Therapeutic efficacy of platelet transfusion treated with amotosalen/UVA pathogen inactivation technology (INTERCEPT™ Blood System) in acute myeloid leukemia patients undergoing chemotherapy with curative intent: a single center experience

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Background - The INTERCEPT™ Blood System (Intercept Blood System, Cerus Europe BV, Amersfoort, the Netherlands) has been used to reduce or inactivate pathogen load in platelet concentrates in France for three years.
Materials and methods - After comparing the transfusion efficiency between pathogen-reduced platelets (PR_PLT) and untreated platelet products (U_PLT), our single-center observational study assessed the effectiveness of PR_PLT for the prevention of bleeding and for therapeutic treatment of WHO grade 2 bleeding in 176 patients undergoing chemotherapy with curative intent for acute myeloid leukemia (AML). The main endpoints were the 24-hour (h) corrected count increment (24h_CCI) after each transfusion, and time to next transfusion.
Results - Whereas the transfused doses tended to be higher in the PR_PLT group compared to U_PLT, there was a significant difference in intertransfusion interval (ITI) and 24h_CCI. In prophylactic transfusions, PR_PLT transfusions of $>0.65\times10^{11}$/10 kg, regardless of the age of the product (day 2 to day 5), resulted in a 24h_CCI similar to that of the untreated platelet product; this meant the patient could be transfused at least every 48h. In contrast, most PR_PLT transfusions of $<0.55\times10^{11}$/10 kg did not achieve a transfusion interval of 48h. In the context of WHO grade 2 bleeding, PR_PLT transfusions $>0.65\times10^{11}$/10 kg and storage of less than 4 days seems more effective in stopping bleeding.
Discussion - These results, which must be confirmed by prospective studies, indicate the need for vigilance regarding the quantity and quality of PR_PLT products used to treat patients at risk of bleeding crisis. Future prospective studies are needed to confirm these findings.

Keywords: *amotosalen, inactivated platelet product, acute myeloid leukemia, CCI, interval transfusions.*

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INTRODUCTION

Platelet (PLT) transfusions are used to prevent (as prophylaxis) and control (treat) bleeding in patients receiving intensive chemotherapy. Recently, the Intercept™ Blood System (Cerus Europe BV, Amersfoort, the Netherlands), which uses a combination of

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the psoralen Amotosalen and UVA light, was added to all French platelet products to reduce the transmission of pathogens (pathogen-reduced platelets [PR_PLT])[1]. This process allows PLT storage time to be extended from 5 to 7 days and for a new production method, the INTERCEPT Dual Storage Processing Set, which can produce one or two PR_PLT products from pools of 8 buffy coats (BC), to be implemented[2-4]. Several studies have shown that the use of PR_PLT products is associated with a shorter interval between two transfusions and a lower 24-hour (h) corrected count increment (24h_CCI) especially in oncohematological patients; these factors suggest impaired in vivo platelet viability and/or reduced circulation capacity[5,6].

Our team recently reported that PR_PLT transfusions in acute myeloid leukemia (AML) patients are less effective than untreated PLT (U_PLT) transfusions[7]. Briefly, in the context of prophylactic transfusions, this study showed that 24h_CCI and intertransfusion interval (ITI) were reduced in PR_PLT transfusions in comparison with U_PLT transfusions, meaning patients can be transfused every day instead of every other day. These two criteria seemed to be dependent on the PR_PLT transfused dose and the date of PR_PLT storage.

Thus, despite many publications of large randomized clinical trials and routine clinical practice in many countries, the optimal quality and quantity of PR_PLT transfusions in oncohematological patients must be assessed before any modifications to PR_PLT transfusion protocols can be made.

This retrospective, observational study describes the efficacy of the quantity and quality of PR_PLT transfusions in AML patients (excluding AML 3) in a setting of prophylactic transfusion and bleeding. The main endpoints were the 24h_CCI after each transfusion and time to next transfusion (intertransfusion interval [ITI]) according to PR_PLT dose and date of storage.

