8.7: Transfusion in haemato-oncology

Many of the principles of transfusion management developed for these patients can be applied to patients with other cancers having treatment of similar intensity.

8.7.1: Transfusion support for myelosuppressive treatment

Intensive combination chemotherapy regimens for acute leukaemia and aggressive lymphoma, with or without haemopoietic stem cell (HSC) rescue, typically suppress the production of blood cells by the bone marrow for 7 to 14 days, during which the patient is likely to require prophylactic or therapeutic transfusions of red cells and platelets. Allogeneic (donor) HSC transplantation after myeloablative chemo-radiotherapy often requires much longer periods of transfusion support, particularly when recovery is complicated by delayed engraftment, acute graft-versus-host disease (GvHD) or severe sepsis.

8.7.2: Red cell transfusion

The ideal red cell ‘transfusion trigger’ for patients undergoing intensive cytotoxic therapy is uncertain. The patients have much in common with patients in critical care in which there is evidence to support a restrictive red cell transfusion policy (see Chapter 7). However, very low haematocrits may increase the risk of bleeding in patients with severe thrombocytopenia. In recent years, most units in the UK have followed a transfusion threshold of 80 or 90 g/L for patients without active bleeding.

8.7.3: Prophylactic platelet transfusion

It has long been standard practice to give prophylactic platelet transfusions to severely thrombocytopenic patients with the objective of preventing bleeding, especially serious or life-threatening bleeding such as intracerebral haemorrhage, although the evidence base for this is incomplete. Over the last decade, most units have used a platelet transfusion threshold of 10×10⁹/L, largely based on an Italian trial comparing thresholds of 10 or 20×10⁹/L. A randomised controlled trial in North America recently showed no significant difference in bleeding rates when patients on prophylaxis were randomised to low, medium or high platelet doses. Thus, there is no justification for the routine administration of ‘double dose’ platelets for prophylaxis.

Most trials of platelet therapy looking at dose or transfusion threshold have shown no difference in bleeding rates between the trial arms, and the routine use of prophylactic platelet transfusion has been questioned. Two recent large randomised controlled trials in haemato-oncology patients compared prophylactic platelet transfusion to a therapeutic policy based on a standardised daily assessment of bleeding and giving platelets only to those with a World Health Organization (WHO) clinically apparent haemorrhage greater than Grade 1 (WHO Grades range from Grade 1 (mild) to Grade 4 (debilitating/life-threatening)). Both trials showed an overall increase in Grade 2 to 4 bleeding in the no-prophylaxis group. However, the 14-centre
UK/Australian TOPPS trial found that the subgroup of patients undergoing autologous HSC transplantation, with relatively short periods of thrombocytopenia, had similar bleeding rates in both treatment arms and platelet use was significantly lower in the no-prophylaxis group.

Although prophylactic platelets are beneficial in most patients receiving intensive chemotherapy they do not prevent all bleeding. Grade 2 to 4 haemorrhage occurred in 43% of patients receiving conventional prophylaxis in the TOPPS trial. Serious bleeds occur above the $10 \times 10^9$/L threshold and current research is investigating clinical and laboratory risk factors.

Based on current evidence:

- Prophylactic platelet transfusions should be given to patients receiving intensive chemotherapy, with a transfusion trigger of $10 \times 10^9$/L.
- One adult therapeutic dose (ATD) should be given once daily to adults and children >15 kg in weight (10–20 mL/kg in children and infants <15 kg).
- In a 70 kg adult, one ATD typically gives an immediate rise in platelet count of 20–40 $\times 10^9$/L. The platelet increment can be measured as early as 10 minutes after completion of the transfusion.
- There is no rationale for the routine use of double dose platelets for prophylaxis.
- It is standard practice to increase the platelet transfusion threshold to $20 \times 10^9$/L in patients who are febrile and/or receiving antibiotic therapy for suspected bacterial or fungal infection, although there is no evidence from randomised trials to support this policy.
- A therapeutic platelet transfusion policy in patients undergoing lower risk procedures such as autologous HSC transplantation may be appropriate, but further research is required before this can be routinely recommended.
- Platelet prophylaxis is not required for bone marrow aspiration or trephine biopsy, but local pressure should be applied.
- For patients requiring lumbar puncture, central-line insertion, percutaneous organ biopsies and most invasive surgeries the platelet count should be increased to $>50 \times 10^9$/L. For adults and children >15 kg, one ATD of platelets should be administered shortly before the procedure and a post-transfusion platelet count should be checked to confirm the count has risen to the desired level.
- There is no evidence to support the practice of once or twice weekly prophylactic platelet transfusions in non-bleeding patients with chronic severe thrombocytopenia.

