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Supportive transfusion therapy in cancer patients with acquired defects of hemostasis

Augusto B. Federici*, Daniela Intini, Antonella Lattuada, Chiara Vanelli, Luisa Arrigoni, Elisabetta Sacchi, Umberto Russo

Hematology and Transfusion Medicine, L. Sacco University Hospital and Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

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ABSTRACT

Bleeding occurs in approximately 10% of patients with cancer: supportive transfusion therapy with Platelets Concentrates (PC), Fresh Frozen Plasma (FFP) and plasma-derived or recombinant concentrates is often required for the cessation and prevention of the bleeding episodes. The most frequent causes of bleeding in cancer is thrombocytopenia followed by liver insufficiency with or without vitamin K deficiency, disseminated intravascular coagulation (DIC) and the inappropriate or excessive use of anticoagulants. Other acquired hemostatic defects such as acquired hemophilia (AHA) and acquired von Willebrand syndrome (AVWS) are rare but they can be life-threatening. Thrombocytopenia in cancer patients may be the consequence of marrow invasion, chemotherapy or platelet auto-antibodies; patients with severe hypoproliferative thrombocytopenia, must be treated with PC and carefully followed to assess refractoriness to PC. The management of the other acquired defects of hemostasis usually requires the use of FFP and specific plasma-derived or recombinant concentrates. PC, FFP and plasma-derived concentrates can induce complications and/or adverse events in cancer patients: these include mainly allergic (ALR) or anaphylactic reactions (ANR), Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD), Trasfusion-transmitted bacteriemia (TTB), Transfusion-Related Acute Lung Injury (TRALI), Acute Hemolytic Transfusion Reactions (AHTR), Febrile Non Hemolytic Transfusion Reactions (FNHTR). Therefore, modifications such as leukocyte-reduction and irradiation of the blood components to be transfused in cancer patients are recommended to reduce the risk of these complications.

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Introduction and general definitions

Acquired hemostatic defects (AHD) may occur in cancer patients and may involve the entire cascade of interactions among vascular endothelium, platelets and the multiple plasma proteins that ultimately results in the conversion of fibrinogen to fibrin, and cross-linking of fibrin by activated FXIII, which stabilizes the formed clot. Qualitative or quantitative deficiencies of any of these hemostatic factors involved in these cascade reactions may be associated with clinical significant bleeding disorders [1-3]. The main acquired defects of hemostasis associated with cancer requiring supportive transfusion therapy because of bleeding are listed in Table 1: they can involve single hemostatic factors or can be more complex, when more hemostatic factors are defective.

Allogeneic Blood Transfusion (ABT) support for cancer patients is a complex and multifaceted medical therapy meant to overcome the complications related to chemotherapy, radiation, transplantation, or widespread metastasis. For these patients, greater attention must be paid to the preparation, modification, and response to blood components to ensure better outcomes [4,5].

Thrombocytopenia and other Platelet Disorders

Thrombocytopenia results from reduced production, increased destruction or sequestration (i.e. from splenomegaly) of platelets, and is the major cause of bleeding in untreated cancer patients. However, low platelet counts in malignancy are most frequently encountered as a result of chemotherapy with cytotoxic medications [1-3]. Other causes include marrow invasion/infiltration or immune thrombocytopenia (ITP). Significant invasion of the marrow by tumor cells may occur in leukemia or in advanced metastatic disease. ITP is most commonly in association with lymphoid malignancies (i.e. chronic lymphocytic leukemia) or with lung, breast and testicular cancers. The overall frequency of this complication in lymphomas is 0.4-1%. In most malignancies, thrombocytopenia is usually the more significant cause of bleeding compared to platelet dysfunction. However, in myeloproliferative neoplasms (MPN) especially in Essential Thrombocythemia (ET) bleeding

* Corresponding author at: Hematology and Transfusion Medicine, L. Sacco University Hospital, Department of Clinical Sciences and Community Health, University of Milan, Via F. Sforza 35, 20122 MILANO, Italy. Tel.: + 39 02 5031 9895; fax + 39 02 5031 9897.
E-mail address: augusto.federici@unimi.it (A.B. Federici).

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Table 1
Acquired defects of haemostasis with bleeding requiring transfusion therapy

A) Deficiencies of single hemostatic factors
1) Thrombocytopenia related to cancer
2) Immune thrombocytopenia associated or concomitant with cancer
3) Ipo-dis fibrinogenemia
4) Circulating anticoagulants: acquired hemophilia A
5) Acquired von Willebrand Syndrome

B) Complex deficiencies with more than one hemostatic factor
1) Disseminated intravascular coagulation
2) Liver insufficiency
3) Vitamin K deficiencies
4) Excessive or inappropriate use of anticoagulant and anti-platelet agents
5) Massive blood transfusion

rather than thrombosis may occur with an elevated platelet counts, due to the association with acquired von Willebrand Syndrome (see below). Dysproteinemia leads to qualitative platelet abnormalities usually as result of paraproteins coating the platelets [1-3]. Platelet dysfunction or thrombocytopenia is observed in IgG Myeloma (15%), IgA Myeloma (38%) and Waldenstrom's Macroglobulinemia (60%).

