Endocrine Care

Acute Ovarian Failure in the Childhood Cancer Survivor Study

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Abbreviations:

AOF
Acute ovarian failure
CCSS
Childhood Cancer Survivor Study
CI
confidence interval
OR
odds ratio

Context: Defined as the loss of ovarian function within 5 yr of diagnosis, acute ovarian failure (AOF) is known to develop in a subset of survivors of pediatric and adolescent cancers. Its precise incidence is unknown, and data concerning its risk factors are limited.

Objective: Our objective was to determine the incidence of and patient/treatment factors associated with AOF in a large cohort of pediatric cancer survivors.

Design and Setting: We conducted a retrospective cohort, multi-center study.

Patients: Female participants from the Childhood Cancer Survivor Study who were greater than 18 yr of age were considered for inclusion. We excluded survivors who received cranial irradiation at doses of more than 3000 cGy, those with hypothalamic/pituitary tumors, and survivors who underwent bilateral oophorectomy. Survivors who reported never menstruating or who had ceased having menses within 5 yr after their cancer diagnosis were considered to have AOF.

Main Outcome: We assessed incidence and risk factors for AOF.

Results: Of a total of 3390 eligible survivors, 215 cases (6.3%) developed AOF. Survivors with AOF were older at diagnosis and more likely to have been diagnosed with Hodgkin's lymphoma or to have received abdominal or pelvic radiotherapy than survivors without AOF. Among survivors with AOF, 116 (54%) had received at least 1000-cGy ovarian irradiation. In a multivariable logistic regression model, increasing doses of ovarian irradiation, exposure to procarbazine, and exposure to cyclophosphamido at ages 13–20 yr were independent risk factors for AOF.

Conclusions: AOF develops in a small subset of survivors, especially those treated with at least 1000-cGy ovarian radiation. These results will facilitate patient counseling and selection of candidates for newer fertility preservation techniques. (J Clin Endocrinol Metab 91: 1723–1728, 2006)

SURVIVAL RATES FOR children and adolescents with cancer have increased markedly over the past 30 yr as a result of advances in supportive care and changes in cancer therapies. The use of multimodality therapy (e.g. combining surgery, multiagent chemotherapy, and radiotherapy) is now routine in the treatment of children with cancer. The 5-yr survival rates currently exceed 70% in children and adolescents, are near 80% in those treated for acute lymphoblastic leukemia, and are above 90% in those treated for Hodgkin's lymphoma. Beyond survival, attention is increasingly drawn to the consequences of cancer and its treatments and to the different health issues surrounding cancer survivorship. In particular, abdominal, pelvic, and spinal radiotherapy and certain chemotherapeutic drugs, especially alkylating agents, have been shown to increase the risk of ovarian failure in female cancer survivors.

Depending on the extent of damage to the ovaries, two forms of premature ovarian failure can be distinguished. The subset of survivors that loses ovarian function during cancer therapy or shortly after its completion is classified as having acute ovarian failure (AOF). For survivors who retain ovarian function after the completion of cancer treatment, a subset will go on to experience menopause before age 40 yr and is classified as having premature menopause. Subjects at high risk of developing AOF may benefit from the newer techniques of fertility preservation (e.g. ovarian tissue cryopreservation) and need to be counseled accordingly. However, the data on the incidence of and risk factors for AOF are somewhat limited. Furthermore, previous studies are often based on small cohorts of patients, and generally the data regarding therapeutic exposures are incomplete.

In the present work, we have assessed the incidence of AOF as well as the patient and treatment factors associated with AOF in a large cohort of subjects enrolled in the Childhood Cancer Survivor Study (CCSS). A unique strength of this cohort, beyond its size, is the availability of detailed treatment information,
including cumulative doses of key chemotherapeutic agents and estimates of radiation dose to the ovaries.

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Subjects and Methods

CCSS

The details of the conduct and characteristics of the CCSS, also known to study participants as the Long-Term Follow-Up Study, have been published previously. In brief, the CCSS is a retrospective cohort of 5-yr survivors of childhood cancer diagnosed before the age of 21 yr between the years 1970 and 1986 and treated at one of the 26 contributing centers located in the United States or Canada (see Acknowledgments). The primary aim of the study is to determine late adverse outcomes that follow treatment for childhood and adolescent cancer. The CCSS has been approved by the Institutional Review Board at the University of Minnesota (the study coordinating center) and each of the participating centers.

