Platelet transfusion for cancer secondary thrombocytopenia: Platelet and cancer cell interaction

Juan Wang [a], Pan Zhou [b], Yunwei Han [c,*], Hongwei Zhang [d,*]

[a] Class 2016 Clinical Medicine, Southwest Medical University, Luzhou 646000, Sichuan, China
[b] Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan, China
[c] Department of Oncology, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan, China
[d] Department of Blood Transfusion, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan, China

ARTICLE INFO

ABSTRACT

Chemoradiotherapy and autoimmune disorder often lead to secondary thrombocytopenia in cancer patients, and thus, platelet transfusion is needed to stop or prevent bleeding. However, the effect of platelet transfusion remains controversial for the lack of agreement on transfusion strategies. Before being transfused, platelets are stored in blood banks, and their activation is usually stimulated. Increasing evidence shows activated platelets may promote metastasis and the proliferation of cancer cells, while cancer cells also induce platelet activation. Such a vicious cycle of interaction between activated platelets and cancer cells is harmful for the prognosis of cancer patients, which results in an increased tumor recurrence rate and decreased five-year survival rate. Therefore, it is important to explore platelet transfusion strategies, summarize mechanisms of interaction between platelets and tumor cells, and carefully evaluate the pros and cons of platelet transfusion for better treatment and prognosis for patients with cancer with secondary thrombocytopenia.

Introduction

Chemoradiation is widely known to be one of the main treatments for cancer; yet, it is likely to cause bone marrow suppression in cancer patients. Myelosuppression is dictated by both chemotherapy regimen and patient characteristics. The rates of anemia, thrombocytopenia, and neutropenia differ for each chemotherapy regimen [1,2]. Thrombocytopenia is estimated to occur in 10-36% of patients with solid tumors [3]. Patients with severe thrombocytopenia will develop skin and mucocutaneous hemorrhage and even intracranial hemorrhage (ICH) [4,5]. Moreover, the frequency of ICH is approximately 0.5% in children and 1.5% in adults, and the risk increases with age [6]. Severe bleeding is distinctly uncommon when the platelet count is $>30 \times 10^9/L$ and usually occurs only when the platelet count falls $<10 \times 10^9/L$ [6]. Platelet transfusion can significantly reduce the mortality of bleeding caused by platelet reduction after radiotherapy and chemotherapy, and is an irreplaceable immediate hemostasis method [7]. The commonly used platelet products in clinical practice are apheresis platelets and concentrated platelets, both having similar effects on platelet increase, hemostatic effect, and side effects after transfusion [8,9]. On the other hand, the function of platelets extends from blood coagulation to their important regulation of both innate and adaptive immunity. Platelets demonstrate their anti-tumor immune regulation through the TGF-β/GARP axis. The TGF-β receptor to which glycoprotein A repetitions predominantly (GARP) have a high affinity is expressed in activated regulatory T cells and platelets, and in turn inhibits specific anti-tumor cytotoxic T cells, which results in immune suppression. [10–12]. Platelet activation gradually increases with the prolonged storage time [13–16]. Activated platelets will release substances with a negative effect on the immune function and tumor growth of cancer patients, including bio-

Table 1

Classification and risk assessment of thrombocytopenia.

Thrombocytopenia Classification*	
Platelet count	Grade
$(75{\sim}99) \times 10^9/L$	I
$(50{\sim}74) \times 10^9/L$	II
$(25{\sim}49) \times 10^9/L$	III
$<25 \times 10^9/L$	IV

Risk assessment	
Platelet count	Danger
$<50 \times 10^9/L$	Skin and mucous membranes can bleed, and patients are at risk to undergo surgery and invasive traumatic examinations
$<20 \times 10^9/L$	High risk of spontaneous bleeding
$<10 \times 10^9/L$	Extremely high risk of spontaneous bleeding

* U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0)

logically active lipids, biochemical factors, chemokines, cytokines, and microparticles [17,18]. For example, vascular endothelial growth factor (VEGF) extracted from stored platelets can contribute to tumor growth [19]; thus, washing platelets before blood transfusion could significantly improve overall survival [20]. Platelet injection into patients with cancer in situ can also significantly increase the tumor proliferation index and promote tumor metastasis and angiogenesis [21]. These studies have indicated that the impact of platelet transfusion on cancer progression may be harmful, including increased tumor recurrence rate and reduced five-year overall survival [22–24]. Activated platelets promote tumor cells growth and metastasis and tumor growth in turn promotes platelet activation [25,26], and such a "vicious circle" of cooperation between platelets and tumors may exist in cancer patients transfused with platelets. However, the specific mechanism is still unclear; therefore, clinicians should carefully evaluate the pros and cons of platelet transfusions when considering this treatment.

Classification and risk assessment of thrombocytopenia

Based on the platelet count, the severity of thrombocytopenia can be categorized into four grades, i.e., grade I to grade IV: Grade I: $(75–99) \times 10^9/L$, Grade II: $(50–74) \times 10^9/L$, Grade III: $(25–49) \times 10^9/L$, and Grade IV: $<25 \times 10^9/L$. In addition to playing a key role in the formation of thrombosis, platelets also protect the integrity of tumor blood vessels, thus helping to determine whether tumor patients have a bleeding tendency or hemostatic ability [27]. When the platelet count is $<50 \times 10^9/L$, bleeding occurs in the skin and mucous membranes, and patients have some risks when undergoing surgery and invasive traumatic examination. The rate of bleeding increased as the platelet count decreased and no clear threshold could be demonstrated. For each sequential decrease in platelet nadir, the rate of bleeding increased by 50–100% [28]. When the platelet count is $<20 \times 10^9/L$, there is a high risk of spontaneous bleeding, while the risk is extremely high when the platelet count is $<10 \times 10^9/L$ (Table 1) [28,29].

Thrombocytopenia associated with solid tumors

Thrombocytopenia caused by chemotherapy

Chemotherapy-induced thrombocytopenia (CIT) refers to the inhibitory effect of anti-tumor chemotherapy drugs on bone marrow, particularly megakaryocytes that result in platelet count in peripheral blood less than $100 \times 10^9/L$. Clinically, CIT is a common dose-limiting

toxic reaction of chemotherapeutic drugs and may result in dose reductions, dose delays, or even discontinuation. Severe thrombocytopenia can cause spontaneous bleeding of important organs, thereby affecting clinical efficacy and patient survival. The degree of thrombocytopenia is related to the category, dose, chemotherapeutic cycle, dose form, and auxiliary measures of chemotherapy drugs as well as individual differences of patients [30]. Furthermore, severity of bone marrow suppression and thrombocytopenia are different when the same drug is applied for different organ tumors [31]. Incidence rates of thrombocytopenia vary with the type of tumor. According to a report of 43995 cases of solid tumors in US, incidence rates for CIT in colorectal cancer, non-small cell lung cancer, ovarian cancer, and breast cancer are 61.7%, 0.5%, 45.6%, and 37.6%, respectively [3]. The preliminary data analysis from January 2016 to June 2017 from the Link Doc database shows that the incidence rate of CIT in liver cancer is higher than 40%, while that in breast cancer is 3.7%, with those in other cancers between 10% and 20%. Concerning the chemotherapy regimen, the incidence of CIT in platinum-containing chemotherapy regimens for many cancers, including lung cancer and gynecological cancer is higher [32–36]. Quinidine, digoxin, valproic acid, quinine, etc. have an incidence at 18% [37,38]. Moreover, polytherapy has a higher incidence than monotherapy. For instance, 4% of the patients receiving only cisplatin may develop Grade III or IV thrombocytopenia, and therapy with gemcitabine alone has an incidence rate of 3.7%. However, a combination of different drugs may have an incidence of thrombocytopenia at 37%, and the rate could be even as high as 79% if an invasive regimen for sarcoma is carried out with ifosfamide, adriamycin, and dacarbazine [3,30].

Immune thrombocytopenia (ITP)

Immune thrombocytopenia (ITP) is an acquired hemorrhagic disease characterized by the excessive destruction of platelets and megakaryocyte dysmaturity mediated by humoral and cellular immunity, mainly manifested as bleeding into the skin and mucous membranes, excessive menstruation, and even internal or intracranial hemorrhage; thus, it can be life-threatening [39,40]. There are two types of ITP, namely, primary immune-mediated thrombocytopenia (pITP) and secondary immune-mediated thrombocytopenia (sITP). pITP is an acquired autoimmune disease characterized by isolated thrombocytopenia without other causes, and sITP refers to all forms of immune-mediated thrombocytopenia except pITP [41]. Despite reports on the association between ITP and cancer, the causality of tumor cells in paraneoplastic ITP pathogenesis and maintenance has not yet been established. Paraneoplastic ITP should be categorized into sITP. The mechanism of sITP may be that certain active metabolites of tumors inhibit the differentiation and maturation of megakaryocytes, and that immune dysregulation of patients produces platelet antibodies [42–44]. In recent years, the clinical diagnosis rate of solid tumors complicated with ITP has gradually increased. Krauth's research has shown that ITP is most common in patients with lung and breast cancers, followed by renal cell and ovarian cancers, but rare in prostate cancer. Additionally, most ITP occurs when tumors recur and metastasize, and 25% of them occur before the diagnosis of tumors. The molecular factors responsible for the association between ITP and carcinogenesis are unclear, but Krauth et al. reported that the following four types of ITP are associated with solid cancers: (i) ITP prior to the diagnosis of cancer, (ii) ITP concurrent with cancer, (iii)ITP at recurrence of cancer or diagnosis of a second/third cancer, and (iv) ITP after chemotherapy and/or radiation therapy for cancer [45].

Thrombocytopenia caused by radiotherapy

As one of the chief treatments for cancer, radiotherapy can control the proliferation and differentiation of cancer cells by irradiating tumor volume. Nevertheless, radiotherapy can also cause adverse effects including leukopenia, anemia, and thrombocytopenia. The throm-

bocytopenia secondary to radiotherapy is hypothesized to be related to generated free radicals from radiotherapy, which are thought to damage hematopoietic stem progenitor cells, causing the destruction of platelets and a low platelet count. Moreover, the DNA repair function of hematopoietic stem progenitor cells is damaged by radiotherapy, which results in platelet dysfunction. When cancer patients receive radiotherapy, particularly radiotherapy for the wider range of the pelvis, the spine, and the whole lung, their hematopoietic system is affected and the platelet count is reduced. If radiotherapy is synchronized with chemotherapy, the suppression of the bone marrow will be exacerbated, causing Grade III or IV thrombocytopenia, bleeding in important organs, and even death [46]. Finally, according to a report in 2017, the lung is also a hematopoietic organ, with the pulmonary megakaryocytes producing over 10 million platelets per hour, so radiotherapy directly affects the function of megakaryocytes in pulmonary circulation, which results in a low platelet count [47].

Platelet transfusion in cancer patients

Platelet transfusion strategy

Platelet transfusion, one of the treatments for patients with severe thrombocytopenia, can effectively reduce the incidence of bleeding and should be considered for most patients with solid tumors, particularly those with a risk of bleeding, such as malignant melanoma, colorectal tumors, bladder cancer, and gynecological tumors. When active bleeding occurs in patients with cancer-related thrombocytopenia, platelet transfusion should be a priority if bleeding is believed to be related to a low platelet count [48,49]. At present, the two main approaches to supplement platelets are platelet transfusion and the use of recombinant human thrombopoietin (rhTPO). When the platelet count is higher than 10×10^9/L, rhTPO is often used. When the platelet count is lower than 10×10^9/L and even when there are any hemorrhagic manifestations, direct platelet transfusion is used and it also may be combined with thrombopoietin (TPO) receptor agonists [48] . Wandt et al. have demonstrated that maintaining a threshold of 10×10^9/L in patients with fever, infection, and concomitant medication does not increase the probability of adverse events [50]. For patients with bleeding, high fever, a rapid drop in the platelet count, or abnormal blood coagulation (such as acute leukemia) who are undergoing invasive surgery or in emergencies where platelets may not be readily available, the higher level (20×10^9/L or 30×10^9/L) of platelet transfusion may be adopted [48] . Randomized clinical trials have also shown that there is no difference in patients with severe bleeding in the use of a threshold of platelet count at 10×109/L or even higher ($\leq 20 \times 10^9$/L or $\leq 30 \times 10^9$/L), while a lower threshold can reduce the number of platelet transfusions. Thus, the threshold at 10×10^9/L is recommended for patients in a stable state or with no symptoms. Therefore, the platelet transfusion monitoring value could be set to be lower than 10×10^9/L or 20×10^9/L if there are additional risk factors. For chronic thrombocytopenia, the threshold could even be $< 5 \times 10^9$/L [49]. Because of the large number and relatively light bleeding of colorectal and bladder tumors, the threshold should be considered to be higher (approximately 20×10^9/L) [48].

