Melita Irving, MBBS MD(Res), FRCPCH, BSc.(Hons)[4].
[1]Murdoch Children's Research Institute, Melbourne, Australia, [2]The Hospital for Sick Children, Toronto, ON, Canada, [3]QED Therapeutics Inc., San Francisco, CA, USA, [4]Guy's and St Thomas' NHS Trust, London, United Kingdom.

Background: ACH, the most common non-lethal form of skeletal dysplasia, is characterized by defective endochondral ossification resulting from gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, a negative regulator of endochondral bone formation. Current treatment options are non-targeted, ineffective, or painful interventions aimed at preventing or treating complications. Infigratinib is an orally bioavailable and selective FGFR1-3 tyrosine kinase inhibitor in development for FGFR-related conditions. *In vitro* data with infigratinib showed inhibition of FGFR1-3 activity with reversal of established growth arrest in chondrocytes. *In vivo* studies revealed dose-dependent improvements in foramen magnum and long bone length in *Fgfr3*$^{Y367C/+}$ mice following treatment with infigratinib. **Methods:** PROPEL2 is a prospective, phase 2, open-label study of infigratinib in children with ACH. Children 3-11 years of age with ACH who have completed at least 6 months of observation in the observational PROPEL study are eligible to participate. PROPEL2 consists of dose escalation with an extended treatment phase, designed as dose finding, followed by a dose-expansion phase to confirm the selected dose and to provide evidence of efficacy. The primary endpoints of the dose-escalation/extended treatment phase are treatment-emergent adverse events and change from baseline in annualized growth velocity. Subjects (n=40) will be enrolled in ascending dose cohorts of approximately 10 subjects/cohort (4 cohorts planned) and treated for 6 months at their assigned dose, continuing for an additional 12 months with dose modifications as required. Up to 20 new subjects will be enrolled in the dose-expansion phase and receive infigratinib (mini-tablets, administered orally once daily) for 12 months. Secondary objectives include: safety/tolerability of infigratinib; changes from baseline in anthropometric parameters, including body proportions; and the pharmacokinetic/pharmacodynamic profile of infigratinib. An exploratory objective is evaluation of changes in ACH disease burden. **Current Status:** PROPEL2 is currently enrolling - the first subject was entered in July 2020. The planned total enrollment is 60 children with ACH (n=40 in the dose-escalation/extended treatment phase; n=20 in the dose-expansion phase). Following completion of PROPEL2, subjects have the opportunity to enroll in an open-label long-term extension study to assess the safety and efficacy of long-term administration of infigratinib in children with ACH.

Pediatric Endocrinology

DISORDERS OF PUBERTY

Late Endocrine Effects After HSCT in Children With Nonmalignant Diseases; A Single Center Cohort Analysis

Liselotte C. de Kloet, MD[1], Joëll E. Bense, MD[1], Eileen van der Stoep-Yap, MSc PharmD[2], Marloes Louwerens, MD[2], Erik GJ von Asmuth, MD[1], Adriaan C. Lankester, MD, PhD, Professor[1], Anne PJ de Pagter, MD, PhD[1], Sabine E. Hannema, MD, PhD[3].
[1]Willem-Alexander Children Hospital, LUMC, Leiden, Netherlands, [2]LUMC, Leiden, Netherlands, [3]Amsterdam UMC, Amsterdam, Netherlands.

Endocrine complications are amongst the most frequent late effects after pediatric hematopoietic stem cell transplantation (HSCT) for malignant diseases. Little is known about the prevalence and risk factors of endocrine complications in children transplanted for nonmalignant diseases. This retrospective study included 134 males and 63 females transplanted for a non-malignant disease between 1997 and 2018 with at least 2 years of follow up. Endocrine late effects and growth were evaluated. Gonadal dysfunction was defined as transient or permanent elevation of gonadotropins or hypogonadotropic hypogonadism.

Median age at HSCT was 5.7 years (IQR 2.8-11.3) and median follow-up was 6.2 years (IQR 3.0-10.4). Underlying diseases were inborn errors of immunity (n=74), hemoglobinopathies (n=66) and bone marrow failure (n=57). The majority of patients had received busulfan-based conditioning (46%) or treosulfan-based conditioning (34%).

Gonadal dysfunction occurred in 24/44 (post)pubertal female patients (55%) and was permanent in 19/44 (43%). 22/44 received hormonal substitution, which could be discontinued in 7. In females who received busulfan-based conditioning 16/17 (94%) developed gonadal dysfunction compared to 5/15 (33%) patients with treosulfan-based conditioning; the odds ratio for permanent gonadal dysfunction was 18.7 (3.61-135, p=0.001).

Gonadal dysfunction occurred in 28/66 (post)pubertal male patients (42%) and was permanent in 23/66 (35%). 6/66 received hormonal substitution, which could be discontinued in 1. Gonadal dysfunction was more common in males (post)pubertal at HSCT, 14/21 (67%), compared to those prepubertal at HSCT, 14/45 (31%), p=0.014. 3/15 treated with a treosulfan-based regimen (20%) developed gonadal dysfunction, all transient, versus 19/39 with a busulfan-based regimen (49%), with 2 transient.

29/187 patients developed hypothyroidism (16%), 7 patients received thyroxine treatment (4%). All patients with persistent primary hypothyroidism (n=6) had positive TPO-antibodies.

17 patients received growth hormone treatment and were excluded from analysis. In patients without growth hormone treatment near adult height (NAH) was -1.2 SDS (median, IQR -2.0- -0.3) below mean parental height (MPH) in males and -0.4 SDS (median, IQR -1.6-0.3) in females. NAH below -2 SDS was seen in 13/43 males (30%) and 2/36 females (6%). The majority of these patients already had a height below -2 SDS before HSCT (73%).

In conclusion, this study on late endocrine effects after HSCT in children with nonmalignant diseases indicates frequent gonadal dysfunction, present in 55% of females and 42% of males. In this cohort, risk of gonadal dysfunction in females was higher after busulfan-based conditioning than treosulfan-based conditioning. Careful long-term endocrine follow-up is indicated.