Italian daily platelet transfusion practice for haematological patients undergoing high dose chemotherapy with or without stem cell transplantation: a survey by the GIMEMA Haemostasis and Thrombosis Working Party

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Background. Following high-dose chemotherapy/bone marrow transplantation, patients are routinely, prophylactically transfused with platelet concentrates (PC) if they have a platelet count $\leq 10\times10^9$/L or higher in the presence of risk factors for bleeding. However, whether such transfusions are necessary in clinically stable patients with no bleeding, or whether a therapeutic transfusion strategy could be sufficient and safe, is still debated.

Materials and methods. The GIMEMA Haemostasis and Thrombosis Working Party sent a questionnaire to Italian haematology departments to survey several aspects of daily platelet transfusion practice, such as the cut-off platelet count for transfusion, the evaluation of refractoriness and the type of PC administered.

Results. The questionnaire was answered by 18 out of 31 centres (58%). A total of 23,162 PC were transfused in 2,396 patients in 2013. The vast majority of centres (95%) transfused PC according to Italian and international guidelines; only a few transfused always at platelet counts $\leq 20\times10^9$/L. The broad agreement on platelet count cut-off for transfusion ($\leq 10\times10^9$/L) was not confirmed when the World Health Organization (WHO) bleeding score was considered: only a third of centres (33%) used transfusions as recommended when the bleeding grade was ≥ 2. Platelet refractoriness was poorly monitored and most centres (89%) evaluated, mostly empirically (67%), response to transfusion only 24 hours later. Thirty percent of centres transfused platelets in asymptomatic refractory patients.

Discussion. Although most Italian haematology departments transfuse PC according to Italian and international guidelines, our survey shows that in routine daily practice physicians do not comply closely with the WHO recommendations on platelet transfusions and monitoring platelet refractoriness. This causes excessive platelet transfusions, with a resulting increase of costs and waste of public health resources.

Keywords: bleeding, platelet transfusion, prophylaxis, high-dose chemotherapy, bone marrow transplantation.

Introduction

Patients with blood malignancies are often treated by myeloablative chemotherapy resulting in severe and prolonged hypo-regenerative cytopenias. Although fatal bleeding is rare, the risk of haemorrhage represents a challenge for patients and physicians and it is a standard of care to support patients with platelet transfusions[1,2]. Platelets are transfused prophylactically if patients have a platelet count below 10×10^9/L or higher in the presence of fever or infection or when grade 2 or higher bleeding, according to the World Health Organization (WHO) scale, is present[3-5] (Table I).

However, whether prophylactic transfusions are necessary in patients who are clinically stable and asymptomatic, or whether a therapeutic transfusion strategy could be sufficient and safe, is still debated[6-8].

Thirty years ago, small controlled studies[9-12] showed favourable results supporting the prophylactic strategy, but there is evidence that a platelet count transfusion trigger of $\leq 10\times10^9$/L is equally as safe as a trigger of $\leq 20\times10^9$/L in controlling bleeding[3].

This practice of prophylactic platelet transfusions, together with the wider diffusion of high-dose chemotherapy and stem cell transplantation programmes, has increased the requests for blood products and more stringent approaches to platelet transfusion have been explored. Two important, recent studies compared prophylactic transfusions to "on demand" transfusions for active bleeding and, although both confirmed the value of prophylactic transfusions, "on demand" treatment might become the standard of care in some subgroups of patients[13,14].

There is a broad consensus regarding the need for prophylactic platelet transfusions when a patient's platelet count is $\leq 10\times10^9$/L, although the debate is still ongoing and some recommendations have tried to reduce the limit further to $\leq 5\times10^9$/L[1,15]. There are economic issues (costs), organisational aspects (supply) and medical concerns associated with platelet transfusions. Although post-transfusion viral infections are now very rare, bacterial infections and sepsis have become more frequent (platelets are blood products stored at room temperature) and the risks of plasma allergic reactions and immunogenicity should not be overlooked. Immunological sensitisation to human leucocyte antigens (HLA) and human platelet antigens (HPA) may result in lack of efficacy and refractoriness to platelet transfusions, the latter occurring in approximately 20-30% of patients[16,17].