When patients have no active bleeding, the dose of transfusion depends on the present and expected platelet count before and after transfusion. Generally, an adult receives one therapeutic dose every time. When patients have active bleeding, the dosage is determined by the severity of bleeding and hemostatic effect of transfusion. Usually, the corresponding standard dose is prescribed based on the degree of thrombocytopenia and one full dose is transfused at a time. There have been trials to determine the effect of the dose of prophylactic infusion in patients. The infusion volume was determined according to body surface area and three groups were specified: the low-dose group at 1.1×10^{11}, the intermediate-dose group at 2.2×10^{11}, and the high-dose group 4.4×10^{11}. The results showed that there is no difference in the incidence of bleeding episodes or in the probability of adverse reaction, ex-

cept for a higher incidence of wheezing in the high-dose group [51,52]. Other experiments have evaluated platelet transfusion at a low dose and their results also indicate that there is no difference in the volume of transfusion [53,54]. Therefore, an appropriate reduction of platelet transfusion dose should be considered to reduce the risk of alloimmunization and costs.

Adverse effects of blood transfusion

For patients with cancer, the incidence of side effects of platelet transfusion, such as fever, allergy, bacterial contamination, and transfusion-related acute lung injury, is higher than those of other components of blood, including suspended red blood cells, suspended leukocytes, and plasma [55]. Some people believe that platelet transfusion in cancer patients may not be associated with an increased risk of thrombosis. In a large retrospective cohort study that evaluated the risk of thrombosis associated with blood transfusion requirements, 15237 patients (3%), out of the total 504,208 consecutively hospitalized cancer patients from 1995 to 2003, received at least one platelet transfusion besides red blood cell transfusions. In the multivariate analysis, during the follow-up examinations, however, platelet transfusion (OR 1.2 and CI 1.11–1.29) was not associated with the increased risk of venous thromboembolism or arterial thromboembolism (OR 1.55 and CI 1.40–1.71), but it increased the hospital mortality rate (OR 2.40; CI 2.27–2.52; and $P < 0.001$) [46]. Furthermore, the in vitro storage of platelet concentrate (with white blood cells removed) will promote the increase of many growth factors (such as VEGF and platelet-derived growth factor, (PDGF)), fibroblast growth factor-2, brain-derived nerve growth factor, EGF, and TGF-β1, etc [56]. Additionally, the amount of soluble proinflammatory and thrombotic factors in the supernatants increase, and these factors may compensate for the loss of platelet function to a certain extent, but they may also lead to the formation of thrombus [57–60].

The incidence of adverse reactions of blood transfusion can be reduced through ABO blood type matching, cross-matching, reducing white blood cells, blood irradiation, and other measures [61–65]. The incidence of side effects of platelet supernatants can be reduced by washing platelets [19]. However, it is now believed that platelets are not only cell debris that promote thrombosis and hemostasis, but also multifunctional immune blood cells. Studies have found that platelets themselves interact with tumor cells. Platelets in storage will be activated, and then promote the growth and metastasis of tumor cells. The growth of tumor cells can promote the production of platelets and activation at a larger range. Therefore, attention to the interaction of platelets and tumor cells is of great importance to evaluate platelet transfusion in cancer patients.

Mechanisms of interaction between platelets and tumor cells

Platelets promote tumor cells metastasis in the circulation to form a "positive feedback loop"

Platelets promote tumor cells metastasis in circulation. On the one hand, tumor cells themselves transit into an aggressive mesenchymal-like phenotype (epithelial to mesenchymal transition, EMT), before they attract activated platelets around the tumor cells to form heterotypic platelet tumor cell aggregates(Fig. 1①). Thus, platelets help tumor cells to obtain a phenotype very similar to platelets, thereby protecting tumor cells from damage by natural killer cells so that metastasis of tumor cells in vivo is enhanced (Fig. 1②) [66–68]. On the other hand, platelets in the blood circulation system stimulate tumor cells to overexpress substances, including IL-1, IL-3, IL-6, and leukemia inhibitory factors (Fig. 1③) [69–72], and these substances in turn induce the liver to produce TPO (Fig. 1④). In response to the stimulation of TPO, bone marrow enhances platelet production and releases platelets into circulation (Fig. 1⑤). Furthermore, tumor cells can also activate platelets through direct interaction with platelets [23,73–76]. Platelet aggregation, like a protective thrombus, can prolong the survival time of tumor
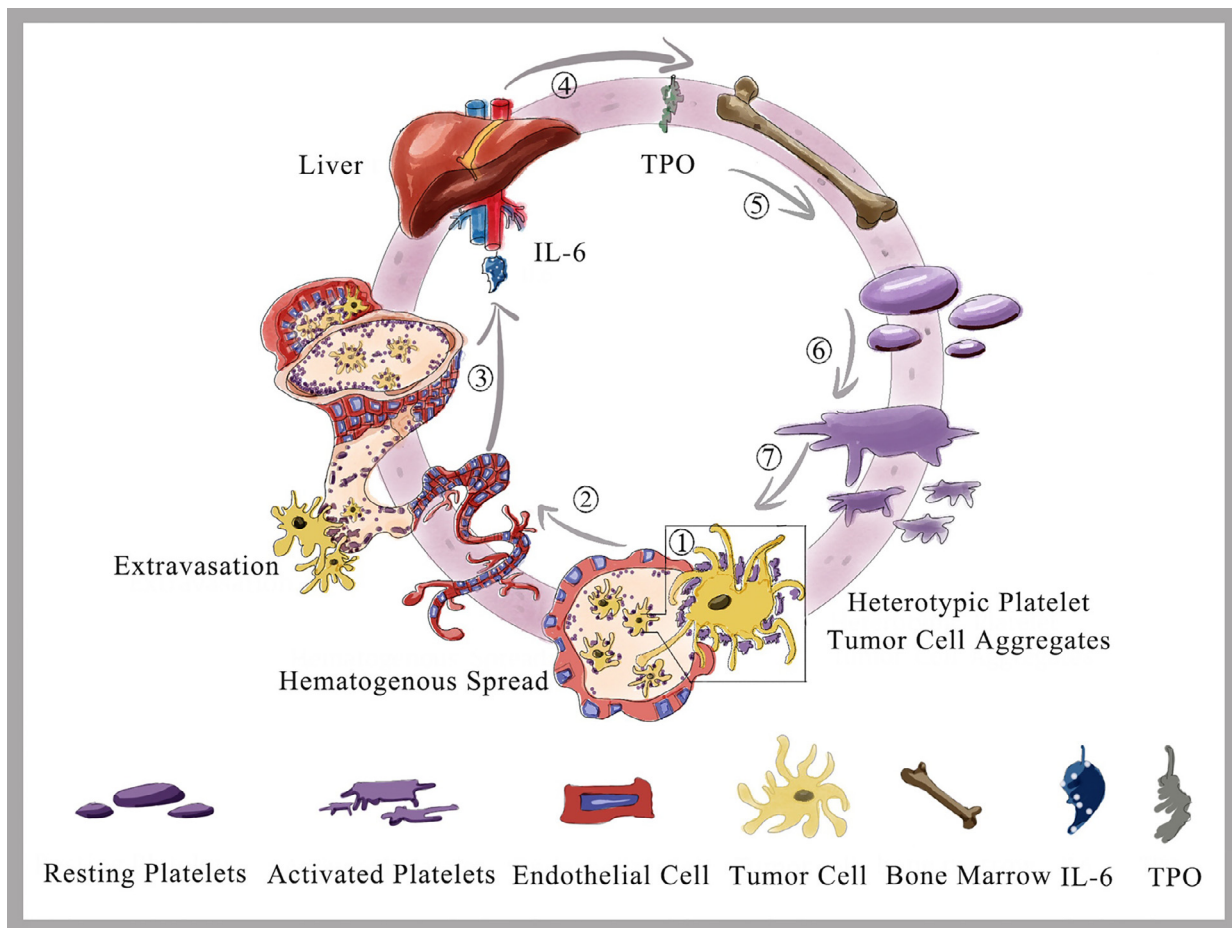
Fig. 1. Platelets promote metastasis of tumor cells to form a "positive feedback loop" in circulation.

cells in the circulatory system and thus protect tumor cells immunologically [77]. As the increased production of platelets promotes the activation of more platelets (Fig. 1⑥), and then induces further production and metastasis of tumor cells (Fig. 1⑦), leading to more platelet numbers and the stimulation of activity levels, platelets eventually promote metastasis of tumor cells to form a "positive feedback loop" in circulation (Fig. 1).

"Vicious circle" of cooperation between platelets and tumor cells

Mechanisms of tumor cell-induced platelet activation

The ability of tumor cells to induce platelet activation and promote metastasis of tumor cells is closely related to their ability to attract platelet aggregation. Tumor cells induce platelet aggregation to form heterotypic platelet tumor cell aggregates, thus protecting circulating tumor cells (CTCs) from death induced by NK cell and tumor necrosis factor α. Through a multistep synthesis process, arachidonic acid in activated platelets is converted into thromboxane TXA2, and activates TXA2 receptors on other platelets and endothelial cells; thus, platelets are activated [78]. Furthermore, to assist their own internal and external transport, tumor cells release complements C3a, C5a, prostaglandin E2 (PGE2), IL-1α, and matrix metalloproteinases (MMPs) that participate in the inflammatory response and indirectly promote platelet activation. Egan et al. have found that ovarian cancer tumor cells release adenosine 5'-diphosphate to mediate platelet activation. This effect has been shown to be blocked by 5'-adenosine diphosphate receptors P2Y12 and P2Y1 antagonists [79]. Recently, Mitrugno et al. have demonstrated that tumor cells can directly induce platelet activation through platelet Fcγ Receptor IIa [80]. These findings have strength-

ened our understanding of the mechanism by which tumor cells induce platelet activation; yet, more mechanisms await to be explored (Fig. 2).

