New Strategies for Prophylactic Platelet Transfusion in Patients with Hematologic Diseases

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ABSTRACT

There is an increasing demand for platelet transfusions due to intensive chemotherapy and blood stem cell or bone marrow transplantation for the treatment of hematologic and oncologic diseases. There has been a long-lasting debate over whether the traditional threshold for prophylactic platelet transfusion of 20,000/µl is really necessary to prevent hemorrhagic complications. During the last 10 years several studies with more than 1,000 patients together have proven the safety of a platelet transfusion trigger of 10,000/µl or even lower when patients are clinically stable without active bleeding. This experience has been mostly gathered in patients with acute leukemia. But this stringent platelet transfusion policy can be used also after blood stem cell and bone marrow transplantation. In stable patients with aplastic anemia and myelodysplasia, prophylactic transfusions should be replaced in most patients by a therapeutic transfusion strategy. Such restrictive platelet transfusion strategies decrease the risk of infectious disease transmission, immunization, and febrile transfusion reactions. Besides reduced hospital visits and a shorter hospital stay for the patients, the costs for platelet transfusions are lowered by 20%-30% compared with traditional transfusion strategies. The decision to administer platelet transfusions should incorporate individual clinical characteristics of the patients and not simply be a reflexive reaction to the platelet count. Further clinical studies are needed to answer the still open question of whether patients with acute leukemia should also be transfused therapeutically rather than prophylactically when they are in stable condition without signs of active bleeding. The Oncologist 2001;6:446-450

INTRODUCTION

Since the 1960s, platelet transfusion therapy has played a major role in the management of patients with hematologic and oncologic disorders with intermittent or long-lasting thrombocytopenia. Platelet transfusion is used therapeutically, to achieve hemostasis in the bleeding patient with nonimmunologically mediated thrombocytopenia, or prophylactically, to prevent hemorrhagic complications by maintaining the platelet count above a predetermined threshold. Based on a landmark study by Gaydos et al. [1], the threshold was set at a platelet count of 20,000/µl. However, this study did not support the concept of a clear threshold for prophylactic platelet transfusion.

According to a survey of the Transfusion Practice Committee of the American Association of Blood Banks in 1992, more than 70% of hospitals transfused prophylactic platelets primarily for prophylaxis. More than 80% of these hospitals set the threshold at 20,000/µl or even higher [2]. There is an increasing demand for platelet transfusions, and it remains an ongoing challenge for most blood centers to maintain an adequate platelet inventory. Between 1989 and 1992, the number of platelet concentrates decreased in the U.S. by 8.9%, whereas the number of apheresis platelets administered increased by 75% [3]. There is no doubt that platelet transfusions are beneficial and that they have permitted the use of more aggressive chemotherapy, and bone marrow and peripheral blood stem cell transplantation. However, there was and still is a controversy regarding when platelets should be administered to maximize their benefit while minimizing the risk of bleeding [4-8]. During the last 10 years several studies have brought into question the traditional platelet transfusion policy since older studies were performed when aspirin was still used in
A more stringent transfusion policy has been proven to be safe and cost effective even during induction and consolidation chemotherapy in patients with acute leukemia (acute promyelocytic leukemia excluded). The reduced need for platelet transfusion lowers the risk of complications such as infectious disease transmission, early immunization and other discomfort for the patient like febrile transfusion reactions, frequent hospital visits, or a longer hospital stay. The probability of bacterial contamination of platelet products is about 1,000 times higher compared with red cell units due to the normal storage temperature. Platelets are contaminated mostly by gram-positive skin-derived bacteria that flourish at a 20°C storage temperature [15]. The considerable reduction of costs is the consequence of reduced numbers of transfusions and the economic use of medical personnel. Altogether reduction of platelet transfusions reduces the patient’s risk of complications and charges on one side and increases the quality of life on the other side without increasing the risk of fatal bleeding. Today the use of aspirin and nonsteroidal anti-inflammatory drugs should clearly be avoided during the period of thrombocytopenia.

