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Growth Hormone Treatment of Patients with Fanconi Anemia after Hematopoietic Cell Transplantation

Gregory P. Forlenza, MD¹, Lynda E. Polgreen, MD, MS¹, Bradley S. Miller, MD, PhD¹, Margaret L. MacMillan, MD², John E. Wagner, MD², and Anna Petryk, MD^{1,*}

¹Department of Pediatrics, Division of Pediatric Endocrinology, University of Minnesota, Minneapolis, MN 55455, USA

²Department of Pediatrics, Division of Pediatric Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN 55455, USA

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Short stature is common in patients with Fanconi anemia (FA) and may be due to growth hormone deficiency (GHD) [1–4], especially after hematopoietic cell transplantation (HCT) [5]. Yet, there are no published data on the effectiveness of recombinant human GH treatment in these patients. Therefore, we conducted a retrospective case review study that included 4 patients with FA treated with GH for 2 years who reached near adult height. All patients received allogeneic HCT at the University of Minnesota between 2002 and 2008. We hypothesized that height would increase by at least 0.5 SDS in response to therapy.

Patients who met two of the three criteria: height -1.5 SDS, growth velocity -2.0 SDS, or height SDS >2 SD below the mid-parental height, underwent GH stimulation testing with clonidine and arginine. GHD was defined as a stimulated GH level <10 $\mu\text{g/L}$ [6]. Evaluation included physical examination, bone age radiograph, magnetic resonance imaging (MRI) or computed tomography scan of the brain, thyroid tests, and growth factor levels. This study was approved by the University of Minnesota Institutional Review Board.

The mean age at FA diagnosis was 7.0 ± 1.9 years and was 8.7 ± 2.2 years at HCT. All patients had GHD. Patient 1 had an ectopic pituitary gland with pituitary stalk anomaly and Patient 3 had a pituitary microadenoma on MRI. Patients 2 and 4 had normal brain scans. Patient 2

*Address correspondence to: Dr. Anna Petryk, University of Minnesota Amplatz Children's Hospital, Pediatric Endocrinology, East Building Room MB671, 2450 Riverside Ave., Minneapolis, MN 55454, Phone: 612-624-5409, Fax: 612-626-5262, petry005@umn.edu.

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CONFLICT OF INTEREST STATEMENT

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was diagnosed with premature ovarian failure at 12 years and was treated with estrogen replacement throughout the course of GH therapy. Patients 1 and 4 had a transient subclinical hypothyroidism, which resolved without treatment within a year. Patient 2 had normal thyroid function. Patient 3 had primary hypothyroidism prior to starting GH therapy and was euthyroid on levothyroxine during GH treatment.

Table I shows GH treatment data. The average age at GH start was 10.7 ± 1.8 years. GH dose was 0.28 ± 0.03 mg/kg/week. The initial bone age was delayed (2 SD below the mean) for Patients 1 and 2. The average growth rate was 4.0 ± 1.1 cm/yr (-2.2 ± 1.8 SD) at baseline, 6.6 ± 3.9 cm/yr (1.7 ± 4.9 SD) in year 1, 9.2 ± 3.1 cm/yr (4.0 ± 1.0 SD) in year 2, 5.6 ± 2.0 cm/yr (1.1 ± 3.7 SD) in year 3, and 5.7 ± 1.1 cm/yr (1.2 ± 2.1 SD) in year 4. The mean increase in height was 0.9 ± 0.6 SDS ($p=0.05$). The smallest response to GH therapy was seen in Patient 4 who was the oldest and showed no improvement in insulin-like growth factor-1 (IGF-1) SDS, suggesting that optimization of GH dose based on IGF-1 levels may have improved outcome. There were no adverse events from GH.

In conclusion, GH treatment was well tolerated and had a positive effect on growth, resulting in an increase in height of at least 0.5 SDS in three out of four patients. It should be noted, however, that the long-term risk of GH treatment in these patients is unknown. Although HCT reduces the risk of leukemia, all patients with FA are at increased risk of solid tumors, including head and neck cancers, and gynecological cancers [7–9]. Therefore, continued surveillance is needed.

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Table I

Growth hormone treatment data

Patients	1	2	3	4
Sex	M	F	M	F
Pre-treatment data				
Age at HCT (yr)	5.9	8.7	9.1	11.2
Age at GH start (yr)	8.3	10.4	11.2	12.7
Tanner stage	1	1	1	1
Ht SDS	-2.5	-2.7	-1.9	-2.0
Mid-parental height SDS	0.0	-0.4	0.6	0.3
Growth velocity SDS	-3.8	-2.1	0.3	-3.3
Stimulated GH level (µg/L)	3.3	9.2	9.1	7.0
IGF-1 SDS ^a	-2.1	-1.5	-2.0	-1.8
IGFBP-3 SDS ^a	-1.8	-0.1	-1.5	-1.5
Post-Treatment data				
Age (yr)	14.9	13.7 ^b	15.3	16.3
Bone age (yr)	16.0	12.5 ^b	17.0	14.0
Tanner stage	4	4 ^b	5	4
Years of GH therapy	6.6	3.3	4.1	2.4
GH dose ^c	0.26±0.08	0.28±0.03	0.32±0.09	0.26±0.01
Ht SDS at GH stop	-1.4	-2.1 ^b	-0.3	-1.7
Change in Ht SDS	1.1	0.6	1.6	0.3
IGF-1 SDS ^{a,d}	0.4±1.7	-1.0±0.07	0.0±0.9	-2.2±0.3
IGFBP-3 SDS ^{a,d}	0.0±0.5	0.2±0.3	0.0±0.4	-1.0±0.07

^a quantified by immunoassay,^b at last visit, still on GH;^c mg/kg/week, mean± SD;^d mean value over a period of GH treatment ± SD