

THE THRESHOLD FOR PROPHYLACTIC PLATELET TRANSFUSIONS IN ADULTS WITH ACUTE MYELOID LEUKEMIA

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ABSTRACT

Background Prophylactic platelet transfusions are usually administered to patients receiving myelotoxic chemotherapy when their platelet count falls below 20,000 per cubic millimeter. Some observations suggest that lower platelet counts can be appropriate in patients in stable condition, but the safety of lower thresholds is uncertain.

Methods We evaluated 255 adolescents and adults (age, 16 to 70 years) with newly diagnosed acute myeloid leukemia (but not acute promyelocytic leukemia), who were treated in 21 centers. One hundred thirty-five patients were randomly assigned to receive a transfusion when their platelet count fell below 10,000 per cubic millimeter (or 10,000 to 20,000 per cubic millimeter in those with a temperature above 38°C, with active bleeding, or a need for invasive procedures), and 120 patients were assigned to receive a transfusion when their platelet count was less than 20,000 per cubic millimeter.

Results Patients in the group with a threshold of 10,000 platelets per cubic millimeter received 21.5 percent fewer platelet transfusions than the patients in the group with a threshold of 20,000 platelets per cubic millimeter ($P=0.001$). The numbers of red-cell units transfused were not significantly different between groups. Major bleeding (defined as any bleeding more than petechiae or mucosal or retinal bleeding) occurred in 21.5 and 20 percent of patients, respectively ($P=0.41$), and on 3.1 and 2.0 percent of the days of hospitalization. One episode of fatal cerebral hemorrhage occurred in the group with a threshold of 10,000 platelets per cubic millimeter; none occurred in the other group ($P=0.95$). Actuarial estimates of survival during induction chemotherapy, actuarial estimates of the absence of major bleeding, and the length of hospital stay were not significantly different in the two groups.

Conclusions The risk of major bleeding during induction chemotherapy in adolescents and adults with acute myeloid leukemia (except acute promyelocytic leukemia, which we did not study) was similar with platelet-transfusion thresholds of 20,000 per cubic millimeter and 10,000 per cubic millimeter (or 10,000 to 20,000 per cubic millimeter when body temperature exceeded 38°C, there was active bleeding, or invasive procedures were needed). Use of the lower threshold reduced platelet use by 21.5 percent. (N Engl J Med 1997;337:1870-5.)

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IT is generally accepted that prophylactic platelet transfusions reduce the risk of hemorrhage in patients undergoing chemotherapy for leukemia or cancer.^{1,2} These prophylactic transfusions are usually given when the platelet count falls below 20,000 per cubic millimeter. However, the risk of bleeding depends not only on the platelet count, but also on the underlying disease, the use of drugs that interfere with platelet function, and complications such as fever and infection.^{1,2} Moreover, platelet concentrates are a limited and expensive resource, and they carry a low but nevertheless measurable risk of untoward effects.^{3,4}

These points were considered at the National Institutes of Health Platelet Transfusion Consensus Conference, whose results were published in 1987,⁵ which supported the view that a platelet count of 20,000 per cubic millimeter is an appropriate platelet-transfusion trigger in most cases, although lower values can be safely used in patients in stable condition. A recent survey of 630 hospitals in North America found that a threshold of 20,000 platelets per cubic millimeter was used in 60 percent of them.⁶

In 1991 Gmür et al. reported their 10-year experience with 102 patients with leukemia who received prophylactic platelet transfusions when their platelet count was 5000 per cubic millimeter; in patients with fever or minor bleeding, the threshold for transfusion was 10,000 per cubic millimeter, and in patients with coagulation disorders, those who were receiving heparin therapy, and those who needed invasive procedures, the threshold was 20,000 per cubic millimeter.⁷ There were 28 nonfatal and 3 fatal hemorrhagic episodes among these patients. Gmür et al. concluded that a lower threshold than that

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generally used is practicable during induction chemotherapy for acute leukemia. The results of a randomized study of 78 patients undergoing induction therapy for acute leukemia at a single institution supported these conclusions.⁸

These results, and the clinical importance of the best use of platelet transfusions,^{5,9-11} prompted the current trial, which evaluated the frequency and types of hemorrhage in adolescents and adults with newly diagnosed acute myeloid leukemia who were undergoing induction chemotherapy and who received platelet transfusions either when the platelet count was 20,000 per cubic millimeter or according to a more restrictive protocol.