**ACUTE LEUKEMIAS**

Most experience during the last 10 years was gathered in patients with acute leukemias (acute promyelocytic leukemia without remission excluded). More than 1,000 patients within five published studies were safely transfused using a platelet transfusion trigger of 10,000/µl or even lower [9-12, 16]. Three of these studies prospectively compared the 10,000/µl with the traditional 20,000/µl trigger for prophylactic platelet transfusion without showing an increased risk for bleeding [10-12]. The stringent trigger was used when patients did not show signs of major bleeding, fever >38°C, plasma coagulation factor deficiencies due to sepsis or leukemia, and were without hyperleukocytosis >50,000/µl at the start of chemotherapy. Major bleeding was defined as soft tissue bleedings requiring blood transfusion, melena, hematemeses, macrohematuria, hemoptysis, vaginal bleeding, epistaxis for more than 1 hour with gross blood loss, or retinal hemorrhages with impairment of vision. In such situations platelet transfusions should be given to maintain the platelet count above 15,000/µl or 20,000/µl. The same trigger was used when biopsies (bone marrow biopsies excluded) were to be performed (Table 1).

During the last few years there still has been some concern regarding the safety of such a stringent trigger for prophylactic platelet transfusion because the number of patients in those three prospective studies was still relatively small (230 patients with the 10,000/µl trigger). We therefore prospectively examined this transfusion strategy within the German Cooperative AML-Study Group during the last 4 years in 734 patients [16]. Our recent analysis confirms the safety and cost effectiveness of this strategy. Clinically relevant bleeding did not occur more often than as expected with the traditional trigger. No single fatal bleeding complication was due mainly to the restrictive platelet transfusion policy. About 50% of fatal bleeding events happened

<table>
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<tr>
<th>Diagnosis</th>
<th>Trigger in µl</th>
<th>Clinical status</th>
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<tbody>
<tr>
<td>Acute leukemias and autologous/allogeneic bone marrow or peripheral blood stem cell transplantation</td>
<td>&lt;10,000</td>
<td>Stable, absence of active hemorrhage</td>
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<td></td>
<td>10,000-20,000</td>
<td>Presence of coagulation disorders</td>
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<td>20,000-30,000</td>
<td>Infection with fever &gt;38°C (and rapid decrease of platelets)</td>
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<td>30,000-50,000</td>
<td>Local injuries (e.g., leukemia or infectious organ infiltration)</td>
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<td></td>
<td>&gt;50,000</td>
<td>Severe mucositis, blast count &gt;50,000/µl, active hemorrhage (except petechias)</td>
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<td></td>
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<td>Biopsies (except bone marrow)</td>
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<td>&lt;50,000</td>
<td>Surgical emergencies</td>
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<tr>
<td>Allograft specials</td>
<td>20,000</td>
<td>Acute graft-versus-host disease, veno-occlusive disease, cystitis, treatment with antithymocyte globulin</td>
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<tr>
<td>Aplastic anemia and myelodysplasia</td>
<td>No need for prophylactic transfusion</td>
<td>Stable, absence of active hemorrhage</td>
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<td></td>
<td>5,000-10,000</td>
<td>Recent minor hemorrhage and/or fever &gt;38°C</td>
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<td></td>
<td>&gt;10,000</td>
<td>Major bleeding (&gt;WHO Grade 2)</td>
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<tr>
<td></td>
<td>&lt;50,000</td>
<td>Biopsies (except bone marrow)</td>
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<tr>
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<td>Surgical emergencies</td>
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*No use of aspirin or nonsteroidal anti-inflammatory drugs.

*Acute promyelocytic leukemia without being in remission excluded.
in patients refractory to platelet transfusion, not recovering from thrombocytopenia and in parallel with uncontrolled leukemia or severe infectious complications. Most bleeding episodes occurred during induction chemotherapy when leukemia was not yet in remission. There was absolutely no increased bleeding risk for patients above the age of 60 years.

**Bone Marrow and Peripheral Blood Stem Cell Transplantation**

As shown by two studies in patients after autologous and in one study after allogenic transplantation, the 10,000/µl trigger can also be applied to patients in stable condition after bone marrow or peripheral blood stem cell transplantation [14, 17]. During conditioning therapy in allografted patients with antithymocyte globulin (ATG) the platelet count should be maintained >20,000/µl. Rapid decrease of platelets happens during and after infusion of ATG. Patients with severe mucositis, active graft versus host disease (GVHD), or veno-occlusive disease, fever >38.5°C, infection with organ involvement, or plasma coagulation factor deficiencies require earlier platelet transfusions to maintain a platelet count of >15,000/µl. Severe bleeding and fatal outcome was more often reported for allogenic compared with autologous transplant patients. But bleeding was recorded as the cause of death in a study of 1,402 patients in only a minority of cases. In most cases bleeding was associated with other major toxicities or transplant complications as the direct cause of death [18]. In clinically stable patients with delayed hematopoetic recovery after autologous or allogenic transplantation, the restrictive platelet transfusion policy (<10,000/µl) can safely be applied (Table 1) [19]. In allografted patients the experience is still limited and the decision to administer platelet transfusion must incorporate the clinical situation of the patient. The platelet count should be maintained >15,000/µl especially in patients with gastrointestinal GVHD and cystis [20].