8.7.4: Refractoriness to platelet transfusion

‘Refractoriness’ is the repeated failure to obtain a satisfactory response to platelet transfusion. Control of bleeding is the most clinically relevant marker but, in practice, it is usual to measure the increase in platelet count after transfusion. Formulas to derive platelet recovery or corrected count increment are of limited value outside research as they require knowledge of the platelet content of each unit transfused. In the clinical setting, simpler indicators, such as failure of the immediately post-transfusion (10 to 60 minutes) platelet increment to exceed the transfusion trigger or a rise of less than $10 \times 10^9$/L 20 to 24 hours after transfusion, are used. The diagnosis of refractoriness should only be made after an unsatisfactory response to two or more transfusions. Platelet refractoriness can be due to immunological or, more commonly, non-immunological causes associated with increased platelet consumption or losses (Table 8.4).

Table 8.4 Causes of platelet refractoriness
### Immunological causes

- Antibodies to antigens on platelets (HLA, HPA, ABO)
- Platelet autoantibodies
- Drug-dependent antibodies
- Immune complexes

### Non-immunological causes

- Infection
- Antibiotics (amphotericin B and fluoroquinolones)
- Splenomegaly/hypersplenism
- Disseminated intravascular coagulation (DIC)
- Platelet loss due to bleeding

Platelet refractoriness due to human leucocyte antigen (HLA) alloimmunisation has been less common since universal leucodepletion of blood components was introduced. The typical patient is now a female sensitised by previous pregnancy. If a non-immunological cause has been excluded, the patient should be screened for HLA antibodies after discussion with a transfusion medicine specialist. The presence of HLA antibodies does not prove immunological refractoriness but the response to platelet transfusion from donors matched, as closely as possible, for the patient’s HLA-A and HLA-B antigens should be assessed. The UK Transfusion Services have panels of HLA-typed donors. ABO-compatible platelets should be used wherever possible and HLA-matched platelet transfusions should be irradiated to prevent transfusion-associated graft-versus-host disease. Immediate (10 to 60 minutes) and 24-hour post-transfusion platelet increments should be measured. If a satisfactory response is seen, HLA-matched platelet transfusions should be continued as long as compatible donors are available. HLA antibodies may reduce or disappear during treatment and it may be helpful to repeat the HLA-antibody screen monthly during treatment. If there is no response to HLA-matched platelets it is reasonable to screen for human platelet antigen (HPA) and other less common antibodies after specialist advice.

### 8.7.5: Selection of compatible blood for patients who have received a marrow or peripheral blood HSC transplant from an ABO or RhD-incompatible donor

Up to 25% of HLA-identical sibling donor/recipient pairs have different ABO blood groups (Table 8.5). SHOT reports show that component selection errors for patients who have changed blood group after allogeneic HSC transplant are common and often stem from poor communication between the clinical team and transfusion laboratory or when there is shared care between different hospitals. A clear post-transplant transfusion policy should be developed for all transplant patients and circulated to the clinical and laboratory teams involved in their care. The recommended ABO groups for components transfused in the immediate post-transplant period are shown in Table 8.6.