METHODS

Objectives of the Study

The primary objective of the Platelet Transfusion Trigger Trial was to compare the frequency and severity of hemorrhage in patients who received prophylactic platelet transfusions under two different protocols. All patients were adolescents or adults with acute myeloid leukemia (but not acute promyelocytic leukemia) who received transfusions during the first course of induction chemotherapy. Patients in the control group were treated according to the current practice of transfusing platelets prophylactically when the platelet count falls below 20,000 per cubic millimeter. Patients who were enrolled in the restrictive protocol received platelet transfusions when the platelet count, which was usually measured in the morning with an automated counter, was below 10,000 per cubic millimeter or was 10,000 to 20,000 per cubic millimeter when the body temperature exceeded 38°C, in the presence of fresh minor or major bleeding, or if invasive procedures were necessary. Our secondary objectives were to compare the numbers of platelet and red-cell transfusions, rates of complete remission, and mortality rates.

Study Design and Participating Institutions

The trial was a multicenter randomized clinical trial that was carried out in 21 hematology departments in cooperation with their transfusion services under the auspices of the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA).

Target Sample Size and Recruitment of Patients

We calculated that a total of 230 patients was needed,¹² on the basis of GIMEMA historical data showing that bleeding of World Health Organization (WHO) grade ≥ 2 (mild blood loss or more severe hemorrhage) and ≥ 3 (gross blood loss or more severe hemorrhage)¹³ occurred in approximately 30 and 10 percent, respectively, of 1298 consecutive adult patients with acute myeloid leukemia (but not the promyelocytic type). Enrollment began in March 1994 and ended in March 1996. The progress and safety aspects of the trial were monitored jointly by members of the steering committee who were not involved in treatment of the patients and by an independent data and safety monitoring committee. The trial was scheduled to be stopped if the rate of outcome events reached statistical significance ($P < 0.01$ by the chi-square test).

Study Protocol

The study protocol was approved by the Commission for Human Experimentation of the Health Authority of Regione Lombardia and by the ethics committees of the participating institutions. All enrolled patients gave informed consent. The inclusion criteria were a diagnosis of acute myeloid leukemia, hospital admission for the first course of induction chemotherapy, and an age of 16 to 70 years. Patients were excluded if they had acute

promyelocytic leukemia or secondary acute myeloid leukemia, if they had received a blood transfusion before the diagnosis of acute myeloid leukemia, or if they declined to participate.

Randomization

Patients underwent randomization as soon as the diagnosis and other inclusion criteria were communicated by telephone to the central randomization center at the GIMEMA secretariat in Rome. A random permuted-block design was used in the individual centers. The people who handled randomization, data management, and statistical analysis were not involved in the treatment of the patients.

Other Interventions

Patients received standard antibiotic and supportive care. A standard protocol was used for remission-induction chemotherapy. It consisted of cytarabine (an intravenous bolus of 25 mg per square meter of body-surface area followed by a continuous intravenous infusion of 100 mg per square meter from day 1 to day 10), etoposide (100 mg per square meter intravenously from day 1 to day 5), and idarubicin (10 mg per square meter intravenously on days 1, 3, and 5) or mitoxantrone (12 mg per square meter intravenously on days 1, 3, and 5) or daunorubicin (50 mg per square meter intravenously on days 1, 3, and 5). Red cells were administered when the hemoglobin level fell below 80 g per liter. Acetaminophen was used as an antipyretic agent. Aspirin and nonsteroidal antiinflammatory drugs with effects on platelet function were not used.