Activated platelets further promote tumor cell growth

After being activated, platelets preferentially release proangiogenic proteins, promote tumor angiogenesis, significantly increase the adhesion of tumor cells to blood vessels, and release a large number of dense granules and α granules. On the one hand, α granules release growth factors and small molecules that promote tumor growth and invasion, such as PDGF and VEGF [81–83]. PDGF and VEGF can also be released directly by platelets themselves. On the other hand, platelet-dense granules secrete ATP to activate endothelial cells P2Y2 and increases the permeability of endothelial cells [46,84,85]. Furthermore, platelet-dense granules can also release G protein-coupled receptor agonists such as ADP and serotonin to promote cancer cell migration and spillover, and platelets undergo morphological changes and release ADP, the tumor cells of which also release after being activated. Then, ADP further enhances, particularly when the body is hypoxic, the activation of platelets in the form of autocrine or paracrine, which relies on platelets to express P2Y12 and P2Y1 [75,86,87]. The study of Labell et al. suggested that TGF-β secreted by platelets induces EMT of cancer cells in blood circulation through BF4-B/Smad and nuclear factor-κB pathways, and promotes tumor metastasis [88]. Platelets promote extravasation of CTCs through adhesion molecules, including P-selectin, L-selectin, and focal adhesion kinase (FAK), of which FAK can promote the binding of GPVI to subendothelial collagen [24,89–91]. These mechanisms clarify the "vicious circle" of cooperation between platelets and tumor cells, that
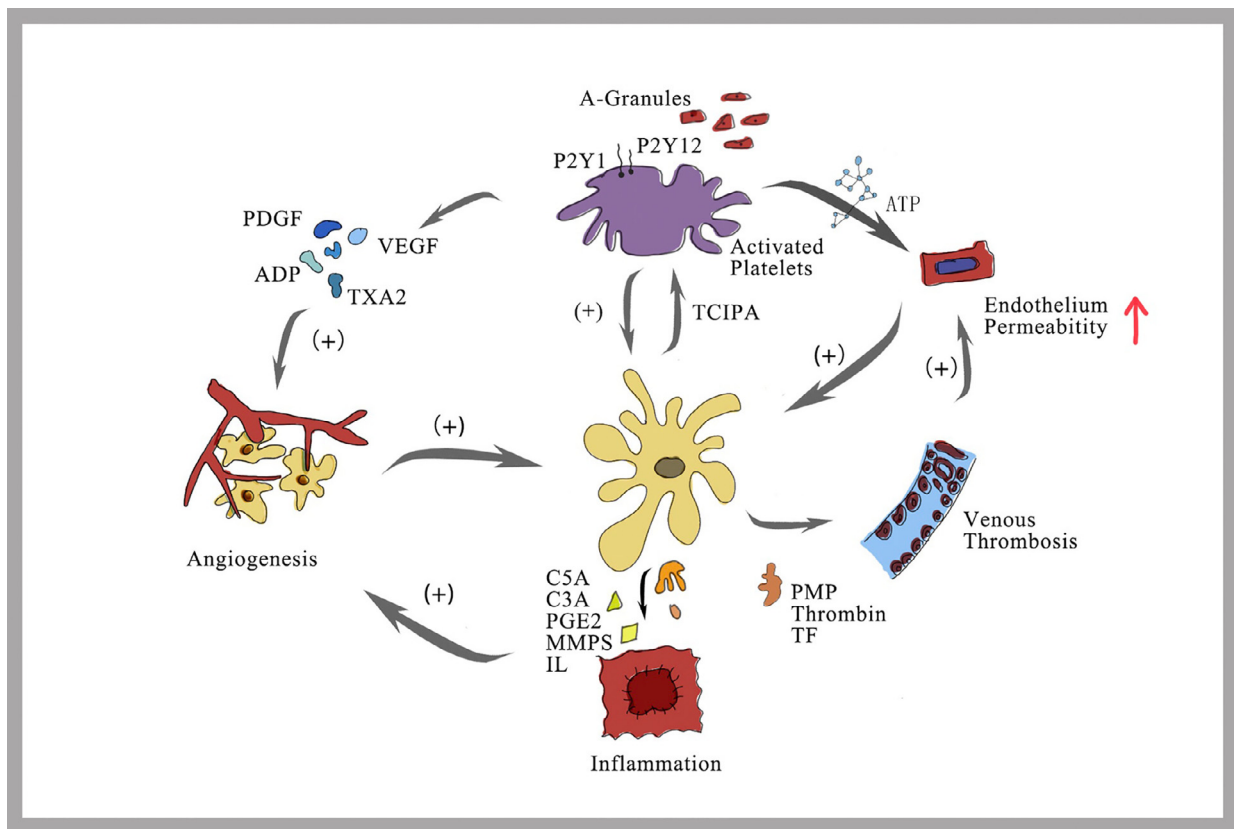
Fig. 2. Biological effects of tumor cells mediated by platelet activation.

is, tumor cells can induce platelet activation and increase platelet production, and platelets can in turn promote tumorigenesis, growth, and distant metastasis (Figure 2).

Platelets become "accomplices" for tumor cells to escape immune surveillance

Tumors must first survive in the circulatory system to metastasize. Platelets also play an important role in immune and inflammatory reactions in addition to hemostasis and coagulation. We already know that tumor cells enter the blood to form platelet-tumor cell aggregate and that platelets prevent tumor cells from death induced by NK cells and TNF-α. Studies have confirmed that platelets promote the induction and differentiation of bone marrow cells by secreting CXCL5 and CXCL7 [92]. Furthermore, transforming growth factor-β (TGF-β) secreted by platelets and PGE2 in the microenvironment can also induce the differentiation of bone marrow-derived stem cells, including myeloid-derived suppressor cells, CD8 cytotoxic T cells, TH1, TH17, and T regulatory cells [75]. A large number of studies have indicated that the main effector of the immune escape of tumor cells is Treg, which is in contact with tumor antigens. Then, macrophages infiltrated by tumor cells secrete chemokines, such as CCL4, CCL11, CCL17, CCL20, and CCL22, and these chemokines can attract CCR3-, CCR4-, CCR6-, and CCR8-positive Treg [93,94]. Moreover, platelet transforming growth factor b (TGF-b) can promote the differentiation of neutrophils and macrophages into an immunosuppressive phenotype, and tumor cells recruit granulocytes to help tumor cells escape immune surveillance. These effects enable platelets to be an "accomplice" of tumor cells for their growth, invasion, and transfer (Fig. 3).

Extracellular vesicles of tumor cells activate platelets indirectly or directly

According to some reports, tissue factor (TF) and platelet microparticles (PMP) expressed in tumor cells can strengthen the procoagulant environment generated by the interaction of platelets and cancer cells, pro-

duce thrombin, activate platelets, form thromboembolism, block blood vessels while it increases endothelial permeability, and promotes tumor metastasis. Tumor-derived TF is associated with a variety of tumor-promoting responses, including primary growth, metastasis, angiogenesis, and tumor-related thrombosis [95–97], and the mechanism is related to TF-dependent thrombin. In certain cancer types, such as pancreatic cancer, there is a clear correlation between elevated circulation of TF-positive microbubble levels and the incidence of thrombosis [98,99]. Emerging studies have shown that exosomes derived from non-small cell lung cancer, glioma, and prostate cancer can directly interact with platelets [100,101], but the mechanisms of this interaction or possible functional changes in platelets remain unknown. Gomes et al. compared the extracellular vesicles produced by two types of breast cancer cell lines with different invasiveness and found that the number of TF vesicles in the high-invasive group was larger than that in the low-invasive group. Moreover, TF vesicles in the high-invasive group were also highly able to form thrombus through TF-dependent thrombin. Furthermore, after the plasma coagulation components were removed from washed platelets, the vesicles in the high-invasive group were found to directly act on platelets through P-selectin, independent of TF, and activate and aggregate platelets [102] (Figure 4).

Platelet-derived extracellular vesicles promote tumor angiogenesis

A large number of studies have shown that platelet-derived extra-cellular vesicles (P-EVs) are most abundant in human blood, accounting for more than 50% of the total amount of peripheral blood extracellular vesicles, and play a very important role in the development of tumors; thus it has become a hot topic in research [103]. Wolf initially named P-EVs as "platelet dust" [104], but this view was quickly changed. P-EVs are of two types: exosomes (diameter 40–100 nm) and microvesicles (diameter 100–1000 nm) [105], both attached to a series of surface receptors, including integrin IIbβ3 (also known as glycoprotein IIIb/iia (gpIIb/iia), gpibα-IX-V receptor complex, P-selectin, lysophosphatidic
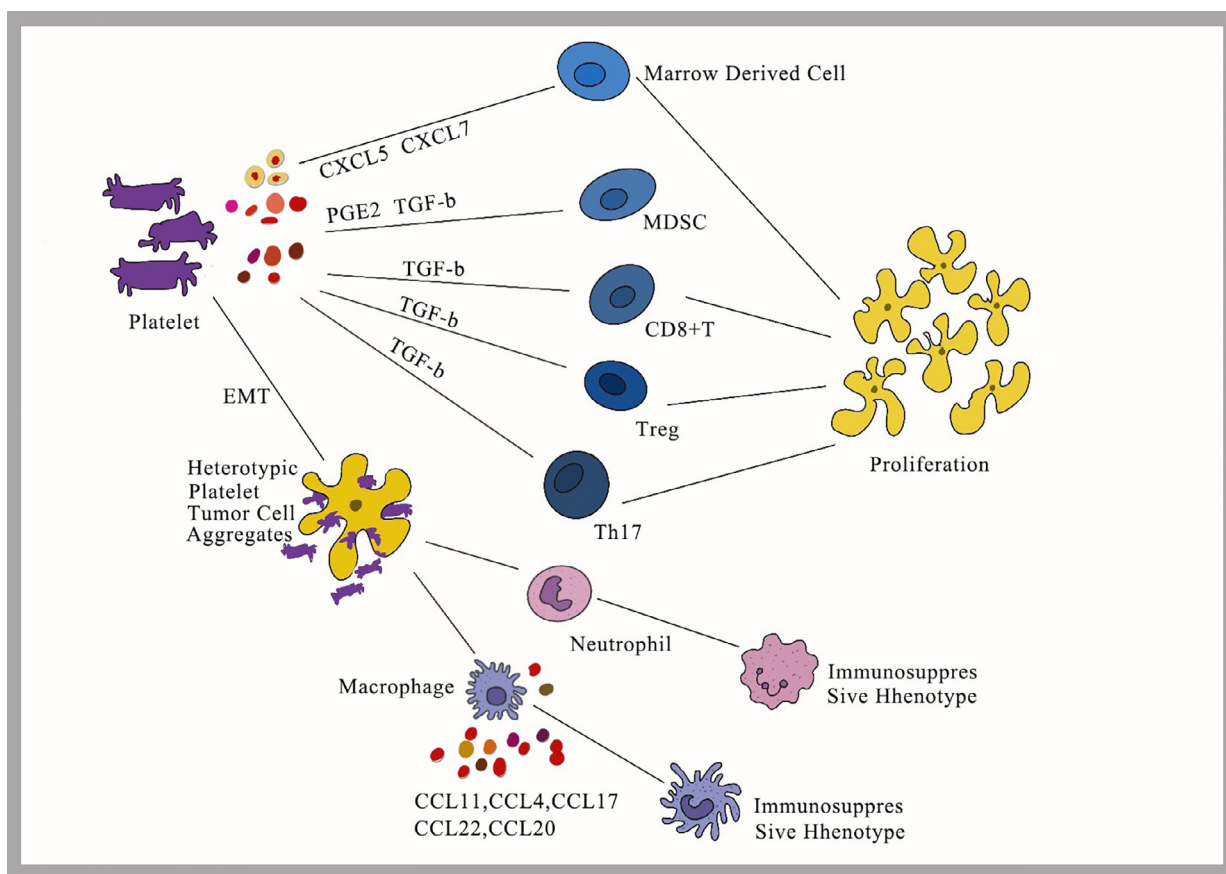
Fig. 3. Platelets help tumor cells escape from immune surveillance.
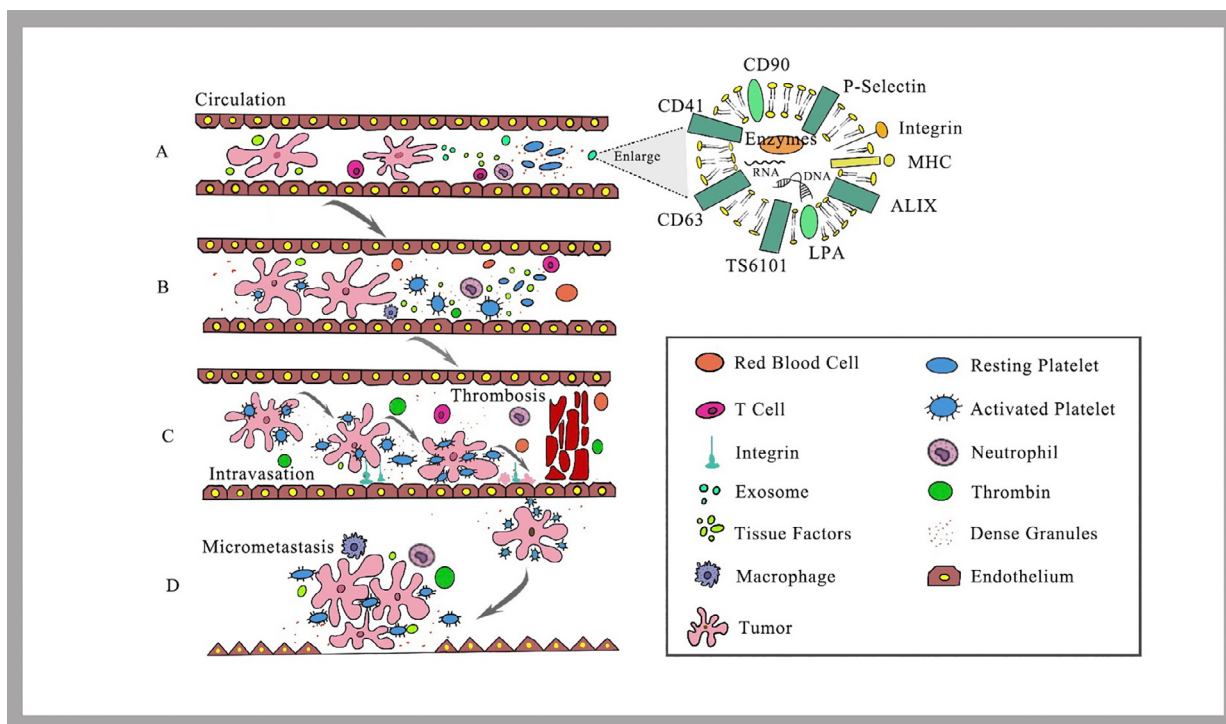
Fig. 4. Vesicles activate platelets to promote tumor cell metastasis and blood vessels. angiogenesis: A. Extracellular vesicles of tumor cells activate platelets indirectly or directly; B. Activated platelets further promote tumor cell growth and platelet-derived extracellular vesicles promote tumor angiogenesis; C. Heterotypic platelet tumor cell aggregates promote migration and spillover of cancer cells. TF and PMP expressed in tumor cells can strengthen the procoagulant environment generated by the interaction of platelets and cancer cells, produce thrombin, activate platelets, form thromboembolism, block blood vessels while they increase endothelial permeability; and D. Platelets promote tumorigenesis, growth, and distant metastasis.

