Clinical effectiveness of platelets in additive solution treated with two commercial pathogen-reduction technologies

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BACKGROUND: Two noninferiority, randomized, controlled trials were conducted in parallel comparing the safety and efficacy of platelets treated with Intercept or Mirasol pathogen-reduction technologies versus standard platelets.

STUDY DESIGN AND METHODS: The primary endpoint was the percentage of hematology patients who developed World Health Organization Grade 2 or greater bleeding. A noninferiority margin of 11% was chosen based on expected Grade 2 or greater bleeding in 20% of controls. The study was closed for financial restrictions before reaching the planned sample size of 828 patients, and an intention-to-treat analysis was conducted on 424 evaluable patients.

RESULTS: In the Intercept trial (113 treated vs. 115 control patients), the absolute risk difference in Grade 2 or greater bleeding was 6.1%, with an upper one-sided 97.5% confidence limit of 19.2%. The absolute risk difference in the Mirasol trial (99 treated vs. 97 control patients) was 4.1%, and the upper one-sided 97.5% confidence limit was 18.4%. Neither absolute risk difference was statistically significant. In both trials, posttransfusion platelet count increments were significantly lower in treated versus control patients. Mean blood component use in treated patients versus controls was 54% higher (95% confidence interval, 36%-74%; Intercept) and 34% higher (95% confidence interval, 16%-54%; Mirasol) for platelets and 23% higher (95% confidence interval, 8%-39%; Intercept) and 32% higher (95% confidence interval, 10%-57%; Mirasol) for red blood cells. Unexpected reactions and adverse events were not reported. Mortality did not differ significantly between treated and control patients.

CONCLUSION: Although conclusions on noninferiority could not be drawn due to low statistical power, the study provides additional information on the safety and efficacy of pathogen-reduced platelets treated with two commercial pathogen-reduction technologies.

ABBREVIATIONS:: AML = acute myeloid leukemia; ITT = intention to treat; PP = per protocol; PR = pathogen reduction; RCT(s) = randomized controlled trial(s); UCL = upper one-sided 97.5% confidence limit.

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Although it is extremely safe, platelet transfusion carries measurable risks of adverse events, including pathogen transmission, alloimmunization to human leukocyte antigens (HLAs), and transfusion-associated graft-versus-host disease. Traditional approaches to reduce these events include improved selection of blood donors and leukoreduction, gamma-irradiation, and bacterial screening of blood components.

Commercial technologies using ultraviolet light to irradiate platelets in the presence of amotosalen or riboflavin have been developed that inactivate pathogens and abrogate leukocyte replication, preventing transfusion-associated graft-versus-host disease.[1,2] The safety of pathogen-reduced platelets has been evaluated in several randomized clinical trials[3-9] and is supported by hemovigilance data.[10,11]

Pathogen-reduction (PR) technologies provide an opportunity to "raise the bar"[12] of transfusion safety, not only by reducing bacterial contamination and septic transfusion reactions[13] but especially in relation to recent concerns of transfusion-transmissible infectious agents such as Zika virus.[14]

Although these technologies for PR of platelets have been evaluated independently using superiority[3,6] and noninferiority trial designs,[4,5,7-9] the two methods have not been tested concurrently in one country. A full technology assessment of these methodologies would provide useful information about risk-based decision making for blood safety.[15,16]

We report on the safety and efficacy of platelets treated with the above-described PR technologies, which were evaluated in parallel in the Italian Platelet Technology Assessment Study. Our specific interest was to collect local data useful for future evaluations of the cost effectiveness of PR technologies and deliberations on their mandatory versus voluntary use in our country. The main objectives of the study were to determine the effectiveness and safety of pathogen-reduced platelets in oncohematology patients undergoing chemotherapy or allogeneic hemopoietic stem cell transplantation.

MATERIALS AND METHODS

Study design

The Italian Platelet Technology Assessment Study was designed as two independent, randomized controlled trials (RCTs) conducted simultaneously in six hematological centers in Italy to assess the effectiveness and safety of PR versus non-PR platelets. The design of each RCT was identical with the exception of the PR technology used in the treatment arms. Three sites evaluated Intercept platelets (Cerus), and three other sites evaluated Mirasol platelets (Terumo BCT). The study was approved by the Institutional Review Board of the clinical coordination site at Foundation Ca' Granda Ospedale Maggiore Policlinico (Milan) and was performed in agreement with the principles of the Declaration of Helsinki (Edinburgh, Scotland, 2000). A Data and Safety Monitoring Board monitored the study for data quality and safety and operational issues. Two formal interim analyses were prespecified to occur after enrolment of 66 and 133 patients in each arm, respectively. Formal stopping rules were not prespecified. The study protocol and the case report forms are available in the supporting information. The study was registered at www.clinicaltrials.gov as National Clinical Trial NCT01642563.

Patients

Patients were eligible for the study if they were adults (aged 18 years or older) with a hematological cancer expected to require two or more platelet transfusions during a single course of remission induction or consolidation chemotherapy or during allogeneic hemopoietic stem cell transplantation. Exclusion criteria included: patients with promyelocytic leukemia, because of the high frequency of coagulopathy and bleeding unrelated to platelet count in this condition; patients who received previous transfusions and had historical documentation of two or more 1-hour posttransfusion platelet corrected count increments (CCIs) below 5000/μL; and patients who had anti-HLA antibodies on admission with greater than 20% panel reactive antibodies. Patients could be enrolled only once and gave written informed consent for participation.

Randomization and masking

There were two levels of randomization: sites and patients. Sites were randomly allocated to the Intercept or Mirasol trial by the administrative coordinating center (Italian National Blood Center, National Institute of Health, Rome). The treatment allocation schedule for patients was prepared by the Italian National Blood Center using a computer-generated assignment sequence stratified by site and whether the patient was receiving chemotherapy or allogeneic hemopoietic stem cell transplantation. Patients were assigned using a 1:1 ratio to one of the two study arms using random permuted blocks with block size equal to 8. Patients were randomized at the time of their first platelet transfusion request by the local blood transfusion service staff using opaque envelopes that contained the treatment assignment. Only the study data manager and the local blood transfusion service staff had knowledge of the patient's randomization arm.