Blood Components

Platelet concentrates were prepared by the platelet-rich plasma method,¹⁴ the buffy-coat method,¹⁵ or apheresis and were stored at 20 to 24°C for a maximum of five days. Each transfusion involved 1 unit of platelet-rich plasma or buffy-coat concentrate per 10 kg of body weight or 1 apheresis concentrate.

Clinical Evaluation

For each patient the physician in charge collected data from the day of admission to the occurrence of complete remission, resistance to chemotherapy, a platelet count of more than 100,000 per cubic millimeter, or death — whichever occurred first. Data included the morning body temperature, complete blood count, the number and type of platelet and red-cell units transfused, and the occurrence and type of hemorrhage and infection (with information on antibiotic therapy). The severity of hemorrhage was graded on an 8-point scale as follows: 0, no bleeding; 1, petechiae or mucosal or retinal bleeding that did not require red-cell transfusion; 2, melena, hematemesis, hematuria, or hemoptysis; 3, any bleeding that required red-cell transfusion; 4, retinal bleeding accompanied by visual impairment; 5, nonfatal cerebral bleeding; 6, fatal cerebral bleeding; and 7, fatal noncerebral bleeding. For the purpose of this analysis, minor hemorrhage was defined as a score of 1 and major hemorrhage as a score of more than 1.

Statistical Analysis

Data were transferred from the patients' records to standard paper forms at participating centers and analyzed at the study secretariat (Centro Trasfusionale e di Immunologia dei Trapianti, Milan). Actuarial curves of overall survival and of the proportion of patients without major hemorrhage were computed with SAS software (SAS, Cary, N.C.) and the log-rank test.¹² Differences in proportions and confidence intervals were computed with Confidence Interval Analysis software.¹⁶ We used the Wilcoxon rank-sum test to compare the numbers of platelet transfusions in the two groups. Unless otherwise noted, a two-sided P level of less than 0.05 was considered to indicate statistical significance. The final report, which formed the basis for this article, was prepared according to the Consolidated Standards of Reporting Trials statement.¹⁷

RESULTS

Table 1 shows the main features of the trial. Overall, 92.4 percent of the 276 randomized patients completed follow-up. During hospitalization, an automated platelet count was available on 91.6 and 90.6 percent of the study days and on 99.2 and 97.7 percent of the days when platelets were transfused in the group with a threshold of 10,000 platelets per cubic millimeter and the group with a threshold of 20,000 platelets per cubic millimeter, respectively. The clinical characteristics of the patients and transfusion data are shown in Table 2. The two groups were similar, but the group with a threshold of 10,000 platelets per cubic millimeter received 21.5 percent fewer transfusions of platelet concentrates than the group with a threshold of 20,000 platelets per cubic millimeter (95 percent confidence interval, 8 to 35 percent; $P=0.001$). The numbers of red-cell units transfused per patient were not significantly different in the two groups. Table 3 shows that the two groups received similar products for platelet transfusion.

Among the patients assigned to the group with a threshold of 10,000 platelets per cubic millimeter, platelet counts were below 10,000 per cubic millimeter for 72 percent of the transfusions and above this level for 22.6 percent, owing to the presence of concomitant risk factors, as prescribed by the study protocol (the presence of fever or fresh bleeding or the need for an invasive procedure). Pretransfusion platelet counts higher than those indicated in the study protocol (protocol violations) were registered in 5.4 percent of transfusions in the group with a threshold of 10,000 platelets per cubic millimeter and in 2 percent of transfusions in the group with a threshold of 20,000 platelets per cubic millimeter.

The major study end points are listed in Table 4. The difference in the numbers of patients with major bleeding episodes in the two groups was not statistically significant ($P=0.41$). Also, the proportions of patients who entered complete remission were not significantly different in the two groups ($P=0.63$). There was one fatal episode of cerebral hemorrhage in a 19-year-old woman who was assigned to the group with a threshold of 10,000 platelets per cubic millimeter; the hemorrhage began when the platelet count was 32,000 per cubic millimeter. No other deaths were attributed to bleeding among the 255 patients who completed follow-up. Of the 21 patients who did not complete follow-up, 2 patients died of cerebral hemorrhage, 1 in each group (Table 1). The death rate was greater in the group with a threshold of 10,000 platelets per cubic millimeter, but this was mainly because of a larger number of deaths due to infection. Despite this difference, actuarial survival up to 49 days after admission, in which deaths due to any cause were included, was not significantly different in the two groups ($P=0.31$).

