Bleeding in children with cancer

Bleeding is characteristic of many types and stages of childhood cancer.

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Before the success story of leukaemia treatment started in the 1950s, many patients succumbed to the disease because of severe haemorrhage. A bleeding tendency is one of the hallmarks of haematological malignancies such as leukaemia, since together with anaemia and an increased susceptibility to infection it completes the picture of bone marrow failure. Almost half of patients with acute lymphoblastic leukaemia present with bleeding.[1] It can also become evident when the bone marrow is infiltrated by a non-haematological malignancy, e.g. neuroblastoma. Thus, easy bruising is one of the St Siluan early warning signs of childhood cancer, compiled by the South African Children's Cancer Study Group (SACCSG). An increased risk of bleeding during the cancer treatment period is almost always present, due to the bone marrow suppressive effect of chemotherapy. Fortunately, death due to bleeding is rare these days.

A bleeding tendency is one of the hallmarks of haematological malignancies such as leukaemia.

History and clinical picture

When evaluating a child with a possible bleeding tendency, one should always distinguish between a mucocutaneous and a clotting factor deficiency bleeding pattern. The mucocutaneous pattern is a superficial bleeding, such as epistaxis, petechiae and ecchymoses (Fig. 1) and the clotting factor deficiency bleeding is haemarthroses and deep-muscle haematomas. If the child is very well and has no other symptoms or signs suggestive of a more sinister disease, a congenital bleeding tendency should be considered.

In a child with cancer, however, the history usually reveals a relatively short period of increased bruising or recurrent episodes of bleeding in a child who is unwell. Sometimes the patient or mother will report that bruising occurred without trauma and in areas not normally involved in trauma-related bruises, e.g. peri-orbital bruising. Recurrent infections, infections not responding to appropriate therapy, fatigue, weight loss, bone pain and pallor are some of the other symptoms that may also be reported, indicating a haematological malignancy.

On examination a petechial or purpuric rash is often present when the platelet count is $<20x10^9$/l. Overt bleeding from the oral mucosa, nose and rectum may occur, as well as haematuria. Intracranial haemorrhage is sometimes present at diagnosis and can of course be catastrophic. A rare presenting symptom in children with leukaemia, called leukaemia cutis, may be confused with ecchymoses, since the lesions may be purplish in colour. The difference is that leukaemia cutis characteristically has nodules that are palpable and non-tender. The lesions may be colourless, blue or light purple. Other signs to be looked for are lymphadenopathy, hepatosplenomegaly and other masses.

Causes and pathophysiology of bleeding (Table I))

Bleeding at presentation is most commonly caused by bone marrow infiltration, whether by the primary haematological malignancy or by metastatic infiltration of a non-haematological malignancy. Proliferation of malignant cells in the bone marrow displaces normal haemopoietic precursor cells, leading to a decrease in haemopoietic precursor cells and peripheral cytopenias, ranging from a single cell line affected to pancytopenia. The most common cause is acute lymphoblastic leukaemia, where the normal bone marrow is being replaced by leukaemic blasts. In metastatic Hodgkin's and non-Hodgkin's lymphomas bone marrow infiltration may be present. Neuroblastoma and rhabdomyosarcoma are examples of solid tumours that can cause non-haematological infiltration of the bone marrow. Metastatic neuroblastoma typically leads to the development of `raccoon eyes' (periorbital ecchymoses due to local periorbital infiltration and probable obstruction of the palpebral blood vessels) (Fig. 2).

Certain characteristics of the malignant cells themselves can trigger bleeding. Acute myeloid leukaemia (AML) notoriously can cause severe, life-threatening bleeding. Thrombocytopenia is commonly present, but a coagulopathy can also occur due to proteins with anticoagulant activity being released by the leukaemic blasts. Disseminated intravascular coagulopathy (DIC) is most frequently seen with acute promyelocytic leukaemia (AML M3), since the promyelocytes contain a high number of these granules. These blasts also express annexin II, which activates plasminogen. DIC triggered by infection may also be present in other malignancies at the time of presentation.

