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Management of thrombocytopenia in cancer

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ABSTRACT

Thrombocytopenia is a common finding in cancer patients and can have different and/or multifactorial pathogenesis. While in solid tumors it occurs often as a consequence of chemotherapy treatment, it is frequently observed at diagnosis in patients with hematological malignancies being aggravated to a potentially life-threatening level during chemotherapy. Other associated conditions (infections, drugs, consumption coagulopathy etc.) can add to influence the degree of thrombocytopenia and the inherent risk of bleeding and they should be recognized and corrected to improve platelet count. Platelet transfusion remains the cornerstone of treatment, but its use should always be weighted taking into consideration the actual risk of bleeding to avoid inappropriate use and wasting of resources. While in hematological malignancies a threshold level of 10,000 platelets/μL is widely accepted as the minimal level prompting prophylactic platelet transfusion, this limit is less frequently observed in patients with solid tumors and platelet transfusions are usually administered for a few days, possibly at a higher platelet level. Alternative treatments for the latter patients including thrombopoietin-mimetic agents are increasingly used and found to be promising.

1. Introduction

Thrombocytopenia in patients with solid tumors is mainly associated with the use of myelotoxic chemotherapy regimens resulting in hypo-proliferative thrombocytopenia, and more rarely with bone-marrow involvement by tumor cells, disseminated intravascular coagulation (DIC) or use of certain drugs (e.g., heparin). Patients with blood malignancies are at higher risk of thrombocytopenia, mostly because of bone-marrow infiltration at diagnosis, and it can be often profound, recurrent and long-lasting with associated chemotherapy treatment. In addition, in certain circumstances DIC, splenomegaly or true immune thrombocytopenia (e.g. during chronic lymphocytic leukemia) resulting in enhanced platelet destruction contribute to the heterogeneity of pathophysiology of thrombocytopenia in hematologic malignancies [1].

In this article, we will concisely review the state of the art of the management of thrombocytopenia in cancer patients, and in particular with blood malignancies, in which thrombocytopenia may significantly influence morbidity and the risk of death.

2. Frequency and factors determining thrombocytopenia and bleeding in cancer patients

In patients with solid tumors, chemotherapy is the main determinant of thrombocytopenia. This often causes delays of subsequent chemotherapy cycles or a reduction of the dose of the agents used, with possible significant impact on outcome. While several regimens have been developed to reduce myeloablative effect of the chemotherapy, in some tumors the combined effect of specific antitumoral drugs may be more relevant in inducing thrombocytopenia. For example, Cisplatin alone may cause grade III (platelet count 25–49.000/μL) or IV (< 25,000/μL) thrombocytopenia in 4% of treated patients and Gemcitabine in 3.7% of patients, while in combination at various dosages they may induce thrombocytopenia in up to 37% of cases [2]. In aggressive protocols for sarcomas including ifosfamide, doxorubicin and dacarbazine, this figure may reach 79% of cases. However, data on 10,582 regimens showed that platelet transfusions have been used in 2.5% of cases only [3].

Nearly all patients with B-cell follicular lymphoma treated with Ibritumomab tiuxetan conjugated with Yttrium-90 have grade III or IV thrombocytopenia while the same grades may be observed in up to 31% of patients with myeloma treated with Bortezomib [1].

Patients with acute leukemia and other hematologic cancers are at highest risk of thrombocytopenia already at diagnosis and platelet count rapidly decreases further during chemotherapy and platelet transfusions invariably administered. This clinical setting has been particularly evaluated in terms of bleeding risk, predictors of bleeding, and quality of treatment results [4]. Several parameters have been suggested to increase the risk of bleeding in thrombocytopenic patients with acute leukemia and bleeding can still persist even after adequate

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supportive treatment. Fever, DIC, minor bleeding the day before severe bleeding onset, amphotericin B administration, and anemia have been suggested among all as useful parameters to predict the risk of severe bleeding in these patients [4,5]. Acute promyelocytic leukemia (APL) stands separately among the different subtypes of acute myeloid leukemia for its peculiar coagulopathy/hyperfibrinolysis associated with the lowest platelet count at diagnosis [6]. Thrombocytopenia has been associated with increased risk of fatal bleeding in some but not all the largest studies on APL so far published, mainly along with high blast cell count, low fibrinogen, creatinine level [6]. The early start of all trans retinoic acid treatment has now significantly shortened this period at risk of severe bleeding mainly improving rapidly the coagulopathy, but yet fatal bleeding may occur during the first days from diagnosis [6].

3. The quality of sources: platelet concentrates

Platelet transfusion is the elective procedure to prevent or treat bleedings in patients with hypo-proliferative thrombocytopenia due to hematological disorders, bone marrow infiltration, chemotherapy or hematopoietic stem cell transplantation [7].

Platelet products for transfusion can be obtained both after platelet separation from whole blood of pooled donors and from apheresis of a single donor. Platelet concentrates (PCs) from pooled donors, usually known as random-donor platelets, are obtained through different methods in USA and Europe, consisting in platelet-rich plasma method and buffy coat method.