MATERIALS AND METHODS

Patient data and study design

This observational study included 186 patients transfused with 1,795 PLT products from November 2016 to April 2020. The patients received transfusions from the time of AML diagnosis to the time of recovery from post-induction chemotherapy aplasia[8,9].

Three cohorts were identified.

1. U_PLT group: 61 patients who received 457 U_PLT from November 2016 to October 2017;
2. PR_PLT group I: 48 patients who received 500 PR_PLT concentrates from November 2017 to May 2018 (during which time platelets were processed with the individual illumination set, and storage was 5 days);
3. PR_PLT group II: 138 patients who received 1,238 PR_PLT concentrates from June 2018 to April 2020 (during which time the dual storage method was implemented and storage time was increased to up to D6/D7).

All patients were transfused according to the indications of the treating physicians, and the PLT products were delivered, as far as possible, in accordance with the recommendations of the French National Authority for Health (Haute Autorité de la Santé [HAS]) concerning ABO compatibility, dosage, and product age. The prophylactic transfusion threshold was 15×10^9/L in non-bleeding, non-febrile patients. Therapeutic transfusions were performed in the presence of a bleeding crisis and/or acute consumption factors, which were systematically reported in the prescription. A single PLT product was delivered for each transfusion, and platelet counts of transfused patients were measured daily.

PR_PLT transfusions for indications such as invasive procedures were excluded from the study (**Figure 1**).

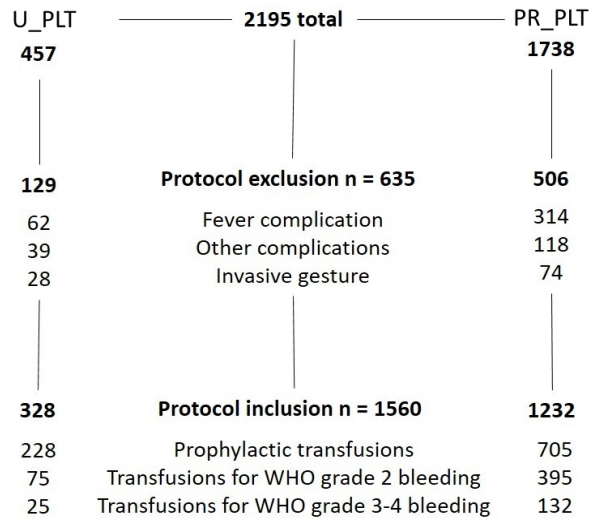

Figure 1 - Selection of untreated platelet products (U_PLT) and pathogen-reduced platelets (PR_PLT) in the comparative and safety analyses

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All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patient ID data were anonymized, and institutional review board approval was obtained from the ethical committee (approval n. IPC 2022-039).

Platelet concentrate production

In this study, 40% of PR_PLT were collected by apheresis, and 60% came from whole blood BC concentrates. The products were suspended in approximately 53-68% platelet additive solution (InterSol, Fenwal Europe [Mont-Saint-Guibert, Walloon Brabant, Belgium] for apheresis and SSP+ [Macopharma, Mouvaux, France] for BC). They contained 2.4×10^{11} platelets/unit or 2.5×10^{11} platelets/unit or greater with 100% leukoreduction (leukocyte count $<1\times10^{6}$/PLT product) following HAS recommendations.

INTERCEPT large-volume and dual-storage processing kits were used. All products were treated with Amotosalen (nominal final concentration 150 µM) and 3 J/cm^2 ultraviolet A radiation according to the manufacturer's instructions, followed by incubation in a compound absorption device for 6-16 h. The INTERCEPT treatment was performed for apheresis components on the day of collection (day [D] 0) or immediately after BC pool preparation on the day after collection (D1). The products were released after receiving the results of testing for infectious diseases. Since June 2019, the PR_PLT products were stored for up to 7 days before transfusion.

Statistical analysis

Data including pre- and post-transfusion platelet counts, transfusion date (day and hour), patient weight and height, and fever or bleeding events at the time of transfusion were prospectively collected and obtained from the electronic records of the Regional Blood Transfusion Service (Inlog software [Limonest, France]) and from two other software programs used in the Institut Paoli-Calmettes Hospital (Hospital Manager for patient data and Cursus for transfusion data).

