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Ovarian Reserve Assessment in Girls and Young Women Following Chemotherapy for Solid Tumors in Childhood

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Abstract

Background: The improved survival rates of children with cancer have raised the need for long-term fertility assessment in this patient group. The aim of the present study was to evaluate the fertility status of survivors of childhood solid tumor malignancies.

Methods: A retrospective cohort study was conducted at a tertiary pediatric medical center. Patients who had undergone chemotherapy for a solid tumor during childhood in 1980-2009 were identified. Data on fertility history and status were collected from the hospital's computerized registry and updated with a standardized telephone survey; patients who consented were referred for pelvic sonography and blood fertility tests. A non-favorable ovarian reserve was defined as antral follicle count<6, basal follicle-stimulating hormone level>8 IU/L, follicle stimulating hormone/luteinizing hormone ratio>2, or anti-mullerian hormone level<1 pg/ml. Findings were analyzed overall and by treatment with or without alkylating agents.

Results: Forty-seven patients met the study criteria. Menarche occurred at the correct chronological age and pubertal stage in all patients expected to be in menarche by the time of the study. Eighteen patients (41.9%) had a non-favorable ovarian reserve: 7/14 (50%) exposed to high-dose alkylating agents, 7/17 (41%) exposed to standard-dose alkylating agents, and 4/12 (33.3%) treated with non-alkylating agents. The between-group difference was not statistically significant (p=0.690).

Conclusions: A diminished ovarian reserve can be expected in a high proportion of patients treated for solid tumors during childhood with either alkylating (high and standard dose) or non-alkylating agents.

Keywords: Solid tumors; Survivors; Late effects

Abbreviations

FSH: Follicle Stimulating Hormone; AMH: Anti-Mullerian Hormone; GnRH: Gonadotropin Releasing Hormone; LH: Luteinizing Hormone; E2: Estradiol; AFC: Antral Follicle Count; CCSS: Childhood Cancer Survivors Study; AA: Alkylating Agents

Introduction

Thanks to advances in therapy and supportive care, the last 3 decades have witnessed an increase in survival rates of children and adolescents with cancer. As a result, attention is being directed toward the long-term consequences of cancer treatment, especially abdominal and pelvic radiotherapy and chemotherapy. Alkylating agents have been shown to increase the risk of ovarian failure in cancer survivors [1-7]. Several means are currently being used for fertility preservation: (1) lowest possible gonado-toxic treatment protocol [8]; (2) oophoropexy or shielding the abdomen or pelvis during radiotherapy [8,9]; (3) pretreatment with GnRH analogue [8]; (4) in vitro fertilization or in vitro maturation and cryopreservation of oocytes or embryos [8,9]; (5) cryopreservation of ovarian tissue for later re-implantation [8-10]; Ovarian reserve following treatment is assessed by blood tests for basal level of Follicle-Stimulating Hormone (FSH), FSH/Luteinizing Hormone (LH) ratio, and levels of follicular inhibin B and Anti-Mullerian Hormone (AMH) [11], in addition to such dynamic instruments as clomiphene citrate challenge test and gonadotrophin-releasing hormone-

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agonist stimulation test [12] and sonographic measurements of antral follicle count, ovarian volume, and maximal blood flow at the ovarian stroma [11,12].

Data on fertility reserve and outcome in patients treated for cancer in childhood are still scarce [5,14-18]. Of the few studies published to date, most focused on hematological malignancies [1,2,4,6,7,13,19,20]. The aim of the present study was to examine the fertility status of survivors of solid tumor malignancies in childhood and the long-term effect of chemotherapy protocols with and without alkylating agents.

Materials and Methods

A retrospective cohort study design was used. The study group consisted of patients who were treated for solid tumors in childhood or adolescence at the tertiary oncology pediatric medical center in 1980 to 2009 and followed by a specialized team of oncologists and endocrinologists at the same institute. Patients lost to follow-up were excluded, as were patients treated with cranial or pelvic radiation and patients with suspected pituitary or hypothalamic damage. To assess fertility status, data were collected from the hospital's computerized registry and updated using a detailed standardized telephone questionnaire, as follows: patient age at diagnosis, duration of follow-up, menstruation and cycle regularity prior to treatment, type of treatment regimen, dosage and field of radiation, basal hormonal profile, use of GnRH agonist during treatment, autologic/allogeneic bone marrow transplantation. The study was approved by the local IRB committee. After signed informed consent was obtained, patients were referred for pelvic sonography and measurement of blood AMH level.