Procedures

Platelets were prepared from whole blood with the buffy-coat method or were collected by apheresis, resuspended in approximately 30% plasma and 70% platelet additive solution, and stored for a maximum of 5 days at 20 to 24°C

under constant agitation. Both PR and control platelets were prepared by each of the six blood transfusion services participating in the study. A platelet dose (total platelet count) was determined in all platelet units at the time of production.

PR platelets were prepared according to manufacturers' instructions using regularly maintained PR devices by staff from the local blood transfusion service. Intersol or SPP+ and Intersol or Composol platelet additive solutions were used for both PR and non-PR platelets in centers that used the Intercept and Mirasol PR technologies, respectively. Each center used only one platelet additive solution throughout the study. PR platelets were not gamma-irradiated or selected to be cytomegalovirus-negative.

Standard platelets, PR platelets, and red blood cells (RBCs) were leukoreduced prestorage with locally validated procedures compliant with the European Union requirement of a final leukocyte count below 1×10^6 per unit. The clinical sites used a RBC transfusion trigger of 80 g/L hemoglobin. Prophylactic platelet transfusion triggers of 10×10^9/L and 20×10^9/L were used for stable patients and for patients who had a rapid fall of the platelet count, documented infection, and/or body temperature greater than 38°C, respectively. Non-PR platelets and RBCs used in both the treatment and control arms were gamma-irradiated and selected based on cytomegalovirus serology according to clinical indication.

Patient observation started on the day of the first platelet transfusion and continued for 28 days or less if the patient did not receive platelet transfusions for 7 days, was discharged, or died. Daily bleeding assessments were performed by a local clinical investigator blinded to the treatment allocation by patient interview, clinical assessment, and chart review. A bleeding grade was assigned according to World Health Organization criteria[17] and the system or organ affected. All bleeding episodes occurring between daily evaluations, including different grades and the system or organ affected, were recorded. The clinical staff at each center was not informed of patient allocation, and the local investigators were instructed to perform bleeding assessments at times different from platelet transfusion administration to avoid possible unblinding due to slight visible differences in platelet products. Body temperature, blood pressure, and heart rate were collected before and after platelet transfusion. After each platelet transfusion, patients were evaluated for adverse events (AEs) that occurred in the next 24 hours. AEs were assessed for relation to the platelet transfusion and graded for clinical severity. Transfusions with AEs possibly, probably, or definitely related to platelet transfusion were defined as transfusions with an acute reaction. Other collected data included: blood product transfusion data, routine laboratory test results, patient demographics, diagnosis and therapies, and baseline HLA screening results. Regular audits were performed by an independent monitor to ensure accuracy and quality of data.

Outcomes

The primary endpoint was the percentage of patients that developed one or more bleeding episodes of Grade 2 or greater.[18] Grade 2 bleeding was defined as oropharyngeal bleeding or epistaxis with total duration greater than 30 minutes in the previous 24 hours, purpura with a diameter greater than 1 inch, spontaneous hematomas in deeper tissues, joint bleeding, melena, hematochezia, hematemesis, gross or visible hematuria, abnormal vaginal bleeding, hemoptysis, blood in bronchopulmonary lavage or blood-tinged sputum, visible blood in body cavity fluid, retinal bleeding without visual impairment, lumbar puncture with blood (>5 RBCs/μL in cerebrospinal fluid on microscopic analysis and nontraumatic tap, no visible red color), and bleeding at invasive sites with total duration greater than 1 hour in the previous 24 hours. Grade 3 bleeding was defined as any bleeding that required RBC transfusion over routine transfusion needs, grossly bloody body cavity fluids and organ dysfunction with symptoms, lumbar puncture with visible red color in the absence of symptoms and nontraumatic tap, or any bleeding associated with moderate hemodynamic instability. Grade 4 bleeding was defined as fatal bleeding from any source; retinal bleeding with visual impairment; central nervous system symptoms with nontraumatic, bloody lumbar puncture; central nervous system bleeding on an imaging study; or any bleeding associated with severe hemodynamic instability.

Secondary outcomes included: time to the episode of Grade 2 or greater bleeding; number of days with Grade 2 or greater bleeding; number of transfused platelets; proportion of patients with acute transfusion reactions; posttransfusion platelet count increments; proportion of patients developing platelet transfusion refractoriness, defined as the detection of 1-hour posttransfusion corrected platelet count increments below 5000/μL after two consecutive ABO-compatible, fresh (≤2 days old) platelet transfusions.

One-hour and 24-hour CCIs were determined using the following formula:

$$\frac{\text{Post}-\text{pre transfusion platelet count } (/\mu\text{L}) \times \text{patient body surface area } (\text{m}^2)}{\text{Platelets dose } (\times 10^{11})}$$

The patient's body surface area was determined according to DuBois and DuBois.[19]

Statistical analysis

Based on local historical data, it was estimated that the frequency of Grade 2 or greater bleeding in the reference group would be 20%. With a noninferiority margin of 11%, which was considered appropriate in relation to the expected benefits of PR, a one-sided Type I error of 0.025, and power of 80%, 207 patients per arm in each trial (828 in total) were required. However, because of financial restrictions, the study was closed before the planned sample size was reached.

The primary analysis was done on the intention-to-treat (ITT) population, including 424 evaluable patients who received at least one platelet transfusion. A prespecified per protocol (PP) analysis was done excluding all treated and control patients who had received at least one non-PR and PR platelet unit, respectively. A post-hoc subgroup ITT analysis was carried out on patients with acute myeloid leukemia (AML) in consideration of the higher proportion of leukemic patients in the treatment arm of the Intercept trial.

No imputation was done for missing data. Secondary outcomes in treated and control patients were compared by determining differences or ratios and their 95% confidence intervals (CI) with no a priori hypothesis of noninferiority, equivalence, or superiority.

