Title	Exploring height outcomes with adjuvant aromatase inhibition in growth hormone–deficient male survivors of childhood cancer
Authors	Pollock, Netanya I.;Song, Minkeun;Wolf, Alexander J.;Li, Yimei;Hawkes, Colin P.;Motamedi, Niloofaralsadat;Denburg, Michelle R.;Mostoufi#Moab, Sogol
Publication date	2024-05-28
Original Citation	Pollock, N. I., Song, M., Wolf, A. J., Li, Y., Hawkes, C. P., Motamedi, N., Denburg, M. R. and Mostoufi#Moab, S. (2024) 'Exploring height outcomes with adjuvant aromatase inhibition in growth hormone–deficient male survivors of childhood cancer', Pediatric Blood and Cancer, 71(8), e31117 (9pp). https://doi.org/10.1002/pbc.31117
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1002/pbc.31117
Rights	© 2024, Wiley Periodicals LLC.This is the accepted version of the following item: Pollock, N. I., Song, M., Wolf, A. J., Li, Y., Hawkes, C. P., Motamedi, N., Denburg, M. R. and Mostoufi#Moab, S. (2024) 'Exploring height outcomes with adjuvant aromatase inhibition in growth hormone–deficient male survivors of childhood cancer', Pediatric Blood and Cancer, 71(8), e31117 (9pp), which has been published in final form at: https://doi.org/10.1002/pbc.31117. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.
Download date	2026-09-19 02:09:17
Item downloaded from	https://hdl.handle.net/10468/16793

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2024 August 02.

Published in final edited form as:

Pediatr Blood Cancer. 2024 August ; 71(8): e31117. doi:10.1002/pbc.31117.

Exploring height outcomes with adjuvant aromatase inhibition in growth hormone deficient male survivors of childhood cancer

Netanya I. Pollock[1], **Minkeun Song**[2], **Alexander J. Wolf**[3], **Yimei Li**[4], **Colin P. Hawkes**[1,5,6,7], **Niloofaralsadat Motamedi**[2], **Michelle R. Denburg**[4,7,8], **Sogol Mostoufi-Moab**[1,2,7]

[1]Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[2]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[3]Division of Nephrology, Stanford Children's Health, Stanford, California

[4]Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[5]Department of Paediatrics and Child Health, University College Cork, Cork, Ireland

[6]INFANT Research Centre, University College Cork, Cork, Ireland

[7]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[8]Division of Nephrology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Abstract

Background: Aromatase inhibitors (AI) may improve height in short stature conditions, however the effect in childhood cancer survivors (CCS) is unknown. We assessed final adult height (FAH) in CCS treated with AI and GH compared to those treated with GH alone.

Methods: Retrospective cohort study of GH deficient male CCS treated between 2007 and 2023. FAH was noted as height at fusion of growth plates or 18 years of age. Multivariable linear regression was used to examine treatment association with FAH, adjusting for other risk factors.

Results: Ninety-two patients were included; 70 were treated with GH and 22 with combination AI/GH. The mean age at GH initiation did not differ between groups. Mean age at AI initiation was 13.7 ± 1.9 years. A greater proportion of patients in the AI/GH group were treated with stem cell transplantation, abdominal radiation, total body irradiation, and *cis*-retinoic acid ($P<0.01$). Multivariable linear regression demonstrated no significant treatment association with final adult height Z-score (β= 0.04, 95% CI −0.9, 0.9). History of spinal radiation (β= −0.93, 95% CI −1.7, −0.2), lower starting height Z-score (β= −0.8, 95% CI −1.2, −0.4), and greater difference between

Corresponding author and reprint requests: Netanya I. Pollock, MD, 3500 Civic Center Boulevard Philadelphia, PA 19104, pollockn@chop.edu, Fax 215-590-3053.

CONFLICTS OF INTEREST STATEMENT

The authors declare that this original research manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICAL STATEMENT: The study received ethical approval from the Children's Hospital of Philadelphia IRB. The study was determined to be exempt (IRB approval number, 20-017796).

bone age and chronological age (β= −0.3, 95% CI −0.5, −0.07) were associated with lower final adult height Z-score.

Conclusions: Adjuvant AI was not associated with increased FAH in male CCS compared to GH monotherapy. Future work is needed to determine optimal adjunctive treatment to maximize final adult height for this population.

Keywords

aromatase inhibitor; growth hormone deficiency; final adult height; childhood cancer survivor

INTRODUCTION

Advances in childhood cancer treatment have significantly improved survival rates, with recent estimates of 5-year overall survival exceeding 80%.[1] However, as childhood cancer survivors (CCS) are living longer into adulthood, the burden of chronic health conditions following cancer treatment is increasing.[1,2] Late endocrinopathies are prevalent, with abnormalities in at least one hormone occurring in more than 50% of childhood cancer survivors.[3] Growth hormone (GH) is the most common pituitary hormone deficiency in CCS, often secondary to tumor location and subsequent treatment with surgery, radiation, chemotherapy, or targeted immunotherapy.[4] Despite GH treatment, many have suboptimal height outcomes due to the impact of other factors on growth, including additional hormone deficiencies, abnormal pubertal timing, compromised nutritional status, or the deleterious direct effects of spinal radiation, total body irradiation (TBI), or *cis*- retinoic acid on the skeleton.[5,6]

Aromatase is a key enzyme in the biosynthesis of estrogen, and in both sexes, estrogen induces growth plate closure following sexual maturation.[7] The use of adjuvant therapy with reversible aromatase inhibitors (AIs), such as anastrozole or letrozole, may support growth potential in the male pediatric cancer survivor population and improve final adult height. As AIs block the conversion of androgens to estrogen, there is the potential to delay growth plate closure and increase time for linear growth. The efficacy of aromatase inhibition is biologically plausible, as patients with aromatase deficiency have tall stature,[7,8] however, the studies of AIs for height indications have shown conflicting results.[9-11] The effectiveness of AI on improving final adult height in the childhood cancer population is unknown. Therefore, the objective of this study was to assess final adult height in CCS treated with AI combined with GH therapy compared to those treated with GH alone.