Cancer treatment regularly causes bleeding, since almost all chemotherapy agents cause bone marrow suppression, and therefore thrombocytopenia, but bleeding is also secondary to DIC in a few cases. The degree of suppression is dependent on treatment dose, the number of treatment courses the patient has already received, as well as individual reactions. The nadir of the platelet count is usually reached 7 - 10 days after chemotherapy, except in the case of carboplatinum/cisplatinum, where prolonged thrombocytopenia is often seen. L-asparaginase, which is used in the treatment of leukaemia, can cause coagulopathy due to a decrease in antithrombin III and fibrinogen. Radiotherapy, when it involves a large field, also causes bone marrow suppression, including thrombocytopenia.

Peripheral destruction of platelets can occur in episodes of febrile neutropenia (fever in the presence of a neutrophil count $<0.5x10^9$/l).

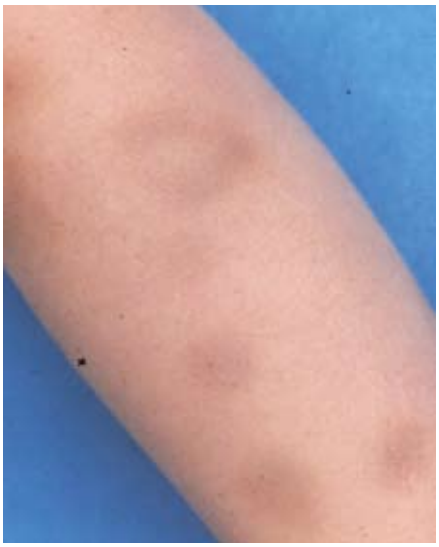

Fig. 1. Ecchymoses on a patient's arm (with thanks to the Tygerberg Children's Tumour Registry).

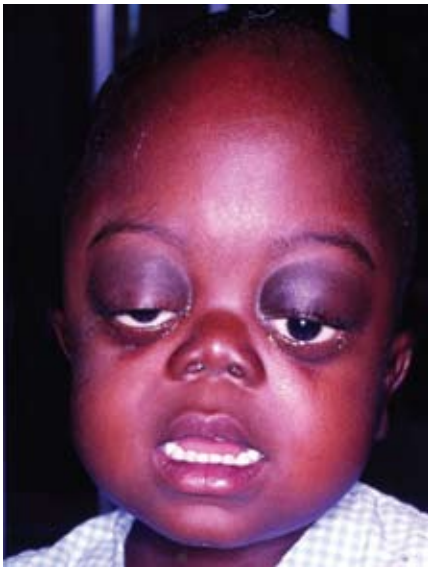

Fig. 2. `Raccoon eyes' in metastatic neuroblastoma (with thanks to the Tygerberg Children's Tumour Registry).

Prophylactic platelet transfusions

Prophylactic platelet transfusions are administered with the aim of reducing the risk of severe bleeding in children with cancer.[3] However, the jury is still out on whether prophylactic transfusions truly are necessary for patients with chronic thrombocytopenia without additional risk factors to prevent haemorrhage or whether it would be safe and effective to transfuse platelets only in the event of bleeding. Since 1966, when a study reported a significant decrease in the number of haemorrhagic deaths in children with leukaemia after the implementation of a prophylactic transfusion programme, clinicians have been prescribing prophylactic platelet transfusions. In 2006 it was reported that platelet transfusions were administered only when bleeding occurred in adult autologous stem cell transplant patients and that this approach was safe.[2] No recent randomised control trials implementing the lower platelet transfusion threshold in children have explored this issue. Currently all paediatric oncology units still employ prophylactic platelet transfusions since authoritative organisations still advocate prophylactic treatment.[3,4]

Table I. Causes of bleeding in a child with cancer

Thrombocytopenia secondary to:
- Bone marrow infiltration
  - Haematological malignancy, e.g. leukaemia, lymphoma
  - Non-haematological malignancy, e.g. neuroblastoma, rhabdomyosarcoma
- Infection
- Disseminated intravascular coagulopathy
- Chemotherapy
- Radiotherapy

Coagulopathy secondary to:
- Anticoagulant activity of the malignant cells, e.g. AML
- Disseminated intravascular coagulopathy
- Hyperleukocytosis (white cell count >100x10^9/l)
- Chemotherapy, e.g. L-asparaginase

