease. In the absence of clear recommendations guiding transfusion in cancer patients, transfusion thresholds are often empiric with great inter- and intra-institutional variability.

Beyond the known reactions and infectious risks of transfusions, transfusion of red blood cell [RBCs], platelets [PLT] and plasma could negatively alter the immune system and have a deleterious effect on cancer, favoring disease progression and relapse.

Moreover, chronic oncology/hematology patients may require specialized or modified components or alternative support presenting newer challenges for suppliers in terms of the selection of the best-fit therapeutic modality delivered in a timely manner.

This theme aims to highlight some of the most challenging issues of transfusion support for oncology patients, based on the problems that are often encountered by both clinicians and components suppliers, where some uncertainty exists also whether we are doing more harm than benefit.

We also briefly discuss the requirements for product selection based on the ABO group; the need for component modification to reduce the potential for alloimmunization/immunomodulation, the role of validated alternative therapies for oncology patients and transfusion/infusion related side effects, based on the reported concise review by W L Schulz & E L Snyder [1].

Finally, in respect to where we are going, emphasis is placed on the need for continual quality improvement of various products/processes, referring to newer technological advances such as proteomics and interatomic analysis of blood components and the roles of some membrane/cytosolic blood cell-derived extracellular vesicles, based on the lessons learned from the current state of the art technologies. The potential role of the microbiota of both donors and transfusion recipients will also be addressed.

2. RBC therapy for cancer patients: indication, product selection/modification

It is well documented that cancer patients with hematological and oncological problems frequently suffer from cancer associated anemia often aggravated by surgical interventions resulting in blood loss as well as chemotherapy or radiotherapy affecting bone marrow production. Patients are, therefore, in need of highly specialized transfusion support, compared to other patient populations [1]. This makes effective transfusion support with minimal side events more challenging for clinicians. Moreover, in view of the fact that oncology patients have more frequent exposures to blood components and are often immunocompromised they are at greater risk of transfusion associated-graft *versus* host disease, alloimmunization to cellular antigens and microparticle-induced immunomodulation, all current focus areas that remain to be fully resolved. Transfusion-induced immunomodulation [TRIM] can furthermore suppress the immune system of oncologic transfusion recipients; a building body of evidence suggests that transfusion can have a negative effect on survival and cancer recurrence rates [2,3].

From a clinical stand point and, in line with all other cases of anemia, we need to increase the oxygen carrying capacity of anemic cancer patients with the most effective available products while maintaining patient safety and hemostatic balance.

Unfortunately, in the absence of evidence based guidelines for transfusion, significant variability is noted in transfusion practices between and even within different cancer treatment centers. The relevant question that rises immediately is the hemoglobin transfusion threshold for this heterogeneous clinically ill patient population and the role of restrictive transfusion policies. There is no evidence to support that Hb levels higher than 70–100 g/L provide any superior therapeutic benefit and in fact "hypetransfusion" or unnecessary transfusions may introduce additional harm and negatively impact clinical outcomes [3]. Oncology

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patients should, hence be treated for systematic anemia with predetermined local hospital policies for oncology patients [1].

Hematopoietic stem cell transplant [HSCT] recipient, represent even more challenges for transfusion services as they require special blood components such as leukocyte-reduced cellular products, cytomegalovirus (CMV)-seronegative, and/or -irradiated components that will add cost and are a burden to transfusion medicine [4]. Products should be delivered in a timely manner with thorough incompatibility assessment. Component alternatives and continuous quality and safety improvements at all levels and adherence to criteria of acceptability is essential and should be aligned with current regulatory surveillance.

During cold storage in an artificial environment, red blood cells undergo time-dependent deterioration in several physiological aspects, collectively known as the "RBC storage lesion". Therefore, improving our understanding of the storage lesion at a molecular level is useful to take a critical step toward the continual improvement of blood processing and storage conditions, though be it these might not be the only causes of the multifaceted storage lesion, as both good storers and bad storers' donors exist and the synergic influence of the recipients health should always be taken into account [5,6]. The role played by the donors and recipients microbiome may also be of importance in the future [7].

As gleaned through multivariate analysis of metabiomics data from different storage media, the mechanisms of the storage lesion of RBCs are multifaceted embodying specific 3-stage metabolic sequences. This includes the influence of oxidative stress on functional proteins such as hemoglobin and anti-oxidant enzymes and energy and redox homeostasis in stored RBCs, such as in the case of alkaline additives or hypoxic storage of erythrocyte concentrates. Finally, the role played by energy and redox metabolic reprogramming during storage, associated with irreversible vesiculation and impaired morphology and functionality translates into *in vivo* survival as well as possible untoward reactions in some individuals and, likely, a negative outcome in cancer patients [5,6,8,9].

