Safety and Cost Effectiveness of a 10 × 10⁹/L Trigger for Prophylactic Platelet Transfusions Compared With the Traditional 20 × 10⁹/L Trigger: A Prospective Comparative Trial in 105 Patients With Acute Myeloid Leukemia

By Hannes Wandt, Markus Frank, Gerhard Ehninger, Christiane Schneider, Norbert Brack, Ali Daoud, Irene Fackler-Schwalbe, Jürgen Fischer, Ringfried Gäckle, Thomas Geer, Peter Harms, Birgit Löffler, Siegfried Öhl, Burkhard Otremba, Monika Raab, Petra Schönrock-Nabulsi, Gerhard Strobel, Rolf Winter, and Hartmut Link

In 105 consecutive patients with de novo acute myeloid leukemia (French-American-British M3 excluded), we compared prospectively the risk of bleeding complications, the number of platelet and red blood cell transfusions administered, and the costs of transfusions using two different prophylactic platelet transfusion protocols. Two hundred sixteen cycles of induction or consolidation chemotherapy and 3,843 days of thrombocytopenia less than 25 × 10⁹/L were evaluated. At the start of the study, each of the 17 participating centers decided whether they would use a 10 × 10⁹/L prophylactic platelet transfusion trigger (group A/8 centers) or a 20 × 10⁹/L trigger (group B/9 centers). Bleeding complications (World Health Organization grade 2-4) during treatment cycles were comparable in the two groups: 20 of 110 (18%) in group A and 18 of 106 (17%) in group B (P = .8). Serious bleeding events (grade 3-4) were generally not related to the patient's platelet count but were the consequence of local lesions and plasma coagulation factor deficiencies due to sepsis. Eighty-six percent of the serious bleeding episodes occurred during induction chemotherapy. No patient died of a bleeding complication. There were no significant differences in the number of red blood cell transfusions administered between the two groups, but there were significant differences in the number of platelet transfusions administered per treatment cycle: pooled random donor platelet concentrates averaged 15.4 versus 25.4 (P < .01) and apheresis platelets averaged 3.0 versus 4.8 (P < .05) for group A versus group B, respectively. This resulted in the cost of platelet therapy being one third lower in group A compared with group B without any associated increase in bleeding risk.

© 1998 by The American Society of Hematology.

THERE IS AN INCREASING demand for platelet transfusions, and it remains an ongoing challenge for most blood centers to maintain an adequate platelet inventory. Platelet transfusions doubled in the United States and in Canada from 1980 to 1987.¹² Between 1989 and 1992, the number of platelet concentrates decreased in the United States 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 transplantation. However, there is still controversy regarding when platelets should be administered to maximize their benefit while minimizing the risk of bleeding.⁵-¹²

In the 1960s, studies demonstrated a relationship between hemorrhage and platelet count in patients with acute leukemia.¹³ Since that time, most hemato-oncologists have used a 20 × 10⁹/L platelet trigger for administering prophylactic platelet transfusions with a considerable interinstitutional heterogeneity in transfusion policies. A study performed in 1992 by the Transfusion Practice Committee of the American Association of Blood Banks reported the current practice for prophylactic platelet transfusion. More than 70% of hospitals transfused platelets primarily for prophylaxis. Eighty percent of these hospitals set the threshold for prophylactic transfusion at 20 × 10⁹/L or even higher.³ During the last 10 years, there has been increasing debate based on both old and more recent data that have brought into question the traditional platelet transfusion policy.⁷,¹¹,¹₄ Those data indicate that there is no real threshold for bleeding complications. Other factors affect bleeding risk, such as platelet function, rapid platelet consumption during febrile episodes, plasma coagulation factor deficiencies, and local factors such as vascular lesions or organ infiltrations. With regard to the safety and practicability of a more restrictive platelet transfusion policy, there has been only one study in the last 10 years that has addressed this question prospectively when we started our trial.¹⁴ In this single-center study, leukemia patients were routinely transfused with platelets if the morning count was <5, <10, or <20 × 10⁹/L, depending on different clinical situations. This transfusion policy was demonstrated to be safe. On the basis of this study and other data available in 1992, we started a prospective multicenter trial in the cooperative acute myeloid leukemia (AML) study group of the Süddeutsche Hämostaseosgruppe evaluating the safety of a 10 × 10⁹/L versus a 20 × 10⁹/L morning trigger for routine prophylactic platelet transfusions. Because half of the centers of our group were reluctant to use this more restrictive platelet transfusion policy, we decided to perform a prospective nonrandomized comparative study. Each center decided to use either the 10 × 10⁹/L or the traditional 20 × 10⁹/L platelet transfusion trigger. Study objectives were to document bleeding complications, the number of platelet and red blood cell (RBC) transfusions, and the costs of transfusion support in the two groups.