Supportive Transfusion Therapy with Platelet Concentrates

Platelet concentrates (PC) can be prepared from more than one unit of whole blood (WB-PC or Pool random donor-PC) or by apheresis of a single blood donor (Single Donor PC or Apheresis PC) and can be used in patients with severe thrombocytopenia or severe inherited or acquired platelet defects. WB-PC or Pool random donor-PC are prepared by centrifugation of whole blood, although the centrifugation techniques used in Europe and Canada differ from those used in USA [4,5]. At least 75% of these units must contain 2.5 X 10^{11} platelets and each blood bank should be able to provide an estimate from their quality control data. Although there is no required volume of this type of PC, the volume is usually about 50 mL. Single Donor PC or Apheresis PC is a suspension of platelets in plasma prepared by cytoapheresis. This type of PC is processed, tested, and labelled in a manner similar to that for WB-Pool-random-donor-PC: this includes ABO and Rh typing, and required testing for all transfusion-transmitted diseases. Each single donor PC contains very few red cells so that red cell crossmatching is not necessary. Apheresis procedures separate leukocytes from platelets, so that Single Donor PC produced by apheresis are usually considered to be leukocyte-reduced PC. The quality of PC sometimes does differ between pooled and apheresis Units. Markers of platelet activation, such as P-selectin, are increased in WB-PC or Pool random donor-PC as compared to Apheresis PC. These changes however, have not correlated with poor in vivo platelet recovery. Therefore, current evidence does not suggest that apheresis PC are a more viable platelet option. As far as PC reactions (see below), large trials have revealed no difference in adverse events between these two types of PC [5].

Transfusion of PC for cancer patients is indicated to stop or prevent bleeding in the setting of thrombocytopenia. The use of PC for acute bleeding in cancer patients with low platelet count or receiving antiplatelet medications is a first line therapy. Rebulla et al reported that, in patients with acute leukemia undergoing first induction of remission, there was no difference in deaths, red cell transfusions or severe hemorrhage, but there was a 21.5% reduction in PC use adopting a transfusion threshold of 10,000/uL compared to 20,000/uL [6]. The guideline of a platelet count of 10,000/uL for prophylactic transfusion applies to the stable, uncomplicated patients: however, many cancer patients are febrile, have severe mucosal bleeding or have other complications that necessitate PC transfusion at higher platelet counts [7]. Much greater controversy exists, however, in the consideration of PC for bleeding prophylaxis. More clinical data on the issue of PC prophylaxis in cancer patients have been collected since 2010. Slichter et al designed a trial of prophylactic PC transfusion to evaluate the effect of the PC dose on bleeding in patients with hypoproliferative thrombocytopenia (PLADO: Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients): they randomly assigned hospitalized patients with cancer to receive prophylactic PC at low (1.1 X 10^{11}), medium (1.1 X 10^{11}) or high (1.1 X 10^{11}) dose when platelet counts were 10,000/uL. They could conclude that low doses of PC administered as prophylaxis led to a decreased number of PC transfused per patient but an increased number of transfusion given: however low and high doses had no effect on bleeding [8]. One important information of the PLADO study was the separate analysis of pediatric patients performed by Josephson who showed that bleeding risks are higher in children than in adults [9]. The therapeutic PC transfusion versus routine prophylaxis approaches in patients with the hematological malignancies were investigated in two different trials [10,11]: Wang et al concluded that the therapeutic strategy could become a new standard of care after autologous stem-cell transplantation but prophylactic PC transfusion should remain the standard for patients with acute myeloid leukemia [10]. In the most recent study, Stanworth et al concluded that there is a need for the continued use of prophylaxis with PC transfusion and could show the benefits of such prophylaxis for reducing bleeding as compared with no prophylaxis: nevertheless, they reported that a significant number of patients had bleeding despite prophylaxis [11].

Because of their immunosuppressed state, many cancer patients are at high risk for transfusion associated graft-vs-host disease (TA-GVHD), since donor lymphocytes generate a profound immune response against the recipient's cells. PC contain contaminating leukocytes that can allommunize transfusion recipients, leading to multiple problems [12], as summarized in Table 2. The indications for leukocyte-reduced PC are all those conditions that are described as complication and/or adverse reactions to blood transfusions (see below for detail): a) prevention of alloimmunization to leukocytes and platelets; b) prevention of transmission of cytomegalovirus (CMV); c) treatment of patients with multiple febrile transfusion reactions; d) prevention of immunomodulatory effects of transfusions. The prevention of TA-GVHD does require also the PC irradiation, usually gamma irradiation. The irradiation results in the generation of electrons which damage DNA of lymphocytes and therefore make the lymphocytes unable to proliferate. Table 3 lists the clear indications, the indications deemed appropriate by most authorities, and the indications for which irradiation is considered unwarranted by most authorities for irradiated PC. The clinical effectiveness of leukocyte reduced PC in plasma or additive solution have been reported in detail in one study [5,13]. There is a dose-response effect from PC transfusion. Within 1 hour after transfusion, the platelet count increases by approximately 10,000/uL when 1 X 10^{11} platelets are transfused into a 70 Kg patient [4,5]. Since PC products contain approximately 3.5-4.0 X 10^{11} platelets, the platelet count should increase by 35,000-40,000/uL in an average size adult. In order to achieve these increases in platelet count, 4-6 WB-Pool random donor-PC or 1 Platelet Apheresis Concentrate are used. The 1-hour post-transfusion platelet count is an excellent predictor of an effective PC transfusion and can be used to calculate the 1-hour Corrected Count Increment (CCI) or the percent recovery. The expected CCI is about 15,000/uL X 10^{11} platelet transfusion per square meter of body surface area. If the CCI is <5,000-7,500, the patient is

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