Late Endocrine Effects Despite Reduced Intensity Chemotherapy for Hematopoietic Stem Cell Transplantation in Children

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Introduction

- The endocrine system is extremely susceptible to damage by high dose chemotherapy and radiation associated with hematopoietic stem cell transplantation (HSCT), which can result in short stature, hypothyroidism, hypogonadism, and disorders of bone metabolism
- Advances in HSCT have allowed for reduced intensity conditioning (RIC) regimens involving less toxic chemotherapy and no radiation
- Little is known about the endocrine effects of RIC in children receiving HSCT

Hypothesis

- Treatment with RIC regimens will result in few endocrine effects in patients receiving HSCT

Population and Methods

- An IRB approved retrospective chart review was performed for 122 children at our center, who received RIC for HSCT between 2004 and 2012 and survived at least 1 year. Patients were excluded if they received a second HSCT.
- All patients received RIC (campath, fludarabine, and melphalan) but no radiation
- For analysis, patients were grouped by diagnosis (see below)
- BMI Z-score (BMI-Z), height for age Z-score (HAZ), thyroid testing, and 25-OH vitamin D levels were measured both prior to and following HSCT.
- Steroid therapy was defined as glucocorticoids administered either before HSCT or beyond 2 months following HSCT.

Results

Table 1. Patient Characteristics

Diagnosis	Number of patients	Male	Age > 12 years	Steroid Therapy	Average age at HSCT (y)	Time between pre & post HSCT measurements (y)
PID	33	19	5	14	5.8	3.4
HLH/XLP	59	41	9	57	6.3	2.9
BMF & Metabolic	30	17	5	3	6.1	3.9
Total	**122**	**77**	**19**	**74**	**6.0**	**3.3**

PID (Primary Immune Deficiencies): autoimmune lymphoproliferative syndrome, combined immune deficiency, common variable immunodeficiency, hypereosinophilic syndrome, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, Langerhans cell histiocytosis, Ommen's syndrome

HLH/XLP: hemophagocytic lymphohistiocystosis & X-linked lymphoproliferative syndrome

BMF & Metabolic: adrenoleukodystrophy, leukemia (ALL, CML, lymphoproliferative disorder), aplastic anemia, familial aplastic anemia, syndromes (Hurler, Kostmann, Krabbe, Shwachman-Diamond, Seckel), other BMF

Results

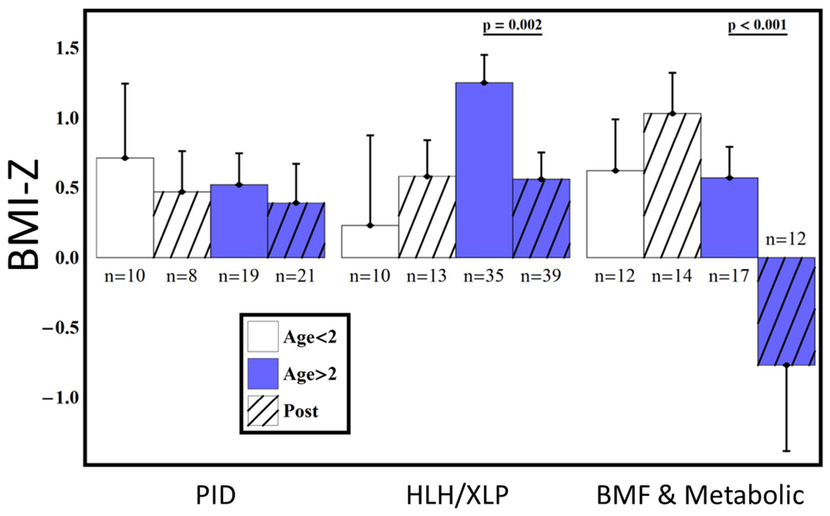

Figure 1. After HSCT, BMI-Z significantly declined in older patients with HLH/XLP and BMF & Metabolic syndromes. There was a trend toward increased BMI-Z among younger children in these same groups. No differences were noted in the PID population.

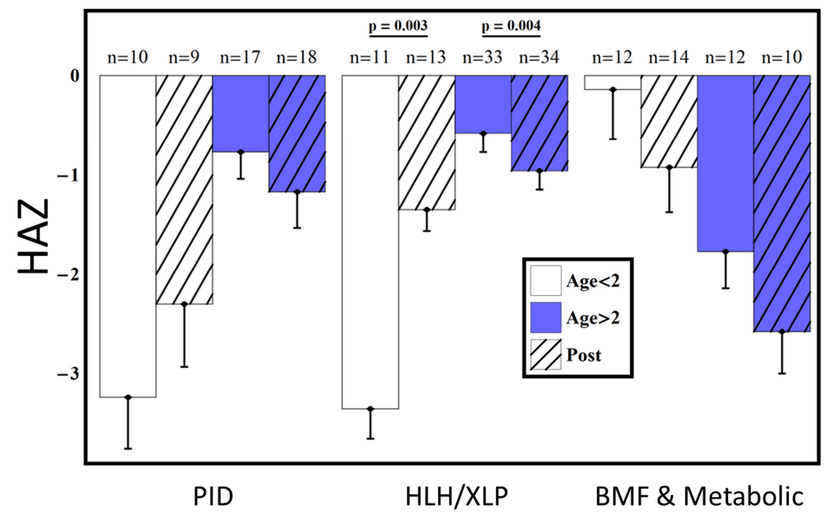

Figure 2. All groups displayed short stature. Younger children with PID and HLH/XLP had more severe short stature than older patients perhaps due to more severe presentation or steroid treatment. The opposite was observed in BMF & metabolic syndromes. After HSCT, HAZ significantly increased in younger children with HLH/XLP, while older children had significant worsening of HAZ.

