HOW I TREAT ACQUIRED HYPOGAMMAGLOBULINAEMIA

Malignancies of the B-lymphocyte lineage are among the most diagnosed haematological malignancies in clinical practice. Dysregulation of the immune system is a common feature in the pathogenesis of these disorders, and secondary immunodeficiencies, in particular hypogammaglobulinaemia, are common.

Review the following hypothetical scenarios in which patients present with hypogammaglobulinaemia alongside other conditions. For each scenario, consider how you would best manage the patient and reflect on the questions provided.

Case Study 1: Elise

Presentation

Elise is a 57-year-old pharmacist presenting with acute lower back pain and trouble walking. A computed tomography (CT) scan of her thoraco-lumbar spine demonstrates pathological collapse of T9 and numerous lytic lesions involving several other vertebrae.

She reports two episodes of infection (maxillary sinus and lower respiratory tract infection) treated with oral antibiotics over the last 6 months. She takes no regular medicines and her health is otherwise unremarkable.

Examination

A magnetic resonance imaging (MRI) scan also demonstrates an epidural mass at T9 that is starting to impinge on the spinal cord. A CT skeletal survey shows widespread lytic lesions in the pelvis, long bones, and vertebral bodies.

Elise's pathology results show:

- full blood count: haemoglobin (Hb) 95 g/L, white cell count 5.9 x 10^9/L (normal differential), platelets 210 x 10^9/L
- biochemistry: creatine 145, calcium 2.85, lactate dehydrogenase 200, beta-2 microglobulin 4.5 mg/dL
- serum protein studies: IgG 2.5 g/L, IgA 57 g/L, IgM 1.0 g/L, IgAK paraprotein 56 g/L, free kappa light chain 55 mg/L, kappa-lambda ratio 5.7
- bone marrow aspirate and trephine: Infiltrate of 65% plasma cells (IgAK) and reduced normal haematopoiesis
- fluorescence in situ hybridisation (FISH) finds no high-risk abnormalities in Elise's cytogenetic profile
- her Revised International Prognostic Score of 2 indicates low risk.

Diagnosis and initial treatment

? HOW WOULD YOU DIAGNOSE ELISE?

- Elise's presentation and reported findings are diagnostic of acute myeloma with spinal cord impingement and significant hypogammaglobulinaemia.

? HOW SHOULD ELISE'S CONDITION INITIALLY BE MANAGED?

- Elise should be started on intravenous (IV) fluids and IV dexamethasone (4 mg 6 hourly) and urgent radiotherapy (20 Gy) to the T9 region and the associated epidural mass. IV zoledronic acid should be administered for control of calcium and ongoing for 'skeletal protection'.
- Start Elise on definitive anti-myeloma therapy with bortezomib, lenalidomide and dexamethasone, aiming for formal reassessment after four courses.
- Elise also requires immediate immunoglobulin (Ig) replacement starting with a loading dose of IVIg (0.4 g/kg). She should receive maintenance Ig replacement during the course of the disease.

Short-term outcome

Elise demonstrates significant neurological improvement following her initial course of treatment, with calcium and creatinine levels returning to within their reference ranges.

? HOW ELSE WOULD YOU TREAT ELISE OVER THE SHORT-TERM?

- Aim to maintain trough levels of IgG ≥ 6 g/L.
- Valaciclovir oral 500 mg twice daily for herpes zoster prophylaxis.
- Continue monthly IV zoledronic acid.

WHAT ARE THE NEXT STEPS?

- After four courses of therapy have been completed, assess performance status, conduct a full blood count, and assess biochemistry.

Elise has a normal peripheral blood smear and only a mild residual neurological deficit. Her laboratory results demonstrate normal levels of calcium and creatinine, and trough levels for IgG of 5.5 g/L and IgA of 0.7 g/L. A trace of IgAK paraprotein is seen on serum protein immunofixation and her bone marrow shows less than 5% of plasma cells with good recovery of normal haematopoiesis.

WHAT ARE THE NEXT STEPS?

- Continue IgG replacement.
- Collect peripheral blood stem cells followed by two further courses of bortezomib, lenalidomide and dexamethasone therapy with the aim of proceeding to an autologous stem cell transplant.
- Elise's autologous stem cell transplant is complicated by an episode of febrile neutropenia.