Fig. 5. Signaling pathway of platelet-promoting tumor metastasis.
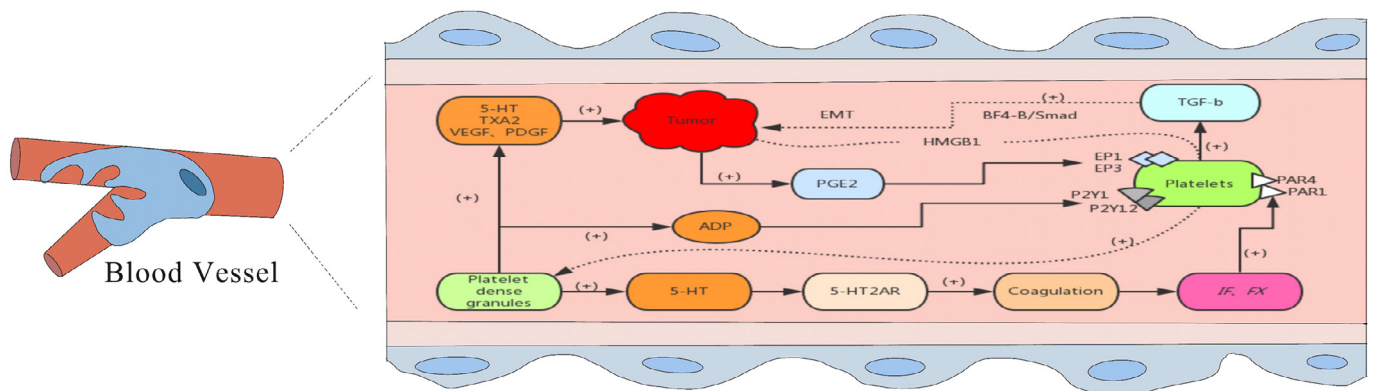
acid, and sphingosine 1-phosphate lipids as well as cytoplasm and secreted proteins [106, 107]. Specific markers such as CD41, CD9, CD63, TSG101, and ALIX are present in exosomes and can promote tissue regeneration by transporting proteins and RNA, thereby promoting angiogenesis, proliferation, anti-inflammatory, and anti-apoptotic effects [108–110]. Subsequent studies have shown that through the interaction between TGF-β and YAP, as well as phosphoinositide 3-kinase-Akt and mitogen-activated protein kinase (MAPK) -ERK signaling, P-EVs promote endothelial repair after vascular injury, thereby they promote tissue regeneration and cell migration [111,112]. Moreover, Janowska-Wieczorek et al. have found that P-EVs can also act on lung cancer cellular MAPK, produce more MMPs, and promote tumor cell proliferation and invasion [113]. P-EVs play an indispensable role in the induction of tumor metastasis, vascular reactivity changes, angiogenesis, and the activation of signaling pathways [114–116]. Nevertheless, the mechanism of P-EVs promoting tumor cell proliferation and invasion is still not very clear. Given the involvement of P-EVs in the occurrence and development of tumors, we believed that platelet transfusion in tumor patients could be new potential therapeutic targets for antitumor angiogenesis (Fig. 4).

Signaling pathway of platelet promoting tumor metastasis

Tumor metastasis is closely related to tissue invasion, blood inflow, intravascular phase, capillary extravasation, and distant growth of tumor cells, all of which are inseparable from the signal transmission between platelets and tumor cells. On the one hand, ADP released by platelet dense particles and tumor cells act on P2Y1 and P2Y12 receptors of platelets [117], and G protein-coupled receptor agonists and 5-hydroxytryptamine (5-HT) released by platelet dense particles promote migration and spillover of cancer cells. At the same time, the tumor cells act on PAR1 and PAR4 on the platelet under the mediation of thrombin produced by TFs VII and X, to jointly activate the platelets to produce a large amount of TGF-b, help to induce the conversion of tumor cells into the epithelial mesenchyme and finally promote metastasis [118,119]. Platelets can also promote tumor metastasis through the interaction of TLR4 with the ligand HMGB1 protein on tumor cells [120]. Moreover, platelets can prevent tumor cells from anoikis and also help tumor cells to successfully metastasize by activating YAP1 signal on tumor cells [121]. Additionally, EP1 and EP3 receptors on platelets are activated by PGE2 produced by cyclooxygenase 2 on tumor cells [122,123]. On the other hand, tumor cells can not only interact with platelet P-selectin through mucin, but also promote the growth of cancer cells through the interaction of the podoplanin with platelet C-type lectin-like receptor-2 (CLEC-2) [124–126]. Furthermore, the TXA2 receptor signal can promote tumor metastasis through the interaction of P-selectin-mediated tumor cells with platelets and endothelial cells [127]. The signal transduction pathway between platelets and tumor cells is essential in the process of platelet-promoting tumor metastasis (Fig. 5).

In summary, platelets play a key role in the development of tumors and have a "dual personality." On the one hand, they are "heroes" that stop bleeding and help repair damaged tissues of the human body. On the other hand, they also form blood clots and assist tumor cells to spread in the circulation, thus becoming "treason officials." The increase and activation of platelets can promote the growth and metastasis of tumors, which in turn promotes platelets to increase and be activated. In other words, platelets and tumor cells are closely related. TF and PMP expressed on tumor cells can strengthen the interaction between platelets and cancer cells. Moreover, tumor extracellular vesicles can indirectly and directly activate platelets, and also promote tumor angiogenesis. The intricate signaling pathways between platelets and tumor cells suggest that the receptors and signaling mechanisms on platelets are potential therapeutic targets for anti-tumor metastasis.

Conclusion

Platelets are closely related to tumors and have a specific target on certain cells, and emerging studies have found that there are a variety of proteins with different functions on the surface of the platelet membrane, such as immunomodulatory function, adhesion function, targeting, and a natural targeted affinity for certain cell types [26,128]. Therefore, there are studies to develop cell combination drug delivery (CCDD) that targets cancer cells in circulation or tissues to reduce the recurrence and metastasis of cancer. [129,130]. For instance, this technology could deliver programmed cell death protein 1 antibody, cut off its combination with programmed death-1 ligand 1 on cancer cells, and activate T cells to identify, attack, and kill tumor cells [131–133]. However, platelets used for CCDD are not easily stored for a long time. Moreover, Anne-Laure et al. have proposed the concept of "cottage platelets" (platelet bait), a platelet shell obtained after platelets are processed. Cottage platelets combine with tumor cells in the circulatory system to reduce the activation of platelets by tumor cells. In this way, it is difficult for tumor cells to escape from immune surveillance without the protection of platelets and thus their metastasis could be effectively inhibited. Furthermore, the patient's own platelets can be used to make "cottage platelets," and this cell therapy may also avoid dangerous immune reactions. Because of their ability to bind tumor cells, "cottage platelets" may have the potential to be transformed into a drug delivery vehicle to treat tumors [134]; however, such a potential is seldom studied, and the effective duration of "cottage platelets" in circulation also needs further study. The angiogenesis of tumor controls its growth and development, and platelets contribute to the angiogenesis of tumor [135]. Platelets store and release angiogenesis regulators, including VEGF, DGF, TGF-β, PF4, and P-selectin, among which are not only VEGF and basic fibroblast growth factor to promote angiogenesis but also anti-angiogenesis modulators (thrombin and PF4) [136,137]. Therefore, we believe that further elucidating the intracellular signal mechanism that controls the release

of platelet proangiogenic or anti-angiogenesis regulator particles can be used to formulate corresponding cancer treatment strategies. Nevertheless, these studies have laid the foundation for the immunotherapy of tumors, and indicate that platelets are a potential target for the treatment of tumors in the future.

Platelets in storage will be activated and they release cytokines. Platelet activation and degranulation may be more severe along with the process of storage [138,139]. Therefore, platelet transfusion likely promotes tumor growth and metastasis and harms the treatment and prognosis of cancer patients. Although the effects of platelet products stored for different times on cancer and the role of platelets in this process have yet to be determined, we suggest that platelets with shorter storage time may have better therapeutic effects. However, the indications of platelet transfusion should be strictly examined to minimize platelet transfusion for cancer patients. If transfusion is really needed, platelets should be treated with leukocyte reduction and irradiation to prevent immune response caused by leukocytes and transfusion-associated graft versus host disease caused by lymphocytes. In addition, the development of a new platelet maintenance solution to inhibit platelet activation is also a worthy topic of research. Given the role of platelets in tumor growth, invasion, and metastasis, it is necessary to study strategies that block platelets to promote tumorigenesis and development.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the PubMed repository. The processed data are available from the corresponding author upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Juan Wang: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Funding acquisition. **Pan Zhou:** Visualization, Investigation, Funding acquisition. **Yunwei Han:** Software, Project administration, Supervision. **Hongwei Zhang:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Funding

Acknowledgments

References

[1] D. Daniel, J. Crawford, Myelotoxicity from chemotherapy, Semin. Oncol. 33 (2006) 74–85 http://dx.doi.org/10.1053/j.seminoncol.2005.11.003.

[2] D. Weycker, M. Hatfield, A. Grossman, A. Hanau, A. Lonshteyn, A. Sharma, D. Chandler, Risk and consequences of chemotherapy-induced thrombocytopenia in US clinical practice, BMC Cancer 19 (2019) 151 http://dx.doi.org/10.1186/s12885-019-5354-5.

[3] Y. Wu, S. Aravind, G. Ranganathan, A. Martin, L. Nalysnyk, Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007, Clin. Ther. 31 Pt 2 (2009) 2416–2432 http://dx.doi.org/10.1016/j.clinthera.2009.11.020.

[4] T. Kuhne, W. Berchtold, L.A. Michaels, R. Wu, H. Donato, B. Espina, H. Tamary, F. Rodeghiero, M. Chitlur, J. Rischewski, P. Imbach, I.T.P.S.G. Intercontinental Cooperative, Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the intercontinental cooperative immune thrombocytopenia study group, Haematologica 96 (2011) 1831–1837 http://dx.doi.org/10.3324/haematol.2011.050799.

[5] G. Moulis, A. Palmaro, J.L. Montastruc, B. Godeau, M. Lapeyre-Mestre, L. Sailler, Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France, Blood 124 (2014) 3308–3315 http://dx.doi.org/10.1182/blood-2014-05-578336.