MATERIALS AND METHODS

Study design and participants

A single center retrospective cohort study of male survivors of childhood cancer or non-cancer diagnosis requiring cancer therapy (e.g. bone marrow failure syndrome treated with allogenic hematopoietic stem cell transplantation) was performed. Survivors were followed in the Endocrine Late Effects of Cancer Therapy (ELECT) program at the Children's Hospital of Philadelphia (CHOP) between 2007 and 2023 and treated with GH for a diagnosis of GH deficiency. We compared height outcome in males treated with GH

alone or with off-label use of AI in an attempt to improve final adult height. Due to the sex-specific effects of AIs, this study was limited to biologically male patients. The study was determined by the Institutional Review board at CHOP to be exempt (IRB approval number, 20-017796).

Anthropometric measurements and physical maturity

Anthropometric measurements including weight, height, and body mass index (BMI) were extracted from endocrinology visits. Sex adjusted mid-parental height was calculated via the Tanner method.[12] Height velocity was calculated during the GH treatment period for both groups. As subjects in the combined GH and AI group were treated with AI for a shorter duration of up to two years, height velocity for this cohort was calculated during GH and AI treatment. Final adult height was noted as height documented at a bone age of 17 years, where there is complete fusion of growth plates, or once patients reached 18 years of age without a history of delayed bone age. Physical maturity and pubertal status were determined based on previous Tanner staging by a pediatric endocrinologist (SMM) and were extracted from the electronic medical record. Subjects were classified as pre-pubertal if Tanner stage 1, pubertal if Tanner stages 2-3, and post-pubertal if Tanner stages 4-5. Given the known impact of alkylating chemotherapy on Sertoli cell function and elevation in gonadotropin levels, puberty was defined by Tanner staging and morning testosterone level > 10 ng/dL without the use of gonadotropins.[13] Bone age interpretations were based on formal left hand radiographic interpretations by radiologists using the Greulich and Pyle methodology and further confirmed by the treating endocrinologist (SMM). Relative skeletal maturation was expressed as bone age minus chronological age. Additionally, patients were categorized with congruent bone ages if within 2 SD of chronological age, delayed bone age if > 2 SD younger than chronological age, and advanced bone age if > 2 SD older than chronological age.

Endocrine disorders

Patients were recorded as having specific endocrinopathies, including GH deficiency, hypothyroidism, hypogonadism, precocious puberty, adrenal insufficiency, or diabetes mellitus, if diagnosed by a pediatric endocrinologist in the medical record. All included patients were on GH therapy for GH deficiency, which was diagnosed based on abnormal growth pattern and supporting laboratory testing including insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP3), and/or GH peak ≤ 10 ng/mL on confirmatory provocative testing, according to institutional standards.[14,15] The GH dose ranged from 0.26 to 0.3 mg/kg/week and was titrated to maintain IGF-1 values within +1 to +2 SD for age, sex, and pubertal maturation. Patients were started on AI at the discretion of the treating endocrinologist.

Biochemical measurements

To evaluate the safety and efficacy of AI treatment, laboratory values prior to and post AI treatment were extracted from the electronic health record. Total serum testosterone (ng/dL) concentration was analyzed by liquid chromatography/tandem mass spectrometry, with a lower limit of detection of 2.5 ng/dL (Esoterix, Inc, Calabasas Hills, CA).[16] IGF-1 (ng/mL) concentrations were analyzed by chemiluminescent immunoassay (Esoterix Inc,

Calabasas Hills, CA). Hemoglobin A1c (%) was analyzed on Vitros 4600 automated chemistry analyzer by Ortho Clinical Diagnostics (CHOP, Philadelphia, PA, USA).

Statistical analysis

All statistical analyses were performed using Stata version 18.0 (StataCorp LLC, College Station, TX, USA). Tests were carried out at a two-sided significance level of 5%. Differences in demographic and clinical characteristics between treatment groups were assessed using the *t*-test or Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for categorical variables. Differences in laboratory values pre and post AI therapy were assessed using the paired *t*-test or Wilcoxon signed rank test.

Age and sex-specific Z-scores for weight, height, and BMI were calculated for individuals less than 20 years of age using the National Center for Health Statistics 2000 Center for Disease Control (CDC) growth data.[17] Mid-parental height Z-scores were calculated by the LMS method, using parameters from 2000 CDC growth tables.[17] The LMS (lambda mu and sigma) method enables exact percentiles and Z-scores to be calculated as a function of age, using Box-Cox transformations to achieve normality of data.[18]

Multivariable linear regression was used to examine the adjusted association of AI/GH vs GH monotherapy with final adult height Z-score, controlling for risk factors including history of radiation to the spine, history of *cis*-retinoic acid treatment, age at start of GH therapy, height Z-score at GH initiation, BMI Z-score at GH initiation, and relative skeletal maturation at GH initiation. Patients treated with total body irradiation (TBI), craniospinal radiation, or abdominal radiation were classified as having radiation effects to the spine.