Participation in the Long-Term Follow-Up Study consisted of completion of a 24-page baseline questionnaire (all CCSS questionnaires are available at http://www.cancer.umn.edu/ccss). A proxy completed the baseline questionnaire if the participant was less than 18 yr at entry or was deceased after achieving 5-yr survivorship but before study entry. In addition, detailed medical information was abstracted from the medical record of each participant. Data collected included all treatments for the primary diagnosis, including the initial treatment for any relapse, and preparatory regimens for bone marrow transplant. Information about cancer treatment included qualitative information on 42 chemotherapeutic agents, quantitative information on 22 selected chemotherapeutic agents, quantitative information on 22 selected chemotherapeutic agents, surgeries performed from the time of diagnosis, and quantitative radiation data on field size, site, and dose.

AOF study

The inclusion criteria consisted of female CCSS participants who were greater than 18 yr of age at the time of completion of the questionnaire (see below) and for whom menstrual history was available. Exclusion criteria were diagnoses associated with ovarian dysfunction (e.g. Turner syndrome), cranial irradiation above 3000 cGy (known to cause hypogonadotropic hypogonadism), tumor located in the hypothalamic-pituitary region, history of bilateral oophorectomy, and incomplete radiation records.

Of the 14,372 participants in the CCSS, 6,079 females were greater than 18 yr and known to be alive as of November 2000. Of those 6079 survivors 4608 (76%) completed a follow-up questionnaire (complete questionnaire is available at www.cancer.umn.edu/ccss) during 2000 and 2001. This questionnaire included a specific section on menstrual status, which requested information on age at menarche, current menstrual status, age at last menstrual period, and etiology of menopause (i.e. surgical vs. nonsurgical) for those who were currently menopausal. From among these 4608 subjects, 1218 patients were excluded. Thus, 3390 survivors were deemed eligible for this study. Survivors who reported never menstruating or who reported that they had ceased having spontaneous menses within 5 yr after their cancer diagnosis were considered to have AOF.

Radiation dosimetry

Radiation dose to the ovaries and pituitary was quantified by a radiation dosimetrist who evaluated radiation therapy records collected by the 26 centers. Complete records included photographs of patients in treatment position or diagrams of treatment fields, beam energy, field size, blocking information, and daily treatment doses. When diagrams were not available, a written description of the treatment from the radiation therapy record or medical record was used to estimate the extent of the treatment and the dose administered. For treatments very near the sites of interest, the records were reviewed to determine oophoropexy status, special gonadal shielding, beam shaping blocks, and field location. Doses from all treatment fields were summed and included the contribution of primary and scatter radiation. If the surgical notes indicated an oophoropexy,
the dose to the ovary was reduced to approximately 10% of the in-beam dose. Doses to right and left ovaries were estimated separately.

Chemotherapy

Seven broad categories of drug classes of chemotherapy were identified from treatment records: alkylating agents, alkaloids, platinum-containing agents, antimetabolites, topoisomerase inhibitors, antibiotics, and steroids. The total exposure to alkylating agents was measured by calculating an alkylating agent score, accounting for both the number of drug exposures as well as the cumulative doses administered. Specifically, for each alkylating agent, the total dose in milligrams per square meter was calculated for each subject. The distribution of the doses received by all subjects in the CCSS cohort was determined for each alkylating agent. Each subject was assigned a score of 0, 1, 2, or 3 for each drug depending on whether the individual received no drug or fell into the lower, middle, or upper tertile of the distribution. The individual scores were summed, and the subjects were assigned an overall alkylating agent score of 0, 1, 2, or 3 depending on where the individual fell in the overall distribution [13]. Exposure to individual alkylating agents was also considered as separate dichotomous variables (yes or no).

Statistical analysis

Study participants were categorized into two groups: survivors with AOF and nonaffected survivors. Furthermore, survivors were divided into two age groups: subjects no more than 12 yr at diagnosis and those more than 12 yr at diagnosis. These age cutoffs were meant to correspond to survivors who were likely prepubertal (≤12 yr) or pubertal (>12 yr) at diagnosis. Cumulative doses of radiotherapy received by the ovaries were calculated and grouped as follows: less than 100, 100–999, 1000–1999, and 2000 cGy and above. Study subjects’ ages at diagnosis and at completion of the menstrual history questionnaire were expressed as the mean ± SD; univariate comparisons between subjects with AOF and nonaffected survivors were made using Student’s t test, and univariate associations of AOF and categorical variables were assessed by χ² test. Logistic regression was used to estimate the odds ratio (OR) with 95% confidence intervals (CI) for having AOF to account for the effect of the different patient characteristics, primary diagnoses, and treatment modalities. A multivariable logistic regression model was then constructed to estimate the effects of independent risk factors for AOF. We included interactions between age at diagnosis and treatment risk factors to investigate whether treatment-related risks varied with age at treatment. The Akaike information criterion was used as a guide in determining a final model that best explained the data [14].