For prophylactic transfusions, 24h_CCI and ITI were calculated. All platelet counts were systematically measured starting at 5 a.m. Pre-transfusion platelet count was measured 1-9 h before transfusion and post-transfusion platelet count was measured 15-20 h after transfusion. The 24h_CCI was calculated as follows: (post platelet count – pre platelet count in 10^9/L) × (body surface area in m^2)/(platelet dose transfused × 10^{11}). According to HAS guidelines, a successful transfusion was defined as CCI >7.

The percentage of 24h_CCI compliance was defined as the reported number of 24h_CCI >7 of the total number of 24h_CCI for a given condition.

The ITI was defined as hours from the onset of the study transfusion to the onset of the subsequent transfusion. An interval of more than 120 h between transfusions was defined as platelet transfusion independence, and such transfusions were excluded from the analysis.

For bleeding crises, therapeutic transfusions were classified according to the WHO bleeding scale. To evaluate WHO bleeding assessments used for daily monitoring of the PLT transfusion effect, the difference in WHO bleeding grade before and after each transfusion was calculated.

To evaluate the platelet dose effect, four groups were determined in accordance with the platelet dose per transfusion:

- Group 0.5: 0.5×10^{11}/10 kg ± 0.5;
- Group 0.6: 0.6×10^{11}/10 kg ± 0.5;
- Group 0.7: 0.7×10^{11}/10 kg ± 0.5;
- Group >0.75: $>0.75\times10^{11}$/10 kg.

In the second step, two other groups were determined:

- Group <0.65: $<0.65\times10^{11}$/10 kg and
- Group >0.65: $>0.65\times10^{11}$/10 kg.

Data are reported as mean, standard deviation and range for continuous data or by frequencies and proportions (%) for categorical data using computer software (XLSTAT, 2021.1.1, Addinsoft [Paris, France]). The comparison of the means of two groups was carried out by the Student *t* test and the proportion was determined by the z test. Two-sided $p\leq0.05$ was considered statistically significant.

RESULTS

Patient and transfusion characteristics

Patient and transfusion characteristics are described in **Table I**.

For all indications of platelet transfusions, age and sex ratios were similar between the different groups. The transfused doses tended to be higher in the PR_PLT

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Table I - *Patient and transfusion characteristics*

