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Chemotherapy induced thrombocytopenia in pediatric oncology

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ABSTRACT

Thrombocytopenia has long been recognized as a significant problem of cancer therapy, but there is still lack of consensus about the optimal approach to prophylaxis and/or treatment of this important complication. In pediatric oncology, since there are very few studies dedicated to this problem, the knowledge gap is even larger and no final conclusions or pediatric evidence based guidelines are available. Those guidelines that are available consist mostly of experts' personal opinions and data extrapolated from the adult studies. In this review we tried to summarize the existing data and approaches in chemotherapy induced thrombocytopenia (CIT) in pediatric oncology.

1. Current evidence

Cancer is an evolving problem and novel treatments are constantly being developed; however, patients with cancer still experience significant morbidity and mortality not only from the disease itself, but also from complications arising from our therapies.

Thrombocytopenia has long been recognized as a significant complication of cancer therapy, but there is still lack of consensus about the optimal approach to prophylaxis and/or treatment of this important morbidity (Bercovitz and Josephson, 2012; Estcourt et al., 2012; Blumberg et al., 2012; Estcourt et al., 2010); some physicians transfuse platelets when the peripheral blood platelet

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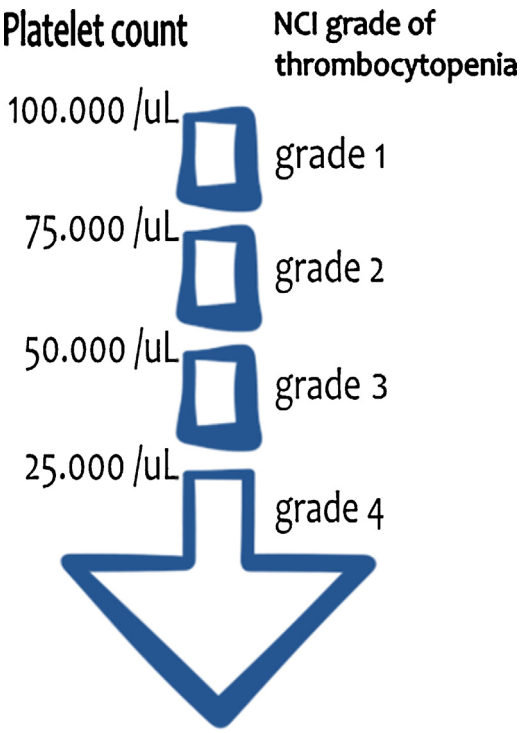

Fig. 1. NCI grading of thrombocytopenia.

count drops below 10×10^3/uL (Schiffer et al., 2001; Rebulla et al., 1997; Slichter, 2007; Liumbruno et al., 2009; Qureshi et al., 2007; Greeno et al., 2007; Eikenboom et al., 2005; Stanworth et al., 2013; Benjamin and Anderson, 2002; Wandt, 2001; Mehta, 2010) or 20×10^3/uL (Qureshi et al., 2007; Greeno et al., 2007; Eikenboom et al., 2005), while others use higher or lower cut off levels (Qureshi et al., 2007; Eikenboom et al., 2005; Rebulla et al., 1997; Lieberman et al., 2014; Cameron et al., 2007), and some transfuse platelets only on demand, i.e., in case of bleeding (Greeno et al., 2007; Wandt et al., 2012). Many studies have been conducted to address this issue, but still many questions remain unanswered.

In pediatric oncology, since there are very few studies dedicated to this problem, the knowledge gap is even larger and no final conclusions or pediatric evidence based guidelines are available. Those guidelines that are available consist mostly of experts' personal opinions and data extrapolated from the adult studies (Bercovitz and Josephson, 2012).