The upper one-sided 97.5% confidence limit (UCL) of the between-arm difference in the occurrence of the primary endpoint was computed according to Santner and Snell.[20] The same approach was adopted to compute two-sided 95% confidence limits of the between-arm differences in the number of deceased or refractory patients or patients who had transfusion reactions. In case of inconsistency between exact test results and exact confidence limits, continuity-adjusted chi-square test and 95% asymptotic confidence limits were adopted. Confidence limits of the odds ratios for the number of days with a leukocyte count less than 1.5×10^9/L (a proxy of bone marrow depression selected post-hoc), the number of days with Grade 2 or greater bleeding, and the number of transfusion reactions were derived from a generalized linear mixed model for binomial variates, using a logit link function. Confidence limits of differences and ratios in the number of platelet and RBC units transfused were derived from a generalized linear model for Poisson variates using an identity link-function for differences and a logarithmic link-function for ratios. Confidence limits of the differences in the other secondary endpoints were derived from an ordinary general linear model. Differences between patients with and without Grade 2 or greater bleeding during the study and the number of blood components used were estimated with a two-factor general linear model with interaction (arm, bleeding, arm × bleeding). All analyses were carried out on a per-patient basis; that is, patients were included in the models as random terms within each arm, and the observations were included as random terms within patient.[21]

Days to the occurrence of the first Grade 2 or greater bleeding and to the onset of refractoriness were expressed in terms of Kaplan-Meier survival curves, and between-arm differences were tested with the log-rank test. Data processing and statistical analyses were carried out with SAS version 9.2 (SAS Institute, Inc.). A p value less than 0.05 was considered statistically significant.

RESULTS

Between October 20, 2010 and June 30, 2014, 360 and 246 patients were assessed for eligibility in the Intercept and Mirasol trials, respectively. In the Intercept trial, 118 patients were randomized to the PR arm, and 119 were randomized to the standard platelets arm. In the Mirasol trial, 102 patients were randomized to receive PR platelets, and 99 were randomized to receive standard platelets (Fig. 1).

General characteristics of patients included in the ITT analysis and the number of days with leukocyte count less than 1.5×10^9/L are shown in Table 1. There was a higher prevalence of patients with leukemia and of males in treated versus control patients in the Intercept and Mirasol trials, respectively.

Statistical significance of the differences between arms in the ITT populations are reported in Table 2. Descriptive statistics are reported in Tables 3 through 6.

The number of patients who had bleeding episodes and the bleeding sites or organs are detailed in Table 3. Because of the low statistical power caused by early study termination, no conclusion was drawn about the noninferiority of PR platelets, and the primary endpoint is reported only for descriptive purposes. The absolute risk differences of proportions of patients with Grade 2 or greater bleeding in the treated versus control arms were +6.1% (UCL, +19.2%) and +4.1% (UCL, +18.5%) in the Intercept and Mirasol trials, respectively (Table 2).

Proportions of patients who were free of Grade 2 or greater bleeding during the study are reported in Fig. 2. Differences between the treated and control arms were not statistically significant.

Characteristics of blood components, duration of the study, and the number of platelets and RBC units transfused are shown in Table 4. More than 80% of the platelets were transfused within 2 days of storage. Protocol violations related to the transfusion of non-PR platelets to patients allocated to the treatment arm occurred in 2.8 and 6.4% of platelet transfusions in the Intercept and Mirasol trials, respectively, because of temporary nonavailability of the specific product. Platelet counts in apheresis

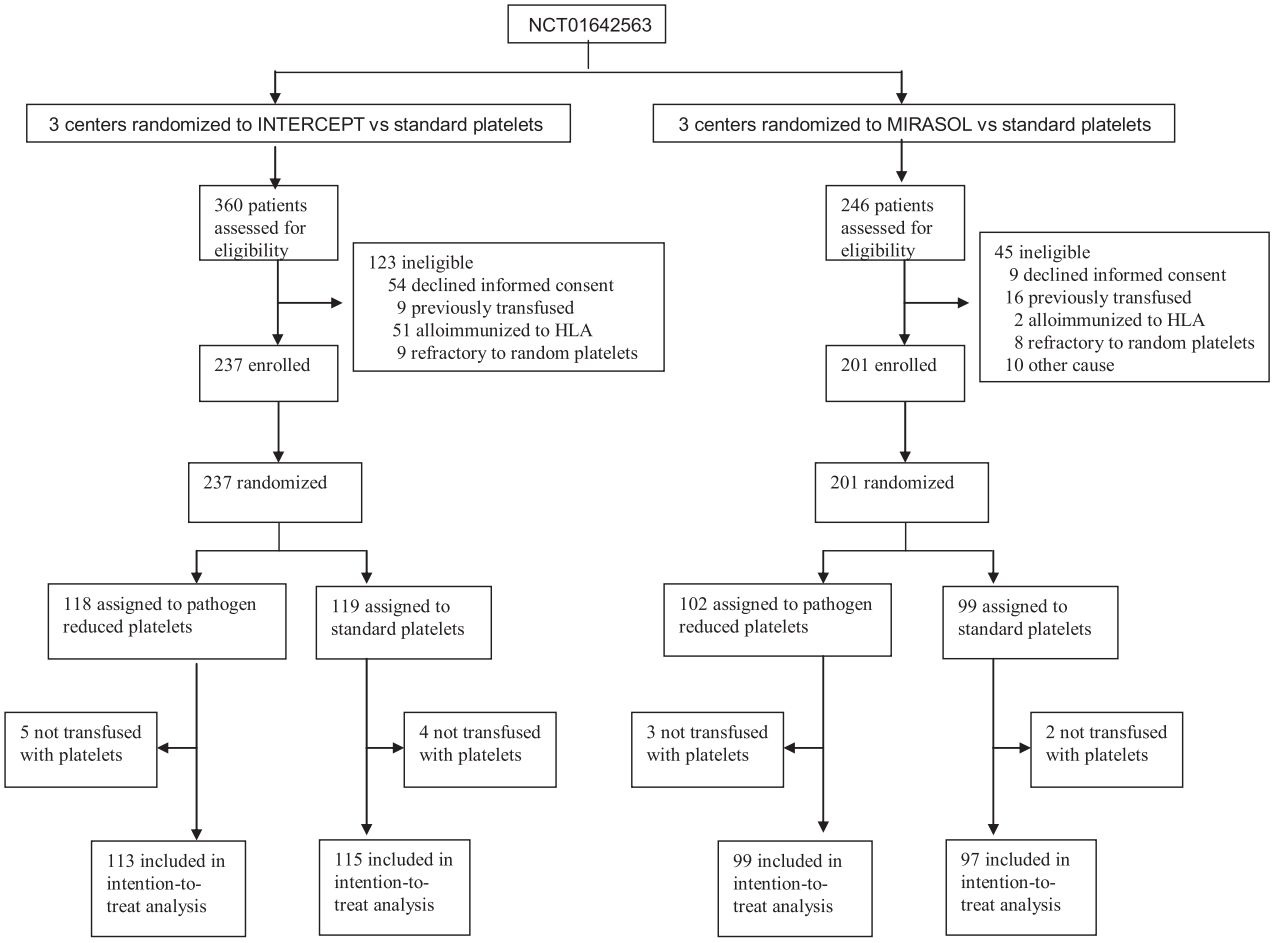

Fig. 1. This flow diagram illustrates the progress through the study phases.

