Lancashire and South Cumbria Haematology CRG

GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF T-LARGE GRANULAR LYMPHOCYTE LEUKAEMIA (T-LGL)

Introduction: T-Large granular lymphocyte leukaemia (T-LGL) is characterised by peripheral blood and marrow lymphocytic infiltration with LGL's, splenomegaly and cytopenias, most commonly neutropenia. The LGL is a morphological distinct lymphoid subset that is larger than most circulating lymphocytes and has characteristic azurophilic granules containing acid hydrolases. LGL's comprise 10-15% of normal peripheral blood mononuclear cells.

Epidemiology: 2% to 5% of chronic lymphoproliferative disorder. Affects adults with a median age of 55 years and equal gender distribution. It arises more commonly in patients with auto-immune disorders, particularly rheumatoid arthritis. Also, association between MGUS, multiple myeloma, myelodysplastic syndrome and post bone marrow transplant.

Clinical Features:

Typically have an indolent clinical behaviour with a median survival of > 10 years.

Neutropenia (84%). Infections typically involve skin, oropharyngeal and perirectal areas but pneumonia can also occur. Opportunistic infections are uncommon.

Anaemia (50%). Transfusion dependent (20%); association with autoimmune haemolytic anaemia and pure red cell aplasia.

Thrombocytopenia (20%).

Lymphocytosis is usually between 2 and 20 x 109/l

B symptoms (30%).

Splenomegaly is seen in about two thirds of patients but lymph node enlargement is rare.

Diagnosis:

Peripheral blood and slides, bone marrow aspirate, trephine and cell markers to be sent to HMDS Leeds.

Peripheral blood - absolute lymphocyte count usually raised but may be normal. Absolute numbers of LGL's usually increased. Characteristic morphology.

Bone marrow may be hypercellular, normocellular or slightly hypocellular with mild to moderate reticulin fibrosis. Monoclonal LGL's usually less than 50% of nucleated cells. Interstitial and or intrasinusoidal infiltration of clonal, CD8 expressing T-Cells accompanied by lymphoid aggregates or nodules comprised of reactive (polyclonal) T and B cells.

Immunophenotype great majority of T – LGL leukaemia's express CD3, CD8, CD16, CD57 and the alpha/beta T-cell receptor (TCR) but do not usually express CD4, CD56 or CD28.

Clonal nature of T-cell LGL leukaemia most easily demonstrated by molecular studies of T-cell receptor. Identification of clonally rearranged T-cell receptor genes is the key factor in the diagnosis of T - LGL leukaemia (to be performed at HMDS Leeds).

Serological findings*:* Rheumatoid factor, the most common abnormality (60%). Antinuclear antibodies 40 – 50%. Serum protein electrophoresis may show hypergammaglobulinemia and a polyclonal pattern in about one half of patients. Also, association with MGUS.

Imaging – CT scan, US scan as indicated.

Treatment:

Not all patients with LGL leukaemia require treatment at the time of diagnosis. Active treatment for symptomatic disease only. Most cases have an indolent clinical behaviour with medium survival over ten years.

Indications for treatment:

- Severe neutropenia (< 0.5 $x10^9$/l)

- Moderate neutropenia (absolute neutrophil counts <1x10^9/l) with recurrent infections.
- Significant symptomatic anaemia (<9 g/dl) and/or the need for transfusion..
- Severe thrombocytopenia (very rare event <20) or bleeding and higher platelet threshold – clinical decision.

Initial Treatment:

Immunosuppressive therapy. Methotrexate, Cyclophosphamide, Cyclosporine. These drugs can be combined with prednisolone as indicated.

Methotrexate (up to 10 mg/m^2 weekly) with or without prednisolone is the most commonly used initial therapy especially for patients with neutropenia as a primary symptom. Response is seen in 50% of patients with time to response ranging from two to twelve weeks. Monitor FBC, renal and liver function tests.

Low dose Methotrexate 5 – 7.5 mg per week gradually increasing to 15 – 20 mg per week over one to three months has similar efficacy.

Cyclophosphamide (50 to 100 mg daily). Overall response rate 55 to 65% in previously untreated patients. One study showed efficacy along with prednisolone in the presence of pure red cell aplasia. Not a good option for neutropenic patients. Monitor FBC and renal function. Alkylating agent so advice regarding fertility, long term small risk of MDS, AML.

Cyclosporine response rate 56% 5-10 mg/kg per day orally in two divided doses for at least three months. Adjusted therapeutic blood level of 200 to 400 ng/mL. Close monitoring of renal function.

Low dose cyclosporine (1 to 1.5 mg/kg orally every 12 hours) with or without low dose GCSF led to a return of normal neutrophil count in one small study where the neutrophil count was less than 0.5

Toxicities include gastrointestinal disturbance, nephrotoxicity, hypertension, neurotoxicity and secondary malignancy. Blood pressure, creatinine, blood glucose, liver function tests, potassium and magnesium should be monitored.

Prolonged treatment (3-4 months) is often necessary to achieve a response and responders usually require long term maintenance.

Methotrexate and Cyclosporine can be continued indefinitely as tolerated. Cyclophosphamide should not be administered for longer than six to twelve months for responders.

Discontinuation of methotrexate and cyclosporine can be considered in patients who achieve complete remission for one to two years but studies show that the disease is likely to return slowly following cessation.

Other treatments: Steroids and growth factors may be beneficial in achieving rapid, but usually short-lived, improvement in cytopenias. Long term steroid therapy should be avoided. Erythropoietin can be given for anaemia only. Both have poor success rates.

Blood transfusion – consider chelation once ferritin > 1000.

Treatment of relapsed or resistant disease

Consider the use of one of the immunosuppressive drugs not previously used.

Patients who fail first-line therapy may benefit from purine analogues (fludarabine, cladribine, pentostatin). Combination therapy with fludarabine, dexamethasone and mitozantrone has been used.

Splenectomy can sometimes assist in relieving refractory cytopenias, especially those related to autoimmune haemolytic anaemia (AIHA) or immune thrombocytopenia (ITP).

Advise discussion with tertiary centre for possible clinical trials. Other drugs with anecdotal benefit: alemtuzumab, tacrolimus, azathioprine, anti lymphocyte globulin (ALG).

References:

- Springael C, Delrieu V, Wu KL, Schroyens W, Bonnet C, Bron D, Janssens A. BHS guidelines for the treatment of large granular lymphocyte and cronic prolymphocytic leukaemias. Belgian Journal of Hematology. 2016;7:103-11.

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