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Review

Hypoplastic thrombocytopenia and platelet transfusion: therapeutic goals

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ABSTRACT

Platelet transfusions consist a major part of the management of hypoplastic thrombocytopenia, the latter occurring mainly among patients with hematological malignancies. Platelet transfusions have led to a reduction of deaths attributable to thrombocytopenia - induced bleeding, despite their possible complications; nonetheless, prophylactic administration of platelets to patients with severe thrombocytopenia or before invasive procedures should be based on specific criteria, as well as therapeutic administration during active bleeding. Recently developed ex-vivo procedures have resulted in producing safer blood products, yet it remains unclear whether these pathogen-inactivated products have sufficient efficacy. What is more, another significant problem that remains to be more effectively addressed is the developing refractoriness to platelet transfusions.

Keywords: hypoplastic thrombocytopenia, platelet transfusion, active bleeding, inactivated blood products, refractoriness

INTRODUCTION

Platelets (PLTs) are the cellular effector and a vital part of hemostasis; they provide the surface where coagulation factors bind and become activated while they also produce and secrete granules with prothrombotic properties. PLTs have been thought as well to provide a supportive function by plugging gaps in the endothelium of otherwise intact blood vessels [1, 2]. Thrombocytopenia on the other hand has been associated with the gradual thinning of the vessel wall endothelium over time, and, if thrombocytopenia persists, gaps gradually occur between adjacent endothelial cells [3], which in turn results in an increased use of circulating PLTs to prevent the loss of red blood cells (RBCs) through these gaps. Therefore, in patients with thrombocytopenia the coagulation process may be deficient, which in turn may result in bleeding. In order to prevent or manage these episodes, PLT administration can be very useful.

PLTs however contain biologically active molecules which carry potential risks for their recipients [4]. PLT units deriving from whole blood units as well as those obtained by apheresis from a single donor unavoidably contain white blood cells (WBCs). The latter are responsible for febrile non-hemolytic transfusion reactions (FNHTRs), alloimmunization and refractoriness to PLT transfusion, infections with intracellular pathogens and transfusion-associated graft-versus-host disease (ta-GVHD). Human platelet antigens (HPAs) can stimulate the production of alloantibodies and the latter may provoke post-transfusion purpura or lead to PLT transfusion refractoriness. PLT units also contain plasma proteins that have been linked to transfusion-related acute lung injury (TRALI - a rare event, but known to be one of the leading causes of transfusion-related death [5]) and allergic reactions [6]. Furthermore, they contain a small number of RBCs that express Rhesus (Rh) blood group antigens on their

surface. These RBCs are significantly fewer in PLT units obtained by apheresis but, as a general rule, PLT transfusion from a Rh(+) donor to a Rh(-) woman of reproductive age should be avoided due to the possible risk of Rh alloimmunization and subsequent hemolytic disease of the newborn, or else RhD negative females receiving RhD positive PLT units should receive RhD immunoglobin (100 IU intramuscularly for every 1 ml of transfused RBCs [7]) soon after the PLT transfusion (to prevent a possible hematoma) or within 72 hours at the most [8]. Moreover, PLT units are stored at room temperature which limits their storage time to five to seven days only, due to the risk of bacterial overgrowth and consequent sepsis [9]. Globalization on the other hand contributes to the rising incidence of new pathogens, potentially transmitted through transfusions. Epidemiological studies have also shown that there may be a relationship between PLT transfusion and thrombosis, possibly due to the accumulation of low pH during their storage that ultimately leads to PLT and WBC activation [10, 11]. Finally, patients who need PLT transfusions most often are those who suffer from hematologic malignancies or solid tumors, e.g., patients that are fragile, immunocompromised and with serious co-morbidities, prone to bleeding complications (Table 1) [12 - 14].

INDICATIONS FOR PLT TRANSFUSION

PLT transfusions have led to a remarkable reduction of deaths attributed to thrombocytopenia – induced bleeding [15 - 17]. Among patients with hematologic diseases the majority of PLT transfusions (69% of them) are given prophylactically to non-bleeding, severely thrombocytopenic patients, while the rest are administered either to thrombocytopenic patients who are expected to undergo invasive procedures in order to reduce the risk of bleeding, or therapeutically, in case of active bleeding [13, 18].