Conventionally refractoriness occurs if the platelet count increase, calculated 1 hour and/or 24 hours after the transfusion, is less than 7.5×10^9/L or 4.5×10^9/L, respectively, using the standard "formula" (Figure 1) and the results are confirmed on at least two consecutive occasions. In fact, a correct platelet count increase, followed by a reduction after 24 hours may be due to increased consumption induced by non-immunological causes such as fever, sepsis, splenomegaly, active bleeding, disseminated intravascular coagulation or administration of amphotericin B[18,19].

Table I - WHO Bleeding Score.

Grade 0	No bleeding
Grade 1	Petechiae, ecchymosis, occult blood in body secretions, etc.
Grade 2	Evidence of gross haemorrhage, not requiring red cell transfusion
Grade 3	Haemorrhage requiring transfusion
Grade 4	Life-threatening haemorrhage

The aim of the present survey was to evaluate the standard trough level at which patients receive platelet transfusions and to assess how "refractory" patients are managed in Italian haematology departments. Currently in Italy approximately 150-200,000 units of platelet concentrates are transfused each year, at a total cost of about 40 million euros. Given that the resources involved are substantial, this survey could contribute to the debate on the best management of platelet transfusions by determining the real-life approach in several Italian haematology departments.

Material and methods

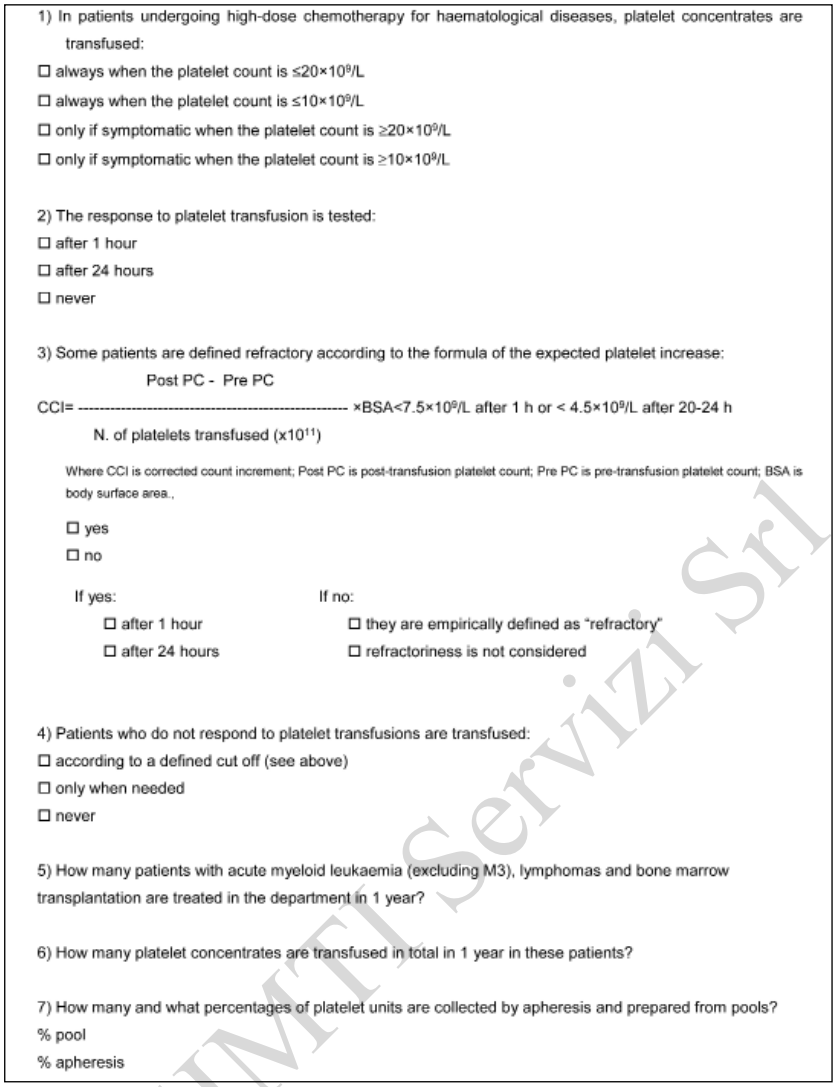
The GIMEMA Haemostasis and Thrombosis Working Party designed a questionnaire (Figure 1) to be delivered to experts in haemostasis and thrombosis working in haematology departments to cover platelet transfusions in the whole of 2013. Thirty-one haematology departments were contacted to investigate daily practice in the transfusion of platelet concentrates, such as the cut-off platelet count for transfusion, the evaluation of refractoriness and the type of platelet concentrates transfused. The platelet transfusion policy in the following circumstances was investigated specifically:

a) patient in a stable condition without complications and platelet count $\leq 10\times10^9$/L;
b) patient with active bleeding, in the presence of fever >38 °C, rapid drop in platelet count, or infection with a platelet count $\leq 20\times10^9$/L.