RESULTS

Baseline Characteristics at GH Initiation

A total of 92 male patients were included in the study; 70 were treated with GH monotherapy and 22 with combination AI/GH. Characteristics at time of GH therapy initiation are summarized in Table 1. There were no significant differences between the two treatment groups in age at start of GH, height Z-score, mid-parental Z-score, or pubertal maturation.

Cancer Treatment and Medical History

Cancer history and endocrine late effects are summarized in Table 2. The most common diagnosis in the combination group was neuroblastoma (N=13; 59.1%), while the most common diagnosis in the GH monotherapy group was central nervous system (CNS) tumor (N=34; 48.6%). The remaining major cancer diagnoses included leukemia, Wilms tumor, and soft tissue sarcoma. Five patients in the GH monotherapy group had other diagnoses including retinoblastoma, Langerhans cell histiocytosis, and bone marrow failure syndrome requiring allogenic hematopoietic stem cell transplantation (HSCT). Nearly all patients in the combination group received chemotherapy (N=22; 100%), radiation therapy (N=21; 95.5%), or a HSCT (N=18; 81.8%). A greater proportion of patients in the combination group received HSCT (81.8% versus 42.9%, P=0.001), abdominal radiation (40.9% versus

15.7%), TBI (68.2% versus 27.1%), or the biologic agent *cis*-retinoic acid (59.1% versus 14.3%, $P<0.001$). The age of cancer diagnosis was considered a proxy for age at radiation exposure; amongst those who received TBI, median age of cancer diagnosis was 3.0 (0.6-12.0) years. Following GH deficiency, hypogonadism and hypothyroidism were the most common endocrinopathies among both combination and monotherapy groups. Within the full cohort, 26 patients (28.2%) were diagnosed with hypothyroidism. Thirty-four (37%) were diagnosed with hypogonadism, and 28 (82%) were treated with testosterone. For males diagnosed with hypogonadism, there was no difference in testosterone treatment between the groups. Due to the greater number of patients in the GH monotherapy group with a history of CNS tumor, a significantly greater number of patients had adrenal insufficiency (37.1% versus 9.1%, $P=0.02$).

Clinical Characteristics at AI Therapy

The AI treatment regimen and clinical characteristics at start and completion of AI therapy are summarized in Table 3. Twenty patients (91%) were treated with letrozole at a dose of 2.5 mg daily, while two patients (9%) were treated with anastrozole at 1 mg daily. Mean age at AI initiation was 13.7 ± 1.9 years. The mean duration of AI treatment was 2.0 ± 0.8 years. The majority of patients were pubertal (Tanner stage 2-3) at start of treatment. The mean relative skeletal maturation (bone age minus chronological age) at start of AI was 0.2 ± 1.8 and was not significantly different than the mean relative skeletal maturation at start of GH for the AI/GH group ($P=0.1$). The mean relative skeletal maturation (bone age minus chronological age) at start of AI did not differ significantly by *cis*-retinoic acid exposure status, with mean 0.7 ± 1.7 in those who received *cis*-retinoic acid therapy (N=13) versus −0.4 ± 1.8 in those who did not (N=9).

Laboratory Evaluation

The mean IGF-1 levels significantly increased from 461 ± 240.49 ng/mL to 587 ± 231.76 ng/mL following GH treatment (95% CI −210.4, −2.99; $P=0.04$), and median testosterone levels significantly increased following AI treatment: median 167 (range 3.6 - 544) ng/dL versus median 204 (range 53 - 1406) ng/dL ($P<0.01$). There was no significant difference in mean hemoglobin A1c levels before and after AI treatment, with hemoglobin A1c levels 5.6 ± 0.2% before and 5.7 ± 0.2% after treatment.

Anthropometric Characteristics at Treatment Completion

Anthropometric characteristics related to height at completion of GH therapy are summarized in Table 4. Duration of GH did not differ between the treatment groups. Mean final adult height in the combination group was 160.8 ± 12.4 cm and did not differ significantly from the monotherapy group with mean 166.6 ± 13.1 cm. Within each group there was a statistically significant increase in mean height (cm) following treatment, with a height improvement of 30.9 cm (95% CI 26.0 - 35.9; $P<0.0001$) in the GH monotherapy group and improvement of 25.0 cm (95% CI 19.3 - 30.8; $P<0.0001$) in the AI/GH group. However, there was a statistically significant increase in height Z-score following treatment only in the monotherapy group (mean height Z-score improvement 0.63, 95% CI 0.2 - 1.0; $P=0.004$). There was no significant change in the mean height Z-score following AI/GH treatment in the combination group (mean Z-score decrease of 0.3, 95% CI −1.0 - 0.3).

Mean final adult height Z-score in the combination group was −2.1 ± 1.5 and did not differ significantly from the monotherapy group with mean −1.3 ± 1.7 (Table 4). This observation held when stratifying by cancer treatment history with *cis*-retinoic acid and spinal radiation (Figure 1). Patients treated with GH monotherapy had a greater height velocity on GH than those in the combination group (median 5.96, range 1.1 - 15.6 cm/year versus median 4.9, range 2.6 - 9.1 cm/year; P=0.02). There was a greater difference between final adult height and mid-parental height in patients in the combination group [median difference −19.1 cm (range - 37.7 to 1.2)] than in the monotherapy group [median difference - 7.3 cm (range - 55.3 to 11.5)] (P=0.03; Table 4).