Outcome measures of the study were rates of menstruation and cycle regularity, basal hormonal profile [FSH, LH, estradiol (E2), progesterone], and AMH level, and sonographic parameters of ovarian volume and Antral Follicle Count (AFC). A non-favorable ovarian reserve was defined as a finding of at least one of the following: AFC<6, basal FSH level>8 IU/L, or AMH level<1 pg/ml. Irregular cycles alone were considered non-favorable ovarian reserve only in the absence of other good prognostic ovarian parameters.

Findings were evaluated overall and by treatment with alkylating agents, standard or high dose, or without alkylating agents. The pediatric oncologists set the criteria defining the maximal standard cumulative dose of alkylating agents: Cisplatin 400 mg/m^2, Ifosfamide 50,000 mg/m^2, Cytoxan 10,000 mg/m^2, Carboplatin 6000 mg/m^2, BCNU 400 mg/m^2.

Statistical analysis

Statistical analysis was performed with SAS 9.2. Analysis of variance (ANOVA) was used to evaluate continuous variables and chi-square test for categorical variables. The association between ovarian reserve and treatment regimen was assessed using multivariate logistic analysis. AP value of <0.05 was considered statistically significant.

Results

During the study period, overall 357 female oncological patients were followed at the hospital's endocrinology clinic. Of the 84 with solid tumors, 47 were eligible for the present study. Their characteristics are shown in Table 1. Age at diagnosis ranged from 3 days to 15 years; only one of the patients had reached menarche by the time of diagnosis. The most prevalent tumor types were Wilms' tumor (15 patients) and neuroblastoma (14 patients).The average lag time from diagnosis to the present study was 14.6 years.

Forty-three of the 47 patients participated in the follow-up telephone survey. Eleven were aged 7-12 years at the time of this study; the other 25 were older than 15 years, and all had reached menarche. None of the post-menarcheal patients had evidence of amenorrhea; 18 reported regular cycles and 7, irregular cycles. Patients who were on oral contraceptives attested to the pre-pill era.

Fourteen patients consented to undergo pelvic sonography. Eight had an AFC of<6. AMH was measured in 9 patients, of whom 2 had a level of<1 pg/ml.

Table 2 presents the ovarian reserve parameters and the lag time from diagnosis to the present study by treatment group. Thirty-one patients received treatment with alkylating agents, 17 standard dose and 14 high dose; the average time from treatment to the present study was 17 years and 15.9 years, respectively. The remaining 12 patients received chemotherapy without alkylating agents; their average lag time to the study was 13.5 years. There was no significant difference in current age or lag time among the groups. A non-favorable ovarian reserve was found in 7/14 (50%) exposed to high-dose alkylating agents, 7/17 (41.1%) exposed to standard-dose alkylating agents, and 4/12 (33.3%) who received non-alkylating chemotherapy. The difference in rates of non-favorable ovarian reserve among the groups was not statistically significant (p=0.690).

Discussion

Solid tumors account for approximately 26% of all malignancies in children [21]. Treatment may include chemotherapy, radiotherapy, surgery, or their combination. We examined the long-term effect of different chemotherapy regimens on the ovarian reserve of survivors of childhood solid tumor malignancies. To avoid bias due to confounding factors for ovarian failure, we excluded patients treated with radiation to the head or pelvis [2-6,19].

Our findings show that a diminished ovarian reserve can be expected in a high proportion of patients treated during childhood with either alkylating agents (high or standard dose) or non-alkylating agents. More than 40% of the patients treated with alkylating agents had poor-prognostic ovarian reserve parameters as did more than 30% of the patients treated with non-alkylating agents. Among the patients treated with alkylating agents, there was a trend toward a higher rate of non-favorable ovarian reserve in those given the high as opposed to the standard dose, but the difference did not reach statistical significance.