The ready availability of PLT concentrates has undoubtedly made a major contribution in allowing the development of intensive treatment regimens for hematological disorders (malignant and non-malignant) and solid tumors. PLT transfusion guidelines in

thrombocytopenic patients with malignancy have been published but their level of evidence and strength of recommendation are not high and strong, respectively, in all instances [8, 19]. The absolute indication for PLT transfusion is severe thrombocytopenia with clinically significant bleeding. In such cases, PLT transfusion should be immediate and the PLT count should be maintained above 50,000/μlt. All other indications should be considered as relative and depend on clinical parameters, such as the reason of thrombocytopenia, the presence of fever, infection or inflammation, other possible coagulation abnormalities and current medication (Figure 1).

Prophylactic PLT transfusion

It was not until the 1970s and 1980s that PLT transfusion became standard treatment for thrombocytopenic patients with bone marrow failure, including those undergoing chemotherapy [20]. The relationship between the severity of thrombocytopenia, the prediction of the occurrence of a possible bleeding and the importance of PLT transfusion remains vague. Among various randomized controlled trials (RCTs) the observed incidence of bleeding varies greatly (5-70%), probably because of the different methods used in order to record the type and the severity of bleeding, the different thresholds for PLT transfusion as well as the number and kind of the transfused units [21]. Certain attempts to minimize such systematic biases have been made, including a standardized recording tool for the existence of bleeding and its severity and the specialized training of the involved personnel.

In the randomized, prospective, non-inferiority TOPPS study (Trial of Prophylactic vs. No-Prophylactic Platelet Transfusions in Patients with Hematological Malignancies)the use of prophylactic PLT transfusions was associated with improved bleeding outcomes compared to no prophylactic transfusions [22]; despite the fact that there were no deaths in either the prophylaxis or the non-prophylaxis group and that the time needed for the recovery of the PLT count had no difference between the two groups, PLT administration led to fewer

transfusions of RBC units, shorter time to the first bleeding episode and decreased duration of bleeding, especially among patients treated with chemotherapy compared to those who had undergone autologous stem cell transplantation. Regarding the latter, Wandt et al had also showed that grade 3 hemorrhage was rare in patients receiving autologous stem-cell transplantation, regardless of PLT transfusion strategy [23]. No grade 4 bleeding was reported, although the prophylactic PLT transfusion approach did reduce the risk of severe bleeding.

In a recurrent event analysis of the TOPPS study [24] these results were confirmed and, additionally, it was shown that bleeding episodes were significantly more frequent among female patients, for unknown reasons and despite women having higher levels of coagulation factors (such as factor VIII, von Willebrand factor and fibrinogen) than men and the same levels of fibrinolytic activity. It was also shown that the risk of severe bleeding increases with a rising body temperature; patients with body temperature >38°C had a statistically significant higher risk of bleeding, compared to those with body temperature <37.5 °C.

Unfortunately, specific diagnostic tests that could precisely and reliably predict the possibility of spontaneous bleeding in patients with severe thrombocytopenia have not been available yet. However, it has been shown that bleeding is common among patients treated with chemotherapy for solid or hematologic malignancies when PLT count is less than 5,000/µlt [25] or less than 10,000/µlt [22, 26], while earlier studies have shown that patients require only approximately 7,100 PLTs/µlt per day to maintain adequate hemostasis [1]. The PLADO Trial, which enrolled 1,272 patients (pediatric and adult), demonstrated that the risk of WHO grade 2-4 bleeding was 25% when morning PLT counts were 5,000/µlt versus 17% at PLT counts more than 5,000/µlt, the last one remaining fairly consistent up to a PLT count of 80,000/µlt [25]. This means that there are a significant number of bleeding episodes that are not being effectively treated by prophylactic PLT transfusions. Conversely, not all patients with low PLT counts suffer from tissue hemorrhage, indicating that other cofactors are probably required as well for the induction of thrombocytopenic bleeding, namely the PLT count during a previous bleeding episode, the presence of mucosal bleeding and epistaxis (which

are predictive for severe bleeding, contrary to the presence of ecchymoses and petechiae), the presence of fever, infection or inflammation, and the underlying cause of thrombocytopenia. For instance, most of the patients with immune thrombocytopenia (ITP) usually tolerate very low PLT counts without any sign of bleeding but others with acute leukemia and coagulation disorders may present with a bleeding episode despite the higher PLT counts (30,000-50,000/μlt).