PATIENTS AND METHODS

Over a 15-month period, all patients with de novo AML (French-American-British [FAB] M3 excluded) and without uncontrolled infection admitted to the participating hospitals were enrolled in the study.

From the 5th Medical Department and Institute of Medical Oncology and Hematology, Nürnberg, Germany; the Department of Internal Medicine, Hematology/Oncology, Medical School Hannover, Hannover, Germany; and the Medical Clinic I, Technical University Dresden, Dresden, Germany.

Supported by Grant No. M 32/90/Li 1 of the Deutsche Krebshilfe e.V.

Address reprint requests to Hannes Wandt, MD, 5th Medical Department and Institute of Medical Oncology and Hematology, Flurstrasse 17, D-90340 Nürnberg, Germany.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1998 by The American Society of Hematology.

0006-4971/98/9101-0026/$3.00/0
Seventeen departments of hematology in 17 different hospitals (4 university and 13 community hospitals, most with university affiliation; 7 departments treating 10 newly diagnosed AML patients per year and 10 departments treating >10 patients per year) participated in the study. Small and large centers were equally distributed to both groups (group A 3 and 5, group B 4 and 5, respectively). Eight centers used the 10 × 10^9/L prophylactic platelet transfusion trigger (group A) and 9 centers used the 20 × 10^9/L trigger (group B). The chemotherapy for induction and consolidation in the two groups was the same. Two induction chemotherapy cycles were followed by two consolidation cycles in patients less than 60 years of age. The induction regime consisted of daunorubicin at 60 mg/m^2/d for 3 days, ara-C at 200 mg/m^2 as a 3-hour infusion daily for 3 days followed by 100 mg/m^2/d as continuous infusion for 5 days, and etoposide at 150 mg/m^2/d for 3 days (DAE). During the second induction cycle, daunorubicin was reduced to two doses. Consolidation I was composed of m-AMSA at 100 mg/m^2/d and ara-C at 2 × 1 g/m^2/d for 5 days. Consolidation II included mitoxantrone at 10 mg/m^2/d for 3 days combined with 6 days of ara-C at the dose of 2 × 3 g/m^2/d for patients up to the age of 50 years, and for patients between 51 and 60 years of age, ara-C in the dose of 2 × 1 g/m^2/d. Induction chemotherapy for elderly patients (>60 years of age) consisted of daunorubicin at 45 mg/m^2/d for 3 days and ara-C at 100 mg/m^2/d for 7 days as continuous infusion for the first cycle followed by a second cycle, in which daunorubicin was reduced to two doses. In patients more than 60 years of age, consolidation therapy was not obligatory and was administered according to clinical indication. When consolidation was administered to older patients, it was analogous to consolidation I of the patient group 51 to 60 years of age. Prophylactic oral antibiotics and antifungics, the initiation of intravenous antibiotics for fevers greater than 38.5°C, and the use of intravenous amphotericin were standardized for all patients. Hematopoietic growth factors were not administered in this study. Aspirin or nonsteroidal anti-inflammatory drugs were avoided. Paracetamol or metamizol were used as antipyretics. All patients were hospitalized during the study. When disseminated intravascular coagulopathy (DIC) or hyperfibrinolysis was clinically suspected in patients with high cell counts (>50 × 10^9/L) or sepsis with bleeding complication, the following coagulation laboratory tests were performed: prothrombin time, partial thromboplastin time, Quick’s test, fibrinogen, antithrombin III, factor XIII, and fibrinogen levels, or by infusion of fresh frozen plasma, as needed.

Daily morning blood counts were performed as long as patients were receiving platelet transfusions or until the platelet count was self-supporting of greater than 25 × 10^9/L for 2 to 3 days. Blood counts were performed on EDTA-anticoagulated blood using a flow cytometer. The patients were examined daily for evidence of hemorrhage. Fundoscopy was performed only in case of impairment of vision.