	U_PLT	PR_PLT Part I	p-value	PR_PLT Part II	p-value	All PR_PLT	p-value U_PLT *vs* all PR_PLT
Patients (n)	61	48		138		182	
Mean age (years)	58±15	57±16		59±14.1		58.3±14.8	0.87
Percent Male (%)	57.4	59.1		55.1		56.04	
ABO compatibility	83.70	87.80	0.0632	86.10	0.3483	86.60	0.0998
Days transfusions (D6-D7)		5		76		81	
Mean PLT dose per transfusion ± SD ($\times10^{11}$)	4.31±0.71	4.28±0.64	0.568	4.61±1.15	0.0019	4.52±1.04	0.1139
Mean number of PLT transfusions per patient ± SD ($\times10^{11}$)	8.28±3.9	9.65±7.3	0.4749	9.08±5.1	0.8123	9.24±5.79	0.4308
Mean interval between PLT transfusions ± SD (hours)	63±44.3	48±40.4	<0.001	53±40.2	0.0028	52±40.33	<0.001
Mean compliance CCI (%)	37.6	25	<0.001	32.9	0.0013	30.6	0.0042
Prophylactic Transfusions							
Number of Transfusions	228	233	0.309	472	0.0011	705	<0.001
Number of Patients	56	48		116		162	
Mean PLT dose per transfusion ± SD ($\times10^{11}$)	4.33±0.74	4.25±0.63	0.2089	4.54±1.12	0.2471	4.44±0.99	0.8371
Mean number of PLT transfusions per patient ± SD ($\times10^{11}$)	4.07±1.94	4.85±2.99	0.2747	4.07±2.85	0.0394	4.35±2.92	0.8309
Mean interval between PLT transfusions ± SD (hours)	73±56	52±29.1	<0.001	58±45.7	0.3742	56±41	<0.001
24h_CCI compliance (%)	41.7	27.9	0.0019	34.5	0.0763	32.3	0.0101
Transfusions for WHO grade 2 bleeding							
Number of Transfusions (%)	75 (16)	98 (20)	0.2004	297 (24)	0.048	395 (23)	**0.0034**
Number of Patients	32	34		108		141	
Mean PLT dose per transfusion ± SD ($\times10^{11}$)	4.33±0.74	4.38±0.69	0.7509	4.69±1.17	0.2052	4.61±1.07	0.1533
Mean number of PLT transfusions per patient ± SD ($\times10^{11}$)	2.31±1.7	2.94±2.44	0.2118	2.75±2.33	0.4826	2.74±2.38	0.4909
Mean interval between PLT transfusions ± SD (hours)	59±34.8	47±30.7	**0.0103**	51±32.9	0.1709	50±32.5	**0.0284**
24h_CCI compliance (%)	34.7	26.5	0.2474	26.9	0.9374	26.8	0.1665
Transfusions for WHO grade 3-4 bleeding							
Number of Transfusions	25 (5)	55 (11)	**0.002**	77 (6)	<0.001	132 (7.5)	0.1168
Number of Patients	11	6		28		34	
Mean PLT dose per transfusion ± SD ($\times10^{11}$)	4.22±0.59	4.31±0.58	0.5087	4.53±0.91	0.4017	4.44±0.79	0.3006
Mean number of PLT transfusions per patient ± SD ($\times10^{11}$)	2.27±1.35	9.17±12.8	**0.0179**	2.75±2.43	0.2614	3.88±5.99	0.6616
Mean interval between PLT transfusions ± SD (hours)	45±25.8	21±20.2	<0.001	42±32.9	<0.001	36±29.7	**0.0311**
24h_CCI compliance (%)	36	20	0.1256	54.55	<0.001	40.15	0.697

In bold: statistically significant data. PR_PLT: pathogen-reduced platelets; U_PLT: untreated platelet products; 24h_CCI: 24-hour corrected count increment; D: day.

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group and the percentage of 24h_CCI compliance (30.6% PR_PLT *vs* 37.6% U_PLT; p=0.003) were significantly lower compared to the U_PLT group. These significant differences were also found in prophylactic transfusions from the PR_PLT group, which had platelet doses comparable to those of the U_PLT group. When PR_PLT group I was compared to PR_PLT group II, the transfusion dose increased the ITI and the percentage of 24h_CCI compliance but did not achieve results similar to the U_PLT group. However, there was no significant difference in the number of PLT transfusions per patient between the PR_PLT group II and the U_PLT group.

In therapeutic transfusion for WHO grades 2 and 3 bleeding, the intervals between transfusions were also reduced in the PR_PLT groups compared to the U_PLT group. The percentage of therapeutic transfusions for WHO grade 2 bleeding (but not the percentage of therapeutic transfusions for WHO grade 3-4 bleeding) was significantly higher in the PR_PLT group than in U_PLT group.

Impact of transfusion dose and days of PR_PLT production in the setting of prophylactic transfusion

A total of 162 patients undergoing prophylactic transfusion were transfused with 705 PR_PLT concentrates. The percentage of 24h_CCI compliance increased as a function of the platelet dose transfused, particularly when the age of platelet production was D3. The platelet recirculation was relatively constant regardless of the age of platelet production until D5, except for platelet doses <0.55 and >0.75. Surprisingly, the recirculation dropped sharply at a PR_PLT dose >0.75 (p=0.03) at D4, obtaining a similar recirculation as that for Group 0.5 (30% for >0.75 *vs* 26.2% for 0.5; p=NS) (**Figure 2a**).