Assessment following transplant

At 8 weeks following her stem cell transplant, Elise is assessed again. Her performance status, haematology and biochemistry are found to be normal. Her IgG trough level is 6.1 g/L, her IgA is 0.5 g/L, and no paraprotein is detected on immunofixation. Her bone marrow shows less than 5% of plasma cells with normal haematopoiesis. Interphase FISH genetic analysis results are all normal.

WHAT ARE THE NEXT STEPS?

- Given the above, Elise can start to plan her return to work.
- She should commence maintenance lenalidomide therapy; zoledronic acid should continue; and 4 weekly IVIg should continue with 3 monthly IgG trough assessments.

Ongoing landmarks

Elise experiences one mild upper respiratory tract infection 9 months following her previous assessment. No antibiotic therapy is required, and revaccination for the flu and pneumococcus are scheduled. Her IgG trough level is 6.1 g/L.

WHAT ARE THE NEXT STEPS?

- Continue 4-weekly IVIg therapy and maintenance lenalidomide.

Two years later, Elise remains in complete remission with a normal bone marrow and interphase FISH genetic analysis, and no evidence of a paraprotein by immunofixation. Her IgG trough level is 6.3 g/L.

WHAT ARE THE NEXT STEPS?

- Elise should receive ongoing lenalidomide.
- Given that Elise has been in remission for 2 years, it may be appropriate to trial cessation of Ig.

During this discussion, Elise expresses hesitation with the plan as she doesn't want to lose the quality of life she has gained back.

HOW WOULD YOU ADDRESS ELISE'S CONCERNS?

- Use a conversation tool to guide your discussion around weaning off Ig – see the NPS MedicineWise tool: Immunoglobulin dose adjustment, weaning and cessation: a conversation guide for health professionals.
- Reassure Elise that she can be restarted on Ig at any point if relapse does occur.

After a long discussion, Elise agrees to trial a dose reduction toward cessation. Her weaning plan involves a 25% reduction in Ig dose each month and frequent reviews. After 6 months, Elise is reviewed and her condition remains in remission.

Practice points

- Patients receiving Ig replacement should be routinely reviewed by their haematologist. While the frequency of visits is determined by clinical status, an initial review within 6 months and reviews annually (at minimum) thereafter are required for ongoing access to government-funded Ig.[1] Reviews should include consideration of treatment efficacy and tolerability, history of infection and disease-specific considerations detailed in the Criteria.[1] Outcomes of each review should be recorded in BloodSTAR.
- Continuation of Ig therapy should depend on evidence of clinical benefit, including adequate replacement of antibodies (IgG, IgA, and IgM) and history of infection. As a generalisation, a trial of Ig cessation should be considered after each 12 months of treatment, and in patients who appear well, have no history of recent serious infection and have serum IgM, IgA and IgG levels approaching normal.[1] Where possible, trial cessation should commence in September or October in line with warmer months and reduced circulation of seasonal viruses.

Case Study 2: Louis

Presentation

Louis is a 69-year-old retired bus driver, known to have had chronic lymphocytic leukemia (CLL) for more than 10 years. At age 62 he developed treatment indications (Binet stage C) and received six courses of rituximab, fludarabine and cyclophosphamide (RFC). His pre-therapy Ig levels were within the normal range. His second course of RFC was complicated by an episode of febrile neutropenia, and he subsequently received granulocyte colony stimulating factor support to maintain an adequate neutrophil count during therapy.

After completion of his sixth course of therapy, Louis had a normal performance status and physical examination. His full blood count was within the reference range, apart from a lymphopenia (0.5 x 10^9/L) and a small residual population of CLL cells were detected in his peripheral blood by flow cytometry. His Ig levels were IgG 6.2 g/L, IgM 1.1 g/L, IgA 1.3 g/L and no paraprotein was detected.

He has regularly received the flu vaccine and pneumococcal vaccine, and takes pneumocystis pneumonia prophylaxis when lymphopaenic.

Six years later, Louis presents to your practice with a gradual onset of lethargy, constitutional symptoms, and lymphadenopathy, with a rising peripheral lymphocyte count (128 x 10^9/L) and falling haemoglobin levels (108 g/L).

His neutrophil count is 2.5 x 10^9/L, platelets 108 x 10^9/L, IgG is 4.61 g/L, his IgA is 0.8 g/L and IgM is 1.0 g/L. His bone marrow examination demonstrates an extensive infiltrate of CLL lymphocytes with a marked reduction in normal haematopoiesis, 11q deletion on FISH, and unmutated heavy-chain variable region gene (both high-risk features). Screening for TP53 is negative.

? WHAT ARE THE NEXT STEPS?