In case of fever, sepsis or acute promyelocytic leukemia or even in case of solid tumors with high bleeding risk (mostly bladder cancer and necrotic tumors, while generally the risk of bleeding is quite low among patients with solid malignancies and thrombocytopenia [25]), the transfusion threshold is higher [8, 27]. More precisely, in patients with acute myeloid leukemia, PLT transfusion is recommended when PLT count is less than 10,000/μlt, while in patients with acute promyelocytic leukemia and coagulation disorders that may result in disseminated intravascular coagulation (DIC) and diffuse hemorrhage, the prophylactic PLT transfusion threshold is higher (30,000-50,000/μlt) [27].

After allogeneic stem cell transplantation, PLT transfusion is recommended when PLT count is less than 10,000/μlt [8, 28]. There has been however a study by Nevo et al [29] that has shown an association of profound thrombocytopenia with reduced survival among hematopoietic stem cell transplant patients, which continued well after the count recovery, suggesting that perhaps more vigorous PLT support may improve the clinical outcome of these patients and that at least some patients may benefit from being maintained at a higher transfusion threshold. Finally, among patients with hepatic disease complicated with cirrhosis and splenomegaly, complex prothrombotic and antithrombotic conditions coexist with thrombocytopenia and PLT transfusion can only be recommended prophylactically when the PLT count is less than 25,000/μlt and during invasive procedures[30].

Ideal dose of PLT transfusions

Low dose prophylactic PLT transfusions have not been shown to be inferior compared to the standard dose PLT transfusions. In a study by Slichter et al [25], no statistically significant difference was found between the groups of patients who were transfused with different PLT doses, regarding both the primary (one or more major bleeding episodes) as well as the secondary end points (higher grade of bleeding, death from bleeding, number of days with major bleeding, number of days to onset of major bleeding, need for RBC transfusions). The above findings were confirmed by a meta-analysis of Estcourt et al, which showed that there was no statistically significant difference between the low dose and the standard dose PLT transfusion arms, regarding both major and grade 4 bleeding episodes [28]. Yet, the noninferiority SToP trial in which thrombocytopenic adults were randomly allocated to standard versus low dose PLT transfusions had to be terminated prematurely because the difference in the grade 4 bleeding reached the prespecified threshold of 5% [31]. According to the above, the use of low dose prophylactic PLT transfusions for intensively treated inpatients and medium to high dose for outpatients could be considered. This would decrease the total PLT utilisation for inpatients, while for outpatients it would decrease the number of hospital visits for transfusions, which could not only improve a patient's quality of life but also have resource and financial implications.

PLT administration before invasive procedures

Before invasive procedures associated with high risk of bleeding, it is recommended that thrombocytopenic patients be transfused with PLTs right before those, aiming at specific PLT counts (although different among relevant papers and guidelines) according to each procedure [8, 19, 32 - 34]. The most commonly used PLT counts considered to be safe before specific invasive procedures are mentioned in Table 2. Bone marrow biopsy for example can be safely performed at PLT counts of ≥20,000/μlt, with DIC being the only possible contraindication to the procedure [8]. A PLT count of 50,000/μlt is often considered safe enough for a major

surgery (provided once more that there are no associated coagulation abnormalities [8]), however more systematic research is needed in order to reach firm conclusions for most procedures. When a PLT transfusion is needed, a nearly post-transfusion (and pre-procedure) PLT count should be obtained in order to verify that an adequate PLT count has been achieved, in order to perform the procedure as soon and as safe as possible [8].