Haemolysis due to ABO incompatibility may occur immediately on stem cell infusion (usually with bone marrow transplants that are heavily contaminated with red cells) or be delayed for 7 to 14 days due to production of antibodies by residual host or transplanted lymphocytes (more common with peripheral blood-derived HSC). It is occasionally life threatening. In RhD-incompatible transplants, the main risk is delayed haemolysis where the donor is RhD negative and the recipient RhD positive.

Table 8.5 Categories of ABO-incompatible HSC transplant
Major ABO incompatibility

The recipient’s plasma contains anti-A, anti-B or anti-A,B antibodies that are incompatible with donor red cells
(e.g. group A donor and group O recipient)

Minor ABO incompatibility

The donor’s plasma contains anti-A, anti-B or anti-A,B antibodies that can react with the recipient’s red cells
(e.g. donor group O and recipient group A)

Bidirectional ABO incompatibility

Both the donor and recipient’s plasma contain anti-A, anti-B or anti-A,B antibodies reactive with recipient and donor red cells respectively (e.g. donor group A and recipient group B)

Immediate haemolysis in major ABO mismatch marrow transplants can be prevented by red cell depletion of the marrow harvest. This is unnecessary with peripheral blood HSC transplants that contain <10 mL red cells. In minor ABO mismatch marrow transplants the harvest can be plasma depleted to remove high-titre donor anti-A or -B (this is unnecessary in peripheral blood HSC transplants where the small amount of plasma is rapidly diluted after infusion).

Table 8.6 Recommended ABO blood group of components transfused in the early post-transplant period
<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Red cells</th>
<th>Platelets</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>O</td>
<td>O</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>O</td>
<td>O</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>O</td>
<td>O</td>
<td>A</td>
<td>AB</td>
</tr>
<tr>
<td>AB</td>
<td>A</td>
<td>A(^a)</td>
<td>A</td>
<td>AB</td>
</tr>
<tr>
<td>AB</td>
<td>B</td>
<td>B(^a)</td>
<td>B</td>
<td>AB</td>
</tr>
</tbody>
</table>

**Major ABO incompatibility**

- A
- B
- AB
- AB

**Minor ABO incompatibility**

- O
- O
- O
- O
- O
- A
- B
- A\(^a\)
- B\(^a\)

**Bidirectional ABO incompatibility**

- A
- B
- B
- A

\(^a\) Group O red cells may also be used.

Once conversion to donor blood group is complete, components of that group can be given. In both major and minor RhD mismatch, RhD negative red cells and platelets are given post-transplant. If, for reasons of availability, RhD positive platelets have to be given to unsensitised RhD negative recipients, 250 IU of anti-D immunoglobulin subcutaneously will cover up to five adult therapeutic doses of platelets over a 5-week period.

### 8.7.6: Prevention of transfusion-associated graft-versus-host disease (TA-GvHD)

This fatal complication can be prevented by the use of irradiated cellular blood components (red cells, platelets and granulocytes) in patients at high risk (see Chapter 5 for a more detailed discussion of TA-GvHD and prophylaxis). It is not necessary to irradiate red cells or platelets for adults or children with acute leukaemia except for HLA-selected platelets or donations from first or second degree relatives. The 2010 British Committee for Standards in Haematology (BCSH) guideline on the use of irradiated blood components [https://b-s-h.org.uk/](https://b-s-h.org.uk/) recommendations for transfusion of irradiated components in haemat-oncology patients are summarised in Table 8.7. The guidelines are regularly reviewed as new immunosuppressive drugs and biologicals are introduced into practice and evidence of risk accumulates. For example, irradiated components are currently recommended for patients, including solid organ transplant recipients, treated
with the lymphocyte-depleting monoclonal antibody alemtuzumab (anti-CD52) but not for those receiving rituximab (anti-CD20).