Association of treatment and risk factors with final adult height Z-score

In the multivariable linear regression model, there was no significant treatment association (AI/GH versus GH monotherapy) with final adult height Z-score (Table 5). History of radiation to the spine, height Z-score at initiation of GH, and relative skeletal maturation were significantly associated with final adult height Z-score. History of radiation to the spine showed the greatest impact on final adult height Z-score, decreasing the height Z-score by 0.93. Lower starting height Z-score at GH initiation was associated with a 0.8 lower adult height Z-score (P<0.001), and greater difference between bone age and chronological age was associated with a 0.3 lower final adult height Z-score (P=0.01).

DISCUSSION

In this first retrospective study of height outcomes in male survivors of childhood cancer treated with GH and AI, the addition of AI to GH therapy did not contribute to improvement in final adult height. Patients treated with GH monotherapy demonstrated statistically significant improvement in overall height Z-score following treatment, while those in the combination AI/GH group did not.

The negative finding in our study population is likely influenced by the profound impact of their cancer history and treatment.[19] As the GH axis is most sensitive to the effects of radiation, GH deficiency is often the first endocrinopathy seen following cranial radiation, and can be diagnosed following lower radiation doses in young patients such as those administered with TBI in the setting of HSCT.[20] Forty percent of the patients in this cohort received cranial or craniospinal radiation, and greater than one-third of patients received TBI. While treatment with GH can significantly improve height outcome in those with GH deficiency, patients may not achieve genetic potential due to other effects of their cancer treatment history. Spinal radiation can directly damage the growth plate, leading to vertebral growth deceleration, with increased damage following radiation at younger ages.[5,21,22] While unable to determine a statistical difference in spinal radiation exposure between the GH and AI/GH groups due to our small sample size and concern for multiple comparisons, a greater proportion of patients in the AI/GH group received spinal radiation, which likely contributed to the worse height outcome in the AI/GH group. Additionally, *cis*-retinoic acid, most often used in treatment of high-risk neuroblastoma, is known to result in premature epiphyseal closure and an advanced bone age, portending worse adult height outcomes.[6,23-25] The majority of patients in this cohort treated with *cis*-retinoic acid were

in the combination AI/GH group. The lower height velocity observed in the AI/GH group compared to the GH group, may also be explained by the greater exposure to *cis*-retinoic acid. Prior studies of AI for height indication have shown that treatment with AI does not decrease growth velocity, positing that high concentrations of androgens have direct effects on the growth plate. However, these studies were in males without pubertal growth spurt prior to treatment with AI, and it is also possible that our finding is also due to suppression of the pubertal growth spurt. Additional factors contributing to the lack of response from treatment with combination AI/GH may include poor nutrition, as evidenced by the lower starting BMI Z-score at treatment initiation in the combination group, and additional endocrinopathies including hypothyroidism, hypogonadism, and precocious puberty, though the frequencies of these complications were the same between treatment groups.

While our finding that AI does not augment final adult height is consistent with the negative studies in the general population,[26,27] there is conflicting evidence in the literature. A few small studies reported a slight benefit of AI in augmenting predicted adult height.[9,28-30] AIs have been used either off-label for height augmentation in male pediatric patients with short stature conditions, or in the context of randomized controlled trials. In a randomized controlled trial of 50 males with GH deficiency, Mauras et al. showed an increase in predicted adult height with AI/GH combination therapy compared to GH and placebo.[9] While there was no difference between groups in the actual height throughout the treatment period, the bone ages at treatment completion were significantly younger in the combination group, leading to a greater predicted height by the Bayley-Pinneau method.[31] Similarly, Hero et al. compared predicted adult height in boys with idiopathic short stature treated with AI versus placebo and found a significant increase in predicted adult height in the AI treated group.[28] Hero et al. also reported that letrozole plus testosterone significantly improved both predicted adult height as well as near final adult height compared to testosterone alone in males with constitutional delay of puberty.[32] Unlike these studies, a strength of this study is the analysis of actual attained adult height rather than predicted heights.

The side effect profile of AIs, recognized following studies of AIs in women with breast cancer, must carefully be considered and includes but is not limited to impaired glucose metabolism, increased risk of cardiovascular events, hepatotoxicity, and osteoporosis.[33,34] In our study, we found that hemoglobin A1c levels in the AI/GH combination treatment group were in the normal range, with no significant differences pre and post AI treatment. However, as laboratory values were obtained following treatment completion, the long-term impact of AI or cancer therapy on hemoglobin A1c in our study population is not known. Prior studies of AI for growth indications in the male pediatric and adolescent population have shown that bone mineral density is not significantly affected,[9,28,30,32] though AI treatment during early puberty may lead to vertebral abnormalities secondary to impaired vertebral body growth.[35] The latter finding underscores the importance of following patients longitudinally, as the long-term implications of aromatase inhibition in male patients for growth indications are not known.

Despite the importance of the study findings, the limitations of this study include the retrospective study design, small sample size, and differences in cancer treatment history between the GH and AI/GH treatment groups. These limitations may account for the lack of

statistically significant differences between GH and AI/GH groups in baseline characteristics including cancer treatment history. In addition, due to the small sample size, our power is limited to definitively conclude the lack of difference in height outcome between treatment with GH and combination AI/GH in this patient population. Furthermore, as this is a retrospective study, selection bias may have played a role in individuals who were offered AI/GH versus GH alone as providers were more likely to prescribe an AI plus GH in patients with GH deficiency and severe short stature with a small window of time for remaining growth. The differences in cancer treatment between the two groups supports this, as there was a greater number of patients in the AI/GH group treated with spinal radiation or *cis*-retinoic acid, which are known to be detrimental to growth. However, this reflects clinical decision making and renders our study generalizable for providers. Finally, while sitting height may be informative, particularly in patients with history of radiation exposure, this measurement was not consistently obtained in patients clinically across the study time frame and so was not incorporated into the study's growth outcomes. Yet, despite its limitations, this study has many strengths including largest study to date to examine GH/AI treatment in survivors of CCS.