Results

Of a total of 3390 survivors included in the study, 215 cases (6.3%) developed AOF. The characteristics of patients with AOF and of the nonaffected survivors are summarized in Table 1. Compared with survivors who did not develop AOF, survivors with AOF were older at diagnosis (9.8 ± 6.0 vs. 8.3 ± 6.0 yr; P < 0.004), were more likely to have been diagnosed with Hodgkin’s lymphoma (30.7 vs. 15.3%; P < 0.001), and were more likely to have been exposed to an alkylating agent (67 vs. 48.6%; P < 0.001) and to abdominal/pelvic radiotherapy (75.3 vs. 21.1%; P < 0.001). Among survivors with AOF, 116 individuals (i.e. 54% of all cases of AOF and 72% of all cases treated with abdominal/pelvic radiation) had received an estimated dose of at least 1000 cGy to the ovary.

The univariate analysis showed that the following variables were all significantly associated with the occurrence of AOF: age at diagnosis above 12 yr; diagnoses of Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, Wilms’ tumor, and soft-tissue sarcoma; exposure of the ovaries to increasing doses of radiotherapy; and treatment with chemotherapy in general as well as exposure to various alkylating agents (Table 2). The multivariable logistic regression model revealed that the independent risk factors for AOF were age at diagnosis, exposure of the ovaries to radiotherapy, and exposure to cyclophosphamide and procarbazine. There were significant interactions between age at diagnosis and high

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**TABLE 1 -- Patient characteristics and treatment variables**

<table>
<thead>
<tr>
<th>Survivors</th>
<th>Nonaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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doses of radiotherapy to the ovary ( \( P = 0.03 \) for dose \( \geq 2000 \) cGy) and between age at diagnosis and treatment with cyclophosphamide ( \( P = 0.0006 \)), with this drug being a significant risk factor only for the older age group. Table 3 shows the treatment-related risk factors obtained by the multivariable model for each age group. Figure 1 illustrates the percentage of subjects who developed AOF according to age and radiation dose delivered to the ovaries. For subjects who developed AOF despite receiving radiation doses to the ovaries of less than 1000 cGy, 55% were older than age 12 yr at diagnosis and 72% had been exposed to alkylating agents.
Discussion

The precise incidence of therapy-related adverse effects and the chances that a particular individual will experience them are of critical importance to patients and families as they embark on cancer treatment. In the current study, we have characterized these parameters for AOF in childhood cancer survivors using data from the multicenter CCSS cohort.

AOF appears to occur in a small subset of childhood cancer survivors. The incidence of AOF in the CCSS cohort was 6.3%. This is substantially lower than the 12% previously reported by Stillman et al., who described data in a cohort of 182 childhood cancer survivors with a large percentage of survivors of Wilms' tumor (29%) and only a small number.

TABLE 2 -- Risk factors associated with AOF: univariate associations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–12</td>
<td>121</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–20</td>
<td>94</td>
<td>1.8</td>
<td>1.4–2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>66</td>
<td>3.8</td>
<td>2.7–5.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NHL</td>
<td>19</td>
<td>3.2</td>
<td>1.8–5.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wilms'</td>
<td>35</td>
<td>3.0</td>
<td>1.9–4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SST</td>
<td>27</td>
<td>2.6</td>
<td>1.6–4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Others</td>
<td>68</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>201</td>
<td>3.3</td>
<td>2.0–6.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>119</td>
<td>1.7</td>
<td>1.3–2.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Busulfan</td>
<td>2</td>
<td>9.9</td>
<td>1.3–60.1</td>
<td>0.01</td>
</tr>
<tr>
<td>CCNU</td>
<td>10</td>
<td>4.1</td>
<td>1.9–8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>6</td>
<td>7.6</td>
<td>2.6–19.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>20</td>
<td>1.7</td>
<td>1.0–2.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>53</td>
<td>3.4</td>
<td>2.4–7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alkylator score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>1.5</td>
<td>1.0–2.2</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>1.7</td>
<td>1.1–2.6</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>2.9</td>
<td>1.9–4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>203</td>
<td>11.2</td>
<td>6.5–21.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pelvis or abdomen</td>
<td>162</td>
<td>25.4</td>
<td>14.7–48.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other sites</td>
<td>41</td>
<td>3.5</td>
<td>1.9–6.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>Minimum ovarian irradiation dose (cGy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–99</td>
<td>40</td>
<td>3.7</td>
<td>2.0–7.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>100–999</td>
<td>38</td>
<td>15.5</td>
<td>8.2–31.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1000–1999</td>
<td>34</td>
<td>61.0</td>
<td>30.8–128.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥2000</td>
<td>82</td>
<td>482.1</td>
<td>233.4–1082.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum ovarian irradiation dose (cGy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of leukemia survivors (5%), a distribution quite different from that observed in the general pediatric population. The higher incidence of AOF reported by this group may be due to the high doses of radiation received by the ovaries in girls treated for Wilms' tumor during this era. In a more recent study, Larsen et al. reported on ovarian function of 100 childhood cancer survivors diagnosed and treated before the age of 15 yr. The distribution of cancer diagnoses was similar to that observed in the CCSS cohort; 8% of the survivors had AOF, if we apply our diagnostic criteria to that population.