There was a significant difference in ITI according to age of platelet production and the quantity of platelets transfused (**Figure 2b**). Indeed, the mean ITI was significantly greater when the age of platelet production at D3 was compared to those at D4, D5, and D6/7, and when the age of platelet production at D3 and D4 was compared to those at D5 and D6/7 (**Figure 3a**). The mean ITI for dose >0.65 were significantly greater than those for <0.65 (63±49 *vs* 49±32 h; p<0.0001), regardless of the age of PR_PLT production, except for D5. Moreover, the ITI of interest (48h) was more often achieved by doses >0.65 (64 *vs* 47%, p<0.0001). Notably, a platelet dose >0.75 at D4 was associated with a significant decrease in ITI (p=0.02) when compared to a platelet dose >0.75 at D3 (**Figure 3a**).

Impact of transfusion dose and days of PR_PLT production on WHO grade 2 bleeding

A total of 141 patients with WHO grade 2 bleeding were transfused with 395 PR_PLT concentrates. The percentages of 24h_CCI compliance were relatively similar between the different platelet dose groups regardless of the age of the product, except for D6/D7 for dose >0.65 (p=0.03). For all products, the mean percentage of 24h_CCI compliance was higher at D3 than at D5, having decreased at D4.

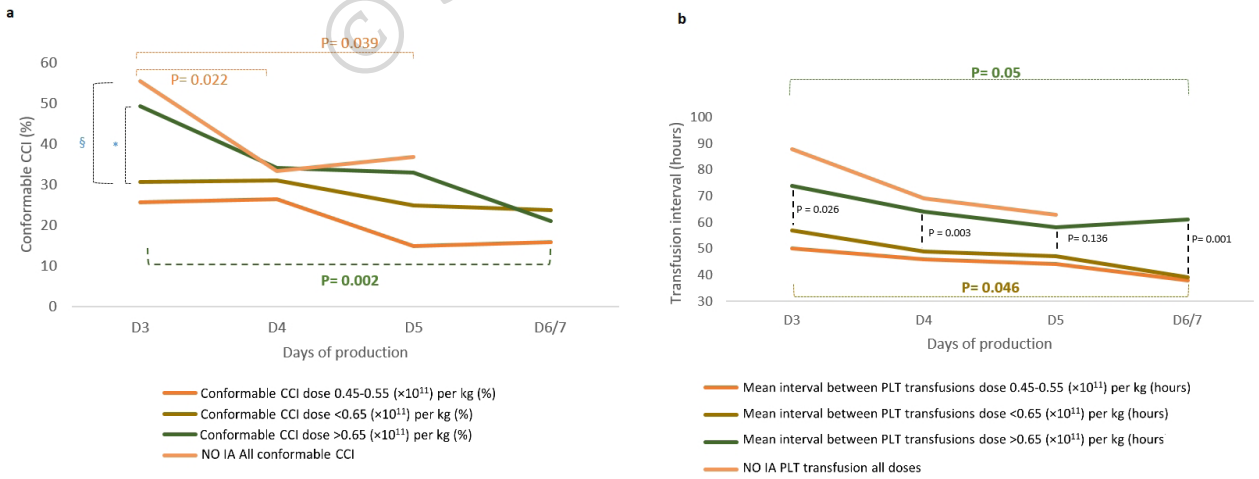

Figure 2 - Percentage of 24-hour corrected count increment (CCI) (2a) and transfusion interval (2b) as a function of dose and age of pathogen-reduced platelets (PR_PLT) and untreated platelet products (U_PLT) in prophylactic transfusion