Endocrine late effects of cancer, particularly growth impairment, are highly prevalent in survivors of childhood cancer. Despite treatment with GH, many patients do not achieve final adult height within genetic potential. While some studies suggest AIs may be effective as monotherapy or in combination therapy for male pediatric patients with short stature, we did not observe a benefit for maximizing final adult height in our study. While our study findings do not support the extrapolation of data in favor of aromatase inhibition to augment height outcomes in the CCS population, further prospective studies with stratification of CCS populations by relevant treatment history are warranted to determine if there are subpopulations within CCS who may benefit or if there is truly no role for adjuvant AI in CCS. Further, given the side effects and unknown long-term risk of AIs, future studies are needed to determine optimal adjunctive medical therapy to maximize final adult height for this high-risk patient population.

ACKNOWLEDGEMENTS

The authors do not have any special acknowledgements.

DATA AVAILABILITY STATEMENT:

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Abbreviation Table

CCS	Childhood cancer survivor
GH	Growth hormone
AI	Aromatase inhibitor

BMI	Body mass index
TBI	Total body irradiation
HSCT	Hematopoietic stem cell transplant
ELECT	Endocrine Late Effects of Cancer Therapy
CHOP	Children's Hospital of Philadelphia
IGF-1	Insulin like growth factor - 1
IGFBP3	Insulin like growth factor binding protein 3
CI	Confidence interval
CDC	Center for disease control
CNS	Central nervous system

REFERENCES

1. Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of Childhood Cancer in the United States: Prevalence and Burden of Morbidity. Cancer Epidemiology Biomarkers and Prevention. 2015;24(4):653–663. doi:10.1158/1055-9965.EPI-14-1418.
2. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study cohort: A review of published findings. Journal of Clinical Oncology. 2009;27:2339–2355. doi:10.1200/JCO.2008.21.1953 [PubMed: 19364955]
3. Brignardello E, Felicetti F, Castiglione A, et al. Endocrine health conditions in adult survivors of childhood cancer: the need for specialized adult-focused follow-up clinics. European journal of endocrinology / European Federation of Endocrine Societies. 2013;168:465–472. doi:10.1530/EJE-12-1043
4. Chemaitilly W, Cohen LE, Mostoufi-Moab S, et al. Endocrine late effects in childhood cancer survivors. Journal of Clinical Oncology. 2018;36(21):2153–2159. doi:10.1200/JCO.2017.76.3268 [PubMed: 29874130]
5. Rose SR, Carlsson M, Grimberg A, et al. Response to GH treatment after radiation therapy depends on location of irradiation. Journal of Clinical Endocrinology and Metabolism. 2020;105(10):1–12. doi:10.1210/clinem/dgaa478 [PubMed: 31511876]
6. Duvalyan A, Cha A, Goodarzian F, Arkader A, Villablanca JG, Marachelian A. Premature epiphyseal growth plate arrest after isotretinoin therapy for high-risk neuroblastoma: A case series and review of the literature. Pediatric Blood and Cancer. 2020;67(8):1–9. doi:10.1002/pbc.28236
7. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab. Dec 1995;80(12):3689–98. doi:10.1210/jcem.80.12.8530621 [PubMed: 8530621]
8. Carani C, Qin K, Simoni M, et al. Effect of Testosterone and Estradiol in a Man with Aromatase Deficiency. New England Journal of Medicine. 1997;337(2):91–95. doi:10.1056/nejm199707103370204 [PubMed: 9211678]
9. Mauras N, De Pijem LG, Hsiang HY, et al. Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: A randomized, placebo-controlled, multicenter trial for one to three years. Journal of Clinical Endocrinology and Metabolism. 2008;93(3):823–831. doi:10.1210/jc.2007-1559 [PubMed: 18165285]
10. Mauras N, Ross JL, Gagliardi P, et al. Randomized trial of aromatase inhibitors, growth hormone, or combination in pubertal boys with idiopathic, short stature. Journal of Clinical Endocrinology and Metabolism. 2016;101(12):4984–4993. doi:10.1210/jc.2016-2891 [PubMed: 27710241]