Our data indicate that radiotherapy to the ovaries was the most significant risk factor for AOF, a finding that is consistent with previous reports. Of survivors who developed AOF, 75% had been previously exposed to abdominal-pelvic

### TABLE 3

- **Age at diagnosis**
- **Risk factor**
- **OR**
- **95% CI**
- **P**

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Exposure to procarbazine</th>
<th>Exposure to cyclophosphamide</th>
<th>Minimum ovarian irradiation dose (cGy)</th>
<th>Exposure to procarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.2</td>
<td>1.3–7.3</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>13–20 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.6</td>
<td>1.4–4.7</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>
Irradiation. Doses of radiotherapy to the ovary of at least 2000 cGy were associated with the highest risk of AOF; more than 70% of patients exposed to such doses developed AOF. Previous data indicate that radiation does affect the ovaries in a dose-dependent fashion (7–17). Several attempts were made in the past to define radiation dose thresholds for ovarian toxicity. Doses in the range of 1000–3000 cGy have been noted to cause AOF in the majority of patients treated during childhood and adolescence (3,17–23). In the current study, smaller doses of radiotherapy to the ovaries were also found to be significant risk factors for AOF, albeit with a weaker statistical association than doses of at least 1000 cGy. Thus, doses of ovarian radiation of less than 1000 cGy are capable of inducing AOF in patients who have additional risk factors, namely concomitant exposure to alkylating agents and older age at diagnosis.

Among chemotherapeutic agents, alkylating agents,
which prevent cell division by interacting with DNA, are known to be associated with the occurrence of ovarian failure [5] [6] [23] [24]. In the current study, we showed that the alkylating agents cyclophosphamide and procarbazine were significant risk factors for AOF. Although exposure to procarbazine was an independent risk factor for AOF, regardless of age at treatment, cyclophosphamide significantly increased that risk only in subjects treated at an older age. As the number of oocytes declines with advancing age, the ovaries of older individuals become more vulnerable to gonadal toxins compared with that seen in younger subjects [3] [22]. Only a small number of patients in our study were exposed to other alkylating agents such as busulfan and chlorambucil, which may explain the weaker association of these agents with the development of AOF (Table 2). Myeloablative chemotherapy regimens, such as high-dose cyclophosphamide combined with busulfan, are being used increasingly as preparation for stem cell transplantation. Several reports indicate a high incidence of AOF in patients exposed to such regimens [5] [6] [21] [24]. Thus, high-dose alkylating-agent chemotherapy may be a more prominent risk factor for AOF in patients treated on select contemporary regimens that incorporate these agents.

In this study, we report on the largest known cohort of female childhood cancer survivors suffering from AOF. However, there are limitations that need to be taken into account when interpreting the study results. The only criterion used to make a diagnosis of AOF was self-reported amenorrhea. Thus, it is possible that we may have included some cases of amenorrhea due to conditions other than primary ovarian failure (e.g., stress-related amenorrhea). Because treatment protocols have changed over time, the results of this study may not be strictly applicable to individuals who were treated more recently.

In conclusion, AOF appears to occur in a relatively small number of childhood cancer survivors. Exposure of the ovaries to irradiation, especially at doses of 1000 cGy and above, and exposure to the alkylating agents procarbazine and cyclophosphamide, at older ages, were identified as significant risk factors for AOF. These data will assist clinicians in counseling patients and their families at the time of diagnosis and before cancer therapy is initiated. Recently, successful pregnancies have been reported in cancer survivors after autotransplantation of cryopreserved ovarian tissue [25] [26]. Understanding which patients are at highest risk of developing AOF will help in defining those most likely to benefit from these novel treatments.
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