When major hemorrhages were analyzed accord-

TABLE 1. FEATURES OF THE TRIAL.*

VARIABLE	THRESHOLD, 10,000 PLATELETS/mm ³	THRESHOLD, 20,000 PLATELETS/mm ³
Total no. randomized	144	132
No. whose study records were not received	9†	8‡
No. not evaluated for other reasons	0	4§
No. (%) who completed the follow-up	135 (94)	120 (91)

*Three hundred twenty-nine patients with acute myeloid leukemia were admitted to participating hematology units during the study period. Of these, 53 were not randomized: 37 had secondary leukemia, 10 had received a transfusion before the diagnosis of acute myeloid leukemia, 4 did not meet the age criteria, and 2 declined to give consent.

†Disseminated intravascular coagulation developed on the day of admission in one patient who was admitted with fever (temperature, $>38^{\circ}\text{C}$), which continued until death, and he died of cerebral hemorrhage on day 5, when his morning platelet count was 13,000 per cubic millimeter. The remaining eight patients were alive at discharge.

‡All eight patients were alive at discharge.

§Two patients died within 24 hours after admission (one of cerebral hemorrhage and one of cardiac arrest), and two patients received a nonmyeloablative course of chemotherapy.

TABLE 2. CHARACTERISTICS OF THE PATIENTS.

	THRESHOLD, 10,000 PLATELETS/mm ³ (N = 135)	THRESHOLD, 20,000 PLATELETS/mm ³ (N = 120)
Male sex — %	53	52
Age — yr		
Median	51	49
Range	16–70	17–70
FAB classification of AML — no. of patients (%)*		
M0	7 (5.2)	5 (4.2)
M1	41 (30.4)	24 (20.0)
M2	28 (20.7)	37 (30.8)
M4	27 (20.0)	31 (25.8)
M5	21 (15.6)	17 (14.2)
M6	1 (0.7)	1 (0.8)
M7	1 (0.7)	0
Undefined	9 (6.7)	5 (4.2)
Days of hospitalization		
Median	29	28
Range	3–64	4–54
Pretransfusion platelet count/mm ³		
Median	9000	14,000
Range	1000–89,000	0–64,000
No. of platelet transfusions/patient		
Mean \pm SD	7.05 \pm 4.56	8.97 \pm 5.17†
Median	6	8
Range	1–22	2–27
No. of red-cell units transfused/patient		
Mean \pm SD	9.57 \pm 5.18	9.07 \pm 4.58
Median	9	8
Range	3–48	2–27

*FAB denotes French–American–British, and AML acute myeloid leukemia.

† $P=0.001$ for the difference between groups.

TABLE 3. CHARACTERISTICS OF PLATELET CONCENTRATES.

VARIABLE	THRESHOLD, 10,000 PLATELETS/mm ³	THRESHOLD, 20,000 PLATELETS/mm ³
Platelet concentrates (%)		
Selected by HLA type	4.8	4.6
Transfused within 2 days of storage	79.9	78.1
Prepared by apheresis	50.5	42.0
Processed to reduce the number of leukocytes	45.0	44.6
Irradiated	40.0	38.7
Platelet count in apheresis concentrates (cells × 10 ⁻⁹ /unit)		
Median	280	290
Range	110–588	130–610
Platelet count in nonapheresis concentrates (cells × 10 ⁻⁹ /pool)		
Median	217	217
Range	140–555	140–505

TABLE 4. MAJOR END POINTS OF THE TRIAL.