Questions were also asked on how to evaluate and reduce the risk of platelet refractoriness or prolong the life of transfused platelets by using ABO-compatible platelet concentrates or selected HLA-matched platelet donors. Finally, costs were compared according to the type of concentrates administered: derived from a pool or obtained by apheresis.

Results

Eighteen out of the 31 (58%) centres involved in this survey answered the questionnaire. The results are reported in Tables II and III. A total of 23,162 platelet concentrates were transfused in 2,396 patients. The vast majority of centres (95%) transfused according to the Italian and international guidelines[3,20,21] while only a few (5%) transfused always when the platelet count was below the level of 20×10^9/L. Interestingly, the broad agreement on the platelet count cut-off for transfusion (10×10^9/L) was not confirmed when WHO bleeding scores were considered (Table I). In fact, only a minor proportion (33%) used transfusions as recommended by the WHO when the bleeding score was ≥2 (Table II).



1) In patients undergoing high-dose chemotherapy for haematological diseases, platelet concentrates are transfused:

☐ always when the platelet count is ≤20×10⁹/L
☐ always when the platelet count is ≤10×10⁹/L
☐ only if symptomatic when the platelet count is ≥20×10⁹/L
☐ only if symptomatic when the platelet count is ≥10×10⁹/L

2) The response to platelet transfusion is tested:

☐ after 1 hour
☐ after 24 hours
☐ never

3) Some patients are defined refractory according to the formula of the expected platelet increase:

$$CCI = \frac{\text{Post PC} - \text{Pre PC}}{\text{N. of platelets transfused } (\times 10^{11})} \times BSA$$

<7.5×10⁹/L after 1 h or < 4.5×10⁹/L after 20-24 h

Where CCI is corrected count increment; Post PC is post-transfusion platelet count; Pre PC is pre-transfusion platelet count; BSA is body surface area.,

☐ yes
☐ no

If yes:
☐ after 1 hour
☐ after 24 hours

If no:
☐ they are empirically defined as "refractory"
☐ refractoriness is not considered

4) Patients who do not respond to platelet transfusions are transfused:

☐ according to a defined cut off (see above)
☐ only when needed
☐ never

5) How many patients with acute myeloid leukaemia (excluding M3), lymphomas and bone marrow transplantation are treated in the department in 1 year?

6) How many platelet concentrates are transfused in total in 1 year in these patients?

7) How many and what percentages of platelet units are collected by apheresis and prepared from pools?

% pool
% apheresis

Figure 1 - Questionnaire on thrombocytopenia after high-dose chemotherapy sent by the GIMEMA Haemostasis and Thrombosis Working Party to Italian Haematology Departments.

Regarding refractoriness to platelet concentrates only a few haematology departments (11%) evaluated the platelet count 1 hour after the end of transfusion, while the vast majority (89%) did so after 24 hours. However, only 28% of these used the corrected count increment formula (Figure 1 and Table III), while empirical assessments, based on laboratory data routinely acquired 24 hours later, were prevalent (67%). Although 70% of haematology departments transfused refractory patients only when bleeding, 30% still continued to transfuse platelets regardless of the increase observed (Table III). These results show that platelet transfusions are more widely used than necessary in clinical practice and that patients are often transfused also in the case of minor bleeding such as petechiae and mild epistaxis.

The detailed responses to the questionnaire on the total amount and the types of platelet concentrates are reported in Tables IV and V.

Discussion

The first randomised trial on a platelet transfusion threshold in patients with blood malignancies, published in the 1990s[3], was performed when there were fewer patients undergoing bone marrow transplantation (BMT) and high-dose chemotherapy and the platelet availability seemed sufficient to ensure transfusions for all those who needed them. The now widespread use of chemotherapy and autologous and allogeneic BMT has led to a dramatic increase in the number of patients potentially requiring platelet transfusion and availability has reached a critical point. This is one of the reasons why some

Table II - Clinical and laboratory data on platelet transfusion criteria in 2013 in Italy.