Further therapeutic approaches concerning the prevention of hemorrhage in patients with hypoplastic thrombocytopenia

In spite of the fact that prophylactic PLT transfusions decrease the incidence of bleeding among patients with thrombocytopenia a certain bleeding risk remains, while this approach necessitates frequent visits to the medical center, is hampered by PLT shortages, and ultimately leads often to alloimmunization and PLT refractoriness. In addition, this approach is ineffective in preventing significant bleeding episodes in 20% to 50% of patients [35]. Therefore, the American Association of Blood Banks (AABB) recommends further prophylactic measures, for example antifibronolytic treatment [4]. It has been well established that epsilon aminocaproic acid (EACA, a synthetic lysine analogue that inhibits fibrinolysis, leads to thrombus stabilization and has antiplasmin activity [36]) may contribute to the prevention as well as the treatment of bleeding episodes in patients with thrombocytopenia [37, 38]. EACA administration is well tolerated and results in fast and significant reduction in bleeding episodes as well as RBC transfusions in patients with thrombocytopenia [37, 38]. Phase II PROBLEMA (PRevention Of BLeeding in hEmatological Malignancies With Antifibrinolytic, NCT02074436) study aims to compare the effectiveness of EACA administration to PLT transfusion in patients with thrombocytopenia and hematological malignancies, regarding the prevention of bleeding episodes [39]. The administration of tranexamic acid, another antifibrinolytic agent, is effective only in the prevention of thrombocytopenia-induced bleeding [40, 41]. Nonetheless, it should be recognized that anti-

fibrinolytics may increase the risk of DIC, of which patients with hematological malignancies are already at an increased risk.

Corticosteroids, estrogens, desmopressin, recombinant factor VIIa, thrombopoietic growth factors and intravenous IgG have also been administered for the prevention of bleeding in thrombocytopenic patients [20, 42–45], with each one of these drugs having potential side-effects (hypertension, psychological disorders, Cushing's syndrome, hyperglycemia and diabetes, weight gain, peptic ulcer, osteoporosis, cataract formation and glaucoma among others for corticosteroids, vaginal hemorrhage, endometrium disease, edema, hypertension, headache, anxiety and depression, rash, pruritus, weight gain, hot flashes and gastrointestinal disorders for estrogens, hyponatremia for desmopressin, thrombosis for recombinant factor VIIa, thrombocytosis, thrombosis, increased bone marrow fibrosis and rebound thrombocytopenia for thrombopoietic growth factors, and headache, thromboembolism, hemolysis and acute renal failure for intravenous IgG) (Table 3). Moreover, a recent study has recently shown that leukocyte extravasation to the site of tissue inflammation increases the bleeding risk in patients with thrombocytopenia and therefore targeted pharmacological interventions (e.g., pertussis toxin) could be of value for these patients [46]. However, a recent meta-analysis and systematic review that examined whether any alternative agent can prevent bleeding better than prophylactic PLT transfusions found insufficient evidence to support an alternative agent [47]. It seems that the most effective approach concerning the avoidance of bleeding among patients with chemotherapy-induced thrombocytopenia would be the development of new cancer treatments that would not cause thrombocytopenia.

Therapeutic administration

The dose and frequency of transfusions depend on the initial PLT count and the severity of bleeding. The latter is evaluated according to the well-known World Health Organization bleeding scale. The WHO bleeding scale (1979) has been used most commonly in PLT

transfusion trials, though it is not considered to be adequate, since it employs terms such as "mild" and "gross" to describe bleeding without explicit definitions of these terms and involves a great degree of subjectivity by default. Bearing this in mind, grade 1 and 2 bleeding is usually attributed to the severity of thrombocytopenia while grade 3 and 4 bleeding is correlated with other coexisting factors, namely anticoagulants, underlying diseases (such as uremia), medication, and vasculature deficits (e.g., in necrotizing tumors). It is due to those confounding factors that PLT transfusions are not able in certain circumstances to prevent or control bleeding episodes.

A new measurement tool (Bleeding Severity Measurement Scale, BSMS) has been proposed for a more precise recording of bleeding episodes among patients with thrombocytopenia due to myelosuppression [48]; in the future, this could be used for all bleeding patients. The BSMS has several potential strengths. It was developed according to input from health care workers involved in the care of the population for whom the bleeding scale was developed (i.e., patients undergoing chemotherapy and presenting with thrombocytopenia). Furthermore, it was developed with the primary goal of being clinically meaningful, while using a clear grading scale and no site-specific bleeding categories or laboratory values. This allows for easier administration of the scale and increases the generalizability of the scale. A possible limitation is the fact that the BSMS classification uses the need for intervention to determine bleeding severity, which may vary by clinician or institution.