[6] D.M. Arnold, Bleeding complications in immune thrombocytopenia, Hematol. Am. Soc. Hematol. Educ. Program 2015 (2015) 237–242 http://dx.doi.org/10.1182/asheducation-2015.1.237.

[7] S.J. Stanworth, C.L. Hudson, L.J. Estcourt, R.J. Johnson, E.M. Wood, T.s. investigators, Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis, Haematologica 100 (2015) 740–747 http://dx.doi.org/10.3324/haematol.2014.118075.

[8] H. Schrezenmeier, E. Seifried, Buffy-coat-derived pooled platelet concentrates and apheresis platelet concentrates: which product type should be preferred? Vox Sang 99 (2010) 1–15 http://dx.doi.org/10.1111/j.1423-0410.2009.01295.x.

[9] J. McCullough, Overview of platelet transfusion, Semin. Hematol. 47 (2010) 235–242 http://dx.doi.org/10.1053/j.seminhematol.2010.04.001.

[10] B.R. Zihai Li, Alessandra Metelli, Anqi Li, Bill X. Wu, The role of platelets in tumor growth, metastasis, and immune evasion, Platelets (2019) 547–561, doi:10.1016/B978-0-12-813456-6.00030-8.

[11] C.N. Morrell, D.N. Pariser, Z.T. Hilt, D. Vega Ocasio, The platelet napoleon complex-small cells, but big immune regulatory functions, Ann Rev Immunol 37 (2019) 125–144 http://dx.doi.org/10.1146/annurev-immunol-042718-041607.

[12] L.S. Ribeiro, L. Migliari Branco, B.S. Franklin, Regulation of Innate Immune Responses by Platelets, Front Immunol. 10 (2019) 1320 http://dx.doi.org/10.3389/fimmu.2019.01320.

[13] C. Caram-Deelder, A.L. Kreuger, J. Jacobse, J.G. van der Bom, R.A. Middelburg, Effect of platelet storage time on platelet measurements: a systematic review and meta-analyses, Vox Sang 111 (2016) 374–382 http://dx.doi.org/10.1111/vox.12443.

[14] A.L. Kreuger, K. Rostgaard, R.A. Middelburg, J.H. Kerkhoffs, G. Edgren, C. Erikstrup, O.B. Pedersen, K. Titlestad, K.R. Nielsen, S.R. Ostrowski, M. Voldstedlund, J.G. van der Bom, H. Ullum, H. Hjalgrim, Storage time of platelet concentrates and risk of a positive blood culture: a nationwide cohort study, Transfusion 58 (2018) 16–24 http://dx.doi.org/10.1111/trf.14401.

[15] C. Saunders, G. Rowe, K. Wilkins, P. Collins, Impact of glucose and acetate on the characteristics of the platelet storage lesion in platelets suspended in additive solutions with minimal plasma, Vox Sang 105 (2013) 1–10 http://dx.doi.org/10.1111/vox.12013.

[16] F.M.A. van Hout, R.A. Middelburg, P.F. van der Meer, A. Pors, J.C. Wiersum-Osselton, M.R. Schipperus, J.L. Kerkhoffs, J.G. van der Bom, Effect of storage of platelet concentrates in PAS-B, PAS-C, or plasma on transfusion reactions, Transfusion 59 (2019) 3140–3145 http://dx.doi.org/10.1111/trf.15497.

[17] V. Henn, J.R. Slupsky, M. Grafe, I. Anagnostopoulos, R. Forster, G. Muller-Berghaus, R.A. Kroczek, CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells, Nature 391 (1998) 591–594 http://dx.doi.org/10.1038/35393.

[18] M.C. Rissoan, V. Soumelis, N. Kadowaki, G. Grouard, F. Briere, R. de Waal Malefyt, Y.J. Liu, Reciprocal control of T helper cell and dendritic cell differentiation, Science 283 (1999) 1183–1186 http://dx.doi.org/10.1126/science.283.5405.1183.

[19] S.P. Dineen, C.L. Roland, J.E. Toombs, M. Kelher, C.C. Silliman, R.A. Brekken, C.C. Barnett Jr., The acellular fraction of stored platelets promotes tumor cell invasion, J. Surg. Res. 153 (2009) 132–137 http://dx.doi.org/10.1016/j.jss.2008.04.013.

[20] N. Blumberg, J.M. Heal, J.M. Rowe, A randomized trial of washed red blood cell and platelet transfusions in adult acute leukemia [ISRCTN76536440], BMC Blood Disord 4 (2004) 6 http://dx.doi.org/10.1186/1471-2326-4-6.

[21] M.S. Cho, J. Bottsford-Miller, H.G. Vasquez, R. Stone, B. Zand, M.H. Kroll, A.K. Sood, V. Afshar-Kharghan, Platelets increase the proliferation of ovarian cancer cells, Blood 120 (2012) 4869–4872 http://dx.doi.org/10.1182/blood-2012-06-438598.

[22] H.A. Goubran, J. Stakiw, M. Radosevic, T. Burnouf, Platelets effects on tumor growth, Semin. Oncol. 41 (2014) 359–369 http://dx.doi.org/10.1053/j.seminoncol.2014.04.006.

[23] H.A. Goubran, T. Burnouf, M. Radosevic, M. El-Ekiaby, The platelet-cancer loop, Eur. J. Intern Med. 24 (2013) 393–400 http://dx.doi.org/10.1016/j.ejim.2013.01.017.

[24] A.T. Nurden, Platelets, inflammation and tissue regeneration, Thromb Haemost 105 (Suppl 1) (2011) S13–S33 http://dx.doi.org/10.1160/THS10-11-0720.

[25] R.J. Lin, V. Afshar-Kharghan, A.I. Schafer, Paraneoplastic thrombocytosis: the secrets of tumor self-promotion, Blood 124 (2014) 184–187 http://dx.doi.org/10.1182/blood-2014-03-562538.

[26] H.A. Goubran, J. Stakiw, M. Radosevic, T. Burnouf, Platelet-cancer interactions, Semin. Thromb Hemost 40 (2014) 296–305 http://dx.doi.org/10.1055/s-0034-1370767.

[27] H.C. Segal, C. Briggs, S. Kunka, A. Casbard, P. Harrison, S.J. Machin, M.F. Murphy, Accuracy of platelet counting haematology analysers in severe thrombocytopenia and potential impact on platelet transfusion, Br. J. Haematol. 128 (2005) 520–525 http://dx.doi.org/10.1111/j.1365-2141.2004.05352.x.

[28] C.A. Schiffer, K.C. Anderson, C.L. Bennett, S. Bernstein, L.S. Elting, M. Goldsmith, M. Goldstein, H. Hume, J.J. McCullough, R.E. McIntyre, B.L. Powell, J.M. Rainey,

S.D. Rowley, P. Rebulla, M.B. Troner, A.H. Wagnon, O. American Society of Clinical, Platelet transfusion for patients with cancer: clinical practice guidelines of the American society of clinical oncology, J. Clin. Oncol. 19 (2001) 1519–1538 http://dx.doi.org/10.1200/JCO.2001.19.5.1519.

[29] K. Adelborg, N.R. Kristensen, M. Norgaard, S. Bahmanyar, W. Ghanima, K. Kilpatrick, H. Frederiksen, C. Ekstrand, H.T. Sorensen, C.Fynbo Christiansen, Cardiovascular and bleeding outcomes in a population-based cohort of patients with chronic immune thrombocytopenia, J. Thromb Haemost 17 (2019) 912–924 http://dx.doi.org/10.1111/jth.14446.

[30] M.J. Ten Berg, P.M. van den Bemt, S. Shantakumar, D. Bennett, E.E. Voest, A. Huisman, W.W. van Solinge, T.C. Egberts, Thrombocytopenia in adult cancer patients receiving cytotoxic chemotherapy: results from a retrospective hospital-based cohort study, Drug Saf. 34 (2011) 1151–1160 http://dx.doi.org/10.2165/11594310-000000000-00000.

[31] F. Tas, I. Yildiz, L. Kilic, R. Ciftci, S. Keskin, F. Sen, Same chemotherapy regimen leads to different myelotoxicity in different malignancies: a comparison of chemotherapy-associated myelotoxicity in patients with advanced ovarian and non-small-cell lung cancer, Am. J. Ther. 23 (2016) e670–e679 http://dx.doi.org/10.1097/MJT.0b013e31828232b8.

[32] J. Jang, H.K. Kim, B.C. Cho, K.H. Lee, H.J. Yun, I.S. Woo, H.S. Song, H.M. Ryoo, C.H. Kim, D.S. Sun, J.W. Shin, Randomized phase II study comparing weekly docetaxel-cisplatin vs. gemcitabine-cisplatin in elderly or poor performance status patients with advanced non-small cell lung cancer, Cancer Chemother Pharmacol. 79 (2017) 873–880 http://dx.doi.org/10.1007/s00280-017-3289-6.

[33] D. Ma, J. Wang, X. Hao, Y. Wang, X. Hu, P. Xing, J. Li, Gemcitabine combined with cisplatin as adjuvant chemotherapy for non-small cell lung cancer: a retrospective analysis, Thorac Cancer 8 (2017) 482–488 http://dx.doi.org/10.1111/1759-7714.12472.

[34] D.H. Moore, J.A. Blessing, R.P. McQuellon, H.T. Thaler, D. Cella, J. Benda, D.S. Miller, G. Olt, S. King, J.F. Boggess, T.F. Rocereto, Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study, J. Clin. Oncol. 22 (2004) 3113–3119 http://dx.doi.org/10.1200/JCO.2004.04.170.

[35] S. Pignata, G. Scambia, G. Ferrandina, A. Savarese, R. Sorio, E. Breda, V. Gebbia, P. Musso, L. Frigerio, P. Del Medico, A.V. Lombardi, A. Febbraro, P. Scollo, A. Ferro, S. Tamberi, A. Brandes, A. Ravaioli, M.R. Valerio, E. Aitini, D. Natale, L. Scaltriti, S. Greggi, C. Pisano, D. Lorusso, V. Salutari, F. Legge, M. Di Maio, A. Morabito, C. Gallo, F. Perrone, Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial, J. Clin. Oncol. 29 (2011) 3628–3635 http://dx.doi.org/10.1200/JCO.2010.33.8566.

[36] L. Wang, Y.L. Wu, S. Lu, L. Deng, M.J. Ahn, F.H. Hsu, N. Iscoe, A. Hossain, T. Puri, P. Zhang, M. Orlando, An East Asian subgroup analysis of PROCLAIM, a phase III trial of pemetrexed and cisplatin or etoposide and cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small cell lung cancer, Asia Pac J. Clin. Oncol. 12 (2016) 380–387 http://dx.doi.org/10.1111/ajco.12513.

[37] Y. Khan, Y. Lyou, M. El-Masry, S. O'Brien, Reassessing the role of chemoimmunotherapy in chronic lymphocytic leukemia, Expert Rev. Hematol. 13 (2020) 31–38 http://dx.doi.org/10.1080/17474086.2020.1697226.

[38] G.A. Soff, Y. Miao, G. Bendheim, J. Batista, J.V. Mones, R. Parameswaran, C.R. Wilkins, S.M. Devlin, G.K. Abou-Alfa, A. Cercek, N.E. Kemeny, D.M. Sarasohn, S. Mantha, Romiplostim treatment of chemotherapy-induced thrombocytopenia, J Clin Oncol 37 (2019) 2892–2898 http://dx.doi.org/10.1200/JCO.18.01931.

[39] A. Zufferey, R. Kapur, J.W. Semple, Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP), J Clin Med 6 (2017) http://dx.doi.org/10.3390/jcm6020016.

[40] RSM Wong, MN Saleh, A Khelif, et al., Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study, Blood 130 (23) (2017) 2527–2536 Blood, 131 (2018) 709 http://dx.doi.org/10.1182/blood-2017-12-823252 .

[41] F. Rodeghiero, R. Stasi, T. Gernsheimer, M. Michel, D. Provan, D.M. Arnold, J.B. Bussel, D.B. Cines, B.H. Chong, N. Cooper, B. Godeau, K. Lechner, M.G. Mazzucconi, R. McMillan, M.A. Sanz, P. Imbach, V. Blanchette, T. Kuhne, M. Ruggeri, J.N. George, Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group, Blood 113 (2009) 2386–2393 http://dx.doi.org/10.1182/blood-2008-07-162503.

