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Review

Platelet transfusion in thrombocytopenic cancer patients: Sometimes justified but likely insidious

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ABSTRACT

The transfusion of platelet concentrates prepared from allogeneic single or pooled donations is a standard procedure in transfusion medicine to stop or prevent bleeding in cancer patients with thrombocytopenia undergoing surgery, chemotherapy and/or radiotherapy. While platelet transfusion may appear reasonable in many instances, greater scientific and medical attention should however be given to the possibly insidious impact of transfused platelets on the outcome of cancers. Indeed platelets and the microvesicles they release possess all the biological ingredients capable of supporting tumor growth, protecting circulating tumor cells, and to contributing to metastatic invasion. Until any randomized controlled trials can objectively document their effects on survival or cancer recurrence, minimizing the use of platelet transfusion in cancer patients appears to represent a reasonable precautionary measure.

Contents

1. Introduction

Systematic reviews conducted on behalf of the U.S. Preventive Services Task Force (USPSTF) investigated current evidence for the benefits and harms of aspirin – the cornerstone antiplatelet agent – for primary prevention of cardiovascular disease, on all-cause mortality for all types of cancer, and, in particular, for colorectal cancer (CRC) [1–4]. These reviews reaffirm the evidence of aspirin's effectiveness in preventing first-time myocardial infarction and ischemic stroke and found convincing evidence indicating its effectiveness in CRC prevention confirming the role played by platelets (PLTs) in the development and progression of at least some cancers.

There is an increasing body of evidence pointing out that PLTs fulfill a wide role in balancing health and disease. PLTs are an important source of active metabolites, growth factors and proteins. They promote heterotypic cell interactions and possess a biologically active surface. They also play an active role in sepsis, inflammation, tissue regeneration and control of infection, including promoting the innate immune response and, through their surface and microvesicle content, provide the necessary medium and promot-

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ers for tumor growth, tethering and spread [5,6]. Within tumor microenvironments, they exert important pro-tumorigenic effects [7].

Most cells can release different classes of vesicles into their environment. PLT extracellular vesicles (PEVs) [or microparticles (PMPs)] are present in high number in PLT concentrates. They have a negatively charged pro-coagulant surface that can support the binding of coagulation factors resulting in activation of the coagulation cascade [8]. PEV membranes are capable of generating 50–100 times more thrombin than resting PLTs due to their phosphatidylserine pro-coagulant phospholipids [9]. Furthermore, PEVs act as reservoirs of growth factors and biological response modifiers (anti-leukocyte antibodies and lipids) in particular soluble (s) CD40L (sCD154), a pro-inflammatory mediator associated with adverse transfusion reactions and TRALI [10].

Transfusion of PLTs in often resorted to, in the oncology world, when thrombocytopenia resulting from chemotherapy, radiation or bone marrow tumor infiltration leads to potential or active bleeding. It is also used to raise the PLT count in anticipation of invasive procedures or when anticoagulation is mandatory. One can therefore assume that PLT transfusion, rich in PEVs, will actually provide a perfect milieu for fueling tumor growth [11,12].

2. PLTs, PEVs – tumor interactions

2.1. PLTs

A complex bidirectional interaction happens between the PLTs and tumor cells. Initially, tumor cells can activate PLTs through multiple mechanisms including the expression of tissue factor on the surface of tumor cells. The process of tumor-cell induced PLT activation (TCIPA) has been described many decades ago [5]. The reciprocal interaction involves the PLT membrane and its receptors, as well as the PLT granules and their contents.

PLT adhesion receptors interact with tumor cells via GPIb-IX-V, the ligand for VWF, thrombin, and factors XI and XII, and through GPIIb/IIIa (αIIbβ3) but mostly through P-selectin [13]. PLT P-selectin binds a large variety of tumor cell lines and shares in their inflammatory potential [14]. Furthermore, P-selectin is crucial for tumor cell permeation to the vascular compartment, their intravascular migration and extravasation to form distant metastasis [11,15].

The sialo-glycoprotein aggrus/podoplanin is often expressed by tumor cells and activates PLTs through C-type Lectin receptors (CLEC2). Reciprocally, in experimental models, tumor growth is promoted with metastatic potential [16]. Following their initial activation by tumors, a secondary amplification response mediated by the release of adenosine diphosphate (ADP) from their dense granules activates more PLTs through P2Y1andP2Y12 receptors [17]. Interestingly, many tumor cells express PLT integrins on their surface [18].