and buffy-coat–derived platelets were comparable in the different arms and in compliance with local standards. Centers that used the Intercept and Mirasol technologies used buffy-coat–derived platelets in approximately 97 and 50% of transfusions, respectively. Table 2 shows that the mean blood component use in treated patients versus controls was 54% (95% CI, 36%-74%; Intercept) and 34% (95% CI, 16%-54%; Mirasol) higher for platelet units, and 23% (95% CI, 8%-39%; Intercept) and 32% (95% CI, 10%-57%; Mirasol) higher for RBC units. On average, patients in the treated arms of the Intercept and Mirasol trials used 2.07 (95% CI, 0.82-3.51) and 1.17 (95% CI, 0.27-2.07) more platelet units than patients in the control arms, respectively (Table 2).

Pretransfusion and posttransfusion absolute platelet counts, posttransfusion count increments, CCIs, and the number of days between platelet transfusions are shown in Table 5. Both 1-hour and 24-hour posttransfusion platelet count increments and CCIs in treated patients were lower than the increments in controls. Differences between the treated and control arms were statistically significant with the exception of 1-hour CCIs in the Intercept trial and 1-hour count increments in the Mirasol trial (Table 2).

Time on study and the number of RBC and platelet units given to patients with and without Grade 2 or greater bleeding are shown in Table S1 (available as supporting information in the online version of this paper). Blood component use was statistically significantly increased in patients with Grade 2 or greater bleeding, with the exception of platelet use in controls on the Mirasol trial. Occurrence of bleeding was associated with statistically significant longer time on study in both treated and control patients.

Data from refractory patients are shown in Table 2, Table S2, and Fig. S1 (available as supporting information in the online version of this paper). Refractoriness was significantly more frequent in recipients of PR platelets versus controls (Intercept trial, 13.3 vs. 4.3%; Mirasol trial, 18.2 vs. 4.1%). Pretransfusion and posttransfusion platelet counts before and after detection of refractoriness did not show clinically relevant differences associated with treatment arm (Table S2, available as supporting information in the online

TABLE 1. Characteristics of the study patients

	Intercept trial		Mirasol trial	
Item	PR platelets	Standard platelets	PR platelets	Standard platelets
No. of enrolled patients	118	119	102	99
No. of patients included in ITT analysis (%)	113 (95.8)	115 (96.6)	99 (97.1)	97 (98.0)
Male sex, no. (%)	68 (60.2)	68 (59.1)	67 (67.7)	50 (51.6)
Age: Median/range, years	53/18-85	53/19-76	56/20-82	54/22-76
Height: Median [IQR], cm	170 [160-174]	170 [164-175]	170 [165-176]	172 [163-178]
Body weight: Median [IQR], kg	73 [61-83]	73 [63-81]	70 [62-80]	72 [60-81]
Disease classification, no. (%)				
Leukemia	84 (74.3)	69 (60.0)	72 (72.7)	69 (71.1)
Lymphoma	16 (14.2)	23 (20.0)	16 (16.2)	22 (22.7)
Other	13 (11.5)	23 (20.0)	11 (11.1)	6 (6.2)
Chemotherapy/allogeneic transplantation	101/12	102/13	85/14	83/14
Total no. (%) of days with leukocyte count $<1.5 \times 10^9$/L/total no. of days with complete blood count	562/789 (71.2)	471/598 (78.8)	474/543 (87.3)	358/409 (87.5)
Percentage of days with leukocyte count $<1.5 \times 10^9$/L, mean $\pm$ SD	49.6 $\pm$ 25.7	42.6 $\pm$ 26.5	39.5 $\pm$ 27.4	38.3 $\pm$ 24.3

IQR = interquartile range.

TABLE 2. ITT analysis: results of statistical analysis, reported as the difference (D), odds ratio (OR), or ratio (R) between the treatment and control arms*

Item	Intercept trial	p	Mirasol trial	p
Primary outcome				
Percentage of patients with Grade $\geq$2 bleeding: D	+6.1% (UCL, +19.2%)	0.1648	+4.1% (UCL, +18.5%)	0.2489
Secondary outcomes				
No. of days with Grade $\geq$2 bleeding: OR	1.55 (0.67; 3.63)	0.3100	1.10 (0.44; 2.74)	0.8414
No. of days with leukocyte count $<1.5 \times 10^9$/L: OR	0.82 (0.48; 1.39)	0.4544	1.00 (0.55; 1.84)	0.9881
No. of days on platelet support: D	+1.88 (+0.04; +3.72)	0.0452	+1.45 (+0.11; +2.80)	0.0342
No. of platelet units transfused: R	1.54 (1.36; 1.74)	$<$ 0.0001	1.34 (1.16; 1.54)	$<$ 0.0001
No. of platelet units transfused: D	+2.07 (+1.49; +2.64)	$<$ 0.0001	+1.17 (+0.61; +1.73)	$<$ 0.0001
No. of platelets transfused, $\times 10^9$/L: D	+556 (+172; +941)	0.0047	+399 (+118; +681)	0.0057
No. of RBC units transfused: R	1.23 (1.08; 1.39)	0.0015	1.32 (1.10; 1.57)	0.0024
No. of RBC units transfused: D	+0.87 (+0.34; +1.41)	0.0014	+0.69 (+0.25; +1.14)	0.0023
1-Hour posttransfusion platelet count increment, $\times 10^9$/L: D	−4.42 (−7.80; −1.04)	0.0105	−8.91 (−18.94; +1.11)	0.0810
24-Hour posttransfusion platelet count increment, $\times 10^9$/L: D	−7.06 (−10.37; −3.75)	$<$ 0.0001	−4.28 (−7.47; −1.08)	0.0090
1-Hour posttransfusion corrected platelet count increment: D	−2004 (−4045; +38)	0.0543	−5282 (−10,436; −128)	0.0446
24-Hour posttransfusion corrected platelet count increment: D	−3066 (−4926; −1206)	0.0014	−2554 (−4212; −896)	0.0027
Percentage of patients with nonhemolytic, febrile transfusion reactions to platelets: D	+2.82 (−9.90; +15.96)	0.5310	−1.22 (−15.44; +12.55)	0.8132
Percentage of patients with allergic transfusion reactions to platelets: D	−0.73 (−13.56; +12.48)	1.0000	+0.99 (−13.24; +15.11)	1.0000
No. of platelet transfusions followed by nonhemolytic, febrile reactions: OR	0.76 (0.35; 1.64)	0.4842	0.76 (0.29; 2.10)	0.6013
No. of platelet transfusions followed by allergic reactions: OR	0.63 (0.24; 1.63)	0.3406	1.50 (0.13; 17.16)	0.7435
Percentage of refractory patients: D†	+8.93 (+1.64; +16.21)	0.0317	+14.06 (+5.49; +22.62)	0.0038
Percentage of patients who died: D	−6.01 (−18.80; +7.26)	0.1286	+4.00 (−10.30; +17.98)	0.2790