Most of the previous studies of ovarian reserve following treatment for childhood cancer focused on hematological malignancies, which are much more prevalent in this age group. In the largest one to data, the Childhood Cancer Survivors Study (CCSS), survivors of childhood cancer (90% hematologic tumors, <10% solid tumors) were interviewed by telephone 5 years after completion of treatment [19]. Ovarian reserve status was defined by rates of secondary amenorrhea, accumulated pregnancy, and premature menopause. The authors found that women treated with pelvic radiation and/or increasing doses of alkylating agents were at risk of acute ovarian failure, premature menopause, and small-for-gestational-age offspring.

A study published in 2014 evaluated ovarian reserve in 105 cancer survivors, 60 of them was diagnosed with solid tumors. The main outcome was basal FSH and LH, E-2, AMH levels, ovarian surface area and AFC. Survivors had lower ovarian surface and lower AMH

Table 1: History of 47 survivors of childhood solid tumors.

Pt. no.	Age at diagnosis (yr)	Menarche status at diagnosis	Diagnosis	Treatment	AA treatment
1	15	Post-menarche	Osteosarcoma	S+C	Yes
2	4	Pre-menarche	Osteosarcoma	S+C	Yes
3	2	Pre-menarche	Ewing	S+C	Yes
4	10	Pre-menarche	Ewing	S+C+R	Yes
5	8	Pre-menarche	Rhabdomyosarcoma	C+R	Yes
6	6.06	Pre-menarche	Rhabdomyosarcoma	S+C	Yes
7	6	Pre-menarche	Rhabdomyosarcoma	S+C+R	Yes
8	1.06	Pre-menarche	Rhabdomyosarcoma	S+C+R	Yes
9	3	Pre-menarche	Rhabdomyosarcoma	C+R	Yes
10	0.08	Pre-menarche	Rhabdomyosarcoma	S+C+R	Yes
11	5.06	Pre-menarche	Rhabdomyosarcoma	S+C+R	Yes
12	8	Pre-menarche	Sarcoma	S+C+R	Yes
13	0.01	Pre-menarche	Sarcoma	S	No
14	1.1	Pre-menarche	Neuroblastoma	S + C	Yes
15	0.01	Pre-menarche	Neuroblastoma	S + C	Yes
16	1.06	Pre-menarche	Neuroblastoma	S + C	Yes
17	2.08	Pre-menarche	Neuroblastoma	C+R+I	Yes
18	3.06	Pre-menarche	Neuroblastoma	C	Yes
19	4	Pre-menarche	Neuroblastoma	C	Yes
20	1.03	Pre-menarche	Neuroblastoma	S+C+R	Yes
21	3	Pre-menarche	Neuroblastoma	S+C	Yes
22	1	Pre-menarche	Neuroblastoma	S+C	Yes
23	1.08	Pre-menarche	Neuroblastoma	S+C	Yes
24	2	Pre-menarche	Neuroblastoma	S+C	Yes
25	0.03	Pre-menarche	Neuroblastoma	S+C	Yes
26	3 .06	Pre-menarche	Neuroblastoma	S+C	Yes
27	7	Pre-menarche	Neuroblastoma	C	Yes
28	3 days	Pre-menarche	Hepatoblastoma	S+C	Yes
29	1.06	Pre-menarche	Wilms	S+C+R	No
30	2.06	Pre-menarche	Wilms	S+C+R	No
31	4.06	Pre-menarche	Wilms	C	No
32	5.06	Pre-menarche	Wilms	S+C+R	Yes
33	5	Pre-menarche	Wilms	S+C	No
34	2.06	Pre-menarche	Wilms	S+C+R	Yes
35	0.06	Pre-menarche	Wilms	C	No
36	8.06	Pre-menarche	Wilms	C+R	No
37	2	Pre-menarche	Wilms	S+C	No
38	4	Pre-menarche	Wilms	S+C	No
39	5	Pre-menarche	Wilms	S+C+R	No
40	2.06	Pre-menarche	Wilms	S+C+R	No
41	5	Pre-menarche	Wilms	S+C	No
42	4	Pre-menarche	Wilms	S+C+R	No
43	1.06	Pre-menarche	Wilms	S+C	No
44	10 days	Pre-menarche	Retinoblastoma	S+C	Yes
45	0.02	Pre-menarche	Retinoblastoma	S+C	Yes
46	4.06	Pre-menarche	Retinoblastoma	S+C	Yes
47	2	Pre-menarche	Meduloblastoma	S+C	Yes

AA: Alkylating Agent; S: Surgery; C: Chemotherapy; R: Radiation; I: radioactive iodine

Table 2: Ovarian reserve parameters and prognosis in survivors of childhood solid tumors.