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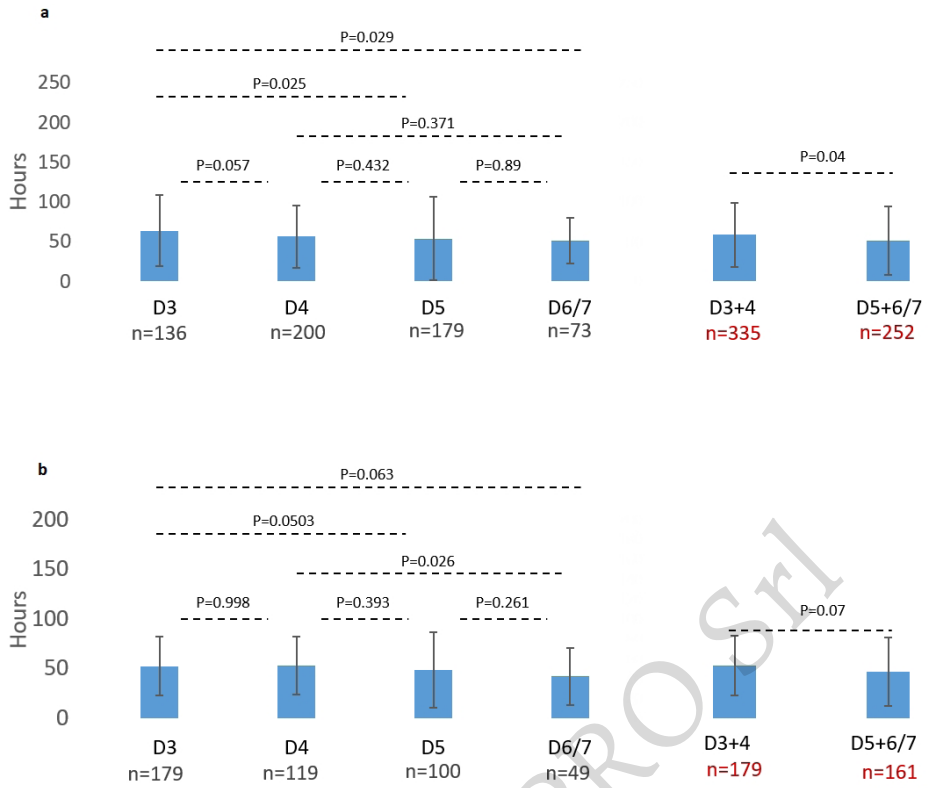

Figure 3 - Variation in transfusion intervals according to the dates of the pathogen-reduced platelets (PR_PLT) in prophylactic transfusions (3a) and in WHO grade 2 bleeding (3b)

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However, there was no significant difference in 24h_CCI compliance between PR_PLT groups I and II, regardless of the age of production up to D5 (**Figure 4a**).

Average ITI for patients undergoing therapeutic transfusion for WHO grade 2 bleeding were not related to the dose of PR_PLT transfused, but a trend of a difference in ITI with age of platelet production was observed when age of PR_PLT at D3 and D4 were compared to those at D5 and D6/7 (p=0.07) (**Figure 3b**). Age of platelets, except for dose <0.55, did not affect the ITI up to D5. The mean interval decreased at D6/D7. Indeed, the >0.65 dose had a significantly higher mean ITI at D3 than the dose >0.65 at D6/7 (p=0.02) (**Figure 4b**).