PATHOGEN-INACTIVATED BLOOD PRODUCTS

Various techniques for pathogen inactivation have been recently deployed. These techniques have the potential of eliminating the residual risk of the window period, reducing the risk of recognizable infectious agents or other emerging ones, and offering global protection against ta-GVHD.

The most widespread one is based on the addition of amotosalen, a psoralen derivative, in the PLT unit which is then exposed to ultraviolet A (UVA) light. Amotosalen molecules that have been bound on the nucleic acids of the microorganisms and the WBCs are then activated and lead to covalent cross-linking, which results in the blocking of replication and the death of bacteria, viruses and protozoa as well as the WBCs. The inactive amotosalen is then removed by absorption. This method is considered to be safe, nontoxic and non-mutagenic [49 - 52]. Evidence from the first randomized clinical trial support the efficacy of the administration of inactivated PLTs and so do subsequent clinical trials [51, 53, 54]. Other studies have shown that the corrected count increment [CCI = (PLT increment per μlt) x (body surface area in m^2)/number of PLTs transfused ($x10^{11}$)], the most commonly used indicator of the effectiveness of PLT transfusions, was lower compared to the transfusion of conventional products [55 - 57]. The results of two meta-analyses are conflicting as well [58, 59]. Finally, in the most recent randomized clinical trial the efficacy of pathogen-reduced PLTs was noninferior to PLTs in additive solution but such noninferiority was not achieved when comparing pathogen-reduced PLTs with PLTs in plasma [60].

Two other systems for inactivating blood products have been developed as well, yet the clinical experience is inadequate. The first is based on the addition of riboflavin that associates with nucleic acids and mediates an oxygen-independent electron transfer upon UV exposure, provoking their irreversible damage [61, 62]. In a recent randomized noninferiority trial comparing the efficacy of pathogen-inactivated PLTs using riboflavin and UV B illumination technology (intervention) compared with standard plasma-stored platelets (control) for the prevention of bleeding in patients with hematologic malignancies and thrombocytopenia [63], the noninferiority criterion for pathogen-inactivated platelets was not demonstrated in the per-protocol analysis, a fact that may suggest that such pathogen-inactivated PLTs have a mitigated hemostatic efficacy. This finding is in accordance with the conclusion of a recent review that included randomised controlled trials involving both the Intercept® as well as the Mirasol® method of pathogen-reduction [64]. The second system uses

UV rays as well (UVC) that directly interacts with nucleic acids causing the formation of nucleotide dimers [65].

EFFECTIVENESS OF PLT TRANSFUSION AND REFRACTORINESS

The assessment of the efficacy of PLT transfusion is challenging. The most frequently used indicator is CCI but, in everyday clinical practice, the persistence of bleeding signs or the occurrence of new ones seem to be more useful. Factors influencing the effectiveness of PLT transfusions are the dose administered, ABO compatibility, storage time, the use of plasma or other solutions for PLTs re-dilution, their irradiation and the procedures for pathogen inactivation as well as clinical conditions, namely fever, infection or sepsis, splenomegaly, DIC, the presence of GVHD, persistent bleeding and medications such as vancomycin, heparin and GPIIb/IIIa antagonists.

Refractoriness to PLT transfusion is defined as an inadequate rise of the PLT count after 2 consecutive PLT transfusions, e.g., a CCI less than 7,500 or 4,500/μlt, determined 1 and 18-24 hours respectively after the transfusion of ABO compatible PLTs which have been stored for less than 3 days. Refractoriness to PLT transfusion is found in 30% of the transfused patients even if they are transfused with HLA compatible and leukodepleted products [66, 67]. Reasons for refractoriness to PLT transfusion are divided into either immune-mediated or non-immune-mediated, with the latter being more frequent. In patients with PLT transfusion refractoriness, non-immunologic factors are present in 63-88% of all cases while alloimmunization occurs in 18-25% of them [68]. Bleeding, sepsis, splenomegaly, medications, and GVHD in patients who underwent allogeneic stem cell transplantation are some of the non-immunologic factors mentioned above. Apart from the production of anti-HLA antibodies, the presence of anti-HPA antibodies and/or their combination are another factor that can lead to PLT transfusion refractoriness [69]. In allogeneic stem cell transplantation, minor histocompatibility antigens may play an important role as well [70].