* Data in parentheses indicate the upper one-sided 97.5% confidence limit (UCL) for primary outcome and the two-sided 95% confidence limits for secondary outcomes.

† Adjusted chi-square and asymptotic confidence limits are shown.

TABLE 3. ITT analysis: number (%) of patients and days with Grade 2 or greater bleeding episodes and bleeding site/organ calculated as the number of patients and days with available bleeding report forms

	Intercept trial		Mirasol trial	
Item	PR platelets	Standard platelets	PR platelets	Standard platelets
No./total no. (%) of patients with Grade ≥2 bleeding episodes	24/109 (22.0)	17/107 (15.9)	13/97 (13.4)	9/97 (9.3)
Reported on 1 day	11	6	7	3
Reported on 2 days*	2	3	2	2
Reported on 3 days*	1	3	1	1
Reported on 4 days*	2	2	1	0
Reported on >4 days*	8	3	2	3
No. (%) of patients with Grade 3 bleeding episodes	0	1 (0.9)	0	0
No. (%) of patients with Grade 4 bleeding episodes	2 (1.8)	0	1 (1.0)	2 (2.1)
No./total no. (%) of days with Grade ≥2 bleeding	116/1266 (9.2)	61/1119 (5.5)	30/1118 (2.7)	39/1065 (3.7)
Mean ± SD no. of days with Grade ≥2 bleeding per patient with Grade ≥2 bleeding	4.83 ± 5.98	3.59 ± 4.03	2.31 ± 1.93	4.33 ± 4.18
No. (%) of patients; no. (%) of days with grade ≥2 bleeding by site/organ				
Oral, nasal	14 (12.8); 28 (2.2)	8 (7.5); 15 (1.3)	4 (4.1); 5 (0.4)	5 (5.2); 9 (0.8)
Skin, soft tissue, musculoskeletal	16 (14.7); 90 (7.1)	8 (7.5); 29 (2.6)	5 (5.2); 8 (0.7)	3 (3.1); 19 (1.8)
Gastrointestinal, genitourinary, gynecologic	10 (9.2)†; 38 (3.0)	6 (5.6); 27 (2.4)	5 (5.2); 14 (1.3)	2 (2.1); 3 (0.3)
Pulmonary	0	1 (0.9); 4 (0.4)	1 (1.0); 1 (0.1)	1 (1.0); 1 (0.1)
Body cavity	0	0	0	0
Neurologic	1 (0.9); 6 (0.5)	0	1 (1.0); 5 (0.4)	2 (2.1); 20 (1.9)
Invasive sites	1 (0.9); 2 (0.2)	0	0	0
Hemodynamic instability	1 (0.9); 1 (0.1)	1 (0.9); 1 (0.1)	0	0

* These episodes were reported on consecutive or nonconsecutive days.
† In one patient who died of hemorrhagic shock, the last platelet count available before death was 26×10^9/L.

version of this paper), suggesting that refractoriness was occasional and transitory.

Transfusion reactions, complete remission in chemotherapy recipients, and frequency and causes of death are reported in Table 6. Differences between treated and control patients were not statistically significant (Table 2). Unexpected reactions and AEs were not reported. Hemorrhagic shock was the cause of death in one recipient of PR platelets who had a platelet count of 26×10^9/L on the day of death. There was no evidence that the cause of death was related to platelet transfusion.

The numbers of transfusion reactions to RBCs are provided in Table S3 (available as supporting information in the online version of this paper).

Results of the PP analysis are shown in Tables S4 through S7 (available as supporting information in the online version of this paper). Results of the post-hoc ITT analysis of patients with AML are provided in Tables S8 through S12 (available as supporting information in the online version of this paper).

The primary ITT, PP, and post-hoc ITT analyses in patients with AML yielded concordant statistical significances for differences and ratios of the number of transfused platelet units and for absolute and corrected posttransfusion platelet count increments at 24 hours.

DISCUSSION

We compared the safety and efficacy of PR versus standard platelets in two parallel RCTs to contribute local data to a national program of transfusion technology assessment designed to assess the costs and benefits of two commercial PR technologies.

The study closure before completion of the planned sample size, which was not related to safety issues, prevented us from drawing conclusions on PR platelets noninferiority. PR platelet recipients displayed a numerically higher but not statistically significantly increased frequency of the composite outcome of mild to severe bleeding, the latter consisting mainly of mild bleeding events. Furthermore, no evidence of unexpected transfusion reactions or AEs was reported. In both trials, per patient analyses showed statistically significant reductions in posttransfusion platelet count increments and increased use of platelets and RBCs in PR platelet recipients. Although our study was not designed to directly compare the two commercial PR technologies, we noted that their performance in relation to local standard platelets was similar.