Both of them allows to obtain PCs with approximately 0.5 to 0.75×10^{11} platelets/unit, in a volume of approximately 50 mL of plasma. The buffy coat method results in less white blood cells (WBC) contamination, but the amount of residual WBC must be considered for immunosuppressed and/or chronic thrombocytopenic patients. Red blood cells (RBC) could also be contained. PCs are usually stored at 20–24 °C using continuous gentle horizontal agitation up to 5 days.

Single donor platelets are produced by apheresis through a blood-cell separator centrifugation system that removes the platelets and returns the plasma and RBC to the donor. A bag of apheresis volume is about 200 mL, and must contain at least 3×10^{11} platelets in the 75% of the tested products.

Because of the presence of few RBC end WBC, platelet apheresis (PA) does not need red cell cross-matching and are considered as leukocyte-reduced. The platelets from apheresis can be stored for up to 5 days at 20 °C to 24 °C in the same manner of random concentrates. The cost of the procedure is generally higher compared to the preparation of PCs [7,8].

4. How to choose between PCs and platelets from PA

The amount of transfused platelets is equivalent by using one apheresis or 4–6 random PCs. There is no evidence of different efficacy of platelet count recovery by using these different products, especially in patients occasionally in need of platelet support. However, for cancer patients who are usually immunosuppressed and that could have low platelet count for long time, the different content in WBC should be considered [9]. Donor leukocytes could produce an immune response against recipient cells and lead to an allo-immunization of transfusion recipient and a transfusion associated graft versus host disease (TA-GVHD) [9].

The expected increase of platelet count in a patient of 70 kg of weight after transfusion of an average amount of $3.5–4.0 \times 10^{11}$ platelets (estimated contents of 4–6 random PCs or 1 PA) is 35,000–40,000/μL. A platelet count after 1 h from platelet transfusion is useful to estimate the effectiveness of the platelet transfusion by calculating the 1-hour Corrected Count Increment (CCI). The CCI is calculated with the following formula: absolute increment of platelet count × body-surface area (m^2)/number of platelets transfused $\times 10^{11}$. The expected CCI is about 15,000/μL $\times 10^{11}$ platelets transfused per square meter of body surface area. If the CCI is $< 7.5 \times 10^9$/L at 1 h or $< 4.5 \times 10^9$/L after 24 h, the patient is to be considered as refractory.

5. Refractoriness to platelet transfusion

Alloimmunization against HLA antigens occurs in about 25–35% patients with new diagnosis of acute myeloid leukemia (AML) receiving random PCs, and is responsible for refractoriness to platelet transfusions [10,11]. A diagnosis of refractoriness should be made after at least two platelet transfusions with ABO-matched products stored for < 72 h. In order to reduce this risk, PA should be preferred due to lower WBC number; if PA is not available, PCs must be filtered at the blood bank or at bedside since it has been demonstrated that leukocyte reduction in blood components reduces the frequency of HLA alloimmunization and platelet refractoriness. However, notwithstanding this preventive approach, up to 18% of patients become HLA alloimmunized and 3% develop immune-mediated platelet refractoriness [12].

Patients who become refractory to platelet transfusions should be treated with HLA –matched products. There are no evidences that transfusion of non-HLA compatible platelets, which do not induce platelet recovery, could produce a clinical benefit in refractory patients. It should be noted however that a recent Italian survey among hematological centers showed that in clinical practice only 11% of Centers monitor platelet count 1 h after platelet transfusion and that 30% of Centers continue to transfuse platelets in refractory patients regardless the presence of bleeding [8].

Other non-immunological causes that could contribute to a reduced efficacy of platelet transfusions are consumption due to active bleeding, fever, drugs (e.g. amphotericin B), micro-angiopathies or DIC and splenomegaly. All these conditions should be evaluated and, when possible, treated.

The prevention of TA-GVHD requires the irradiation of PCs or AP, usually performed with gamma rays that produce leukocyte DNA damage. The conditions with an high risk of TA-GVHD are represented by heavy immunosuppression, like hematopoietic stem cells transplantation (HSCT) and hematological malignancies.

Platelet express surface ABO antigens, suggesting that ABO-matched transfusion should be the best option. However, the limited platelet concentrate availability could make this choice not always feasible. In this case the most important feature to be considered is the presence of anti-A or anti-B antibodies present in the plasma of the PCs or PA, that could produce hemolysis in the recipient. Patient's anti-A or anti-B antibodies against the transfused platelets could impair the platelet recovery after transfusion, but the clinical consequences in this setting are unclear.

Platelets do not express RhD antigen. However, PCs could contain RBCs as contaminant. PCs from a RhD positive donor transfused in a RhD negative recipient could then lead to an alloimmunization against RhD. This should be considered in particular in RhD negative females of childbearing age, who could have indication to receive anti-D immunoglobulin in case of transfusion with RhD-positive platelet units. In other cases the Rh match does not seem to be of relevance [7–9,13].

6. Bleeding prophylaxis and treatment

In case of an active bleeding in patients with cancer related thrombocytopenia, platelet transfusion is the first line of therapy if bleeding is considered related to thrombocytopenia. On the other hand, several studies have been conducted to establish how to prevent bleeding in asymptomatic thrombocytopenic patients.

Two randomized clinical trials have demonstrated that prophylaxis with platelet transfusions reduced the incidence of WHO grade 2 to 4 bleeding events in patients with cancer related hypo-proliferative thrombocytopenia. No clear recommendations were obtained for