Hemoglobin levels were maintained at greater than 80 g/L by packed RBC transfusions.

During each course of chemotherapy, bleeding complications according to World Health Organization (WHO) criteria (0, none; 1, petechial; 2, mild blood loss; 3, gross blood loss; 4, debilitating blood loss) were recorded as well as the number of RBCs and platelet transfusions administered. The bleeding complication scores were recorded in parallel to the treatment of each patient by the treating physician and controlled by a board-certified hematologist responsible for the study at each center. Major bleeding complications (WHO grade 3 and 4) were verified by chart review performed by the study coordinator. Platelet transfusions were administered at the discretion of each center as pooled random donor platelet concentrates (normally 4 to 6) or as apheresis single-donor products. The use was determined by the standard of each center and by the actual availability of the different platelet products. All centers used standardized and quality controlled platelet products according to the “Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie.” It was recommended, but not a study requirement, that platelets be leuko-reduced by filtration at the bedside. Random ABO-compatible (non-HLA-typed) platelet transfusions were administered until a major bleeding episode and alloimmunization necessitated HLA-matched platelet transfusions.

All patients were followed from the beginning of each chemotherapy cycle until discharge with a stable platelet count greater than 25 × 10^9/L, treatment failure, or death.

**Platelet transfusion protocol.** In group A patients, prophylactic platelet transfusions were administered routinely for morning platelet counts less than 10 × 10^9/L. Platelet transfusions were administered for morning platelet counts of less than 15 × 10^9/L if patients had a fever of greater than 38.5°C and a rapid decrease in platelet count (>10 × 10^9/L), if patients had plasma coagulation factor deficiencies due to sepsis or leukemia, or when hyperleukocytosis (>50 × 10^9/L) was present at the start of chemotherapy. In group B patients, platelets were transfused prophylactically for morning platelet counts of less than 20 × 10^9/L (Table 1). The platelet counts were maintained at greater than 20 × 10^9/L in both groups when biopsies (bone marrow biopsies excluded) were performed and in case of major bleeding. Major bleeding was defined as melena, hematemesis, macrohematuria, hemoptysis, vaginal bleeding, epistaxis for more than 1 hour with gross blood loss, retinal hemorrhages with impairment of vision, or soft tissue bleeding requiring blood transfusion.

**Statistics.** Mean values were compared using the Student’s t-test and frequencies of bleeding complications between the two groups were calculated using the χ² test. The duration of thrombocytopenia as well as the number of platelet units administered per treatment cycle or per patient were calculated with the nonparametric Kolmogorov-Smirnov test running on a computer-based program (STATISTICA/α 5.0, Statsoft Inc, Tulsa, OK).

The study was approved by the Institutional Review Board of the Cooperative AML Study Group of the Süddeutsche Hämoblastosegruppe.

**RESULTS**

The study included 105 consecutive patients (mean age, 47 years; range, 17 to 73 years) with AML (FAB-M3 excluded). We evaluated 216 cycles of myelo suppressive chemotherapy and 3,843 days of thrombocytopenia with platelet counts less than 25 × 10^9/L. In group A, results were evaluated in 58 patients during 110 cycles of chemotherapy and 2,198 thrombocytopenia days, and these data were compared with results obtained in 47 patients in group B who received 106 chemotherapy cycles and were thrombocytopenic for 1,645 days.

**Table 1. Protocol for Prophylactic Platelet Transfusion in AML (FAB M 3 Excluded): No Sign of Major Bleeding or Retinal Bleeding With Impairment of Vision**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning platelet count of</td>
<td>Morning platelet count of</td>
</tr>
<tr>
<td>&lt;10 × 10^9 platelets/L</td>
<td>&lt;20 × 10^9 platelets/L</td>
</tr>
<tr>
<td>≤15 × 10^9 platelets/L in case of:</td>
<td></td>
</tr>
<tr>
<td>Fever &gt;38.5°C and rapid decrease in platelet count</td>
<td></td>
</tr>
<tr>
<td>Plasma coagulation factor deficiencies due to sepsis or leukemia</td>
<td></td>
</tr>
<tr>
<td>Hyperleukocytosis &gt;50 × 10^9/L</td>
<td></td>
</tr>
</tbody>
</table>