END POINT	THRESHOLD, 10,000 PLATELETS/mm ³ (N = 135)	THRESHOLD, 20,000 PLATELETS/mm ³ (N = 120)
Patients with major bleeding episodes — no. (%)	29 (21.5)	24 (20.0)
1 episode	21 (15.6)	18 (15.0)
2 episodes	7 (5.2)	3 (2.5)
3 episodes	0	3 (2.5)
4 episodes	1 (0.7)	0
>4 episodes	0	0
Total days in hospital	4006	3330
Days with major bleeding episodes — no. (%)	123 (3.1)	65 (2.0)
Complete remission — no. of patients (%)	76 (56.3)	76 (63.3)
Death — no. of patients (%)	18 (13.3)	9 (7.5)
Infection	12	7
Cardiac failure	2	0
Acute renal failure	0	1
Trauma	1	0
Disseminated intravascular coagulation	1	0
Apoplectic stroke	0	1
Intestinal infarction	1	0
Cerebral hemorrhage	1	0

ing to type (Table 5), gastrointestinal bleeding occurred more frequently in the group with a threshold of 10,000 platelets per cubic millimeter, although overall, the mean numbers of major bleeding episodes per patient were similar in the group with a threshold of 10,000 platelets per cubic millimeter (39 in 135 patients = 0.29) and the group with a threshold of 20,000 platelets per cubic millimeter (33 in 120 patients = 0.27). We considered that the proportion of patients who had no major

bleeding episode represented a valid estimate of the success of prophylaxis because the trial concerned prophylaxis against hemorrhage. Therefore, we used the log-rank test to compare actuarial curves for the proportions of patients without major bleeding during the study. As shown in Figure 1, the difference between the two groups was not statistically significant (P = 0.54).

DISCUSSION

Platelet transfusion is a cornerstone of supportive therapy for patients undergoing cytotoxic chemotherapy.^{1,2,18,19} However, the degree of thrombocytopenia that should trigger the use of prophylactic platelet transfusions — the platelet-transfusion trigger — is still debated. The definition of the platelet-transfusion trigger is important because of increasingly aggressive anticancer treatment,²⁰ the need to avoid transfusion-associated risks,²⁻⁴ and costs.^{9,21}

Studies performed during the past 20 years suggest that the platelet-transfusion trigger could be safely set at platelet counts below the traditional level of 20,000 per cubic millimeter in patients in clinically stable condition. In a heterogeneous setting of 124 patients with cancer, Lawrence et al. reported similar death rates in two consecutive periods during which the threshold for transfusion was decreased from 20,000 to 10,000 per cubic millimeter.²²

Another nonrandomized study was recently performed by Wandt et al.²³ in 105 patients with acute myeloid leukemia (but not the promyelocytic type) who were treated in eight centers using the threshold of 10,000 per cubic millimeter (or 15,000 per cubic millimeter in the presence of sepsis with disseminated intravascular coagulation, a white-cell count of more than 50,000 per cubic millimeter, or a temperature above 38°C with a rapid decrease in the platelet count) and in nine centers using the traditional threshold of 20,000 per cubic millimeter. The group with the lower threshold used 38 percent fewer units of platelets. The rates of bleeding complications of WHO grade 2 were similar: 18 percent in the former group and 17 percent in the latter.

Gil-Fernández et al.²⁴ performed a nonrandomized comparative analysis of 190 patients who underwent bone marrow transplantation at one institution during one period in which the transfusion threshold was 10,000 per cubic millimeter and a second period in which the threshold was 20,000 per cubic millimeter. Although the frequency of bleeding was not significantly different in the two periods, the median platelet requirement during the first 100 days after transplantation was 54 units with the lower threshold, as compared with 73 units with the higher threshold.