**Long-Term Support in Severe Aplastic Anemia and Myelodysplasia**

Many outpatient clinics that care for patients with severe aplastic anemia or myelodysplasia have experienced that those patients do not show bleeding despite platelet counts below 10,000/µl for long periods. The Zürich group in Switzerland published their experience with a stringent threshold policy with the additional goal to lengthen the transfusion intervals to at least 7 days irrespective of the interim course of the platelet count when good tolerance was observed [13]. They used the following criteria for a same-day platelet transfusion: platelet count <5,000/µl in stable patients, from 5,000-10,000/µl in case of recent hemorrhage and/or fever >38°C only, >10,000/µl in case of major bleeding events (World Health Organizatin [WHO] grade ≥2) or before minor surgery. In 78% of all outpatient transfusions an interval of 7 days or even longer could be achieved. Fifty-seven percent of transfusions were given at counts ≤5,000/µl. No fatal bleeding occurred with this restrictive and delayed transfusion policy.

**Other Causes of Thrombocytopenia in Hematologic Diseases**

Besides the treatment of malignancies, routine prophylactic platelet transfusions are not indicated. This is especially true for situations where platelet consumption is accompanied by an increased platelet production at the same time, for example, with immune thrombocytopenia, thrombotic-thrombocytopenic purpura, hemolytic-uremic syndrome, and disseminated intravascular coagulation. In such situations, platelet transfusion should be given therapeutically when major bleeding happens or on an individually based clinical decision.

**Which Platelet Transfusion Product?**

It is quite clear that only products that are leukocyte reduced (either by filtration or by ultraviolet B irradiation) should be given to avoid early alloimmunization and following refractoriness to platelet transfusion [21]. Leukocyte reduction by filtration can also prevent the transmission of cytomegalovirus. The transfusion of four to six pooled random donor platelet concentrates is normally as effective as single-donor apheresis products depending on the content of platelets and the duration of storage of each product. Platelet dose is most important for a good increment [22]. Platelets should normally be given as random AB0-compatible (nonHLA-typed) transfusion. HLA-matched transfusions or cross-matched platelets should only be given in patients refractory to at least two random platelet transfusions.

**Perspectives**

Neither platelet substitutes nor growth factors like thrombopoetin or megakaryocyte growth and development factor are candidates that could replace the need for platelet transfusions in the near future [23, 24]. Although interleukin-11 was recently approved as a thrombopoietic agent, its overall effects are relatively modest [25]. With respect to the new threshold for prophylactic platelet transfusion of 10,000/µl, this effect has no real clinical value. Studies with growth factors for platelets failed to be clinically effective due to two reasons. Endogenous thrombopoetin levels are already high in those patients, and the deep suppression of megakaryocyte precursors as a consequence of intensive chemotherapy cannot be overcome by those growth factors. The risk of viral and bacterial contamination of platelets can...
be eliminated in the near future by inactivating techniques like photodynamic treatment with psoralen. There is a clear tendency in all clinical studies recently published that the number of platelet transfusions can safely be reduced in patients with hematologic diseases. This will reduce unnecessary discomfort for patients and costs at the same time.

New widely accepted standards must be established (Table 1) by hematologists and oncologists as discussed recently by the American Society of Hematology and the American Society of Clinical Oncology [7, 24]. For patients with solid tumors or lymphomas without meningeal and cerebral involvement, those guidelines can be adopted when patients are treated intensively while in remission. Further clinical studies are currently required to answer the still open question of whether there is a real need for prophylactic platelet transfusions in clinically stable patients with leukemia or whether platelet transfusion should be administered only when bleeding is documented in those patients at low risk for hemorrhage. The experience of the Zürich group in patients with aplastic anemia underlines the possibility that such an “only therapeutic” platelet transfusion strategy can safely be used for more patients in stable condition.

REFERENCES

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