Major bleeding is defined in the text.
Patients’ characteristics were well balanced in the two groups (Table 2). The characteristics of the treatment cycles were also quite comparable for the two groups (Table 3) with regard to the ratio of induction to consolidation therapy and the ratio of the different platelet products, as well as the use of leukocyte filters in both groups. There were statistically significant differences in favor of group B versus group A patients for platelet counts ($< 10^9 /L$ or $> 100 \times 10^9 /L$) at the beginning of each chemotherapy cycle and, as a consequence, in the median duration of thrombocytopenia ($P < .05$ for both). The median platelet count at study entry was $72 \times 10^9 /L$ in group A and $151 \times 10^9 /L$ in group B, respectively. The median duration of thrombocytopenia was 5 days longer in group A compared with that in group B (Table 3). This finding was independently seen whether we looked to all patients or to patients in complete remissions.

**Bleeding complications.** Bleeding complications of WHO grade 1 were regarded as clinically insignificant and were counted together with WHO grade 0. Hemorrhages of WHO grade 2-4 occurred in 20 of 110 (18.2%) and 18 of 106 (17.0%) chemotherapy cycles and in 19 of 58 (32.8%) and 13 of 47 (27.7%) patients in groups A and B, respectively. Both differences are statistically not significant ($P = .8$ and $P = .6$, respectively). Bleeding complications during chemotherapy cycles in group A patients were all grade 2, whereas those in group B patients were grade 2 in 9.4%, grade 3 in 6.6%, and grade 4 in 1%. For all study patients, there was no clear increase in bleeding risk (WHO grades 2-4) during induction compared with consolidation chemotherapy; 31 bleeding events during 159 induction cycles (20%) versus 7 events during 47 consolidation cycles (15%), respectively ($P = .5$). Platelet refractoriness of clinical significance related to alloimmunization was not reported in the two groups.

WHO grade 3 and 4 hemorrhages were seen exclusively in 7 patients in group B, despite the higher threshold for platelet transfusions. We examined these hemorrhages in detail (Table 4). In 5 of these 7 patients, significant morbidity related to the bleeding complication was stated by the treating physician. Four patients developed major bleeding complications in parallel with serious infections and sepsis. In 1 patient, sepsis was related to pneumonia. In a second patient, sepsis was related to a local infection of the central venous line. Both patients showed no sign of DIC or hyperfibrinolysis. Bleeding (WHO grade 3) could be stopped in these 2 patients due to a combined therapeutic approach with antibiotics, removal of the venous line, and transfusion of platelets. Two other patients died. One patient developed septic shock related to a severe pneumonia needing mechanical ventilation on an medical intensive care unit. Gastrointestinal bleeding (grade 4) occurred after 1 day of ventilation related to a stress ulcer of the stomach. The patient showed signs of DIC [fibrinogen $< 100$ mg/dL, antithrombin III $< 50\%$, and positive fibrin(ogen) degradation products]. The hemoglobin level could be maintained at greater than 80 g/L due to the transfusion of 6 RBC packs. Despite intensive treatment with dopamine, antibiotics, antimycotics, transfusion of fresh frozen plasma, and antithrombin III, the patient died in persistent septic shock with adult respiratory distress syndrome (ARDS). The platelet count at the end was $36 \times 10^9 /L$. The treating physician stated that death was clearly not related to the bleeding complication. The other patient who died related to septic shock also had a progressive pneumonia with signs of DIC [fibrinogen $< 200$ mg/dL, antithrombin III $< 60\%$, and positive fibrin(ogen) degradation products] and hemorrhagic diarrhea (grade 3). The platelet count was $50 \times 10^9 /L$ at that time. Despite intensive treatment, including fresh frozen plasma, antithrombin III, and platelet and RBC transfusions, the rectal bleeding persisted. The patient died from causes related to unresolved septic shock with multiorgan failure. Also, in this patient, bleeding was not the cause of death, despite the fact that the bleeding could not be stopped.

In 4 of these 7 patients, bleeding (WHO grade 3 and 4) occurred while their platelet counts were greater than $20 \times 10^9 /L$ (36 to $58 \times 10^9$ platelets/L). Five of 7 patients had local lesions. Five of the patients had AML FAB type M4 or M5. These subtypes are more frequently associated with hyperleucocytosis (Table 4), leukostasis, and organ infiltration, which may be additional risks for bleeding, as shown in other studies. In the subgroup of patients with grade 3 and 4 bleeding, 6 of 7 (86%) experienced this complication during induction chemotherapy.