11. McGrath N, O'Grady MJ. Aromatase inhibitors for short stature in male children and adolescents. Boletin Medico del Hospital Infantil de Mexico. 2015;10:1–48. doi:10.24875/BMHIM.20000353
12. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for heights of parents. Arch Dis Child. Dec 1970;45(244):755–62. doi:10.1136/adc.45.244.755 [PubMed: 5491878]
13. Antal Z, Sklar CA. Gonadal Function and Fertility Among Survivors of Childhood Cancer. Endocrinology and Metabolism Clinics of North America. 2015;44(4):739–749. doi:10.1016/j.ecl.2015.08.002 [PubMed: 26568489]
14. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Hormone Research in Paediatrics. 2017;86(6):361–397. doi:10.1159/000452150
15. Shalet SM, Toogood A, Rahim A, Brennan BMD. The Diagnosis of Growth Hormone Deficiency in Children and Adults. Endocrine Reviews. 1998;19(2):203–223. doi:10.1210/edrv.19.2.0329 [PubMed: 9570037]
16. Travison TG, Vesper HW, Orwoll E, et al. Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe. J Clin Endocrinol Metab. Apr 1 2017;102(4):1161–1173. doi:10.1210/jc.2016-2935 [PubMed: 28324103]
17. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. May 2002;(246):1–190.
18. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med. Jul 1992;11(10):1305–19. doi:10.1002/sim.4780111005 [PubMed: 1518992]
19. Chemaitilly W, Cohen LE, Mostoufi-Moab S, et al. Endocrine late effects in childhood cancer survivors. Journal of Clinical Oncology. 2018;36:2153–2159. doi:10.1200/JCO.2017.76.3268 [PubMed: 29874130]
20. van Santen HM, Chemaitilly W, Meacham LR, Tonorezos ES, Mostoufi-Moab S. Endocrine Health in Childhood Cancer Survivors. W.B. Saunders; 2020. p. 1171–1186.
21. Shalet SM, Gibson B, Swindell R, Pearson D. Effect of Spinal Irradiation on Growth. Pediatric Research. 1986;20(11):1180–1180. doi:10.1203/00006450-198611000-00038
22. Clayton PE, Shalet SM. The evolution of spinal growth after irradiation. Clin Oncol (R Coll Radiol). Jul 1991;3(4):220–2. doi:10.1016/s0936-6555(05)80744-7 [PubMed: 1931763]
23. Standeven AM, Davies PJA, Chandraratna RAS, Mader DR, Johnson AT, Thomazy VA. Retinoid-induced epiphyseal plate closure in guinea pigs. Fundamental and Applied Toxicology. 1996;34(1):91–98. doi:10.1006/faat.1996.0179 [PubMed: 8937896]
24. Hobbie WL, Mostoufi-Moab S, Carlson CA, Gruccio D, Ginsberg JP. Prevalence of Advanced Bone Age in a Cohort of Patients Who Received cis-Retinoic Acid for High-Risk Neuroblastoma. Pediatric Blood & Cancer. 2011;56:474–476. doi:DOI 10.1002/pbc.22839 [PubMed: 21072832]
25. Noyes JJ, Levine MA, Belasco JB, Mostoufi-Moab S. Premature Epiphyseal Closure of the Lower Extremities Contributing to Short Stature after cis-Retinoic Acid Therapy in Medulloblastoma: A Case Report. Hormone Research in Paediatrics. 2015;85(1):69–73. doi:10.1159/000441140 [PubMed: 26457578]
26. Shams K, Cameo T, Fennoy I, et al. Outcome analysis of aromatase inhibitor therapy to increase adult height in males with predicted short adult stature and/or rapid pubertal progress: a retrospective chart review. Journal of Pediatric Endocrinology and Metabolism. 2014;27(0):725–730. doi:10.1515/jpem-2013-0470.Outcome [PubMed: 24756052]
27. Tonyushkina KN, Likki SR, Allen HF, Knee A. Use of letrozole to augment height outcome in pubertal boys: a retrospective chart review. Journal of Pediatric Endocrinology and Metabolism. 2022;35(10):1232–1239. doi:10.1515/jpem-2022-0177 [PubMed: 36169241]
28. Hero M, Norjavaara E, Dunkel L. Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: A randomized controlled trial. Journal of Clinical Endocrinology and Metabolism. 2005;90(12):6396–6402. doi:10.1210/jc.2005-1392 [PubMed: 16189252]

29. Rohani F, Zaeri H, Moarefian S, Moradi S, Alaii MR. Effect of letrozole on the predicted adult height in boys with constitutional delay of growth and puberty: A clinical trial. Biomedical Research (India). 2017;28(15):6813–6817.

30. Wickman S, Sipilä I, Ankarberg-Lindgren C, Norjavaara E, Dunkel L. A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: A randomised controlled trial. Lancet. 2001;357(9270):1743–1748. doi:10.1016/S0140-6736(00)04895-9 [PubMed: 11403810]

31. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: Revised for use with the greulich-pyle hand standards. The Journal of Pediatrics. 1952;40(4):423–441. doi:10.1016/S0022-3476(52)80205-7 [PubMed: 14918032]

32. Hero M, Wickman S, Dunkel L. Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. Clinical Endocrinology. 2006;64(5):510–513. doi:10.1111/j.1365-2265.2006.02499.x [PubMed: 16649968]

33. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. Diabetes After Hormone Therapy in Breast Cancer Survivors: A Case-Cohort Study. J Clin Oncol. Jul 10 2018;36(20):2061–2069. doi:10.1200/jco.2017.76.3524 [PubMed: 29688833]

34. Mukherjee AG, Wanjari UR, Nagarajan D, et al. Letrozole: Pharmacology, toxicity and potential therapeutic effects. Life Sci. Dec 1 2022;310:121074. doi:10.1016/j.lfs.2022.121074 [PubMed: 36243120]

35. Hero M, Toiviainen-Salo S, Wickman S, Mäkitie O, Dunkel L. Vertebral morphology in aromatase inhibitor-treated males with idiopathic short stature or constitutional delay of puberty. Journal of Bone and Mineral Research. 2010;25(7):1536–1543. doi:10.1002/jbmr.56 [PubMed: 20200972]