In patients who are refractory to PLT transfusion, non-immunologic underlying causes should be initially excluded. If an immunologic mechanism is suspected, a search for possible anti-HLA antibodies should take place. In case of positive findings, HLA class I donors should be typed and similar HLA PLT units or products which do not show any cross-linking with the patient's HLA or products from donors who do not express the HLA against which the patient has been sensitized should be administered. Due to these limitations, only 50-60% of the primarily PLT transfusion refractory patients respond satisfactory to PLT transfusions [71 - 73]. The difference between success rates of managing alloimmunization regarding PLT or RBC units is attributed to non-immune-mediated mechanisms, as well as the production of alloantibodies against soluble plasma antigens [74]. In such cases, antifibrinolytic factors could be administered or PLT transfusion could be avoided while the patients are under close medical supervision. In the case of alloimmunized patients with active bleeding, repeated transfusions of large numbers of pooled random-donor PLTs may be of some benefit [8].

PLT TRANSFUSION CONTRAINDICATIONS

It cannot be overemphasized that PLTs should not be withheld in bleeding patients due to fear of "fueling the fire" of thrombus formation. So, rather relative contraindications to PLT transfusion are thrombotic thrombocytopenic purpura (TTP) and other microangiopathic hemolytic disorders [hemolytic-uremic syndrome (HUS), HELLP syndrome] and possibly heparin-induced thrombocytopenia (HIT) [8, 19, 75].

CONCLUSIONS

PLT transfusion has become a major therapeutic aid in clinical practice, especially in the management of myelotoxicity – induced thrombocytopenia, despite the fact that PLT count thresholds for spontaneous bleeding are not completely determined and therefore many other

clinical aspects should be considered before deciding their administration. In cases of major bleeding, DIC, CNS bleeding and retinal hemorrhage, PLT transfusion can be life-saving and should not be delayed despite any possible contraindications. Finally, prophylactic PLT transfusion before invasive procedures has been well-established in clinical practice, notwithstanding the fact that there are differences among the recommendations of various expert groups.