**Platelet and RBC transfusions.** Beside the comparison of transfusions in group A and group B patients, we performed additional comparisons between group A and a subgroup of group B patients omitting the 7 patients with WHO grade 3 and 4 bleeding episodes. We did this additional comparison because we wanted to see whether the differences between group A and B could still be seen when we omitted patients with WHO grade 3 and 4 bleeding complications, which occurred exclusively in group B.

The number of platelet transfusions administered per chemotherapy cycle was significantly different between group A and B.

---

**Table 2. Patient’s Characteristics (n = 105), Leukemia Subtypes, and Leukocyte Count at Diagnosis in the Two Groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 58)</th>
<th>Group B (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>46 (17-72)</td>
<td>49 (25-73)</td>
</tr>
<tr>
<td>Female/male</td>
<td>29/29</td>
<td>23/24</td>
</tr>
<tr>
<td>FAB M 4,5/0/other</td>
<td>25/33</td>
<td>21/26</td>
</tr>
<tr>
<td>Leukocytes $&gt; 50 \times 10^9 /L$</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 3. Characteristics of Treatment Cycles (n = 216)**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 110)</th>
<th>Group B (n = 106)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction I/II v consolidation I/II</td>
<td>51/33 v 17/9</td>
<td>46/29 v 19/12</td>
<td>NS</td>
</tr>
<tr>
<td>Complete remission rate</td>
<td>52%</td>
<td>68%</td>
<td>.09</td>
</tr>
<tr>
<td>Platelet count before each cycle: ($&lt; 100 \times 10^9 /L$)</td>
<td>64/46</td>
<td>41/65</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Median duration of thrombocytopenia ($&lt; 25 \times 10^9 /L$ in days)</td>
<td>18 (1-113)</td>
<td>13 (0-56)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Platelet transfusions: Apheresis/pooled concentrates</td>
<td>1/5.13</td>
<td>1/5.28</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets leukoreduced by filtration</td>
<td>87%</td>
<td>95%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.
patients related to both single-donor apheresis products \((P < .05)\) as well as to pooled random donor concentrates \((P < .01)\). These differences were still observed even when we compared group A with the subgroup of non–major-bleeding group B patients (Table 5). The mean number of apheresis platelets and platelet concentrates administered in group A were 3.0 (0 to 16) and 15.4 (0 to 152), in group B were 4.8 (0 to 33) and 25.4 (0 to 188), and in the subgroup of group B were 4.4 (0 to 21) and 23.2 (0 to 160), respectively. Platelet use was one third lower in group A compared with group B patients. This difference between the two groups was still more evident when platelet transfusions administered were not calculated per chemotherapy cycle but rather per thrombocytopenic day: apheresis platelets averaged 0.15 versus 0.31 per day and platelet concentrates averaged 0.77 versus 1.65 per day for group A versus group B, respectively. The mean number of RBC transfusions administered to group A patients was 7.3 (0 to 22), group B patients received 8.3 (2 to 28), and the subgroup of group B patients received 7.6 (2 to 28). RBC usage did not differ among the groups (Table 5).

Cost calculation for platelet and RBC transfusions. The calculation of costs for the platelet transfusions, RBC transfusions, leukocyte filters, and medical personal in the two groups is based on data for Germany (data not shown here). There was a cost reduction for platelet transfusion per treatment cycle of about one third for group A patients compared with group B patients. Because costs for RBC transfusion did not differ significantly, this led to a mean overall cost reduction of one third for transfusions. Concerning the total costs for transfusions, one has to calculate not only the charges for transfusions, but also the costs for medical personnel administering transfusions to the patients.