Parameters	AA treatment		No AA treatment (n=12)	P value
	High dose (n=14)	Standard dose (n=17)		
Age (yr), Mean±SD (range)	20.5±5.8 (11-30)	19.9±8.9 (9-41)	17.2±7.3 (7-32)	0.507
Time from diagnosis (yr), Mean±SD (range)	15.9±6.6 (6-29)	17.0±9.0 (6-40)	13.5±6.8 (4.5-24.5)	0.476
Irregular menstrual cycles, n (%)	1/9 (11.1)	2/10 (20)	1/6 (16.6)	0.209
FSH ≥8 IU/L, n(%)	3/9 (33.3)	3/13 (23.0)	1/11 (9.0)	0.178
Antral folliclecount <6, n (%)	2/4 (50)	3/6 (50)	3/4 (75)	0.429
Anti-mullerian hormone level <1 pg/ml, n (%)	1/2 (50)	1/4 (25)	0/3	0.171
Non-favorable ovarian reserve prognosis, n (%)*	7/14 (50)	7/17 (41.1)	4/12 (33.3)	0.690

*Defined as at least one low ovarian-reserve parameter
AA-Alkylating Agent; FSH-Follicle Stimulating Hormone

levels in all survivors. Ovarian markers were worse in patients with high dose AA compared with standard dose. The protocols were divided to Cyclophosphamide, Ifosfamide, Procarbazine and high dose chemotherapy. There is no data regarding other AA such as Cisplatin, Carboplatin and BCNU and no information regarding cycles regularity [7].

In the present study, all but one of the 47 patients were diagnosed and treated for a solid tumor malignancy before reaching menarche. None had evidence of primary amenorrhea. At the end of follow-up, complete data were available for 36 patients. All those who were more than 15 years old had reached menarche. For the remaining 11 patients, follow-up needs to be extended until complete sexual puberty to determine if their fertility is impaired. A larger study with longer follow-up is also warranted to verify recent findings that in survivors of childhood cancer, age at menopause is inversely correlated with age at diagnosis [4].

Alkylating agents act by attaching an alkyl group to the guanine base of DNA, thereby affecting cancer cells. However, they also affect other highly proliferative cells, such as primordial follicles in the gonads, which leads to a diminished ovarian reserve. Three studies recently reported an association between treatment with alkylating agents and reduced AMH and increased gonadotropin levels; However, the study populations consisted mainly of patients with hematologic cancers [6-7,20]. The first, by Charpentier et al., included 6 survivors of childhood solid tumor malignancies, of whom 4 had abnormally low levels of AMH [6]. The second study, by El-Shalakany et al., reported higher levels of LH and FSH levels in the 11 patients with solid tumors than in the remaining two-thirds of the study group with hematological tumors [20]. Levels of AMH in the whole study group were similar to control levels but were not evaluated separately in the patients with solid tumors. In addition, there was no information on the cumulative dose of chemotherapy [20].

The strengths of the present study are the homogeneity of the study patients, all of whom had solid tumors treated at the same institution using the same diagnostic criteria and standard chemotherapy protocols. Baseline and follow-up blood measurements were performed by the same laboratory and were therefore comparable. Furthermore, besides the detailed telephone survey, additional tests were performed to assess ovarian reserve (sonographic measurements of ovarian volume and AFC and follow-up AMH blood test). The median duration of follow-up in our study was 15.4 years, far longer than previous studies [1,6,13,20].

The limitations of the study are the small sample size and incomplete evaluation of some of the parameters due to partial patient compliance. In addition, the fact that all patients but one was in the pre-menarchal pubertal stage at the time of treatment limited our ability to assess permanent ovarian damage. An even longer follow-up in these cases could reveal further, if any, residual damage.

In summary, our preliminary findings show that diminished ovarian reserve can be expected in a high proportion of patients treated during childhood for solid tumors with either alkylating (high or standard dose) or non-alkylating agents, therefore these patients should be followed for ovarian reserve markers and in appropriate cases fertility preservation measures such as oocyte freezing may be recommended. Additional studies are needed to detect the dosage tipping point at which alkylating and non-alkylating chemotherapy cause permanent ovarian damage in this patient population.

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