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FIGURE 1

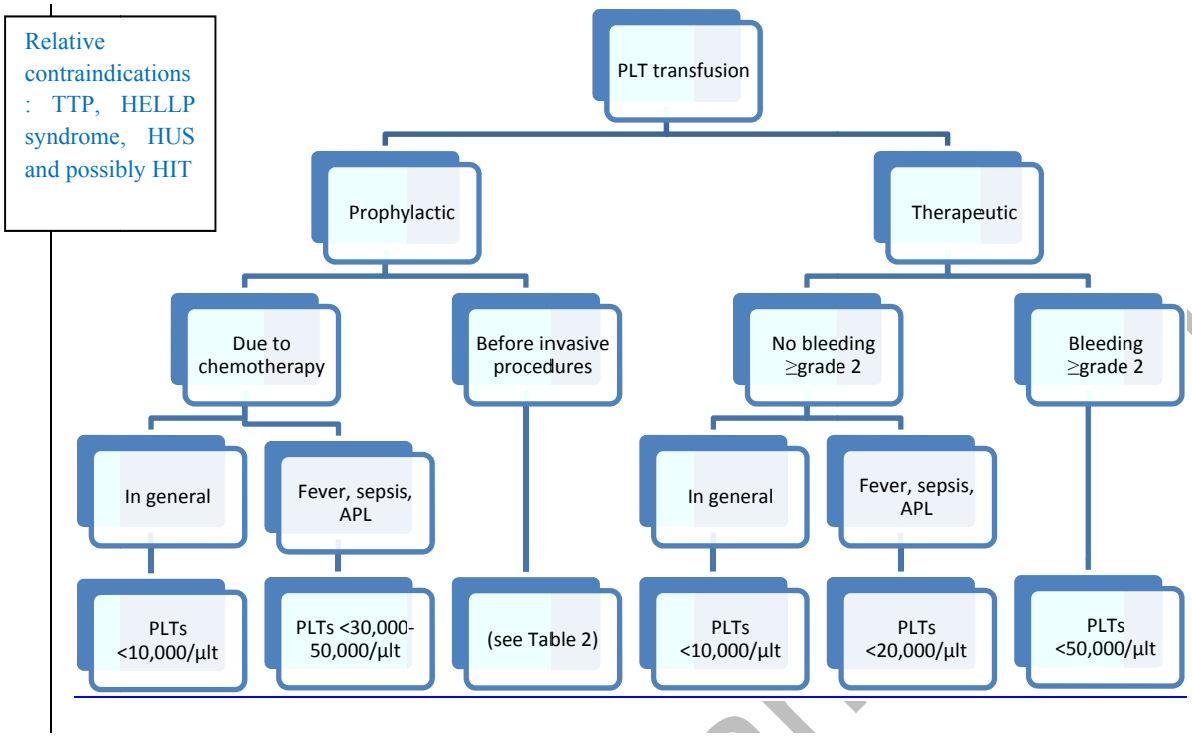

Figure 1. Indications for PLT transfusion, corresponding post-transfusion targets and contraindications. APL, acute promyelocytic leukemia; HELLP, hemolysis, elevated liver enzyme levels, and low platelet levels syndrome; HIT, heparin-induced thrombocytopenia; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

TABLE 1

Hospital service	**Percentage of total PLT transfusions**
Hematology/Oncology	34.4-67%
Cardiac	11-17%
Paediatric	4.8-13%
Intensive Care Unit	9-12.4%
Hepatobiliary	10%
Gastrointestinal	9%
Vascular	4%
Trauma	2-4.4%
Obstetrics	0.6-3%

Table 1. Common indications for PLT transfusion. Data extracted from [9]-[11].

TABLE 2

Type of procedure	**PLT count threshold (/µlt)**
Neurosurgery or ocular surgery	100,000
Major surgery	40,000-50,000
Therapeutic endoscopy	50,000
Diagnostic endoscopy	20,000
Lumbar puncture in stable pediatric patients with hematologic malignancies	20,000
Lumbar puncture in other patients	40,000
Epidural anesthesia	50,000-80,000
Tooth extraction	20,000
Central venous catheter insertion and removal	20,000
Percutaneous liver biopsy	50,000

Table 2. Prophylactic PLT transfusion thresholds among common invasive procedures. Data extracted from [8], [19], [32]-[34].

TABLE 3

PLT transfusion alternatives	**Advantages**	**Possible harms (selected)**
Antifibronolytic agents	EACA may contribute to the prevention as well as the treatment of bleeding episodes in patients with thrombocytopenia EACA administration is well tolerated and results in fast and significant reduction in bleeding episodes as well as RBC transfusions potential enhancement of intrinsic hemostatic function	tranexamic acid is effective only in the prevention of thrombocytopenia-induced bleeding DIC risk
Corticosteroids	potential enhancement of intrinsic hemostatic function	hypertension, psychological disorders, Cushing's syndrome, hyperglycemia and diabetes, weight gain, peptic ulcer, osteoporosis, cataract formation and glaucoma
Estrogens	potential enhancement of intrinsic hemostatic function	vaginal hemorrhage, endometrium disease, edema, hypertension, headache, anxiety and depression, rash,

		pruritus, weight gain, hot flashes and gastrointestinal disorders
Desmopressin	potential enhancement of intrinsic hemostatic function well-tolerated	hyponatremia facial flushing
Recombinant factor VIIa	enhancement of hemostatic function	thrombosis
Thrombopoietic growth factors	improvement of the intrinsic PLT count	thrombocytosis, thrombosis, increased bone marrow fibrosis and rebound thrombocytopenia
Intravenous IgG	rather rapid response	headache, thromboembolism, hemolysis and acute renal failure

Table 3. PLT transfusion alternatives. DIC, disseminated intravascular coagulation; EACA, epsilon aminocaproic acid.

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