Table 5. Mean Number of Platelet and RBC Transfusions Per Treatment Cycle in Group A Compared With Group B and the Nonbleeding Subgroup of B Patients

<table>
<thead>
<tr>
<th>Apheresis platelets</th>
<th>Pooled random donor platelet concentrates</th>
<th>RBC packs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>3.0 (0-16)</td>
<td>15.4 (0-152)</td>
</tr>
<tr>
<td>Group B</td>
<td>4.8 (0-33)</td>
<td>25.4 (0-188)</td>
</tr>
<tr>
<td>Group B*</td>
<td>4.4 (0-23)</td>
<td>23.2 (0-160)</td>
</tr>
<tr>
<td>(P) Value</td>
<td>A/B &lt; .05</td>
<td>A/B &lt; .01</td>
</tr>
<tr>
<td></td>
<td>A/B* &lt; .05</td>
<td>A/B* &lt; .01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abbreviation: NS, not significant.</th>
</tr>
</thead>
</table>

This multicenter study shows that a platelet transfusion trigger of \(10 \times 10^9/L\) for routine prophylactic platelet transfusion therapy during induction and consolidation chemotherapy for AML is safe and not associated with a higher bleeding risk than the more generally used threshold of \(20 \times 10^9/L\). The significantly longer duration of thrombocytopenia in group A patients transfused at the lower trigger did not result in a higher bleeding risk. The longer duration of thrombocytopenia in group A reflects the significantly lower platelet count at study entry for these patients. Significantly more patients in group A started their chemotherapy with platelet counts less than \(100 \times 10^9/L\) (Table 3). This imbalance is related to the comparative, nonrandomized design of our study. This negative factor for group A was certainly seen by chance on one side. On the other side, it underlines the safety of the lower trigger for prophylactic platelet transfusion observed in our study. The trend to higher complete remission rates \((P = .09)\) in group B compared with group A patients in our study was clearly not related to the different triggers for platelet transfusion, because all data available indicate that different transfusion policies do not lead to different remission rates despite the same chemotherapy in those groups.\(^7,16\) Despite the fact that bleeding complications (WHO grade 2-4) were seen at the same rate in both groups, bleeding of WHO grades 3 and 4 was seen exclusively in group B patients who were being transfused at the higher platelet trigger. This unexpected observation occurred by chance, we suppose. The analysis of these serious bleeding episodes showed clearly that they were not related to a platelet count less than \(10 \times 10^9/L\). These observations are in line with the results reported by two other centers using a comparably low trigger level.\(^14,16\) These bleeding episodes were mainly associated with local lesions (in 5 of 7 patients). Patients with M4 and M5 leukemias may be at a higher risk for bleeding (Table 4) at the beginning of chemotherapy, because these leukemias are more often associated with organ infiltration and high leukocyte counts. In 2 patients, major bleeding could be recorded in parallel with DIC caused by sepsis. In these 2 patients with persistent septic shock, bleeding could not be stopped despite adequate intensive therapy. These 2 patients died both related to septic shock and not as a consequence of the bleeding complication. In the study by Gmürr et al.,\(^14\) there were 3 fatal bleeding episodes in 102 patients. None of these hemorrhagic deaths was related to the use of stringent prophylactic platelet transfusion policy. Two of the bleeding deaths were mainly related to associated coagulation factor deficiencies. In 1 of these 2 patients, cerebral bleeding occurred at a platelet count of greater
than 50 × 10^9/L in parallel with a white blood cell count of 430 × 10^9/L (M5 leukemia). The third patient died because of refractoriness to platelet transfusions and the lack of an HLA-identical platelet donor.

Eighty-six percent of serious bleeding episodes (WHO grade 3-4) in our study occurred during induction chemotherapy. In contrast, WHO grade 2 bleeding episodes occurred with equal frequency during induction and consolidation chemotherapy. This result is in accord with prior studies demonstrating that the risk of bleeding in acute leukemia is clearly increased during induction chemotherapy when the patient is not yet in complete remission.14,15,17

Patients with acute promyelocytic leukemia were excluded from our study, because these patients were being treated in a separate European protocol including all-transretinoic acid. This type of leukemia is associated with a well-known high bleeding risk during induction chemotherapy because of severe plasma coagulation factor deficiencies. However, we think that our data collected during consolidation chemotherapy show that the stringent platelet transfusion policy can be safely used even in these patients during consolidation chemotherapy after they have achieved a complete remission.