2. How do we define thrombocytopenia and what are the clinical consequences?

Thrombocytopenia is a decrease of platelet counts in peripheral blood below 100×10^3/uL. According to NCI criteria there are 4 grades of thrombocytopenia (Fig. 1) (Anon., 2014a). Although there is a continuum of bleeding risk and there is not really a "safe" platelet number, generally the risk of bleeding increases as the platelet count decreases; grade 3–4 thrombocytopenia has the highest importance from the clinical perspective, because of increased bleeding tendency in these patients starting below 50×10^3/uL (Schiffer et al., 2001; Slichter and Harker, 1978; Gaydos et al., 1962; Hitron et al., 2011; Vadhan-Raj, 2009). Mostly, in CIT, the nadir blood count is seen 7–10 days after chemotherapy with recovery occurring by 2–3 weeks (Sekhon and Roy, 2006).

Thrombocytopenia in CIT can result in variable bleeding ranging from petechiae and ecchymosis up to debilitating bleeding, and even life-threatening hemorrhage (Drozd-Sokolowska and Wiktor-Jedrzejczak, 2011). In addition to morbidity and mortality resulting from bleeding, however, there are additional costs of thrombocytopenia including delays or dose and cycle reductions in therapy that result in decreased efficacy of treatment regimens (Vadhan-Raj, 2009; Kaushansky, 1996; Liou et al., 2007; Elting et al., 2001a, 2001b; Savarese et al., 1997), and platelet transfusions (Liou et al., 2007; Parker, 2014) and the risks of that intervention. In fact, the most common indication for platelet transfusion in the United States (US) is myelosuppressive chemotherapy (Anon., 2014b). Not only do transfusions result in considerable potential risk to patients (transfusions reactions, infection, alloimmunization), but increased transfusions may also be associated with increased cancer related mortality in adult studies (Blumberg et al., 2012; Gantt, 1981; Vamvakas, 2014; Blumberg et al., 2008).

Table 1
WHO bleeding scale (WHO, 1979).

Bleeding grade	Description of bleeding
0	None
1	Petechial
2	Mild blood loss
3	Gross blood loss
4	Debilitating blood loss

Minor hemorrhage—score of 1; major hemorrhage—score of 2 or greater.

3. What is "clinically significant bleeding"?

As stated by Bercovitz and O'Brien (2012), who summarized all available bleeding scales, "currently, there is neither a universally agreed upon definition of clinically significant bleeding nor a consensus on the best method to quantify bleeding".

The most commonly used scale in pediatric cancer is the WHO (World Health Organization) scale published in 1979 in the WHO Handbook for Reporting Results of Cancer Treatment (WHO, 1979). With the WHO scale, the definitions are quite relative allowing for interpretation between investigators/clinicians (Table 1: WHO Scale) (WHO, 1979). In the Bercovitz study (Bercovitz and O'Brien, 2012), they recommended the Bleeding Severity Measurement Scale (BSMS) (Table 2: BSMS Scale) designed by Webert et al. (2012), which is a simple tool for assessing bleeding in CIT patients in which there are two grades of bleeding: Grade 1—not clinically significant and Grade 2—clinically significant. Clinically significant bleeding was defined as "bleeding resulting in morbidity, requiring interventions, or directly causing death" (Webert et al., 2012).

4. How does chemotherapy induced thrombocytopenia (CIT) occur?

Given that CIT results in clinically significant bleeding, and thrombocytopenia has other consequences including delay of therapy and platelet transfusion, it is important to understand the reasons that CIT occurs. Unfortunately, much of the literature in this area is sparse, assuming that all thrombocytopenia is due to myelosuppression. Indeed, some chemotherapy drugs in normal doses can induce bone marrow hypoplasia, which is the main cause of the CIT. Thrombocytopenia also can occur because of immune mediated mechanisms of chemotherapy agents (Egberts, 2011), splenic sequestration due to liver toxicity (Jardim et al., 2012), direct effect on platelet release (Lonial et al., 2005), inhibition of PDGF and apoptosis of megakaryocytes (Shu et al., 2011), or release of megakaryocyte toxic mediators into the bone marrow milieu (Lambert et al., 2007).