2018 ASH Highlights

December 6, 2018 – The 2018 American Society of Hematology meeting was held in San Diego Nov. 30 – Dec. 4. Below are some of the highlights of the meeting which are of particular interest to the thalassemia community. Note: The following is largely drawn from ongoing trials or includes information that is still being developed and evaluated in studies and may not be considered as definitive at this time.

Thalassemia gene therapy trials

Franco Locatelli reported on bluebird bio's ongoing Phase 3 Northstar-2 and Northstar-3 studies. Northstar-2 looks at transfused thalassemia patients with a non-β^0/β^0 genotype, with a primary endpoint of achieving transfusion independence. 11 patients have been treated as of Sept. 14, 2018. Ten of the 11 patients had stopped receiving transfusions and had hemoglobin levels of 11.1 – 13.3 g/dL at the time of the last study visit (3 – 18 months post-treatment). As of Sept. 14, 3 patients with a β^0/β^0 genotype or the equivalent had been treated in the Northstar-3 trial. All three patients, as of November 19, 2018, had total hemoglobin of greater than 10 g/dL at their last assessment, including a pediatric patient. Patient 1 had no transfusions following treatment and their last assessment at month 12, Patient 2 had their last transfusion 1.9 months post-treatment and last assessment at month six, Patient 3 had their last transfusion at 1.4 months post-treatment and last assessment at month three.

In reporting results from a separate bluebird bio gene therapy trial in sickle cell, it was reported that one sickle cell patient had developed myelodysplastic syndrome (MDS). The company has stated that analysis of the patient's cells indicate the disorder was not caused by the lentiviral vector used in the study.

Luspatercept

Data from the ongoing BELIEVE trial were reported by Maria Domenica Cappellini. This ongoing Phase 3 randomized, placebo-controlled trial is evaluating Luspatercept, an erythroid maturation agent, in transfusion-dependent thalassemia and e beta thalassemia patients. The primary endpoint is a reduction in transfusion burden of at

least 33% 13-24 weeks after treatment. 21.4% of patients in the Luspatercept arm achieved the primary endpoint. 19.6% achieved a 33% reduction later, during weeks 37-48.

Managing alpha thalassemia major

Douglas Higgs presented “Potential new approaches to the management of the Hb Bart’s hydrops fetalis syndrome: the most severe form of α-thalassemia.” The z form of hemoglobin is produced early in the embryonic stage and then typically silenced. Mouse models suggest that continued expression of this hemoglobin could ameliorate the severity of α-thalassemia. Current therapy includes in utero transfusions, as well as a new experimental method involving in utero transplantation.

Cardiovascular and endocrine complications

Alessia Pepe presented two papers on relationship between age and cardiac and endocrine complications; one paper focused on transfusion-dependent patients from Italy and one on non-transfusion-dependent patients from Italy.

In the transfusion-dependent study, patients were divided into 3 groups: those under 12 years of age, those 13-17 and those 18 and older. Among the stated results: younger patients had more hepatic iron, despite the significant lower transfusional burden. Cardiac iron overload occurs early in TDT patients but it is more frequent in older patients. Cardiac iron overload occurs early in TDT patients but it is more frequent in older patients. Endocrinopathies (excluding diabetes) and cardiac complications become clinically evident during the second decade and are time-dependent processes. The data suggest the need for an effective strategy to prevent iron overload since early childhood, in order to reduce its toxic effect and prevent the development of long-term complications.

In the non-transfusion-dependent study, the patients were divided into six age groups: under 18, 18-30, 30-40, 40-50, 50-60, and older than 60. Only one patient showed cardiac iron (T2*<20 ms). Diabetes appeared only in patients more than 50 years and showed a trend toward increasing with increasing age. Hypothyroidism and osteoporosis were not present in pediatric patients and were not associated with age. Hypogonadism was not present in patients of less than 30 years and its frequency was comparable among the age groups. Only patients older than 30 years showed a cardiac

complication (heart failure or arrhythmias), but the rate did not significantly increase with increasing age. Liver iron became overloaded at an early age.

Hematopoietic cell transplantation (HCT)

Emanuele Angelucci reported on HCT for thalassemia and sickle cell, using data from a European registry. 2936 thalassemia patients and 920 sickle cell patients in this registry received transplants between 2000 and 2017. For the thalassemia patients, the 2-year overall survival (OS) rate was 90%; the event-free survival (EFS) rate was 84%. Broken down further, the OS and EFS were 93% and 86% for sibling identical matched donors; 85% and 78% for other relative donors; 87% and 81% for unrelated donors; and 82% and 73% for related haploidentical donors.(Haploidentical means half-matched; donor is typically a parent of the patient.) Bone marrow was the source of hematopoietic cells for 70% of the thalassemia patients.

Bone health

A study of bone health in Thai thalassemia patients was presented by Pokpong Piriyakhunt. 89 transfusion-dependent and 51 non-transfusion dependent patients were screened. Thalassemia-associated osteoporosis was found in about 75% of the patients. Almost 23% of the patients had vertebral fractures. Low hemoglobin levels and high non-transferrin-bound iron were associated with thalassemia-associated osteoporosis and fractures.

Rapamycin

Rapamycin is a drug which has several uses, including preventing organ transplant rejection and fighting a rare lung disease. Christophe Lechauve reported on a study looking at using rapamycin in thalassemia. Cells taken from both transfusion-dependent and non-transfusion-dependent thalassemia patients were treated and studied. The rapamycin appeared to reduce free α-globin, which could potentially benefit b-thalassemia patients. Further studies are needed.