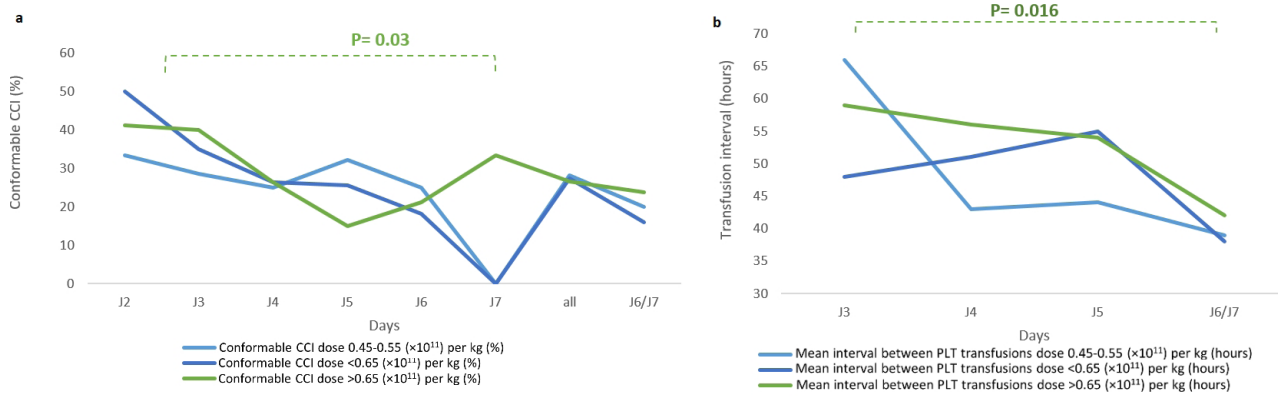

Figure 4 - Percentage of 24-hour corrected count increment (24h_CCI) compliance (4a) and transfusion interval (4b) as a function of dose and age of pathogen-reduced platelets (PR_PLT) in WHO grade 2 bleeding

DISCUSSION

PR_PLT contribute to the safety of platelet transfusions and are currently widely used in most European countries. Several studies have shown that PR_PLT, although less efficient than U_PLT, seem to have therapeutic efficacy, as measured by clinical outcome parameters, such as the occurrence of bleeding. Results from previous studies in clinical conditions other than AML indicated that the time to the next transfusion shortens as the age of transfused BC-derived PLT concentrates increases[10]. However, to our knowledge, no studies have been published on the specific impact of the doses and the days of production of PR_PLT in AML patients undergoing induction treatment.

In this study, the target number of platelets in the patient before prophylactic transfusion was 15 g/L, which differs from international recommendations and other publications[11]. Indeed, the American Association of Blood Banks (AABB) recommends the prophylactic transfusion of a platelet unit when thrombocytopenia is <10 g/L, or <20 g/L in unfavorable conditions. This threshold of 10 g/L platelets mainly concerns hospitalized patients, and higher values should probably be used in patients treated on an outpatient basis to limit the risk of bleeding, such as during febrile events. In addition, to facilitate patient management and in order to carry out a routine transfusion every 48h, the threshold of 15 g/L for all patients was chosen. However, the variation in platelet numbers before PR_PLT transfusions observed in our study did not seem to impact a differential result for patients who have a transfusion target of 10 g/L, because most patients probably had a platelet count <10 g/L at the start of this study before transfusion.

Our observational study shows that PR_PLT in prophylactic transfusion in AML patients have a decreased recirculation level compared to U_PLT. A lower 24h_CCI after PR_PLT compared to U_PLT has been a consistent finding in several studies of patients with other diseases[12,13], although the reason for this is not completely understood. One hypothesis is that Amotosalen treatment increases the activation status of platelets more in PR_PLT compared to U_PLT, inducing increased platelet consumption[14]. Our results showed that PR_PLT doses >0.65, regardless of age (except for D6/D7), partially compensated for these reductions. Interestingly, ITI were also compatible with using these doses when transfusing hospitalized patients. Indeed, PR_PLT doses >0.65 allowed 64% of AML patients to be transfused every 48h, the ITI corresponding to that of platelet products without Amotosalen. On the other hand, 73% of AML patients receiving PR_PLT doses <0.55 did not achieve a 48h ITI.

It should be noted that, during the study period, some study conditions changed, such as the new implementation of dual storage and of storage up to D7. Clearly, these modifications, especially dual storage, allowed the PR_PLT doses to be increased and satisfactory ITI to be obtained.

As in other clinical trials, 24h_CCI was relatively low for PR_PLT transfusion with doses >0.75 from D4[6]. The variations in 24h_CCI are due to many factors, principally PR_PLT products and patient profiles[15]. In this case, the mean PR_PLT was $5.0\pm1\times10^{11}$ from 18 dual storage products (40% of PR_PLT) (data not shown). Dual storage from D4 may be associated with an increase in storage lesions, such as increasing P-selectin expression and reducing agonist-induced aggregation, or with platelet activation, which would explain the faster clearance of PR_PLT, leading to lower recirculation rates and ITI[16,17].

In contrast to other studies, PR_PLT were more often associated with WHO grade 2 bleeding complications than U_PRL[5].