Data from 18 haematology departments	
Patients undergoing high-dose chemotherapy/BMT	2,396
PC transfused per high-dose chemotherapy/BMT (ratio)	3.9
Total transfused PC	23,162
Platelet count triggers for transfusion	**N (%)**
Always with platelet count ≤10×10⁹/L	17 (95%)
In symptomatic patients with platelet count between 10×10⁹/L and 20×10⁹/L	13 (72%)
Always with platelet count ≤20×10⁹/L	1 (5%)
Definition of "symptomatic"	**N (%)**
Fever, even <38 °C	3 (17%)
Fever >38° C	13 (72%)
All bleeding	11 (61%)
According to WHO bleeding score (WHO≥2)	6 (33%)

PC: platelet concentrate; BMT: bone marrow transplantation.

Table III - Efficacy assessment and platelet transfusion criteria*.

Efficacy assessment (platelet count)	**N (%)**
After 1 hour	2 (11%)
After 24 hours	16 (89%)
Never	2 (11%)
Corrected count increment*	**N (%)**
Yes, after 1 hour	2 (11%)
Yes, after 24 hours	5 (28%)
No, refractoriness assessed only empirically	12 (67%)
No, refractoriness not considered	2 (11%)
Platelet transfusion in patients defined refractory	**N (%)**
When platelet count ≤10×10⁹/L	3 (15%)
When platelet count between 10x10⁹/L and 20×10⁹/L	2 (10%)
When platelet count ≤20×10⁹/L	1 (5%)
Only in the case of bleeding	14 (70%)

*The total number of answers exceeds the number of Haematology Departments as some departments gave multiple answers.

recent studies have focused on the possibility of reducing platelet transfusions in routine daily practice. Wandt *et al.*[13] analysed 391 patients, 201 undergoing autologous BMT and 190 receiving intensive chemotherapy for acute myeloid leukaemia, who were randomised to receive platelet transfusions either prophylactically at a platelet count of ≤10×10⁹/L or as "on demand" treatment. The rate of WHO grade 2 bleeding was higher in the "on demand" group, the incidence of grade 3 or 4 bleeding was similar in the two groups, and seven out of 13 grade 4 bleeds in the treatment group occurred in patients with a platelet count between 56×10⁹/L and 11×10⁹/L. This means that

Table IV - Platelet concentrates should contain, in accordance with current legislation, at least 2-3×10¹¹ platelets independently of whether they are produced from pooled buffy coats or apheresis[19,20].

Platelet count in PCs	
Type of PCs	**Plts standard content**
PC from a single unit of whole blood	0.45-0.85×10¹¹
PC from a buffy coat pool: minimum content	2.5×10¹¹
PC from apheresis: minimum content	3×10¹¹
PC from plasma-platelet-apheresis or from a multicomponent sample: minimum content	2×10¹¹

PC: platelet concentrate; plt: platelet.

Table V - Total number, source and ABO compatibility of platelet concentrates transfused in 18 Italian Haematology Departments during 2013.

Total platelet concentrates (average 1,287/centre; range, 300-4,100)	23,162
Type of concentrate	
Pool	38%
Apheresis	62%
ABO-compatible	**N (%)**
Yes	4 (25%)
No	3 (20%)
Partially	11 (55%)

about half of the bleeds could have occurred equally in the group given prophylactic transfusions on the basis of the threshold platelet count of 10×10⁹/L. The authors concluded that prophylaxis should still be the standard of care and that although "therapeutic transfusions only" might become daily practice, this should only be the case in selected centres for patients undergoing autologous BMT. Furthermore, the 10×10⁹/L cut-off should remain for patients with acute myeloid leukaemia as the bleeding rate was higher in patients with leukaemia than in those who underwent autologous BMT[13].

Similarly, in another recent, large trial[14], patients undergoing autologous BMT or chemotherapy for cancer (420 and 178, respectively) were randomly assigned to receive either prophylactic platelet transfusions, or no prophylaxis, if the platelet count was <10×10⁹/L. The results again supported the need for continued use of prophylactic platelet transfusions and showed the benefit of prophylaxis, as compared with no prophylaxis, in reduce bleeding. A recent Cochrane review stated that, while it is reasonable to transfuse platelets to prevent bleeding according to the current transfusion policy, the evidence supporting this practice is often of low quality[22].

Although the WHO bleeding score grades the type of intervention according to the severity (Table I), grade 2 events are heterogeneous and may be considered to have significantly different clinical impact. On this background, the patients' and doctors' "perception" of the bleeding may play a major role in administering platelet concentrates even for mild haemorrhages.