Other than the reassuring evidence that the use of PR platelets was not associated with unexpected reactions or

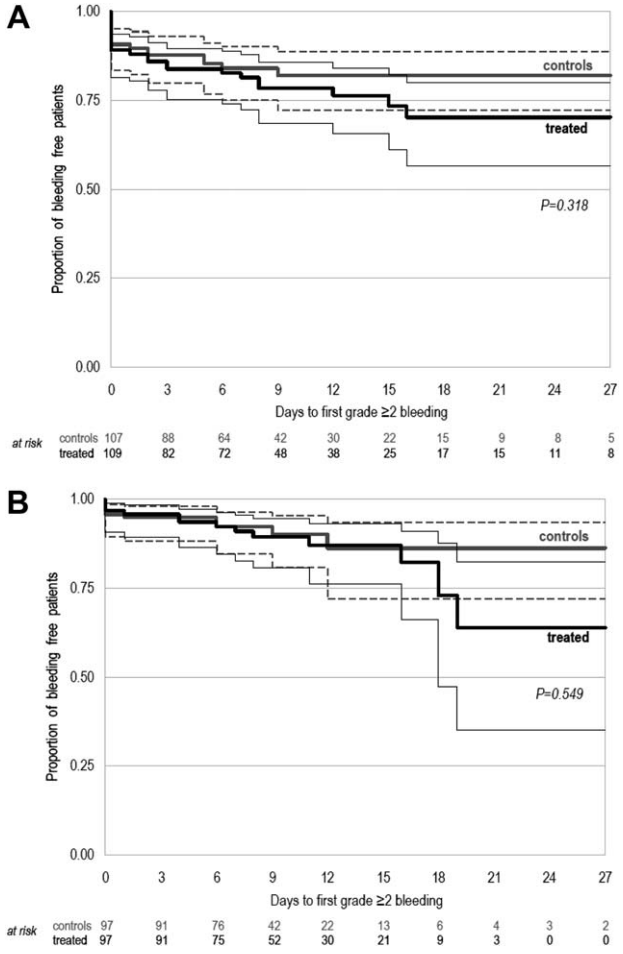

Fig. 2. ITT analysis. The proportions of patients who were free of Grade 2 or greater bleeding in the (A) Intercept and (B) Mirasol trials are shown. Thin solid and dashed lines represent 95% confidence bands in treated and control patients, respectively.

severe hemorrhagic events with significantly greater frequency than those observed in recipients of standard platelets, our data confirm lower posttransfusion platelet count increments in PR platelet recipients versus controls, as reported in other studies. Our data suggest that lower increments were a possible cause of a slight shortening of the platelet transfusion interval, in turn translating into a mean of one or two more platelet units given to PR platelet recipients versus controls. Although this absolute mean increment per patient may appear small, it corresponded to 54 and 34% greater platelet use in the recipients of Intercept-treated and Mirasol-treated platelets, respectively.

We have no clear interpretation for the increased RBC use in the treatment arms of both trials, because most bleeding episodes detected in the treatment arms were World Health Organization Grade 2 or lower, which usually are considered of little clinical significance. However, it is possible that repeated minor bleeding may have required greater RBC support in some patients.

The finding of significantly increased proportions of patients who were refractory to platelet support in the treatment arms of both trials was not unexpected, because this was clearly associated with significantly inferior posttransfusion platelet count increments. This deficiency could be corrected by increasing the platelet dose in units undergoing PR, as performed in two RCTs.[3,9] Additional studies are in progress to investigate the presence of anti-HLA antibodies in the serum of refractory patients.

Operationally, we collected reassuring evidence that the additional step of PR along with routine procedures of platelet preparation was not associated with undesirable prolongation of platelet storage and transfusion of older platelets, as supported by comparable platelet ages at transfusion in the treatment and control arms. Moreover, staff training, qualification, and maintenance of the PR devices did not outline particular problems or difficulties.

Our findings should be considered within the broad context of the results from other RCTs that have tested PR versus standard platelets.[3-9] Their methodological similarities and differences have been carefully analyzed by Cook and Heddle.[22]

Similar to our study, most trials performed with the Intercept technology evaluated multiple transfusions of PR platelets obtained by apheresis or from buffy-coat pools, suspended in a mixture of plasma and commercially available platelet-additive solutions, and stored for 1 to 5 days.[3-7] Control platelets were stored in plasma/platelet additive solutions[3,7,9] or 100% plasma.[4,6,7] Two studies extended platelet storage to 7 days,[7,9] and one study limited the evaluation to one transfusion per patient receiving PR or standard platelets stored for 6 or 7 days.[9] An increase in the platelet dose to account for expected loss due to pathogen reduction was performed only in one center that participated in the euroSPRITE trial[3] and in the study reported by Lozano and colleagues.[9] The robustness and generalizability of the conclusions of these trials vary not only in relation to many methodological differences but also in relation to their sample size, ranging from 43[6] to 645[4] patients. Although most trials used a surrogate marker of clinical efficacy, such as the posttransfusion platelet count increment, only the SPRINT trial,[4] similar to our study, selected bleeding, that is, a "patient-based outcome"[22] as the primary outcome. Despite several existing similarities, a direct comparison of the results from our Intercept trial with those of the above-described studies[3-7,9] is hampered by methodological differences. First, mean platelet age at transfusion was less than 2 days in our trial, whereas it was 3 or 4 days in four studies,[3,4,6,7] and 6 or 7 days in one[9] previously published Intercept RCT. Second, policies for platelet gamma-irradiation had significant variations among the RCTs, because gamma-irradiation was not used for PR platelet

TABLE 4. ITT analysis: characteristics of blood components, duration of study, number of platelets and RBC units transfused (total and per patient)*