Platelet transfusions are very expensive and have several side-effects. It is therefore important to adhere strictly to transfusion guidelines so as to balance the risk versus benefit see-saw. Guidelines as to the transfusion threshold have become more conservative and currently suggest platelet transfusion for a platelet count less than 10 x 10^9/l in a patient without additional risk factors for bleeding.[3-8] A Cochrane review has concluded that there was no statistical difference in mortality, remission rate, number of severe bleeding episodes or red cell transfusion requirements between patients where a cut-off value of 10 x 10^9/l and patients where 20 x 10^9/l was used.[8] It was unclear though whether the studies had sufficient power to demonstrate that the lower threshold was safe. There is a paucity of evidence-based guidelines in children, but the available guidelines also advocate the use of the lower transfusion threshold of <10x10^9/l in a low-risk setting.[4]

Several clinical factors need to be taken into account when considering platelet transfusion, and if any of the following are present one should have a lower threshold for ordering a platelet transfusion (<20x10^9/l): sudden drop in platelet count, previous life-threatening bleeding, severe anaemia, fever, infection, DIC, liver disease, disease factors (e.g. AML M3 causing coagulopathy) and medication that could exacerbate bleeding. The phase of therapy and the risk of allo-immunisation (development of antibodies to donor proteins) should also be considered. The availability of platelets and how rapidly they could be sourced is an important factor to take into account.[3] Allo-immunisation has been shown to adversely affect outcome in certain patients, e.g. patients eligible for a bone marrow transplant,[9] so it is important to keep the number of transfusions as low as possible.

For most surgical procedures a platelet count of >50x10^9/l is sufficient, provided no additional risk factors are present.[3,5,6] A count of >100x10^9/l is required for major surgery and any neurosurgical procedure.[5,6] Bone marrow aspiration and biopsy can be performed safely even in the presence of severe thrombocytopenia, provided adequate pressure is applied to the puncture sites.[3] Prior to intrathecal administration of chemotherapy it must be ensured that the platelet count is >20x10^9/l.[4] For a diagnostic lumbar puncture in a patient with leukaemia a higher count of >100x10^9/l is required to minimise the risk of bleeding and introducing blasts into the cerebrospinal fluid.[10,11] The generally accepted platelet transfusion threshold for neonates is <30x10^9/l.[12]

There are good evidence-based guidelines for platelet transfusion thresholds in different situations, but the limitations must be taken into account, namely that data are extrapolated from studies on adults, doctors must be able to identify additional risk factors of bleeding in patients, and the lower thresholds can only be followed if platelets are readily available and patients are able to rapidly access medical services. A paediatric haematologist/oncologist should be consulted whenever there is doubt.

Easy bruising is one of the St Siluan early warning signs of childhood cancer.

Therapeutic platelet transfusions

Therapeutic platelets are administered to stop active bleeding. The World Health Organization (WHO) has advised the following grading system for any patient with haemorrhage:[13]
- WHO grade 0: none
- WHO grade 1: petechiae, ecchymosis, occult blood in body secretions, vaginal spotting
- WHO grade 2: gross bleeding (e.g. epistaxis, haematuria, haematemesis) that does not require additional transfusion support
- WHO grade 3: bleeding requiring ≥1 units of packed cells/day
- WHO grade 4: life-threatening bleeding.

Grades 1 and 2 usually correlate with the degree of thrombocytopenia, while grades 3 and 4 are often associated with additional risk

Table II. Complications of platelet transfusion[5]

Infectious
- Human immunodeficiency virus
- Hepatitis B and C
- Cytomegalovirus
- Bacterial transmission, resulting in septicaemia or septic shock

Immunological
- Allo-immunisation: Rh, ABO, HLA
- Febrile reactions
- Transfusion-related acute lung injury (TRALI)
- Anaphylaxis
- Graft-versus-host disease
- Hypotension
- Haemolysis

factors for bleeding, e.g. septicaemia. Thus not all bleeding episodes of grades 3 and 4 may be controlled only by a platelet transfusion.[6] Therapeutic platelet transfusions are usually indicated for bleeding ≥WHO grade 2.[6]