All blood components, without exception, undergo a variable loss of potency during storage [10]. This is of critical importance in cancer patients, as even a loss of potency of about 20% with modern additive solutions has some clinical significance because 6 units of red cells must be given to achieve the effect of 5 fully potent units, which is against the goal of restricted blood usage.

3. Platelet support for cancer patients: indication; products selection/modification and reduction of potential untoward effects

Platelet (PLT) support is a first line therapy for acute hemorrhage in thrombocytopenic patients with hematological or non-hematologic malignancies to prevent or stop bleeding.

Storage-related potency loss is once again on center stage as the discrepancy between the amounts of PLTs recovered after transfusion is even greater than in RBCs. About one-third of the transfused platelets become sequestered in the spleen and about 30% of the remainder is reportedly lost due to storage lesions. Therefore, approximately 50% loss must be due to degeneration during storage [10].

Moreover, the use of ABO – mismatched platelets in oncology patients leads to decreased therapeutic benefit or adverse reactions such as refractoriness, mediated by ABO antibodies clearing platelets from the circulation minutes to hours after infusion [11]. ABO incompatibility also promotes HLA alloimmunization in multi-transfused patients and could potentially cause hemolytic transfusion reactions. Accordingly, ABO-matched platelets are recommended for oncology patients with low platelet counts, and the use of apheresis products, which lower red cell contamination is preferred.

Since leukocytes contaminants remain the main reason for alloimmunization and hence refractoriness, the best strategy to reduce immune- related refractoriness is prevention of HLA and platelet antigen exposure by conservative transfusion, rather than seeking remedial action. Moreover, it is highly desirable that PLT units are modified to maximize their safety for oncology patients by using leukocyte reduction, volume reduction, and gamma irradiation as for red cell support. Although of questionable efficacy, cross matched ABO-Compatible and HLA-matched PLT transfusions remain the cornerstone of therapy in thrombocytopenic patients refractory to regular PLT transfusion [12]. The deleterious effects of platelet transfusion on cancer growth and metastasis have been widely highlighted in the literature but have not been demonstrated by controlled randomized trials [13].

4. Newer approach in the use of enriched granulocytes in support of oncology patients with severe neutropenia

Granulocyte support is not addressed in a separate article in this theme.

A healthy individual produces approximately $2–3 \times 10^{11}$ polymorph nuclear cells/m^2 per day, enabling them to clear significant bacterial or fungal infections. For patients whose marrow cannot support such a level of production, doses of 1×10^{11} granulocytes per square meter of body area are used as supportive replacement.

It is well established that G-CSF stimulation in healthy donors is modestly effective for treatment of bacterial and fungal infection, though there is no difference in success rates between antibiotic and granulocyte therapy [1]. The later must be ABO-compatible with the intended recipient and products cross matched before transfusion as such products may have up to 6–12% red cell contaminants. The products may also contain large number of platelets and white cells with the potential risk of alloimmunization and patients alloimmunized to HLA often demonstrate reduced response to granulocyte infusion requiring antigen matching.

Whilst currently granulocyte transfusion support is becoming popular, the decision to initiate such a therapy is only made when all other forms of therapeutic modalities have failed and only is relevant for patients with a reasonable chance of sustainable marrow recovery after resolution of the underlying infection. Oncology patients are still at risk of CMV exposure from transfusion; leukocyte reduction filters must never be used and the infusion must be done through a 150–260 μm filter.

Finally, it should be noted that oncology patients receiving multiple hematopoietic stem cell units are more susceptible to a toxic event associated with DMSO, a chemical used in majority of cryopreservatives which allows for the controlled freezing and thawing of mononuclear cells while maintaining membrane integrity. The granulocyte content also needs to be controlled in view of potential transfusion – acute lung injury – like events [1]. While considerable progress has been made so far with technological advances producing safer and cleaner products, much remains to be done.

5. Plasma and plasma-derived products for transfusion support

Plasma is the liquid part of blood separated by centrifugation that carries nutrients, waste products, antibodies, proteins, lipids, hormones, endothelial cell permeability factor and, of course, all blood cells and their fragments through the body. Evidence is accumulating that the presence of at least 30% residual plasma in platelet storage media leads to better functionality during prolonged storage. From the laboratory stand point plasma is a