Guidelines for management of autoimmune haematological disorders for adults with lymphoproliferative disease

Definition

Autoimmune haemolytic anaemia and immune thrombocytopenia are relatively common amongst patients with lymphoproliferative disease (LPD). This guidance outlines the diagnosis and management of these autoimmune conditions for patients with LPD.

Warm autoimmune haemolytic anaemia (wAIHA)

Diagnosis

Diagnosis of wAIHA should follow the wAIHA guidelines. Examination of the blood film can help resolve diagnostic uncertainty for patients with co-existing LPD as anaemia, thrombocytopenia, elevated LDH and positive DAT are all common in LPD.

Low haptoglobin and elevated bilirubin may occur in hepatic impairment, which may be directly disease related, drug-induced or due to infection.

Consider bone marrow aspirate and trephine if there is diagnostic uncertainty over whether anaemia is directly due to LPD or wAIHA.

Treatment:

1. If there is an indication for directed treatment for LPD-directed then this should be given first. In order to achieve control over both wAIHA and the LPD, steroid treatment may need to run concurrently with a treatment directed against the lymphoma. This is especially true for LPD-directed treatments that work slowly.
2. For non-Hodgkin lymphoma, the response rates are higher with LPD-directed therapy than with wAIHA-directed therapy, although both can be considered.
3. If there is no indication for LPD treatment but there is for AIHA treatment then treatment in the following order recommended:
    1. First line: Prednisolone 1mg/kg (80mg maximum) once a day following wAIHA dosing regimen
    2. Second line: Rituximab 375mg/m2 weekly for four doses
    3. Third line: Consider LPD-directed therapy (alternatives would be azathioprine, ciclosporin or mycophenolate)

All patients should be offered folic acid 5mg once a day until their haemoglobin normalises. During active haemolysis, thromboprophylaxis (inpatient and outpatient) is recommended as the risk of venous thrombosis is high.

Cold agglutinin disease (CAD)

Diagnosis

Diagnosis should follow the CAD guidelines. As with wAIHA, exercise caution at diagnosis because anaemia, thrombocytopenia, elevated LDH and positive DAT are all common in LPD. Examination of the blood film is helpful to distinguish CAD from other causes. Low haptoglobin and elevated bilirubin may occur in hepatic impairment, which may be directly disease related, drug-induced or due to infection (especially CMV reactivation or parvovirus). Bone marrow aspirate and trephine is recommended in all cases

Treatment

1. If there is an indication for LPD-directed treatment then this should be given first.
2. If there is no indication for LPD treatment but there is for treatment of haemolysis then treatment in the following order is recommended:
    1. First line: Rituximab 375mg/m2 weekly for four doses following AIHA guidance
    2. Second line: LPD-directed treatment. Case series show high response rates for Rituximab-bendamustine and Rituximab-fludarabine

All patients should be offered folic acid 5mg once a day until their haemoglobin normalises. Erythropoietin can be considered as a supportive measure. Patients should be advised to avoid exposure to cold and if they require intravenous fluids including blood, this should be given through a warmer.

Immune thrombocytopenia (ITP)

Diagnosis

Diagnosis should follow the ITP guidelines. In some cases it can be challenging to distinguish ITP from other causes of thrombocytopenia. In particular, thrombocytopenia may be due to marrow infiltration, chemotherapy or infection (especially CMV reactivation or parvovirus).

Consider bone marrow aspirate and trephine if there is diagnostic uncertainty over whether anaemia is directly due to LPD or ITP

Treatment

If there is an indication for LPD-directed treatment, then this should be given first. For chemotherapy regimens with slow onset of action, prednisolone can be given alongside initial treatment to control ITP if required.

If there is no indication for LPD treatment but there is for ITP treatment then treatment in the following order is recommended:

1. First line: Prednisolone 1mg/kg (80mg maximum) once a day following ITP dosing regimen
2. Second line: Rituximab 375mg/m2 weekly for four doses
3. Third line: Consider LPD-directed therapy or a thrombopoietin mimetic such as romiplostim, eltrombopag or avatrombopag

Pure red cell aplasia (PRCA)

Diagnosis should follow the PRCA guidelines. If an LPD is present, then treatment directed at the LPD is recommended with caution over myelosuppressive agents.

For all the above associated disorders, when LPD-directed treatment is considered, priority should be given to agents with rapid time to deep response e.g. BCL2i-based treatment.

Autoimmune haematological conditions in patients in remission from LPD
The presence of a new autoimmune haematological condition should lead to assessment for relapse. Consideration should be given to cross-sectional imaging (CT or PET CT as appropriate for underlying LPD) and bone marrow aspirate and trephine.

Prevention of infection for patients with immune cytopenia and LPD:
Patients with an underlying LPD who require steroids and/or rituximab to control their immune cytopenia are at increased risk of opportunistic infection. This is particularly notable in patients requiring concurrent LPD treatment. As a pragmatic step, consider:

- Prophylactic aciclovir 200mg three times a day in all patients to continue until 90 days after completing immunosuppression
- *Pneumocystis jirovecii* prophylaxis (for instance co-trimoxazole 480mg three times a week) for the duration of immunosuppression for patients with chronic lymphocytic leukaemia, patients on concurrent immune cytopenia and LPD treatment, and patients with who have had previous chemotherapy for LPD.

References

- Gurani and Maciejewski. How I manage pure red cell aplasia in adults. Blood 2021; 137: 2001-9
- Hendrick et al. Auto-immune haemolytic anaemia – a high risk disorder for thromboembolism? Hematology 2002; 8: 53-6
- Hill et al. The diagnosis and management of primary autoimmune haemolytic anaemia. Br J Haematol 2017; 176: 395-411
- Hill et al. Guidelines on the management of drug induced immune and secondary autoimmune, haemolytic anaemia. British Journal of Haematology 2017; 177: 208-20.
- Proven et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Advances 2019; 3: 3780-17
- Schuh et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. British Journal of Haematology 2018; 182: 344-59

Name	Revision	Date	Version	Review date
Dr Mike Desborough, Dr Niamh Appleby, Dr Sue Pavord, Dr Toby Eyre	New protocol	June 2024	V1.0	June 2027