Original Study

Evidence to Incorporate Inclusive Reproductive Health Measures in Guidelines for Childhood and Adolescent Cancer Survivors

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A B S T R A C T

Objective: Female childhood cancer survivors are at an increased risk of reproductive health impairment. We compared reproductive health outcomes with the recommended standard in a cohort of childhood cancer survivors.

Study Design and Participants: A retrospective chart review of 222 female childhood cancer survivors aged 21 years or younger that presented to a tertiary referral center between 1997-2008 was initiated. The main outcome measures were the compliance with the American Society of Clinical Oncology guidelines for childhood cancer survivor management of reproductive health. In particular, we evaluated menstrual cycle regularity, fertility preservation counseling, and endocrine profile, as defined by follicle stimulating hormone (FSH) and anti-mullerian hormone (AMH) levels as surrogate markers for ovarian reserve. Secondary outcomes were to study the contribution of survivor clinics in enforcing these guidelines.

Results: Of 136 patients older than 13 years at their last visit, 58 patients (43%) had FSH data available and none had AMH data. Patients were stratified into 3 groups according to FSH levels. Forty of 58 patients (69%) have normal ovarian reserve (FSH level < 10), 10 of 58 patients (17%) have decreased ovarian reserve (FSH levels 10-40), and 8 of 58 patients (14%) have premature menopause, defined as FSH > 40. Most patients with amenorrhea have elevated FSH levels indicating primary ovarian insufficiency, while 3 patients (2.2%) have low FSH levels consistent with hypothalamic amenorrhea. None of the patients were counseled on fertility preservation.

Conclusions: Reproductive health follow-up in children with cancer, including FSH and AMH measurement when indicated, should be established and strictly adhered.

Key Words: Childhood cancer, Fertility preservation, Reproductive health, Ovarian reserve, Survivor clinics

Introduction

The advent of cancer treatment in the past 25 years has led to a huge success in increasing survival of cancer patients today to over 83%, as compared to 45% in the early 1970s.[1] As a consequence, successfully treated children are expected to survive longer. This miraculous improvement of cancer treatment came with a high price—evidence has shown that cancer treatment, in particular chemotherapy and pelvic radiotherapy, has detrimental effects on reproductive function in both male and female childhood cancer survivors.[2,3] Alkylating agents and procarbazine have been found to be highly gonadotoxic[4,5] and direct dose and scattered doses of radiotherapy and bone marrow radiation carry high risks of ovarian damage.[6] While guidelines for fertility preservation and assessment of reproductive health in childhood cancer survivors have been emphasized by multiple national and international organizations, including American Society of Clinical Oncology (ASCO) and American Society of Reproductive Medicine (ASRM), the adherence to these guidelines in oncology clinics is not well documented.[7]

One of the grave consequences of cancer treatment is ovarian hormone deficiency. It is predicted that 1 in 800 young women will be childhood cancer survivors by 2020.4 Roughly 6.3% of childhood cancer survivors suffer from acute ovarian failure as compared to 0.8% of their siblings.[8] Of childhood cancer survivors, 22.6% suffer from imminent ovarian failure and this is strongly related to the age when the diagnosis is made.[9] Primary ovarian insufficiency (POI) causes estrogen deficiency, which leads to failure of pubertal development in prepubescent girls and increases the risk of long-term health complications, including osteoporosis, mental health disorders, cardiovascular disease, and urogenital dysfunctions in older women.[10,11] A small longitudinal and cross-sectional study of young cancer patients demonstrated that gonadotoxic chemotherapy impacts serum hormones, with anti-müllerian hormone (AMH), follicle stimulating hormone (FSH), and antral follicle count (AFC) levels being the most affected.5 Cancer survivors continue to have significantly impaired FSH, AMH, AFC, and ovarian volume when measurements are adjusted for age, BMI, and race.[12] In addition, survivors who experienced spontaneous menstrual cycles were found to have a smaller ovarian volume than controls (4.8 and 6.8 cm median, respectively) and less antral follicles in each ovary as compared to controls (7.5 and 11 median, respectively).[13] Survivors who experienced radiation in the abdomen/pelvis region are more apt to having a premature, low-birth

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weight infant or neonatal death, but were not at increased risk of malformations or deaths compared to those who underwent surgery.[14]

Female cancer survivors have an increased risk of infertility, defined as >1 year of attempts at conception without success. Clinical infertility was most pronounced at early reproductive ages, with a relative risk of 2.92 in participants ≤24 years, a relative risk of 1.61 in those aged 25-29 years, and a relative risk of 1.37 in those aged 30-40 years, as compared to normal individuals.[13] Although female cancer survivors are equally likely to seek treatment for infertility, compared to the control group, they are less likely to be prescribed drugs for treatment of infertility than other patients with no history of cancer.[13]