It has recently been argued that platelet microRNA might be as vulnerable to the effects of pathogen reduction as the nucleic acids of the pathogens themselves, and Amotosalen could alter the proteome of platelets stored following pathogen reduction by inhibiting protein synthesis during storage[18]. However, this may not always be the case. Indeed, a study using riboflavin+UV demonstrated for the first time that platelets can still synthesize proteins despite riboflavin and UV treatment, and suggested that platelets may possess a mechanism to protect their mRNA from damage by the treated product[19].

WHO grade 3 bleeding after PR_PLT transfusions has not been the subject of studies so far because these bleeding events often have multifactorial origins and are linked, in particular, to complications of chemotherapy. In the context of WHO grade 2 bleeding, the percentage of 24h_CCI compliance was higher when the PR_PLT product storage had been shorter, especially when they were no more than 3 days old. However, average ITI was over 48h for doses >0.55 up to D6/D7, suggesting an active

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transfusion treatment for bleeding in these conditions. Most authors (but not all) have reported longer intervals between transfusions with higher doses; however, the number of donor exposures was also increased, and it was not clear whether the risk of bleeding was correlated with the platelet dose[20].

In conclusion, in the event of serious bleeding, a platelet transfusion can be given, on the assumption that the platelets will be used to stop the bleeding; therefore, it is to be expected that increments will be lower, and the ITI shorter.

This study stems from concerns voiced by clinical hematologists about a decrease in ITI after prophylactic platelet transfusions with inactivated products in AML patients. It does not call into question the safety of transfused products using the Intercept method, which prevents the growth of pathogens in the product, offers an additional level of safety against contaminating pathogens not detected by current donor screening, and allows storage to be extended for up to 7 days. On the contrary, use of this method made it possible to consolidate the rational use of these products in a specific clinical condition. Indeed, the younger PR_PLT with doses >0.6 are favored in prophylactic transfusions and the D6/7 PR_PLT are directed to other transfusion indications, including WHO grade 2 bleeding. This resulted in a satisfactory increase in the platelet doses transfused (+40%) during our study, supporting its continued use (data not show).

This study has some limitations. The number of patients in the different clinical groups was not homogeneous, and this, along with changes made during the study (such as the implementation of dual storage) could have resulted in statistical biases. Furthermore, the number of platelets for each production date differed, and studies in larger cohorts are needed to confirm the results obtained from the platelet products. As in other studies, we used the CCI, originally used to define a refractory state to platelet transfusion, as a biological measurement of quantitative comparison between the different transfusion groups. Interestingly, the results of the percentage of 24h_CCI compliance were associated with clinical ITI. Indeed, a rich and young PR_PLT product had the longest ITI. The analysis of ITI for curative indications is problematic, because it can be influenced by many factors related to disease or treatment, such as consumption and the range of indications for which it can be used.

CONCLUSIONS

This observational study has improved our understanding of the clinical implementation of the Intercept™ Blood System in the production of PR_PLT. This can lead to a higher quality PR_PLT production process and greater clinical efficacy of the PR_PLT product, both of which can reduce costs. In agreement with other studies, our results show that there is a difference in terms of the clinical and biological efficacy of PR_PLT *vs* U_PLT, and this suggests a transfusion strategy that reduces the impact of Amotosalen. In the context of prophylactic transfusions in AML patients, PR_PLT doses $>0.65\times10^{11}$/10 kg, especially on D3 and D4, have higher 24h_CCI than PR_PLT doses $<0.65\times10^{11}$/10 kg, and are associated with a more reassuring ITI for clinicians. In WHO grade 2 bleeding, a transfusion of rich PR_PLT ($>0.65\times10^{11}$/10 kg) with young platelets (up from D3) is more applicable. These data must be confirmed by prospective multicenter studies that need to take into account the multitude of factors that potentially affect 24h_CCI. Such studies should include a rigorous evaluation of bleeding episodes in order to make recommendations, and to allow greater clinical and economic control of PR_PLT transfusions.

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AUTHORSHIP CONTRIBUTIONS

PL, JC, NV and CC designed and carried out the study; JME, PP and CP conducted the statistical analysis. All Authors contributed to writing the manuscript.

The Authors declare no conflicts of interest.

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