PLTs contain a myriad of growth factors, which are delivered to the tumor milieu favoring tumor growth through various mechanisms. PLT-derived growth factor (PDGF) signaling through cell surface tyrosine kinase receptors (PDGFR) stimulates various cellular functions including growth, proliferation, and differentiation. They correlate with the invasiveness and metastatic potential of malignant cells [19]. PLTs are a major source of vascular endothelial growth factor (VEGF) with the PLT pool comprising more than 80% of total circulating VEGF in patients with cancer as well as healthy individuals [20]. VEGF is the promotor of vasculogenesis and angiogenesis needed to maintain an adequate blood supply and is essential for the survival of primary as well as secondary tumors – it is also an important target therapy in metastatic disease [21,22]. The α-granule mitogen transforming growth factor β (TGF-β) interplays with tumor cells both directly and immunologically. It also plays an important role in osteoclastic degeneration of bone matrix to allow for the settling of bone metastasis. TFG-β triggers complex immunomodulatory reactions favoring, again, tumor growth and spread [5]. Paradoxically, PLTs contain and release small quantities of angiogenic inhibitors including endostatin and PLT factor 4 (PF4) [23]. Therefore, the role played by the PLT in the tumor milieu is mostly pro-tumorigenic favoring tumor growth and dissemination [7,11].

2.2. PEVs

Cancer cells are capable of inducing PEV generation through the activation of PLTs via multiple mechanisms namely TCIPA, reciprocally, and similar to the action of their PLT precursors, PEVs are capable of interacting with tumors through multitude direct and indirect means resulting in their proliferation, tethering and dissemination. Activated PLTs and the ensuing microparticles and PEVs expose receptors and release procoagulant and growth factors that trigger cancer progression and metastasis in a pathological pro-oncogenic pattern [11,12,24]. Plasma is also often a rich source of EVs and particularly PEVs [25]. Fig. 1 illustrates the interaction of cancer cells, PLTs and PEVs.

3. Indications and threshold of PLT transfusion in cancer patients

Red blood cell transfusion is based on relatively rigorous criteria, such as the hemoglobin level, whereas PLT transfusion is often biased by the perceived risks of bleeding. PLT transfusion is often indicated in oncology patients receiving myelo-suppressive chemotherapy resulting in significant thrombocytopenia with or without bleeding. It is also often used in patients receiving radiation and when heavy bone marrow infiltration by metastasis results in impaired PLT production.

In a national survey conducted in the USA in 2011, 2,516,000 apheresis PLT units and 130,000 pooled units from whole blood were delivered to meet the needs for PLT transfusion [26]. A recent nationwide survey conducted in France revealed that hematologic and cancer pathologies included 46% of transfused patients, 34% of the patients had transfusions in a surgical context, and 32.4% of transfused patients were receiving medication with an impact on transfusion. PLT transfusions for a prophylactic indication were prescribed with PLT counts of less than 20×10^9 and 50×10^9/L in 56.9 and 86.6% of patients, respectively [27]. Considerable advances have been made in PLT transfusion therapy in the last decades.

Although transfusion of PLT to thrombocytopenic patients with active bleeding is less-debatable, the use of prophylactic PLT transfusions for the prevention of thrombocytopenic bleeding continues to provoke debate. Low to moderate grade evidence suggests that a therapeutic-only PLT transfusion policy is associated with increased risk of bleeding when compared with a prophylactic PLT transfusion policy in hematology patients who are thrombocytopenic due to myelo-suppressive chemotherapy or HSC [28].

In a recent Cochrane review in hematology patients who are thrombocytopenic due to myelo-suppressive chemotherapy or HSCT, there was no evidence to suggest that a low-dose PLT transfusion policy is associated with an increased bleeding risk compared to a standard-dose or high-dose policy, or that a high-dose PLT transfusion policy is associated with a decreased risk of bleeding when compared to a standard-dose policy [29]. Findings from this review suggested changing from current practice, with low-dose PLT transfusions used for in-patients receiving treatment for their hematological disorder and high-dose PLT transfusion strategies not being used routinely [29].