The field of oncofertility was founded to find solutions regarding the reproductive future of cancer survivors.[15] Embryo and oocyte cryopreservation is approved for female fertility preservation; however, these fertility preservation options are not yet viable for prepubescent or adolescent girls and do not preserve endogenous estrogen.[16-20] While ovarian tissue cryopreservation is available for children, it is still considered experimental.[21] Research has shown that ovarian tissue cryopreservation is largely safe for childhood cancer survivors to reproduce. We have found 1 reported case of auto-transplantation of cancer in a patient with breast cancer and another with cervical cancer.[22] Currently, gonadotropin-releasing hormone (GnRH) agonists are used to preserve ovarian reserve. While GnRH agonists are effective in preventing uncontrolled menstrual bleeding during chemotherapy, their efficacy for preventing POI has given mixed results. New ovoprotection drugs are currently being investigated. Some of these drugs, such as Sphingosine-1-Phosphate, prevent ovarian cell death and apoptosis,[23,24] while other drugs, such as Dexrazoxane and Bortezomib, inhibit the toxic effects of chemotherapy earlier at the level of drug transport and DNA intercalation prior to DNA damage in the ovary.[25]

At present, there is no standard of care regarding counseling and offering fertility preservation options for every age group prior to commencing with cancer therapy, which results in a wide variation of utilization of available services. Twenty-three percent of oncologists seldom or never discuss any fertility preservation guidelines with their patients.[26] In a survey of oncologists from the United Kingdom, only 38% admitted to giving written information on fertility preservation to their patients and 66% consulted a fertility specialist.[27,28] Furthermore, only one-third of women with hematologic cancer pursue fertility preservation and half of those patients have already been exposed to chemotherapy.[29] The reasons for not having a discussion about fertility preservation are lack of time, lack of knowledge, perceived poor success rates of fertility preservation, poor patient prognosis, patient already had children, was single, or could not afford fertility preservation costs.[28]

Considering the overreaching and devastating effects of cancer and cancer treatment on reproductive health in children and adolescents, we initiated this cohort study to assess the current compliance with available reproductive health national guidelines in cancer patients and investigate additional measurements to include in these guidelines.

Materials and Methods

Study Design and Protocol

A retrospective cohort study of all patients who presented to the pediatric oncology clinic in a tertiary referral center (diagnosed 1997-2008) was initiated. The electronic medical records of 222 female patients were reviewed. Information regarding initial diagnosis, management, and follow-up was gathered. General demographic data as well as tumor type, treatment, reproductive health (fertility preservation counseling, menstrual history, and hormonal contraception) was collected. The study was approved by the Institutional Review Board of the University of Wisconsin # M-2009-1006.

Outcome Measures

The primary outcome measure was compliance with ASCO guidelines for reproductive health preservation and assessment in childhood cancer survivors. In particular we investigated ovarian reserve. A secondary outcome measure was the contribution of survivor clinics in enforcing these guidelines. We evaluated the effect of participation in the multidisciplinary survivor clinic. To evaluate ovarian reserve, the surrogate markers of menstrual cycle regularity, amenorrhea following chemotherapy, and FSH levels (the highest value for a patient if more than 1 value exists) were used. None of the patients had AMH measured; hence this was not included in the analysis. Pubertal and reproductive information was also recorded, including: age of menarche, most recent menstrual history including history of irregular cycles, oligomenorrhea, amenorrhea, and pregnancy outcomes following chemotherapy. History of premature ovarian insufficiency hormone therapy, including hormonal contraception and hormone replacement therapy, were recorded. Finally, written evidence of conversations between clinician and patients regarding reproductive health counseling was also recorded. This includes counseling regarding fertility preservation, contraception and hormone therapy, referral to reproductive endocrinologist when desired, and embryo, oocyte, and ovarian tissue cryopreservation when appropriate. The standard chemotherapy and radiation consent forms include all risks, including potential effects on ovarian reserve and ovarian failure. This site uses these forms and therefore each patient was given written information about reproductive risks of chemotherapy. Recording data about additional counseling allows evaluation of conversations outside of this setting.

Statistical Analyses

Categorical variables were summarized in tabular format using frequencies and percentages. Variables on a continuous scale were summarized in terms of medians and ranges. The comparisons of categorical variables between groups, eg, FSH ≤10 vs >10, survivor clinic attendance versus no attendance, etc, were conducted using chi-square analysis with continuity correction, Fisher exact test, or