Supplement 1. Management options for specific clinical complications in non-transfusion-dependent thalassemia (NTDT) patients.

Pulmonary hypertension: sildenafil citrate, a potent inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase-5 and a selective smooth muscle relaxant, showed promising results for the management of pulmonary hypertension in small studies in β-thalassemia intermedia patients.[1-3] More recently, a multicentre trial on patients with thalassemia including β-thalassemia intermedia showed that sildenafil therapy may improve cardiopulmonary hemodynamics in patients at risk for pulmonary hypertension.[4] Bosentan (endothelin receptor antagonist) and epoprostenol (prostacyclin) were also reported to be effective in some patients.[5-7] Results from ongoing and future clinical trials will help structure management guidelines for PH in β-thalassemia, which have not yet been established.[8]

Extramedullary hematopoietic pseudotumors: Management options include blood transfusion therapy which helps decrease the demand for extramedullary hematopoiesis, radiotherapy of the tumors, or fetal hemoglobin induction by hydroxyurea. Combinations of these modalities have also been used. There is no evidence as to the best treatment and this remains individualized depending on severity of symptoms, size of the mass, clinical condition, and previous treatment.[9-11] Surgery is not always possible due to the diffuse nature of the mass and the likelihood of recurrence. Furthermore, immediate total resection of extramedullary hematopoietic masses can lead to clinical decompensation and deterioration because these masses play a crucial role in maintaining an adequate hemoglobin level.[12]

Leg ulcers: These ulcers are often very painful and indolent, and blood transfusions may provide some relief.[13] Simple measures may be beneficial, such as keeping the patient's legs and feet raised above the level of the heart for 1-2 hours during the day or sleeping with the end of the bed raised. Pentoxifylline which alters the rheological properties of the red blood cell[14] can accelerate the healing of ulcers. Hydroxyurea also has some benefit, either alone or in combination with erythropoietin.[13, 15] The use of an oxygen chamber can also provide moderate relief where tissue hypoxia may be an underlying cause of the ulceration.[16]

Endocrine disease and pregnancy: Fractures and bone pain can be devastating consequences of osteoporosis in NTDT patients. Different regimens of vitamin D and calcium are frequently prescribed to patients with NTDT, but with careful monitoring of renal function.[17-18] Although the efficacy and safety of bisphosphonates has been proven in patients with β-thalassemia major, data on patients with NTDT are limited.[19] Other endocrine complications can be treated as with patients with β-thalassemia major. In pregnant women with NTDT, experience reveals an increased risk of abortion, pre-term delivery, intrauterine growth restriction, Caesarean section delivery, and thromboembolic events.[20] Although the use of blood transfusions may be required to address these complications, the risk of alloimmunization in never transfused women should always be taken into consideration. Splenomegaly can interfere with the enlargement of the uterus and can be complicated by hypersplenism. Splenectomy can therefore become necessary during gestation or

after delivery. Anticoagulation should be considered especially in women with additional prothrombotic risk factors.[21]

Thrombotic disease: Unfortunately, there are no available results from trials on anticoagulant or antiplatelet therapy in patients with thalassemia. However, a lower recurrence rate of thrombotic events in β-thalassemia intermedia patients who took aspirin after their first event, when compared to those who did not, suggests a potential role for aspirin in this setting.[22] Moreover, the high prevalence of silent strokes in patients with elevated platelet counts calls for interventional trials evaluating the role of aspirin therapy.[23]

Hemolytic crisis: These commonly occur in hemoglobin H disease, but more so in non-deletional forms. Sudden, severe anemia following even mild febrile illness frequently occurs. In addition to febrile events, pregnancy often is associated with unexpected falls in hemoglobin levels. Immediate intervention is necessary and management includes blood transfusion, adequate hydration, correction of blood electrolytes, control body temperature, and identifying and treating the cause of infection.[24]

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