- Given lymphocyte doubling time and anaemia, re-treatment is indicated and Louis is commenced on ibrutinib.

Ibrutinib treatment leads to a gradual resolution of symptoms and lymphadenopathy, normalisation of his Hb (131 g/L), and a reduction in peripheral lymphocyte count.

Four months later, Louis is admitted to hospital with an episode of bronchopneumonia *(S. pneumoniae)* with tachypnoea and low PaO_2. He receives IV antibiotics and high-flow nasal oxygen supplementation. His neutrophil count is 1.9 and his IgG is 2.5 g/L.

? WHAT ARE THE NEXT STEPS?

- Given the severity of his presentation and the IgG level, Louis should receive a loading dose of 0.4 g/kg IVIg along with ongoing maintenance doses aimed at stabilising his trough level of IgG at > 6 g/L.

Follow-up

Louis' CLL remains stable with the combination of ibrutinib and IVIg.

? WHAT ARE THE NEXT STEPS?

- Measure Louis' IgG trough levels every 3 months, and adjust dose as required to maintain appropriate trough levels.
- Initiate a discussion with Louis regarding a possible transition to SCIg to reduce the need for hospital visits.

Practice points

- In contrast to IVIg, SCIg can be administered at the patient's home, and in much smaller doses. Since weekly SCIg injections produce more consistent, steady-state serum IgG levels, trough levels may not fall as low as IVIg and potential wear-off effects may be avoided.[2] The smaller doses at each administration and the relatively gradual systemic absorption of SCIg also lead to significantly fewer systemic adverse reactions compared to IVIg.
- Since both routes of administration have been shown to be effective and safe, the most appropriate option requires an assessment of the risks and benefits of each approach for a given patient, alongside logistical issues, patient preferences and individual pharmacokinetics.
- The BloodSTAR dose calculator can be used to determine the appropriate dose of Ig based on the patient's indication and body weight.

Note: In addition to meeting the clinical and diagnostic criteria for access (as defined in the Criteria), patients must access SCIg through an approved SCIg facility. This ensures that SCIg is appropriately managed, including making sure that patients are appropriately supported to use the product at home. There may be a waiting list to receive training, and SCIg clinics may not be available in all geographic locations.[3]

Access to IVIg in Australia

In Australia, the National Blood Authority's (NBA) Immunoglobulin Governance Program provides the framework for access to Ig products currently funded under the National Blood Agreement (the Agreement). The NBA manages contracts with suppliers to ensure a safe, secure, adequate, and affordable supply of blood and blood-related products such as Ig sourced from domestic and imported plasma. The NBA has contracted the Australian Red Cross LifeBlood to assess, authorise, and provide clinical advice on established or emerging therapeutic medical conditions identified in the Criteria for the clinical use of immunoglobulin in Australia (the Criteria).[1] The Criteria also define the conditions for which Ig can be used in exceptional circumstances.

Ig products are funded by governments and are provided to eligible patients at no direct cost. To access Ig under the Agreement, approved health providers (medical officers) are required to request product through the National online system BloodSTAR. The system manages the authorisation request and review process and ensures that access to Ig products is consistent with eligibility, as defined by the Criteria. Patients who are ineligible to access Ig under the Criteria may be able to access Ig through a Jurisdictional Direct Order, at a cost to the approved health provider or can be self-funded by the patient.

Additional resources

- NPS MedicineWise Immunoglobulin replacement therapy for acquired hypogammaglobulinaemia secondary to haematological malignancies: Clinical Guidance Article
- A full list of the conditions that are eligible for government-funded Ig: *Criteria for the clinical use of immunoglobulin in Australia*
- NPS MedicineWise: Immunoglobulin Management and Wellbeing Plan
- NPS MedicineWise Acquired hypogammaglobulinaemia and the role of immunoglobulin: consumer factsheet
- Immunoglobulin dose adjustment, weaning and cessation: a conversation guide for health professionals

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3. National Blood Authority. Access to subcutaneous immunoglobulin (SCIg). Canberra: Commonwealth of Australia. https://www.blood.gov.au/SCIg (accessed 24 March 2022).

VALUE IN PRESCRIBING PROGRAM – IMMUNOGLOBULIN PRODUCTS

Increasing the awareness and understanding amongst health professionals of access to immunoglobulin products in Australia, and improving health outcomes for patients through access to better health information to manage their health conditions. Funded by the Australian Government Department of Health through the Value in Prescribing Program: Immunoglobulins Products Grant.

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