Our study confirms the results of the three other platelet transfusion trials published during the last 15 years that have shown that prophylactic platelet transfusion therapy can be safely postponed until platelets decrease to less than 10 × 10^9/L.14,16,17 The single center study by Gmüör et al18 used an even more stringent transfusion protocol with three different platelet transfusion triggers based on the clinical condition of the patient as well as their platelet count. The lowest trigger used in this study was a platelet count of 5 × 10^9/L. This policy proved to be safe in an experienced leukemia center. Our study was performed in 17 different centers, including large and small departments of hematology and university and community hospitals, an approach that represents the real heterogeneity in the treatment of leukemia patients. Additional support for the safety of the 10 × 10^9/L trigger in the multicenter setting comes from an interim analysis of a randomized Italian multicenter study.18

In a study of 92 children with acute leukemia performed 35 years ago, the investigators stated that they could not determine a threshold platelet level to prevent bleeding. Serious bleeding was more often associated with a platelet count less than 5 × 10^9/L, but from 5 to 100 × 10^9/L there was little difference in the frequency of serious bleeding complications.13 These clinical observations of a serious bleeding risk were gathered when aspirin was still used in thrombocytopenic patients. A clinical study that involved patients with aplastic anemia evaluated fecal blood loss as an indicator of bleeding in 1978, when aspirin was no longer used in thrombocytopenic patients. Stool blood loss did not increase substantially until platelet counts were less than 5 × 10^9/L.19

The number of platelet transfusions in our study was reduced by one third using the lower trigger, whereas the number of RBC transfusions administered was similar in the two different trigger groups. This result is in line with comparable studies.16,18 In our study, the 10 × 10^9/L platelet trigger was increased to 15 × 10^9/L only in certain clinical situations when platelet consumption was increased due to fever greater than 38°C or, when plasma coagulation factor deficiencies were present, due to sepsis or leukemia or in case of hyperleukocytosis (≥50 × 10^9/L) at the start of induction chemotherapy. The use of different platelet products (random donor and apheresis platelets) did not influence our results, because they were equally distributed in both groups (Table 3). The reduction in the use of platelet transfusions shown in patients transfused at the lower trigger, as in our study, has important economic consequences. Calculated (according to the study results presented here) for the expected frequency of newly diagnosed AML in adults per year in the United States, assuming that two thirds of them will be treated by two cycles of chemotherapy, leads to a saving of 83,200 random donor platelet concentrates and 14,976 apheresis products.20

A more stringent platelet transfusion policy is not only safe and cost effective, but it is also less harmful to patients. Blood transfusions can never be made entirely safe because of the risk of transmitting viral and bacterial diseases.21,22 However, this risk is much greater for platelet than for RBC transfusions, because platelets are often pooled from 4 to 8 donors.10,23

Further debate and additional clinical studies will be required to answer the question of whether there is even a need for prophylactic platelet transfusion therapy or whether platelet transfusions should be administered only when active bleeding is documented. Previous studies comparing bleeding risks in patients who received therapeutic rather than prophylactic transfusions indicated that bleeding was corrected in all patients. Thus, a therapeutic platelet transfusion policy is a promising approach, but its actual efficacy is unproven because of the small numbers of patients included in these prior studies.7,8,24

ACKNOWLEDGMENT

The authors thank Dr Dorle Messerer for supporting the study analysis by her statistical expertise.

REFERENCES

13. Gaydos LA, Freireich EJ, Mantel N: The quantitative relation between platelet count and haemorrhage in patients with acute leuke-
18. Rebulla P: Interim report from the Platelet Transfusion Trigger Trial (PTTT): A prospective controlled study on bleeding risk in acute myeloblastic leukemia (AML) patients randomized to be transfused at <10 versus <20 × 10⁹/L platelets. Blood 88:443a, 1996 (abstr, suppl 1)
Safety and Cost Effectiveness of a $10 \times 10^9$/L Trigger for Prophylactic Platelet Transfusions Compared With the Traditional $20 \times 10^9$/L Trigger: A Prospective Comparative Trial in 105 Patients With Acute Myeloid Leukemia

Hannes Wandt, Markus Frank, Gerhard Ehninger, Christiane Schneider, Norbert Brack, Ali Daoud, Irene Fackler-Schwalbe, Jürgen Fischer, Ringfried Gäckle, Thomas Geer, Peter Harms, Birgit Löfler, Siegfried Ohl, Burkhard Otremba, Monika Raab, Petra Schönrock-Nabulsi, Gerhard Strobel, Rolf Winter and Hartmut Link