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POSTER ABSTRACTS

509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Long-Term Hematopoietic Dysfunction in Patients with Single Large-Scale Mitochondrial DNA Deletion Syndromes

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Pearson syndrome (PS) is the only single large-scale mitochondrial DNA deletion syndrome (SLSMDs) presenting substantial hematologic manifestations, usually a severe though transient cytopenia of childhood. Recently, progression to myeloid malignancies has been described among PS patients. Older PS patients, as well as patients with SLSMDs presenting with Kearns-Sayre syndrome (KSS) or with progressive external ophthalmoplegia (PEO), do not display hematologic abnormalities. Since the underlying mitochondrial DNA deletion is similar in all SLSMDs, we hypothesized that bone marrow (BM) dysfunction is a common and persistent manifestation in these patients.

We studied 16 patients with molecular-confirmed SLSMDs: 13 with PS, and three with KSS. The median age at diagnosis was 25 months (range 2-136 months). Seventy-five percent of patients presented with cytopenia in infancy, and 56% required blood products. Resolution of cytopenia occurred in 92% of this subgroup, at a median age of 24 months (range 12-39 months).

BM studies were performed in all patients, and 56% of patients had multiple BM evaluations. All BM biopsies examined showed signs of marrow dysfunction, including in patients without a history of cytopenia. Median BM cellularity was 50% (range 30-80%) at a median age of 5 years. BM samples showed a paucity of precursor myeloid cells, signs of dyserythropoiesis, and abnormal or missing megakaryocytes. We report low hematopoietic stem and progenitor cell functionality in patients with SLSMDs: The median CD34+ count was 0.68% (range 0.27-1.92%, expected range 1-2%). BM colony forming unit (CFU) capacity was reduced in SLSMD patients: the median CFU in patients was 280 per 10^6 cells compared to 1090 per 10^6 cells in healthy controls (p=0.004). Conventional cytogenetic analysis was done on 10 patients (62%), and FISH analysis was done on 15 patients (93%). Monosomy 7 was identified in seven patients (44%): in one patient the monosomy 7 resolved in a follow-up BM assay. Another patient with signs of myelodysplasia and 30% of the BM cells having monosomy 7 was referred to an allogeneic bone marrow transplantation.

To conclude, long-term BM dysfunction is evident in all patients with SLSMD and includes a risk of developing clonal evolution and monosomy 7. This data, combined with other recent publications, highlights the ongoing marrow failure and suggest that SLSMD syndromes should be included under inherited BM failure syndromes.

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