	Intercept trial		Mirasol trial	
Item	PR platelets	Standard platelets	PR platelets	Standard platelets
Total no. of adult platelet doses	667	441	457	334
Transfusions received within 2 days of storage/no. with data	596/665 (89.6%)	358/434 (82.5%)	367/456 (80.5%)	262/334 (78.4%)
ABO compatible/no. with data	552/631 (87.5%)	309/346 (89.3%)	357/441 (81.0%)	123/147 (83.7%)†
Prepared by apheresis/no. with data	4/667 (0.6%)	12/441 (2.7%)	214/457 (46.8%)	174/324 (53.7%)
Leukoreduced/no. with data	666/667 (99.9%)	439/441 (99.6%)	457/457 (100%)	334/334 (100%)
Gamma irradiated/no. with data	3/667 (0.5%)	243/441 (55.1%)	13/457 (2.8%)	195/334 (58.4%)
Pathogen reduced/no. with data	648/667 (97.2%)	9/441 (2.3%)	428/457 (93.6%)	0/334 (0%)
Platelet content in apheresis platelets, $\times 10^9$ [no. with data]	351 ± 95 [4]	307 ± 68 [11]	331 ± 45 [214]	323 ±57 [174]
Platelet content in pooled platelets, $\times 10^9$ [no. with data]	292 ± 35 [654]	309 ± 43 [385]	325 ± 70 [238]	328 ± 58 [143]
Days of storage of platelets at transfusion [no. with data]	1.29 ± 0.79 [665]	1.48 ± 0.92 [434]	1.66 ± 1.04 [457]	1.73 ± 0.96 [334]
No. of leukoreduced RBC units/no. with data	533/533 (100%)	434/442 (98.2%)	275/286 (96.2%)	204/213 (95.8%)
No. of gamma-irradiated RBC units/no. with data	204/533 (38.3%)	261/442 (59.0%)	273/286 (95.5%)	204/213 (95.8%)
No. of days from first platelet transfusion to study end (total)	15.75 ± 6.94 (1780)	14.29 ± 6.32 (1643)	13.90 ± 4.97 (1376)	12.97 ± 4.71 [1258]
No. of days from first to last platelet transfusion (total)	9.96 ± 8.23 (1126)	8.04 ± 7.44 (925)	7.62 ± 5.50 (754)	6.23 ± 4.84 [604]
No. of days on platelet support (total)‡	9.04 ± 7.56 (1022)	7.17 ± 6.50 (824)	7.02 ± 5.47 (695)	5.57 ± 3.92 [540]
No. of adult platelet doses transfused (total)	5.90 ± 5.84 (667)	3.83 ± 3.40 (441)	4.62 ± 3.96 (457)	3.44 ± 2.13 [334]
No. of platelets transfused, $\times 10^9$	1751 ± 1674	1194 ± 1093	1515 ± 1222	1115 ± 702
No. of RBC units transfused (total)	4.72 ± 5.0 (533)	3.84 ± 4.0 (442)	2.89 ± 2.90 (286)	2.20 ± 2.0 (213)

* Data are given as numbers, percentages, and means ±SD.
† Data were missing from two centers in the Mirasol trial.
‡ The sum of days is indicated from the first to last platelet transfusion with the exclusion of inter-transfusion intervals 5 days or longer.

TABLE 5. ITT analysis: pretransfusion and posttransfusion platelet counts ($\times 10^9$/L), posttransfusion platelet count increments, CCIs and number of days between platelet transfusions

	Mean ± SD (no. with data)			
	Intercept trial		Mirasol trial	
Item	PR platelets	Standard platelets	PR platelets	Standard platelets
Pretransfusion platelet count	14.4 ± 7.4 (661)	14.1 ± 7.7 (439)	10.2 ± 3.6 (456)	11.1 ± 4.6 (326)
1-Hour posttransfusion platelet count	29.9 ± 14.0 (573)	33.6 ± 16.7 (357)	33.9 ± 29.4 (426)	43.2 ± 35.8 (306)
24-Hour posttransfusion platelet count	24.5 ± 11.9 (646)	31.4 ± 16.8 (423)	21.8 ± 10.2 (449)	26.9 ± 13.1 (320)
1-Hour posttransfusion count increment (CI)	15.5 ± 9.2 (571)	19.9 ± 12.9 (356)	23.7 ± 29.8 (426)	32.6 ± 38.0 (304)
24-Hour posttransfusion CI	10.1 ± 8.0 (644)	17.2 ± 14.1 (422)	11.5 ± 9.1 (449)	15.8 ± 12.5 (320)
1-Hour posttransfusion corrected CI (CCI)	9,387 ± 5,263 (554)	11,391 ± 7,037 (313)	12,357 ± 14,592 (423)	17,639 ± 19,843 (304)
24-Hour posttransfusion CCI	6,087 ± 4,512 (621)	9,153 ± 6,703 (363)	6,051 ± 4,484 (445)	8,605 ± 6,696 (319)
No. of days between platelet transfusions	2.03 ± 0.76	2.49 ± 0.82	1.98 ± 0.88	2.14 ± 0.86

recipients in our study and in euroSPRITE,[3] but it was partially[6,7,9] or systematically[4] performed in others.

Despite the methodological differences, it is worth noting that all Intercept trials show highly concordant decrements of mean posttransfusion platelet CCI with PR platelets compared with control platelets. More specifically, mean 24-hour CCIs with PR platelets were 30.2,[3] 33.7,[4] 29.8,[6] 31.9,[7] 30.0,[9] and 33.5% (this study) lower compared with control platelet CCIs. This finding, which also was confirmed in our study using relatively fresher platelets, may be clinically and economically relevant, because lower posttransfusion platelet counts detected on the day after transfusion may cause increased platelet use. Lower posttransfusion platelet count increments in PR recipients

TABLE 6. ITT analysis: transfusion reactions to platelets, remission in chemotherapy recipients, frequency, and causes of death*

	Intercept trial		Mirasol trial	
Item	PR platelets	Standard platelets	PR platelets	Standard platelets
No./total no. (%) of platelet transfusions with premedication	221/667 (33.1)	138/441 (31.3)	5/457 (1.1)†	34/334 (10.2)‡
No. (%) of patients with nonhemolytic, febrile transfusion reactions	14 (12.4)	11 (9.6)	9 (9.1)	10 (10.3)
No. (%) of patients with allergic transfusion reactions	9 (8.0)	10 (8.7)	2 (2.0)	1 (1.0)
No. (%) of nonhemolytic, febrile transfusion reactions	15 (2.2)	13 (2.9)	18 (3.9)	18 (5.4)
No. (%) of allergic transfusion reactions	11 (1.6)	12 (2.7)	2 (0.4)	1 (0.3)
No. of patients with other transfusion reactions [no. of reactions]	1 [1]	2 [4]	1 [1]	1 [1]
Remission in chemotherapy recipients: complete/partial/refractory/not available, no. of patients	40/31/18/12	40/26/20/16	15/34/2/34	15/33/4/31
No. of patients who died (%)	5 (4.4)	12 (10.4)	6 (6.1)	2 (2.1)
Cause of death				
Hemorrhagic shock	1	0	0	0
Septic shock	2	0	1	0
Pulmonary insufficiency	1	1	0	0
Cardiac failure	1	3	2	2
Stroke	0	2	0	0
Disease progression	0	3	1	0
Hepatic failure	0	0	1	0
Not recorded	0	3	1	0

* No cases of hemolytic transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-associated graft-versus-host disease, or posttransfusion reactions were reported. Other reactions included chills and headache.
† Five patients received five transfusions.
‡ Eight patients received 34 transfusions.

were associated with 54, 36, 35, and 12% higher mean numbers of platelet transfusions per patient in our Intercept trial, the euroSPRITE trial,[3] the SPRINT trial,[4] and the HOVON[7] trial, respectively. Despite lower posttransfusion platelet count increments, an opposite finding of 20% lower platelet use in the PR arm was reported by Janetzko and coworkers[6] in a small RCT with 22 PR platelet recipients and 21 controls, most of whom underwent autologous or allogeneic hemopoietic stem cell transplantation.