**Table 8.7 Indications for irradiated cellular blood components\(^a\) in haemato-oncology patients**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Irradiated blood components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults or children with acute leukaemia</td>
<td>Not required (except for HLA-selected platelets or donations from first or second degree relatives)</td>
</tr>
<tr>
<td>Recipients of allogeneic (donor) HSC transplantation</td>
<td>From the start of conditioning chemo-radiotherapy. Continue while receiving GvHD prophylaxis (usually for 6 months post-transplant) If chronic GvHD or on immunosuppressive treatment, continue irradiated blood components</td>
</tr>
<tr>
<td>Bone marrow and peripheral blood stem cell donors</td>
<td>Provide irradiated cellular components during and for 7 days before the harvest</td>
</tr>
<tr>
<td>Bone marrow or peripheral blood HSC harvesting for future autologous reinfusion</td>
<td>Provide irradiated cellular components during and for 7 days before the harvest</td>
</tr>
<tr>
<td>Autologous HSC transplant patients</td>
<td>From start of conditioning chemo-radiotherapy until 3 months post-transplant (6 months if total body irradiation was used)</td>
</tr>
<tr>
<td>Adults and children with Hodgkin lymphoma at any stage of the disease</td>
<td>Irradiated cellular components indefinitely</td>
</tr>
<tr>
<td>Patients treated with purine analogues (fludarabine, cladribine and deoxycoformicin)(^b)</td>
<td>Irradiated cellular components indefinitely</td>
</tr>
<tr>
<td>Patients treated with alemtuzumab (anti-CD52) therapy(^c)</td>
<td>Irradiated cellular components indefinitely</td>
</tr>
</tbody>
</table>

\(^a\) Red cells, platelets and granulocytes

\(^b\) Irradiated components are recommended for newer purine analogues and related compounds, such as bendamustine, until further data are available

\(^c\) Irradiated components are also recommended for solid organ transplant patients receiving alemtuzumab
Patients at risk of TA-GvHD should be given clear written information. Patient information leaflets, cards and warning stickers for the hospital notes are available from the UK Blood Services. SHOT annual reports show that failure to prescribe or administer irradiated components is a common cause of incorrect blood component transfused incidents. Many of these are due to poor communication between clinical teams, transfusion laboratories and shared-care hospitals. SHOT (http://www.shotuk.org) has made a series of recommendations concerning better clinical communication and documentation, and improved laboratory and clinical information systems (including IT links with pharmacy and diagnostic services), which should be incorporated into local policies and regularly audited.

**8.7.7: Prevention of cytomegalovirus transmission by transfusion**

Cytomegalovirus (CMV) can be transmitted by cellular blood components and may produce fatal infection in immunocompromised patients, especially allogeneic HSC transplant recipients. The risk can be reduced by blood donor CMV antibody screening (CMV negative components) or pre-storage leucocyte-depleted blood. Current evidence-based recommendations for different patient groups are discussed in detail in Chapter 5. In summary, standard pre-storage leucodepleted components are suitable for adult and paediatric HSC transplant patients.

**8.7.8: Long-term transfusion support for patients with myelodysplasia**

There are increasing numbers of elderly patients with ‘low-risk’ myelodysplasia who are transfusion dependent for months or years. Tolerance of anaemia varies widely between patients and severe fatigue is a commonly reported symptom. Transfusion plans in individual patients should be designed to minimise symptoms of anaemia and improve health-related quality of life rather than achieve an arbitrary Hb concentration. For example, some patients may benefit from higher mean Hb levels and others from smaller, more frequent transfusions to prevent wide fluctuations in Hb concentration. Transfusion triggers designed for perioperative or critical care patients are unlikely to be appropriate.

Up to 16% of patients eventually become alloimmunised to red cell antigens and this may be delayed by selecting Rh and K-compatible donations. Long-term transfusion is also associated with transfusional haemosiderosis and organ damage due to iron overload. Chelation therapy with agents such as desferrioxamine may be indicated in selected patients, carefully balancing the benefits against impairment of quality of life from frequent overnight subcutaneous infusions.