[42] G. Vial, E. Riviere, A.A. Raymond, C. James, S. Di-Tommaso, N. Dugot-Senant, J.W. Dupuy, M. Yacoub, M. Parrens, F. Saltel, J.F. Viallard, Antigenic mimicry in paraneoplastic immune thrombocytopenia, Front. Immunol. 10 (2019) 523 http://dx.doi.org/10.3389/fimmu.2019.00523.

[43] Q. Zeng, L. Zhu, L. Tao, J. Bao, M. Yang, E.K. Simpson, C. Li, D.E. van der Wal, P. Chen, C.M. Spring, M. Wang, L. Zhang, C. Ruan, M. Hou, R. Xia, H. Ni, Relative efficacy of steroid therapy in immune thrombocytopenia mediated by antiplatelet GPIIbIIIa versus GPIbalpha antibodies, Am. J. Hematol. 87 (2012) 206–208 http://dx.doi.org/10.1002/ajh.22211.

[44] S. Shrestha, I. Nazy, J.W. Smith, J.G. Kelton, D.M. Arnold, Platelet autoantibodies in the bone marrow of patients with immune thrombocytopenia, Blood Adv. 4 (2020) 2962–2966 http://dx.doi.org/10.1182/bloodadvances.2020001846.

[45] M.T. Krauth, J. Puthenparambil, K. Lechner, Paraneoplastic autoimmune thrombocytopenia in solid tumors, Crit Rev Oncol Hematol 81 (2012) 75–81 http://dx.doi.org/10.1016/j.critrevonc.2011.02.004.

[46] D.V. Pachito, C.O.C. Latorraca, R. Riera, Efficacy of platelet-rich plasma for nontransfusion use: overview of systematic reviews, Int. J. Clin. Pract. 73 (2019) e13402 http://dx.doi.org/10.1111/ijcp.13402.

[47] E. Lefrancais, G. Ortiz-Munoz, A. Caudrillier, B. Mallavia, F. Liu, D.M. Sayah, E.E. Thornton, M.B. Headley, T. David, S.R. Coughlin, M.F. Krummel, A.D. Leavitt, E. Passegue, M.R. Looney, The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors, Nature 544 (2017) 105–109 http://dx.doi.org/10.1038/nature21706.

[48] C.A. Schiffer, K. Bohlke, M. Delaney, H. Hume, A.J. Magdalinski, J.J. McCullough, J.L. Omel, J.M. Rainey, P. Rebulla, S.D. Rowley, M.B. Troner, K.C. Anderson, Platelet Transfusion for patients with cancer: American Society of clinical oncology clinical practice guideline update, J Clin Oncol 36 (2018) 283–299 http://dx.doi.org/10.1200/JCO.2017.76.1734.

[49] H. Wandt, K. Schafer-Eckart, A. Greinacher, Platelet transfusion in hematology, oncology and surgery, Dtsch Arztebl Int 111 (2014) 809–815 http://dx.doi.org/10.3238/arztebl.2014.0809.

[50] H. Wandt, K. Schaefer-Eckart, K. Wendelin, B. Pilz, M. Wilhelm, M. Thalheimer, U. Mahlknecht, A. Ho, M. Schaich, M. Kramer, M. Kaufmann, L. Leimer, R. Schwerdtfeger, R. Conradi, G. Dolken, A. Klenner, M. Hanel, R. Herbst, C. Junghanss, G. Ehninger, L. Study Alliance, Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study, Lancet 380 (2012) 1309–1316 http://dx.doi.org/10.1016/S0140-6736(12)60689-8.

[51] S.J. Slichter, R.M. Kaufman, S.F. Assmann, J. McCullough, D.J. Triulzi, R.G. Strauss, T.B. Gernsheimer, P.M. Ness, M.E. Brecher, C.D. Josephson, B.A. Konkle, R.D. Woodson, T.L. Ortel, C.D. Hillyer, D.L. Skerrett, K.R. McCrae, S.R. Sloan, L. Uhl, J.N. George, V.M. Aquino, C.S. Manno, J.G. McFarland, J.R. Hess, C. Leissinger, S. Granger, Dose of prophylactic platelet transfusions and prevention of hemorrhage, N Eng. J. Med. 362 (2010) 600–613 http://dx.doi.org/10.1056/NEJMoa0904084.

[52] R.M. Fasano, C.D. Josephson, Platelet transfusion goals in oncology patients, Hematol. Am. Soc. Hematol. Educ. Program 2015 (2015) 462–470 http://dx.doi.org/10.1182/asheducation-2015.1.462.

[53] A. Tinmouth, I.F. Tannock, M. Crump, G. Tomlinson, J. Brandwein, M. Minden, D. Sutton, Low-dose prophylactic platelet transfusions in recipients of an autologous peripheral blood progenitor cell transplant and patients with acute leukemia: a randomized controlled trial with a sequential Bayesian design, Transfusion 44 (2004) 1711–1719 http://dx.doi.org/10.1111/j.0041-1132.2004.04118.x.

[54] N.M. Heddle, R.J. Cook, A. Tinmouth, C.T. Kouroukis, T. Hervig, E. Klapper, J.M. Brandwein, Z.M. Szczepiorkowski, J.P. AuBuchon, R.L. Barty, K.A. Lee, S.T.S.I.o.t.B. Collaborative, A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia, Blood 113 (2009) 1564–1573 http://dx.doi.org/10.1182/blood-2008-09-178236.

[55] M.C. Katus, Z.M. Szczepiorkowski, L.J. Dumont, N.M. Dunbar, Safety of platelet transfusion: past, present and future, Vox Sang 107 (2014) 103–113 http://dx.doi.org/10.1111/vox.12146.

[56] C. Durante, F. Agostini, L. Abbruzzese, R.T. Toffola, S. Zanolin, C. Suine, M. Mazzucato, Growth factor release from platelet concentrates: analytic quantification and characterization for clinical applications, Vox Sang 105 (2013) 129–136 http://dx.doi.org/10.1111/vox.12039.

[57] J. Sahler, S. Spinelli, R. Phipps, N. Blumberg, CD40 ligand (CD154) involvement in platelet transfusion reactions, Transfus Clin Biol 19 (2012) 98–103 http://dx.doi.org/10.1016/j.tracli.2012.02.003.

[58] C.S. Lasta, N. Hlavac, N.A. Marcondes, M.L. Dalmolin, S.R. Terra, L. de Almeida Lacerda, G.A.M. Faulhaber, F.H.D. Gonzalez, Quality control in veterinary blood banks: evaluation of canine platelet concentrates stored for five days, BMC Vet Res 16 (2020) 25 http://dx.doi.org/10.1186/s12917-020-2254-5.

[59] T. Burnouf, H.A. Goubran, M.L. Chou, D. Devos, M. Radosevic, Platelet microparticles: detection and assessment of their paradoxical functional roles in disease and regenerative medicine, Blood Rev 28 (2014) 155–166 http://dx.doi.org/10.1016/j.blre.2014.04.002.

[60] H. Goubran, W. Sabry, R. Kotb, J. Seghatchian, T. Burnouf, Platelet microparticles and cancer: an intimate cross-talk, Transfus Apher Sci 53 (2015) 168–172 http://dx.doi.org/10.1016/j.transci.2015.10.014.

[61] B.A. O'Connell, E.J. Lee, K. Rothko, M.A. Hussein, C.A. Schiffer, Selection of histocompatible apheresis platelet donors by cross-matching random donor platelet concentrates, Blood 79 (1992) 527–531.

[62] T. Nagasawa, B.K. Kim, M.G. Baldini, Temporary suppression of circulating antiplatelet alloantibodies by the massive infusion of fresh, stored, or lyophilized platelets, Transfusion 18 (1978) 429–435 http://dx.doi.org/10.1046/j.1537-2995.1978.18478251236.x.

[63] C. Gleeson, D. Spencer, Blood transfusion and its benefits in palliative care, Palliat Med. 9 (1995) 307–313 http://dx.doi.org/10.1177/026921639500900405.

[64] S. Eisenberg, Refractory response to platelet transfusion therapy, J. Infus. Nurs. 33 (2010) 89–97 http://dx.doi.org/10.1097/NAN.0b013e3181cfd392.

[65] J. Chubak, E.P. Whitlock, S.B. Williams, A. Kamineni, B.U. Burda, D.S. Buist, M.L. Anderson, Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the US preventive services task force, Ann. Intern Med. 164 (2016) 814–825 http://dx.doi.org/10.7326/M15-2117.

[66] A.A. Khorana, G.C. Connolly, Assessing risk of venous thromboembolism in the patient with cancer, J. Clin. Oncol. 27 (2009) 4839–4847 http://dx.doi.org/10.1200/JCO.2009.22.3271.

[67] S. Karpatkin, E. Pearlstein, Role of platelets in tumor cell metastases, Ann. Intern Med. 95 (1981) 636–641 http://dx.doi.org/10.7326/0003-4819-95-5-636.

[68] S. Asghar, F. Parvaiz, S. Manzoor, Multifaceted role of cancer educated platelets in survival of cancer cells, Thromb Res. 177 (2019) 42–50 http://dx.doi.org/10.1016/j.thromres.2019.02.026.

[69] G. Hudes, S.T. Tagawa, Y.E. Whang, M. Qi, X. Qin, T.A. Puchalski, M. Reddy,

M. Cornfeld, M. Eisenberger, A phase 1 study of a chimeric monoclonal antibody against interleukin-6, siltuximab, combined with docetaxel in patients with metastatic castration-resistant prostate cancer, Invest. New Drugs 31 (2013) 669–676 http://dx.doi.org/10.1007/s10637-012-9857-z.

[70] Y. Guo, F. Xu, T. Lu, Z. Duan, Z. Zhang, Interleukin-6 signaling pathway in targeted therapy for cancer, Cancer Treat. Rev. 38 (2012) 904–910 http://dx.doi.org/10.1016/j.ctrv.2012.04.007.

[71] M.C. Cheung, L.K. Hicks, J. Pendergrast, Thrombocytosis, N. Eng. J. Med. 350 (2004) 2524–2525 author reply 2524-2525 http://dx.doi.org/10.1056/NEJM200406103502420 .

[72] D. Buergy, F. Wenz, C. Groden, M.A. Brockmann, Tumor-platelet interaction in solid tumors, Int J Cancer 130 (2012) 2747–2760 http://dx.doi.org/10.1002/ijc.27441.

[73] M.B. Wire, X. Li, J. Zhang, W. Sallas, V. Aslanis, T. Ouatas, Modeling and simulation support eltrombopag dosing in pediatric patients with immune thrombocytopenia, Clin Pharmacol Ther 104 (2018) 1199–1207 http://dx.doi.org/10.1002/cpt.1066.

[74] J.F. Rossi, S. Negrier, N.D. James, I. Kocak, R. Hawkins, H. Davis, U. Prabhakar, X. Qin, P. Mulders, B. Berns, A phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer, Br J Cancer 103 (2010) 1154–1162 http://dx.doi.org/10.1038/sj.bjc.6605872.

[75] M. Haemmerle, R.L. Stone, D.G. Menter, V. Afshar-Kharghan, A.K. Sood, The platelet lifeline to cancer: challenges and opportunities, Cancer Cell 33 (2018) 965–983 http://dx.doi.org/10.1016/j.ccell.2018.03.002.

[76] J. Coward, H. Kulbe, P. Chakravarty, D. Leader, V. Vassileva, D.A. Leinster, R. Thompson, T. Schioppa, J. Nemeth, J. Vermeulen, N. Singh, N. Avril, J. Cummings, E. Rexhepaj, K. Jirstrom, W.M. Gallagher, D.J. Brennan, I.A. McNeish, F.R. Balkwill, Interleukin-6 as a therapeutic target in human ovarian cancer, Clin. Cancer Res. 17 (2011) 6083–6096 http://dx.doi.org/10.1158/1078-0432.CCR-11-0945.