Complications of platelet transfusion (Table II)[5]

Since platelet products are stored at 20 - 24˚C rather than 4˚C as red cells are, the risk for transmission of bacteria is higher than with packed red cells.[6] This is potentially lethal, but is fortunately unusual. High-quality tests currently used to exclude viral infections in donated platelets have decreased the risk of transmission to a very low level. Allo-immunisation (the formation of antibodies to donor proteins) can occur in three situations: in the event of ABO incompatibility, Rhesus incompatibility or when the patient is exposed to platelets that have not undergone leucocyte reduction and HLA antibodies are formed. The development of allo-immunisation causes the patient to be refractory to platelet transfusion. This can also be caused by non-immune factors, namely splenomegaly, drugs (ciprofloxacin, vancomycin, amphotericin, heparin), fever and infection, bleeding and DIC. It can be diagnosed when there is a poor response after transfusion on two subsequent occasions. Other immune-mediated complications include allergic reactions, febrile reactions, transfusion-related acute lung injury (TRALI), graft-versus-host disease (GVHD), anaphylaxis and haemolysis.

Management of a bleeding episode

The first priority is rapid assessment of the haemodynamic status of the patient (including clinical assessment and a side-room haemoglobin determination) and appropriate resuscitation when necessary. Gross bleeding should be controlled by local measures. The next step would be to gain as much knowledge about the patient's diagnosis, treatment and medication as is possible. It is important to identify whether additional risk factors such as septicaemia are present. A decision about which product(s) to transfuse can then be taken. The laboratory work-up should include a full blood count, a peripheral smear and a clotting profile in order to ascertain the haematological cause of the episode (thrombocytopenia v. DIC). The peripheral smear provides important information: presence of blasts indicating relapse, fragments and other signs of DIC, signs of infection and to confirm thrombocytopenia if present on the full blood count. If the clotting profile is abnormal, DIC and drugs precipitating DIC should be considered, as well as disease-specific factors, e.g. coagulopathy caused by AML, and liver disease due to the malignancy or secondary to drugs. Fresh frozen plasma (10 - 15 ml/kg) is indicated for clotting abnormalities and cryoprecipitate should be administered in massive haemorrhage to supplement fibrinogen as well.

Which platelet product is the best for my patient?

Two types of platelet products are available: random/pooled platelets (prepared from 4 - 6 donors' blood) and single-donor/mega unit/apheresis platelets (prepared from a single donor's blood). Both of these are available in infant (±50 ml) and adult (±300 ml) sizes. Random platelets (pooled unit) roughly cost R3 800, while a single-donor unit costs about R5 150. Filtering effectively reduces the numbers of leucocytes in random/pooled platelets in order to decrease the risk of allo-immunisation, febrile reactions and the transmission of cytomegalovirus (CMV). This process of leucocyte reduction will further increase the cost by R830. Studies have shown that the two products are similar in terms of the post-transfusional rise in the platelet count, the haemostatic effect and platelet survival.[3] Irradiation is only indicated for patients receiving allogeneic stem cell transplants, patients receiving products from related donors and severely immunocompromised patients.

Single-donor platelets are indicated for patients where allo-immunisation and refractoriness have occurred. The ideal for patients with these complications would be HLA-matched platelets, but this is rarely available to most patients due to cost and genetic diversity. In practice, single-donor platelets are currently used when a patient is eligible for a stem cell transplant in order to limit the exposure of the patient to multiple donors. However, the TRAP study concluded that the risk for allo-immunisation was the same when random/pooled versus single-donor platelets were used.[14] Further studies are needed to confirm this. In most treatment units this product will also be used when a patient has had multiple transfusion reactions. In all other situations filtered random platelets must be used. Random platelets are usually more readily available than single-donor platelets and in the event of severe haemorrhage would be the product of choice for any patient. The traditional dose of 10 - 15 ml/kg should serve as a guideline whether to order one or more of the infant units or alternatively to order an adult unit. Platelets should never be wasted, since the complete unit can be safely transfused.

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