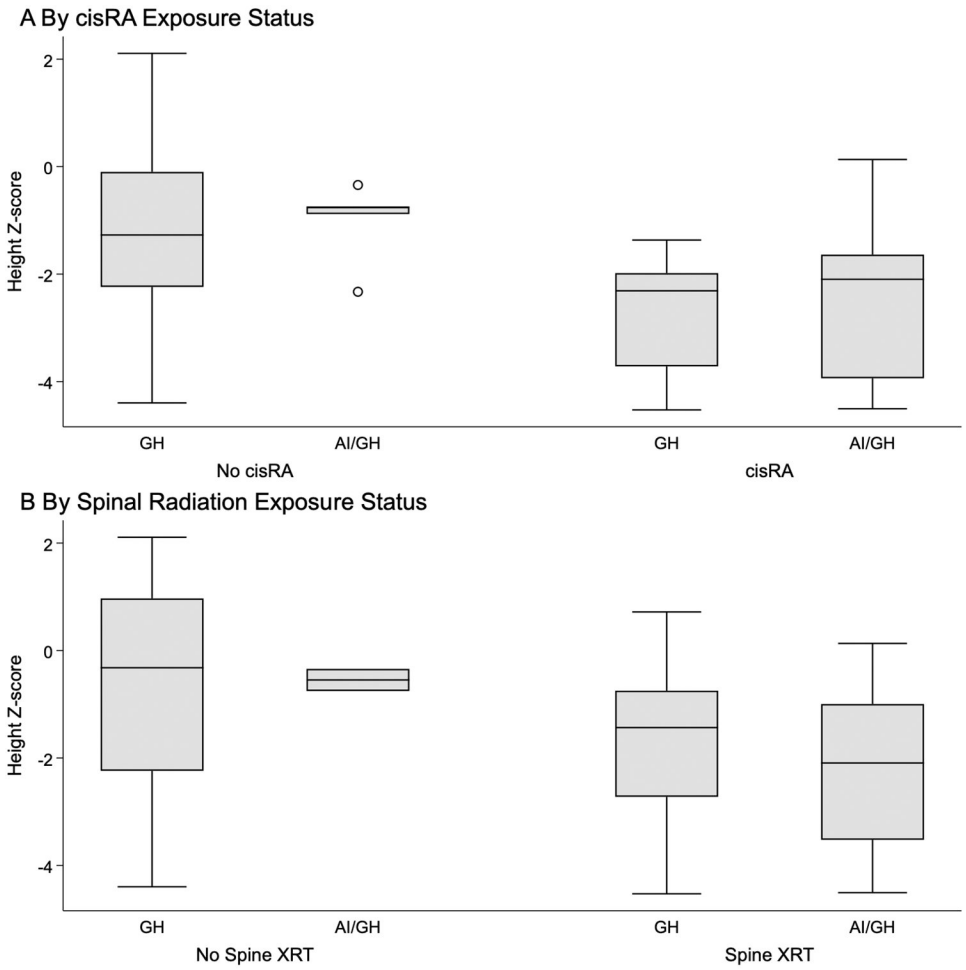

FIGURE 1. Final Adult Height Z-score by GH versus AI/GH treatment, stratified by *cis*-retinoic acid and spinal radiation exposure

There was no significant difference in final adult height Z-score between treatment groups when stratifying by cancer treatment exposure (GH versus AI/GH treatment in patients without *cis*-retinoic acid exposure P=0.9; GH versus AI/GH in patients with *cis*-retinoic acid exposure P=0.6; GH versus AI/GH in patients without spinal radiation exposure P=0.9; GH versus AI/GH in patients with spinal radiation exposure P=0.3).

Abbreviations: GH growth hormone; AI aromatase inhibitor; cisRA *cis*-retinoic acid, XRT radiation therapy

TABLE 1

CLINICAL CHARACTERISTICS AT GROWTH HORMONE (GH) INITIATION

	AI/GH (n =22)	GH (n =70)	*P*-value
Age in years at GH start	11.5 ± 3.5 (3.5 – 18.1)	11.5 ± 2.8 (4.4 – 20.5)	0.9
Ethnicity			0.3
Hispanic	1 (4.6%)	4 (5.7%)	
Non-Hispanic	20 (90.9%)	66 (94.3)	
Unknown/Not reported	1 (4.6%)	0	
Race			0.3
Asian	2 (9.1%)	1 (4%)	
Black or African American	3 (13.6%)	10 (41.7%)	
White	16 (72.7%)	56 (80%)	
Other	1 (4.6%)	3 (4.3%)	
Height Z-score at GH start	−1.7 ± 1.0 (−3.99 – 0.2)	−1.9 ± 1.1 (−4.5 – 0.7)	0.6
BMI Z-score at GH start median (range)	−0.2 (−1.95 – 1.6)	0.5 (−4.2 – 2.3)	0.05
Mid-parental height Z-score	0.03 ± 0.8 (−1.3 – 1.95) N=18	0.14 ± 0.9 (−1.6, 1.95) N=59	0.6
Pubertal Stage at GH start			
Pre-Pubertal (Tanner 1)	11/22 (50%)	45/62 (72.6%)	0.1
Pubertal (Tanner 2-3)	9/22 (41%)	15/62 (24.2%)	
Post-Pubertal (Tanner 4-5)	2/22 (9%)	2/62 (3.2%)	
Unknown	0	8	
BA minus CA median (range)	0.15 (−3.1 – 3.1)	−0.48 (−7.4 – 2.4)	0.4

Data are n (%) or mean ± SD (range), except where indicated.