These data are in keeping with previous results showing that appreciable spontaneous bleeding does not occur until the platelet count falls below 5000 per cubic millimeter² and that the frequency and se-

verity of bleeding in patients with acute leukemia depend not only on the platelet count, but also on the type of leukemia; the presence of fever, infection, or coagulopathy; and the administration of drugs that interfere with platelet function.²⁵ For these reasons, the indications for prophylactic platelet transfusion must take into account the patient's condition and the clinical setting in which thrombocytopenia occurs.²

Until now, the safety of decreasing the usual threshold for platelet transfusion has not been determined in a large, randomized, multicenter clinical trial. This design reduces the dependence of the results on the specific characteristics of a single institution¹² and supports their transferability to other settings. To reduce the effect of potentially confounding factors further, we selected for our trial one disease, acute myeloid leukemia, in which the treatment is given over a well-defined period.

In our study there was one case of fatal hemorrhage in a patient with a platelet count of 32,000 per cubic millimeter among the 135 patients who underwent transfusion when their platelet count fell below 10,000 per cubic millimeter and none in the 120 control patients who received transfusions according to the usual threshold of 20,000 platelets per cubic millimeter. There was evidence that patients in the group with a threshold of 10,000 platelets per cubic millimeter had major bleeding during 3.1 percent of all days of hospitalization, as compared with 2.0 percent of hospital days in the patients in the group with a threshold of 20,000 platelets per cubic millimeter. However, this difference amounted to an average of about eight additional hours during a median hospitalization of 29 days, and we do not know whether it is clinically significant. We also found that a platelet-transfusion threshold of 10,000 per cubic millimeter could be used in 72 percent of transfusions; in 22.6 percent of transfusions the patients had concomitant risk factors that we thought would increase the probability of clinically significant bleeding, such as a temperature above 38°C and the need for invasive procedures. Furthermore, our study showed that the restrictive protocol used 21.5 percent fewer transfusions of platelets than the usual protocol.

The studies of Hanson and Slichter²⁶ may explain why patients in stable condition with platelet counts as low as 10,000 per cubic millimeter can have little risk of spontaneous bleeding. They found that a small, fixed number of platelets, about 7100 per cubic millimeter of blood per day, is removed randomly from the circulation and suggested that this fraction may participate in the endothelial repair that contributes to the prevention of bleeding. It thus seems that a level of 10,000 platelets per cubic millimeter may be sufficient for endothelial repair and the prevention of spontaneous bleeding.

TABLE 5. NUMBER OF MAJOR BLEEDING EPISODES ACCORDING TO TYPE.

TYPE OF EPISODE	THRESHOLD, 10,000	THRESHOLD, 20,000
	PLATELETS/mm ³	PLATELETS/mm ³
	no. of episodes (no. of patients)	
Gastrointestinal bleeding	12 (10)	5 (3)
Hematuria	5 (5)	6 (4)
Metrorrhagia	3 (3)	2 (2)
Epistaxis requiring transfusion	2 (2)	2 (2)
Retinal hemorrhage with visual impairment	3 (3)	2 (2)
Gingival hemorrhage requiring transfusion	0	2 (2)
Hemoptysis	1 (1)	1 (1)
Nonfatal cerebral hemorrhage	0	1 (1)
Fatal cerebral hemorrhage	1 (1)	0
System or organ affected not reported	12 (10)	12 (10)
Total*	39 (29)	33 (24)

*Some patients had more than one type of episode.

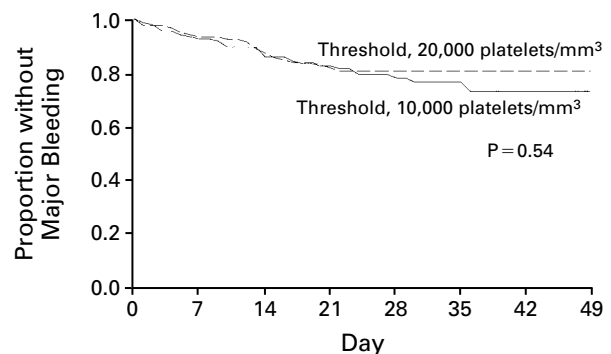


Figure 1. Proportion of Patients without Major Bleeding.

The relative risk of major bleeding was 1.1 in the group with a threshold of 10,000 platelets per cubic millimeter (95 percent confidence interval, 0.7 to 2.0) as compared with the group with a threshold of 20,000 platelets per cubic millimeter.