Refractoriness is a major, severe side effect of platelet transfusion and it is highly recommended that a platelet count is determined 1 hour after the end of transfusion in order to evaluate this effect[23,24]. However, this seems very uncommon with our survey finding that this is being done in only 11% of centres, while the platelet count is checked 24 hours after the transfusion in most haematology departments. Thus, our data seem to suggest that while bleeding is particularly feared, the risks of immunisation and refractoriness are underestimated. Although this accounts for a more cautious approach in clinical practice in Italy, it is at variance with recent literature as the transfusion/patient ratio was higher in our survey (3.6 *vs* 2.4 and 3.0)[13,14]**.** This seems to reflect the different approach in clinical practice compared to that in standardised clinical trials. In fact, patients in our survey were often transfused for minor bleeding (in 11 out of 18 centres, Table II), a practice more likely to be related to prudence than to the WHO bleeding score recommendations.

Transfused platelets may have a shortened life-span as a result of alloimmunisation to platelet and leucocyte antigens (HLA class I and platelet-specific antigens, mainly HPA1) and transfusion of fresh platelet concentrates or 2 hours after amphotericin B infusion[19,20] is recommended to prevent refractoriness and to prolong platelet survival. The transfusion of HLA-matched platelets does not seem to be a first-line strategy because it would need a large number of typed donors and would only be feasible in large centres (actually, only one in Italy), where there are donors whose HLA system has been characterised.

Another strategy to save platelets might be to transfuse at a lower platelet count, possibly below the 5×10^9/L cut-off. This has been addressed by the British Committee for Standards in Haematology[1], but it seems difficult to propose, in part because of poor accuracy of laboratory counts when the number of platelets is very low. The possibility that platelet transfusion is performed only on demand or on the basis of a lower cut-off (5×10^9/L) raises ethical considerations (risks) and practical problems (platelet counts). However, the "on demand only strategy" might find further support from an analysis of other clinical scenarios. For example, prophylactic platelet transfusions are not indicated in patients with autoimmune thrombocytopenia, who may often have a platelet count $<10\times10^9$/L for long periods, except to stop a life-threatening bleed and yet major bleeding is reported in only 3/1,000 patients despite the severity of the thrombocytopenia[25]. Other useful experience comes from Jehovah's Witnesses, who refuse therapy with blood components. There are reports in the literature describing the possibility of these patients undergoing intensive chemotherapy and stem cell transplantation without transfusions[26,27]**.**

In its recent guidelines[21], the American Association of Blood Banks still recommends transfusing hospitalised adult patients with a platelet count of $\leq10\times10^9$/L to reduce the risk of spontaneous bleeding. Using this clinical practice, approximately 2.2 million platelet units are transfused annually in the USA at an expense of nearly one billion dollars[28].

In Italy during 2013 about 200,000 platelet transfusions were carried out, 38% prepared from pooled buffy coats (cost approximately 123 Euro each) and 62% obtained by apheresis (245 Euro each), giving a total cost of around 40 million Euros. As there is no evidence that apheresis-derived platelets are better than pooled platelets, the cheaper option should be used in clinical practice[29].

Although no data are available from our survey, recent literature suggests that the "on demand" treatment strategy could become a new standard of care after autologous stem-cell transplantation while prophylactic platelet transfusions should remain the standard of care for patients with acute myeloid leukaemia. The new strategy should only be used by some haematology centres in which the staff are well trained and experienced in the new approach and can react in a timely way to the first signs of central nervous system bleeding.

Conclusions

Our survey suggests that, in routine daily practice, Italian haematologists adopt the worldwide criterion of a platelet count cut-off when deciding whether to transfuse platelet concentrates, but they pay less attention to the WHO recommendations on platelet transfusions for bleeding and on monitoring refractoriness. This causes an excess of platelet transfusions, more frequently prepared by apheresis than from pooled donors, with a resulting increase of costs and waste of public health resources. The GIMEMA Haemostasis and Thrombosis Working Party should collect more data and propose a national strategy to improve platelet transfusion practice, thereby saving money and reducing inappropriate use of this blood component.

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Authorship contributions

GT, GC, AF, MN, RS, SS, DV, ABF, and VDS, conceived and planned the study. GT, CT, LC, and MB collected and processed data. GT and GC wrote the draft and all co-Authors reviewed the manuscript and approved its final version.

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