Less extensive published information is available on the clinical effectiveness of PR platelets prepared with the Mirasol technology. In total, 118 patients were randomized to receive PR or standard platelets in a noninferiority RCT carried out in France.[8] That study showed mean 1-hour posttransfusion CCIs (primary outcome) equal to 11,725 and 16,939 in recipients of PR platelets and standard platelets, respectively, corresponding to a 30.8% reduction in PR platelet recipients. This reduction is very similar to the 30% reduction of mean 1-hour CCI with PR platelets observed in our Mirasol trial. The French study reported a higher median number of on-protocol platelet transfusions in PR versus standard platelet recipients within the 28-day treatment period (4.5 vs. 3.0 respectively; i.e., 50% greater in PR recipients). However, although the authors noted that several study limitations caused difficulties in the analysis of overall blood product utilization, they reported no significant differences between the treatment and control arms. The authors concluded that the study failed to show noninferiority of PR platelets and that more studies were required to determine whether the lower CCI observed with PR platelets "translates into an increased risk of bleeding."[8]

The data described above provide strong evidence of lower posttransfusion platelet count increments with PR platelets compared with standard platelets. This decrement is also supported by our finding that both technologies were tested with relatively fresher platelets compared with the other published RCTs.

Despite the lower posttransfusion platelet count increments, PR platelets prepared with both technologies have a high safety and efficacy record,[3-11,23-26] because the frequency and type of AEs and the risk and type of bleeding reported in the literature and documented in our study did not appear to differ between PR and standard platelets.

Considering the economic restrictions that affect health systems in many jurisdictions, the increased margin of microbiological and immunological safety of PR platelets must be balanced with the cost of the procedures and with the possibility that lower posttransfusion platelet count increments generate increased blood component utilization. In this regard, it is encouraging to note that a

careful, retrospective analysis carried out in Belgium did not disclose an "adverse impact on blood component use during a 3-year observation period of routine practice" of Intercept-treated platelets.[27] Further independent studies will be useful to corroborate this finding. Moreover, careful analyses of selected recipient types in different settings should be done using several methodological approaches to economic evaluations related to the implementation of PR platelets that have been reported in the literature.[28-34] In parallel, strategies could be developed to investigate public acceptability of PR technologies.[35]

In conclusion, our findings provide additional evidence—in the first study to test both commercial technologies with a unique protocol—on the clinical safety and efficacy of non-gamma–irradiated PR platelets in a large group of thrombocytopenic adult patients with hematologic cancers who received prophylactic transfusion. This evidence, together with previously reported results from the clinical trials that used the Intercept and Mirasol technologies, could be used by blood transfusion regulatory bodies in charge of deciding whether the use of PR will remain voluntary or should become mandatory. Not only may this decision be particularly urgent in light of the recent Zika epidemic and possible additional future threats to blood transfusion safety, but it also may become warranted in view of the promising reports of laboratory studies and clinical trials on pathogen-reduced RBCs and whole blood.[36,37]

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CONFLICT OF INTEREST

Institutions using the Intercept and Mirasol technologies received research funds from Cerus and Terumo BCT that were used for data collection by independent local staff, respectively. Paolo Rebulla received honoraria from Terumo BCT and Macopharma. Silvano Milani received honoraria from Terumo BCT. No other authors have conflicts to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Fig. S1A. ITT analysis: proportion of nonrefractory patients in the Intercept trial.
Fig. S1B. ITT analysis: proportion of nonrefractory patients in the Mirasol trial.
Table S1. ITT analysis: time on study (no. of days) and the number of blood components used in patients with (B) and without (NB) 2 grade or greater bleeding. Data are given as mean (SD) and differences (95% CI) between B and NB patients. Interaction term was statistically significant for the number of platelet units in Mirasol trial only.
Table S2. ITT analysis: data from refractory patients. Data are given as percentage, mean (SD), or median [range]. n.d. = not determined.
Table S3. ITT analysis: transfusion reactions to red blood cells. No cases of transfusion-related acute lung injury, circulatory overload, graft-versus-host disease, or posttransfusion purpura were reported.
Table S4. Number of off-protocol and total platelet units transfused to patients included in the ITT analysis and excluded from the per protocol (PP) analysis of the Intercept trial. Each row identifies one patient.

Table S5. Number of off-protocol and total platelet units transfused to patients included in the ITT analysis and excluded from the PP analysis of the Mirasol trial. Each row identifies one patient.
Table S6. PP analysis: the number of patients in each study arm; percentage of days with leukocyte counts less than 1.5×10^9/L; number (%) of patients and days with grade 2 or greater bleeding; patients with nonhemolytic, febrile, and allergic transfusion reactions; and refractory and deceased patients.
Table S7. PP analysis: results of statistical analysis, reported as the difference (D), odds ratio (OR), or ratio (R) between the treatment and control arms and their upper one-sided 97.5% confidence limits (UCL) for primary outcome and two-sided 95% confidence limits for secondary outcomes.
Table S8. ITT analysis: characteristics of patients with AML. Data are given as mean (SD).
Table S9. ITT analysis: results of statistical analysis of patients with AML reported as the difference (D), odds ratio (OR), or ratio (R) between the treatment and control arms and their upper one-sided 97.5% confidence limits (UCL) for primary outcome, and two-sided 95% confidence limits for secondary outcomes.
Table S10. ITT analysis: number (%) of patients with AML and days with grade 2 or greater bleeding episodes, calculated based on the number of patients and days with available bleeding report forms. IQR = interquartile range.
Table S11. ITT analysis: duration of study and the number of platelets and RBC units received via transfusion by patients with AML. Data are given as mean (SD) and [total].
Table S12. ITT analysis: pretransfusion and posttransfusion platelet counts ($\times 10^9$/L), posttransfusion platelet CIs, CCIs, and number of days between platelet transfusions in patients with AML. Data are given as mean (SD).
Study protocol
Case report forms