We would caution against overinterpreting our results. Obviously, further study is needed to ascertain whether the restrictive protocol can be used in other diseases and other clinical settings. We must also acknowledge that gastrointestinal bleeding occurred twice as often in the group with a threshold of less than 10,000 platelets per cubic millimeter as in the other group; even so, there were no significant differences between the two groups with respect to red-cell transfusions. We believe that the reduction in overall platelet use that might result from lowering the platelet-transfusion threshold may be sub-

stantial; McCullough et al. reported that a small proportion of patients (15 percent, most of whom had hematologic diseases) used most of the platelets (62 percent), which were administered prophylactically in approximately two thirds of the patients.²¹

Although some authors have suggested that a pretransfusion threshold of 5000 platelets per cubic millimeter may be adequate for many patients,²⁷ we selected a level of 10,000 platelets per cubic millimeter because the accuracy of platelet counts at lower levels may be insufficient with some automated counters²⁸ and reliance on manual platelet counts may be impractical. Furthermore, we were uncertain whether a threshold of 5000 platelets per cubic millimeter would be safe in settings in which the immediate availability of good-quality platelets could not be ensured.

In conclusion, this trial supports the safety of decreasing the usual prophylactic platelet-transfusion threshold in adolescents and adults with acute myeloid leukemia (except the promyelocytic type, which we did not study) during induction chemotherapy to an automated platelet count of 10,000 per cubic millimeter in patients in stable condition and 20,000 per cubic millimeter in patients with a temperature above 38°C or those undergoing invasive procedures. Although the use of the lower threshold can have a number of advantages, it should be viewed as a general reference value rather than an absolute one. Expert clinical judgment and careful monitoring of the patient remain the cornerstones of platelet-transfusion practice.

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APPENDIX

The members of the Platelet Transfusion Trigger Trial conducted by the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto are as follows: *Steering committee*: T. Barbui (Bergamo), F. Mandelli (Roma), G. Sirchia (Milano); *Executive committee*: G. Avvisati (Roma), G. Finazzi (Bergamo), L. Gugliotta (Bologna), P. Rebulla and A. Zanella (Milano); *Monitoring committee*: A. Del Favero (Perugia), S. Murphy (Philadelphia), G. Tognoni (Milano); *Data-management committee*: F. Marangoni, M. Pappalètera, and P. Rebulla (Milano); *Principal investigators and data collectors*: A. Alberti, F. Juliano, A. Veratti (Catanzaro); E. Ascari, A.M. Iannone, L. Salvaneschi (Pavia); T. Barbui, M. Buelli, G. Scudeller (Bergamo); B. Bizzzi, T. Lanti, G. Adorno, G. Minunno, F. Mandelli, P. Pontis, G. Girelli (Roma); A. Cajozzo, M. Musso (Palermo); G. Corneo, M. Mangiagalli, G. Sciorelli (Monza); P. Coser, O. Prinoth (Bolzano); L. De Riu, S. Guarino, C. Serafini (Latina); E. Gallo, M. Grasso, S. Fenoglio (Cuneo); I. Iori, F. Merli, P. Rivasi (Reggio Emilia); G. Lambertenghi Deliliers, E. Pozzoli, G. Sirchia (Milano); P. Leoni, D. Capelli, G. Cantelli (Torrette di Ancona); G. Lucarelli, D. D'Adamo, G. Bechelli (Pesaro); F. Nobile, G. Console, M. Donato (Reggio Calabria); A. Porcellini, G. Bisceglie, G. Romanini (Cremona); F. Ricciuti, M. Pizzuti, S. D'Angelo (Potenza); V. Rizzoli, C. Almici, E. Talarico Bianchi (Parma); F. Rodeghiero, A. Schiavotto, M. Belloni (Vicenza); B. Rotoli, M. Picardi, S. Formisano (Napoli); and S. Tura, N. Vianelli, R. Conte (Bologna).

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