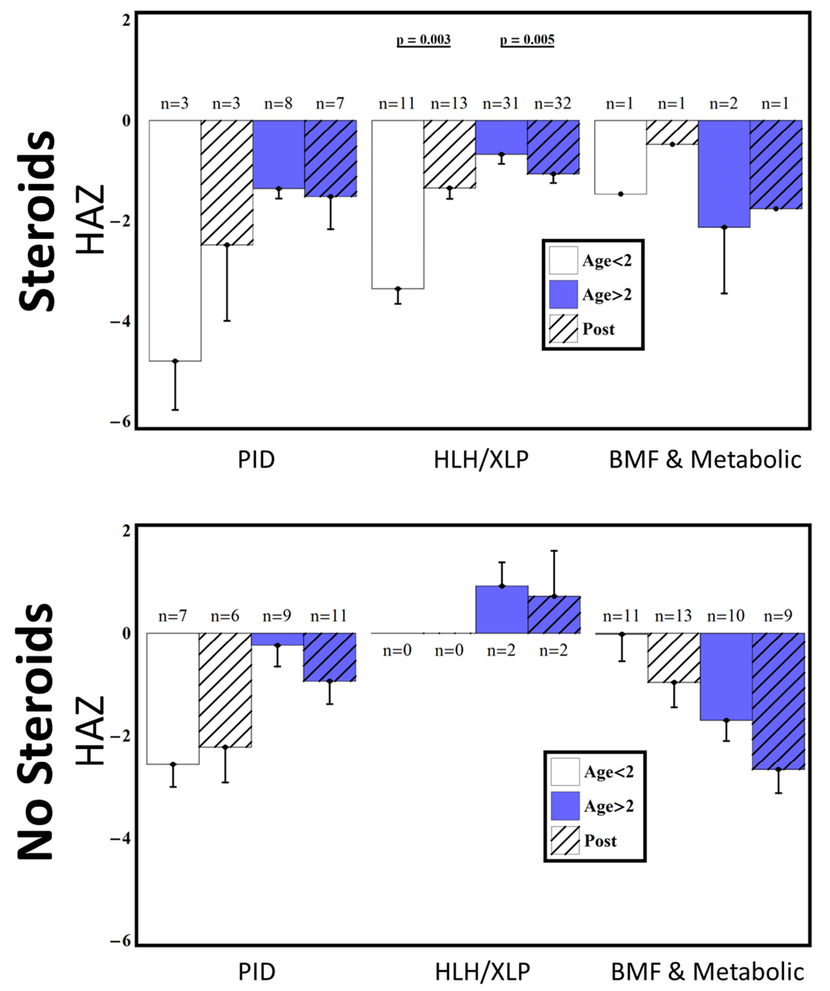

Figure 3. Overall, patients receiving steroid therapy were shorter than untreated patients ($p = 0.02$). However, when analyzed by diagnosis groups, no additional significant differences were noted between pre- and post-HSCT populations.

Results

Table 2. Post-HSCT thyroid disease among children with RIC

Diagnosis	Post-HSCT thyroid function tests	Normal (% total)	Primary Hypothyroid (% total)	Central Hypothyroid (% total)	Primary Hyperthyroid (% total)
PID	17	13 (76%)	1 (6%)	1 (6%)	2 (12%)
HLH/XLP	43	33 (77%)	7 (16%)	3 (7%)	--
BMF & Metabolic	17	13 (76%)	3 (18%)	1 (6%)	--
Total	**77**	**59 (77%)**	**11 (14%)**	**5 (7%)**	**2 (3%)**

Table 3. Post-HSCT vitamin D deficiency among children with RIC

Diagnosis	Post-HSCT 25-OH Vitamin D levels	Normal ≥30 ng/mL (% total)	Low <30 ng/mL (% total)
PID	15	7 (47%)	8 (53%)
HLH/XLP	33	6 (18%)	27 (82%)
BMF & Metabolic	18	7 (39%)	11 (61%)
Total	**66**	**20 (30%)**	**46 (70%)**

Table 4. Extreme HAZ or BMI-Z events within the study population (not included in analysis)

Diagnosis	Pre-HSCT HAZ <-5 SD or >+3 SD	Post-HSCT HAZ <-5 SD or >+3 SD	Pre-HSCT BMI-Z <-5 SD or >+5 SD	Post-HSCT BMI-Z <-5 SD or >+5 SD
PID	2	2	--	--
HLH/XLP	2	1	3	--
BMF & Metabolic	1	1	--	--
Total events*	5	4	3	--

*Total number of patient s with extreme measurements = 10

Conclusions

- Endocrine complications, including short stature, hypothyroidism, hyperthyroidism, and vitamin D deficiency still occur after HSCT despite reduced intensity chemotherapy and no use of total body irradiation
- Overall, steroid treatment resulted in shorter stature; however numbers were not sufficient to perform a complete analysis of the effects of steroids by diagnostic group.
- Prospective follow-up is necessary for detection of further endocrine manifestations. Likewise, comparison is needed of post-HSCT endocrine complications after reduced intensity vs. standard myeloablative protocols.