[77] Y. Li, L.Y. Miao, Y.L. Xiao, H.R. Cai, D.P. Zhang, Elevated platelets enhance cancer cell migration, promote hematogenous metastasis and associate with a poor prognosis in advanced non-small cell lung cancer cases, Asian Pac J. Cancer Prev. 15 (2014) 139–143 http://dx.doi.org/10.7314/apjcp.2014.15.1.139.

[78] J. Liu, M.E. Fitzgerald, M.C. Berndt, C.W. Jackson, T.K. Gartner, Bruton tyrosine kinase is essential for botrocetin/VWF-induced signaling and GPIb-dependent thrombus formation in vivo, Blood 108 (2006) 2596–2603 http://dx.doi.org/10.1182/blood-2006-01-011817.

[79] K. Egan, D. Crowley, P. Smyth, S. O'Toole, C. Spillane, C. Martin, M. Gallagher, A. Canney, L. Norris, N. Conlon, L. McEvoy, B. Ffrench, B. Stordal, H. Keegan, S. Finn, V. McEneaney, A. Laios, J. Ducree, E. Dunne, L. Smith, M. Berndt, D. Kenny, J. O'Leary, Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells, PLoS One 6 (2011) e26125 http://dx.doi.org/10.1371/journal.pone.0026125.

[80] A. Mitrugno, D. Williams, S.W. Kerrigan, N. Moran, A novel and essential role for FcgammaRIIa in cancer cell-induced platelet activation, Blood 123 (2014) 249–260 http://dx.doi.org/10.1182/blood-2013-03-492447.

[81] J.E. Italiano Jr., J.L. Richardson, S. Patel-Hett, E. Battinelli, A. Zaslavsky, S. Short, S. Ryeom, J. Folkman, G.L. Klement, Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet alpha granules and differentially released, Blood 111 (2008) 1227–1233 http://dx.doi.org/10.1182/blood-2007-09-113837.

[82] G.M. Gersuk, B. Westermark, A.J. Mohabeer, P.M. Challita, S. Pattamakom, P.K. Pattengale, Inhibition of human natural killer cell activity by platelet-derived growth factor (PDGF). III. Membrane binding studies and differential biological effect of recombinant PDGF isoforms, Scand J. Immunol. 33 (1991) 521–532 http://dx.doi.org/10.1111/j.1365-3083.1991.tb02522.x.

[83] E.M. Battinelli, B.A. Markens, R.A. Kulenthirarajan, K.R. Machlus, R. Flaumenhaft, J.E. Italiano Jr., Anticoagulation inhibits tumor cell-mediated release of platelet angiogenic proteins and diminishes platelet angiogenic response, Blood 123 (2014) 101–112 http://dx.doi.org/10.1182/blood-2013-02-485011.

[84] D. Schumacher, B. Strilic, K.K. Sivaraj, N. Wettschureck, S. Offermanns, Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor, Cancer Cell 24 (2013) 130–137 http://dx.doi.org/10.1016/j.ccr.2013.05.008.

[85] D.Y. Heng, W. Xie, M.M. Regan, M.A. Warren, A.R. Golshayan, C. Sahi, B.J. Eigl, J.D. Ruether, T. Cheng, S. North, P. Venner, J.J. Knox, K.N. Chi, C. Kollmannsberger, D.F. McDermott, W.K. Oh, M.B. Atkins, R.M. Bukowski, B.I. Rini, T.K. Choueiri, Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study, J. Clin. Oncol. 27 (2009) 5794–5799 http://dx.doi.org/10.1200/JCO.2008.21.4809.

[86] K.A. Kim, W.G. Song, H.M. Lee, H.J. Joo, J.Y. Park, Effect of P2Y1 and P2Y12 genetic polymorphisms on the ADP-induced platelet aggregation in a Korean population, Thromb Res. 132 (2013) 221–226 http://dx.doi.org/10.1016/j.thromres.2013.06.020.

[87] A.J. Gareau, C. Brien, S. Gebremeskel, R.S. Liwski, B. Johnston, M. Bezuhly, Ticagrelor inhibits platelet-tumor cell interactions and metastasis in human and murine breast cancer, Clin. Exp. Metastasis 35 (2018) 25–35 http://dx.doi.org/10.1007/s10585-018-9874-1.

[88] M. Labelle, S. Begum, R.O. Hynes, Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis, Cancer Cell 20 (2011) 576–590 http://dx.doi.org/10.1016/j.ccr.2011.09.009.

[89] M. Haemmerle, J. Bottsford-Miller, S. Pradeep, M.L. Taylor, H.J. Choi, J.M. Hansen, H.J. Dalton, R.L. Stone, M.S. Cho, A.M. Nick, A.S. Nagaraja, T. Gutschner, K.M. Gharpure, L.S. Mangala, R. Rupaimoole, H.D. Han, B. Zand, G.N. Armaiz-Pena, S.Y. Wu, C.V. Pecot, A.R. Burns, G. Lopez-Berestein, V. Afshar-Kharghan,

[90] A.K. Sood, FAK regulates platelet extravasation and tumor growth after antiangiogenic therapy withdrawal, J. Clin. Invest. 126 (2016) 1885–1896 http://dx.doi.org/10.1172/JCI85086.

[90] L. Borsig, R. Wong, R.O. Hynes, N.M. Varki, A. Varki, Synergistic effects of L- and P-selectin in facilitating tumor metastasis can involve non-mucin ligands and implicate leukocytes as enhancers of metastasis, Proc. Natl. Acad. Sci. USA 99 (2002) 2193–2198 http://dx.doi.org/10.1073/pnas.261704098.

[91] A.K. Azab, P. Quang, F. Azab, C. Pitsillides, B. Thompson, T. Chonghaile, J.T. Patton, P. Maiso, V. Monrose, A. Sacco, H.T. Ngo, L.M. Flores, C.P. Lin, J.L. Magnani, A.L. Kung, R. Carrasco, A.M. Roccaro, I.M. Ghobrial, P-selectin glycoprotein ligand regulates the interaction of multiple myeloma cells with the bone marrow microenvironment, Blood 119 (2012) 1468–1478 http://dx.doi.org/10.1182/blood-2011-07-368050.

[92] K. Rajarathnam, M. Schnoor, R.M. Richardson, S. Rajagopal, How do chemokines navigate neutrophils to the target site: dissecting the structural mechanisms and signaling pathways, Cell Signal 54 (2019) 69–80 http://dx.doi.org/10.1016/j.cellsig.2018.11.004.

[93] D. Mrizak, N. Martin, C. Barjon, A.S. Jimenez-Pailhes, R. Mustapha, T. Niki, J. Guigay, V. Pancre, Y. de Launoit, P. Busson, O. Morales, N. Delhem, Effect of nasopharyngeal carcinoma-derived exosomes on human regulatory T cells, J. Natl. Cancer Inst. 107 (2015) 363 http://dx.doi.org/10.1093/jnci/dju363.

[94] A.W. Mailloux, M.R. Young, Regulatory T-cell trafficking: from thymic development to tumor-induced immune suppression, Crit. Rev. Immunol. 30 (2010) 435–447 http://dx.doi.org/10.1615/critrevimmunol.v30.i5.30.

[95] J. Zhang, X. Song. C. Li, Y. Tian, Expression and clinical significance of SLP-2 in ovarian tumors, Oncol. Lett. 17 (2019) 4626–4632 http://dx.doi.org/10.3892/ol.2019.10116.

[96] W. Ruf, J. Disse, T.C. Carneiro-Lobo, N. Yokota, F. Schaffner, Tissue factor and cell signalling in cancer progression and thrombosis, J. Thromb Haemost 9 (Suppl 1) (2011) 306–315 http://dx.doi.org/10.1111/j.1538-7836.2011.04318.x.

[97] L.G. Lima, R.Q. Monteiro, Activation of blood coagulation in cancer: implications for tumour progression, Biosci Rep 33 (2013) http://dx.doi.org/10.1042/BSR20130057.

[98] J.I. Zwicker, H.A. Liebman, D. Neuberg, R. Lacroix, K.A. Bauer, B.C. Furie, B. Furie, Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy, Clin. Cancer Res. 15 (2009) 6830–6840 http://dx.doi.org/10.1158/1078-0432.CCR-09-0371.

[99] A.A. Khorana, C.W. Francis, K.E. Menzies, J.G. Wang, O. Hyrien, J. Hathcock, N. Mackman, M.B. Taubman, Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer, J. Thromb Haemost 6 (2008) 1983–1985 http://dx.doi.org/10.1111/j.1538-7836.2008.03156.x.

[100] R.J. Nilsson, N. Karachaliou, J. Berenguer, A. Gimenez-Capitan, P. Schellen, C. Teixido, J. Tannous, J.L. Kuiper, E. Drees, M. Grabowska, M. van Keulen, D.A. Heideman, E. Thunnissen, A.M. Dingemans, S. Viteri, B.A. Tannous, A. Drozdowskyj, R. Rosell, E.F. Smit, T. Wurdinger, Rearranged EML4-ALK fusion transcripts sequester in circulating blood platelets and enable blood-based crizotinib response monitoring in non-small-cell lung cancer, Oncotarget 7 (2016) 1066–1075 http://dx.doi.org/10.18632/oncotarget.6279.

[101] R.J. Nilsson, L. Balaj, E. Hulleman, S. van Rijn, D.M. Pegtel, M. Walraven, A. Widmark, W.R. Gerritsen, H.M. Verheul, W.P. Vandertop, D.P. Noske, J. Skog, T. Wurdinger, Blood platelets contain tumor-derived RNA biomarkers, Blood 118 (2011) 3680–3683 http://dx.doi.org/10.1182/blood-2011-03-344408.

[102] F.G. Gomes, V. Sandim, V.H. Almeida, A.M.R. Rondon, B.B. Succar, E.D. Hottz, A.C. Leal, B.R.F. Vercoza, J.C.F. Rodrigues, P.T. Bozza, R.B. Zingali, R.Q. Monteiro, Breast-cancer extracellular vesicles induce platelet activation and aggregation by tissue factor-independent and -dependent mechanisms, Thromb Res. 159 (2017) 24–32 http://dx.doi.org/10.1016/j.thromres.2017.09.019.

[103] R. Flaumenhaft, A.T. Mairuhu, J.E. Italiano, Platelet- and megakaryocyte-derived microparticles, Semin Thromb Hemost 36 (2010) 881–887 http://dx.doi.org/10.1055/s-0030-1267042.

[104] P. Wolf, The nature and significance of platelet products in human plasma, Br J. Haematol. 13 (1967) 269–288 http://dx.doi.org/10.1111/j.1365-2141.1967.tb08741.x.

[105] S.M. Schoenwaelder, Y. Yuan, E.C. Josefsson, M.J. White, Y. Yao, K.D. Mason, L.A. O'Reilly, K.J. Henley, A. Ono, S. Hsiao, A. Willcox, A.W. Roberts, D.C. Huang, H.H. Salem, B.T. Kile, S.P. Jackson, Two distinct pathways regulate platelet phosphatidylserine exposure and procoagulant function, Blood 114 (2009) 663–666 http://dx.doi.org/10.1182/blood-2009-01-200345.

[106] A.S. Lonsdorf, B.F. Kramer, M. Fahrleitner, T. Schonberger, S. Gnerlich, S. Ring, S. Gehring, S.W. Schneider, M.J. Kruhlak, S.G. Meuth, B. Nieswandt, M. Gawaz, A.H. Enk, H.F. Langer, Engagement of alphaIIbbeta3 (GPIIb/IIIa) with alphanu-beta3 integrin mediates interaction of melanoma cells with platelets: a connection to hematogenous metastasis, J. Biol. Chem. 287 (2012) 2168–2178 http://dx.doi.org/10.1074/jbc.M111.269811.

[107] L.J. Gay, B. Felding-Habermann, Contribution of platelets to tumour metastasis, Nat. Rev. Cancer 11 (2011) 123–134 http://dx.doi.org/10.1038/nrc3004.

[108] P.M. van der Zee, E. Biro, Y. Ko, R.J. de Winter, C.E. Hack, A. Sturk, R. Nieuwland, P-selectin- and CD63-exposing platelet microparticles reflect platelet activation in peripheral arterial disease and myocardial infarction, Clin. Chem. 52 (2006) 657–664 http://dx.doi.org/10.1373/clinchem.2005.057414.