AI: aromatase inhibitor; GH: growth hormone, BMI: body mass index, BA: bone age; CA: chronological age

TABLE 2

PATIENT CHARACTERISTICS – CANCER TREATMENT AND MEDICAL HISTORY

	AI/GH (n =22)	GH (n =70)	*P*-value
Age at cancer diagnosis in years median (range)	3.2 (0.4- 10.8)	5.5 (0.1 - 14.4)	0.1
Cancer diagnosis			0.001
CNS tumor	3 (13.6%)	34 (48.6%)	
Leukemia	6 (27.2%)	18 (25.7%)	
Wilms tumor	0	1 (1.4%)	
Soft tissue sarcoma	0	1 (1.4%)	
Neuroblastoma	13 (59.1%)	11 (15.7%)	
Other	0	5 (7.1%)	
Chemotherapy*			0.1
No	0	9 (13%)	
Yes	22 (100%)	60 (87%)	
Radiation			0.1
No	1 (4.5%)	15 (21.4%)	
Yes	21 (95.5%)	55 (78.6%)	
Cranial/Craniospinal	6 (27%)	37 (52.9%)	
Neck/Chest	0	1 (1.4%)	
Abdominal	9 (40.9%)	11 (15.7%)	
Pelvic	3 (13.6%)	2 (2.9%)	
TBI	15 (68.2%)	19 (27.1%)	
HSCT			0.001
No	4 (18.2%)	40 (57.1%)	
Yes	18 (81.8%)	30 (42.9%)	
Cis-retinoic acid			<0.001
No	9 (40.9%)	60 (85.7%)	
Yes	13 (59.1%)	10 (14.3%)	
Hypothyroidism	5 (22.7%)	21 (30%)	0.6
Hypogonadism	8 (36.4%)	26 (37.1%)	>0.99
Precocious Puberty	3 (13.6%)	14 (20%)	0.8
Central Adrenal Insufficiency	2 (9.1%)	26 (37.1%)	0.02
Type 2 Diabetes Mellitus	1 (4.6%)	2 (2.9%)	0.6

Data are n (%)

*One patient with missing data in GH monotherapy group.

AI: aromatase inhibitor; GH: growth hormone, CNS: central nervous system; HSCT: Hematopoietic stem cell transplantation; TBI: total body irradiation

TABLE 3

CHARACTERISTICS OF AROMATASE INHIBITOR THERAPY, N=22

Aromatase Inhibitor Used	
Letrozole, 2.5 mg daily	20 (91%)
Anastrozole, 1 mg daily	2 (9%)
Age in years at AI start	13.7 ± 1.9 (10.1 – 17.7)
Age in years at AI end	15.7 ± 1.5 (14.1 – 19.3) N=21[a]
AI Treatment Duration in years	2.0 ± 0.8 (0.8 – 4.2)
Height Z-score at AI start	−1.3 ± 1.3 (−3.7 – 2.3)
BMI Z-score at AI start	−0.3 ± 0.99(−1.8 – 1.6)
Pubertal Stage at AI start	
Pre-Pubertal (Tanner 1)	1/22 (4.5%)
Pubertal (Tanner 2-3)	17/22 (77.3%)
Post-Pubertal (Tanner 4-5)	4/22 (18.2%)
BA at AI Start [b]	
Delayed	1/22 (4.6%)
Congruent	15/22 (68.2%)
Advanced	6/22 (27.3%)
BA minus CA (relative skeletal maturation)	0.2 ± 1.8

Data are n (%) or mean ± SD (range) except where indicated.

[a]One patient still on AI. BA: bone age; CA: chronological age

[b]Bone age categories: delayed if > 2 SD younger than chronological age, congruent if within 2 SD of chronological age, advanced if > 2 SD older than chronological age

AI: aromatase inhibitor; BMI: body mass index.

TABLE 4

ANTHROPROMETRIC CHARACTERISTICS AT TREATMENT COMPLETION

	AI/GH (n =22)	GH (n =70)	*P*-value
GH Treatment Duration in years	4.7 ± 2.8 (0.8 to 11.4)	4.6 ± 2.6 (0.2- to 1.23)	0.9
Age at GH end	16.1 ± 1.9 (13.3 to 19.6) N=21	16.2 ± 1.98 (10.2 to 21.9) N=69	0.8
Height velocity on GH treatment (cm/year) [a] median (range)	4.9 (2.6 to 9.1)	5.96 (1.1 to 15.6)	0.02
FAH Z-score[b]	−2.1 ± 1.5 (−4.5 to 0.1) N = 20	−1.3 ± 1.7 (−4.5 to 2.1) N= 53	0.09
Difference between FAH and MPH in cm median (range)	−19.1 (−37.7 to 1.2)	−7.3 (−55.3 to 11.5)	0.03

Data are n (%) or mean ± SD (range) except where indicated.

[a]Height velocity is height velocity while on GH for both groups as duration of AI treatment is included in GH treatment.

[b]FAH available as height documented at fusion of growth plates or once subjects reached 18 years of age without history of delayed bone age and therefore was not available for all patients

AI: aromatase inhibitor; GH: growth hormone, MPH: mid parental height; FAH: final adult height.

TABLE 5

ASSOCIATION OF GH VERSUS AI/GH TREATMENT WITH FINAL ADULT HEIGHT Z-SCORE

Univariable Analysis			
Exposure	**Beta Coefficient**	**95% Confidence Interval**	***P*-value**
AI/GH Therapy*	−0.74	−1.6, 0.14	0.098
Multivariable Analysis			
Exposure or Risk Factor	**Beta Coefficient**	**95% Confidence Interval**	***P*-value**
AI/GH Therapy*	0.04	−0.9, 0.9	0.9
Age at GH initiation	0.03	−0.1, 0.2	0.7
History of radiation to spine	−0.93	−1.7, −0.2	0.01
History of *cis*-retinoic acid	−0.48	−1.3, 0.4	0.3
Height Z-score at GH start	0.8	0.4, 1.2	<0.001
BMI Z-score at GH start	0.06	−0.2, 0.4	0.7
Bone age minus chronological age	−0.3	−0.5, −0.07	0.01

*GH monotherapy as reference group