[109] K. Denzer, M. van Eijk, M.J. Kleijmeer, E. Jakobson, C. de Groot, H.J. Geuze, Follicular dendritic cells carry MHC class II-expressing microvesicles at their surface, J. Immunol. 165 (2000) 1259–1265 http://dx.doi.org/10.4049/jimmunol.165.3.1259.

[110] H. Liang, X. Yan, Y. Pan, Y. Wang, N. Wang, L. Li, Y. Liu, X. Chen, C.Y. Zhang, H. Gu, K. Zen, MicroRNA-223 delivered by platelet-derived microvesicles promotes

lung cancer cell invasion via targeting tumor suppressor EPB41L3, Mol. Cancer 14 (2015) 58 http://dx.doi.org/10.1186/s12943-015-0327-z.

[111] S.C. Guo, S.C. Tao, W.J. Yin, X. Qi, T. Yuan, C.Q. Zhang, Exosomes derived from platelet-rich plasma promote the re-epithelization of chronic cutaneous wounds via activation of YAP in a diabetic rat model, Theranostics 7 (2017) 81–96 http://dx.doi.org/10.7150/thno.16803.

[112] M. Baj-Krzyworzeka, M. Majka, D. Pratico, J. Ratajczak, G. Vilaire, J. Kijowski, R. Reca, A. Janowska-Wieczorek, M.Z. Ratajczak, Platelet-derived microparticles stimulate proliferation, survival, adhesion, and chemotaxis of hematopoietic cells, Exp Hematol. 30 (2002) 450–459 http://dx.doi.org/10.1016/s0301-472x(02)00791-9.

[113] A. Janowska-Wieczorek, M. Wysoczynski, J. Kijowski, L. Marquez-Curtis, B. Machalinski, J. Ratajczak, M.Z. Ratajczak, Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer, Int. J. Cancer 113 (2005) 752–760 http://dx.doi.org/10.1002/ijc.20657.

[114] S.C. Tao, S.C. Guo, C.Q. Zhang, Platelet-derived extracellular vesicles: an emerging therapeutic approach, Int. J. Biol. Sci. 13 (2017) 828–834 http://dx.doi.org/10.7150/ijbs.19776.

[115] H.A. Goubran, T. Burnouf, J. Stakiw, J. Seghatchian, Platelet microparticle: a sensitive physiological "fine tuning" balancing factor in health and disease, Transfus Apher Sci. 52 (2015) 12–18 http://dx.doi.org/10.1016/j.transci.2014.12.015.

[116] T. Burnouf, M.L. Chou, H. Goubran, F. Cognasse, O. Garraud, J. Seghatchian, An overview of the role of microparticles/microvesicles in blood components: are they clinically beneficial or harmful? Transfus Apher Sci. 53 (2015) 137–145 http://dx.doi.org/10.1016/j.transci.2015.10.010.

[117] M. Aslam, D. Sedding, A. Koshty, S. Santoso, R. Schulz, C. Hamm, D. Gunduz, Nucleoside triphosphates inhibit ADP, collagen, and epinephrine-induced platelet aggregation: role of P2Y(1) and P2Y(1)(2) receptors, Thromb Res. 132 (2013) 548–557 http://dx.doi.org/10.1016/j.thromres.2013.08.021.

[118] Y.C. Lin, Y.C. Ko, S.C. Hung, Y.T. Lin, J.H. Lee, J.Y. Tsai, P.H. Kung, M.C. Tsai, Y.F. Chen, C.C. Wu, Selective inhibition of PAR4 (protease-activated receptor 4)-mediated platelet activation by a synthetic nonanticoagulant heparin analog, Arterioscler Thromb Vasc Biol 39 (2019) 694–703 http://dx.doi.org/10.1161/ATVBAHA.118.311758.

[119] L. Jiang, Y. Luan, X. Miao, C. Sun, K. Li, Z. Huang, D. Xu, M. Zhang, F. Kong, N. Li, Platelet releasate promotes breast cancer growth and angiogenesis via VEGF-integrin cooperative signalling, Br. J. Cancer 117 (2017) 695–703 http://dx.doi.org/10.1038/bjc.2017.214.

[120] L.X. Yu, L. Yan, W. Yang, F.Q. Wu, Y. Ling, S.Z. Chen, L. Tang, Y.X. Tan, D. Cao, M.C. Wu, H.X. Yan, H.Y. Wang, Platelets promote tumour metastasis via interaction between TLR4 and tumour cell-released high-mobility group box1 protein, Nat. Commun. 5 (2014) 5256 http://dx.doi.org/10.1038/ncomms6256.

[121] M. Haemmerle, M.L. Taylor, T. Gutschner, S. Pradeep, M.S. Cho, J. Sheng, Y.M. Lyons, A.S. Nagaraja, R.L. Dood, Y. Wen, L.S. Mangala, J.M. Hansen, R. Rupaimoole, K.M. Gharpure, C. Rodriguez-Aguayo, S.Y. Yim, J.S. Lee, C. Ivan, W. Hu, G. Lopez-Berestein, S.T. Wong, B.Y. Karlan, D.A. Levine, J. Liu, V. Afshar-Kharghan, A.K. Sood, Platelets reduce anoikis and promote metastasis by activating YAP1 signaling, Nat. Commun. 8 (2017) 310 http://dx.doi.org/10.1038/s41467-017-00411-z.

[122] A.G. Paul, B. Chandran, N. Sharma-Walia, Cyclooxygenase-2-prostaglandin E2-eicosanoid receptor inflammatory axis: a key player in Kaposi's sarcoma-associated herpes virus associated malignancies, Transl Res. 162 (2013) 77–92 http://dx.doi.org/10.1016/j.trsl.2013.03.004.

[123] D. Iyu, J.R. Glenn, A.E. White, A.J. Johnson, S.C. Fox, S. Heptinstall, The role of prostanoid receptors in mediating the effects of PGE(2) on human platelet function, Platelets 21 (2010) 329–342 http://dx.doi.org/10.3109/09537101003718065.

[124] K. Suzuki-Inoue, N. Tsukiji, T. Shirai, M. Osada, O. Inoue, Y. Ozaki, Platelet CLEC-2: Roles Beyond Hemostasis, Semin. Thromb Hemost 44 (2018) 126–134 http://dx.doi.org/10.1055/s-0037-1604090.

[125] B.H. Herzog, J. Fu, S.J. Wilson, P.R. Hess, A. Sen, J.M. McDaniel, Y. Pan, M. Sheng, T. Yago, R. Silasi-Mansat, S. McGee, F. May, B. Nieswandt, A.J. Morris, F. Lupu, S.R. Coughlin, R.P. McEver, H. Chen, M.L. Kahn, L. Xia, Podoplanin maintains high

[126] endothelial venule integrity by interacting with platelet CLEC-2, Nature 502 (2013) 105–109 http://dx.doi.org/10.1038/nature12501.

[126] K.A. Becker, N. Beckmann, C. Adams, G. Hessler, M. Kramer, E. Gulbins, A. Carpinteiro, Melanoma cell metastasis via P-selectin-mediated activation of acid sphingomyelinase in platelets, Clin. Exp. Metastasis 34 (2017) 25–35 http://dx.doi.org/10.1007/s10585-016-9826-6.

[127] Y. Matsui, H. Amano, Y. Ito, K. Eshima, T. Suzuki, F. Ogawa, A. Iyoda, Y. Satoh, S. Kato, M. Nakamura, H. Kitasato, S. Narumiya, M. Majima, Thromboxane A(2) receptor signaling facilitates tumor colonization through P-selectin-mediated interaction of tumor cells with platelets and endothelial cells, Cancer Sci. 103 (2012) 700–707 http://dx.doi.org/10.1111/j.1349-7006.2012.02200.x.

[128] J.W. Semple, J.E. Italiano Jr., J. Freedman, Platelets and the immune continuum, Nat. Rev. Immunol. 11 (2011) 264–274 http://dx.doi.org/10.1038/nri2956.

[129] P. Xu, H. Zuo, R. Zhou, F. Wang, X. Liu, J. Ouyang, B. Chen, Doxorubicin-loaded platelets conjugated with anti-CD22 mAbs: a novel targeted delivery system for lymphoma treatment with cardiopulmonary avoidance, Oncotarget 8 (2017) 58322–58337 http://dx.doi.org/10.18632/oncotarget.16871.

[130] J. Li, Y. Ai, L. Wang, P. Bu, C.C. Sharkey, Q. Wu, B. Wun, S. Roy, X. Shen, M.R. King, Targeted drug delivery to circulating tumor cells via platelet membrane-functionalized particles, Biomaterials 76 (2016) 52–65 http://dx.doi.org/10.1016/j.biomaterials.2015.10.046.

[131] X. Zhang, C. Wang, J. Wang, Q. Hu, B. Langworthy, Y. Ye, W. Sun, J. Lin, T. Wang, J. Fine, H. Cheng, G. Dotti, P. Huang, Z. Gu, PD-1 blockade cellular vesicles for cancer immunotherapy, Adv. Mater. 30 (2018) e1707112 http://dx.doi.org/10.1002/adma.201707112.

[132] C. Wang, W. Sun, Y. Ye, H.N. Bomba, Z. Gu, Bioengineering of artificial antigen presenting cells and lymphoid organs, Theranostics 7 (2017) 3504–3516 http://dx.doi.org/10.7150/thno.19017.

[133] Q. Hu, W. Sun, J. Wang, H. Ruan, X. Zhang, Y. Ye, S. Shen, C. Wang, W. Lu, K. Cheng, G. Dotti, J.F. Zeidner, J. Wang, Z. Gu, Conjugation of haematopoietic stem cells and platelets decorated with anti-PD-1 antibodies augments anti-leukaemia efficacy, Nat Biomed Eng 2 (2018) 831–840 http://dx.doi.org/10.1038/s41551-018-0310-2.

[134] A.L. Papa, A. Jiang, N. Korin, M.B. Chen, E.T. Langan, A. Waterhouse, E. Nash, J. Caroff, A. Graveline, A. Vernet, A. Mammoto, T. Mammoto, A. Jain, R.D. Kamm, M.J. Gounis, D.E. Ingber, Platelet decoys inhibit thrombosis and prevent metastatic tumor formation in preclinical models, Sci Transl Med 11 (2019) http://dx.doi.org/10.1126/scitranslmed.aau5898.

[135] R. Leblanc, O. Peyruchaud, Metastasis: new functional implications of platelets and megakaryocytes, Blood 128 (2016) 24–31 http://dx.doi.org/10.1182/blood-2016-01-636399.

[136] J. Kisucka, C.E. Butterfield, D.G. Duda, S.C. Eichenberger, S. Saffaripour, J. Ware, Z.M. Ruggeri, R.K. Jain, J. Folkman, D.D. Wagner, Platelets and platelet adhesion support angiogenesis while preventing excessive hemorrhage, Proc Natl Acad Sci U S A 103 (2006) 855–860 http://dx.doi.org/10.1073/pnas.0510412103.

[137] E.M. Battinelli, B.A. Markens, J.E. Italiano Jr., Release of angiogenesis regulatory proteins from platelet alpha granules: modulation of physiologic and pathologic angiogenesis, Blood 118 (2011) 1359–1369 http://dx.doi.org/10.1182/blood-2011-02-334524.

[138] X. Wang, Y. Fan, R. Shi, J. Li, S. Zhao, Quality assessment of platelets stored in a modified platelet additive solution with trehalose at low temperature (10 degrees C) and in vivo effects on rabbit model of thrombocytopenia, Platelets 26 (2015) 72–79 http://dx.doi.org/10.3109/09537104.2013.872772.

[139] V. Salunkhe, I.M. De Cuyper, P. Papadopoulos, P.F. van der Meer, B.B. Daal, M. Villa-Fajardo, D. de Korte, T.K. van den Berg, L. Gutierrez, A comprehensive proteomics study on platelet concentrates: platelet proteome, storage time and Mirasol pathogen reduction technology, Platelets 30 (2019) 368–379 http://dx.doi.org/10.1080/09537104.2018.1447658.