Title: Acute Ovarian Failure (AOF) in Survivors of Childhood and Adolescent Cancer: Data from the Childhood Cancer Survivor Study (CCSS)

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Background: Defined as the loss of ovarian function within 5 yr of diagnosis, 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**: To determine the incidence of and patient/treatment factors associated with AOF in a large cohort of pediatric cancer survivors. **Design/Methods**: Female participants from the multicenter CCSS who were ≥18 years of age and who completed a special menstrual history questionnaire were considered for inclusion. We excluded survivors who received cranial irradiation at doses > 30Gy, those with hypothalamic/pituitary tumors and survivors who underwent bilateral oophorectomy. Survivors who had never menstruated or ceased menses within 5 years after their cancer diagnosis were considered to have AOF. **Results**: Of a total of 3390 survivors included in the study, 215 cases (6.3%) developed AOF. Survivors with AOF were older at diagnosis (9.8 $\pm$ 6.0 vs 8.3 $\pm$ 6.0, p <0.05) and more likely to have been diagnosed with Hodgkin lymphoma (31%, p<0.0001); 75 % had received abdomino-pelvic irradiation (p<0.0001). In a multivariate Poisson-regression model, increasing doses of ovarian radiotherapy (ORT), older age at diagnosis (AD), and exposure to the highest doses of alkylating agents (AA) were independent risk factors for AOF. Survivors treated with 1-99 cGy ORT had a rate ratio (RR) of AOF of 3.9 (95%CI 1.9-8.7, p=0.0003), those treated with 100-999 cGy ORT had a RR of AOF of 15.6 (95%CI 7.6-35.4, p<0.0001) and those treated with doses ≥1000 cGy ORT had a RR for AOF of 207.4 (95%CI 104.0-463.3, p<0.0001) compared to those treated with no ORT. The other independent risk factors for AOF were: AD > 12 yr (RR 2.4 [95%CI 1.5-3.7, p<0.0001]) compared to AD ≤12 yr, and an AA score of 3 (RR of 2.3 [95%CI 1.3-4.2, p=0.003]) compared to an AA score of 0. See *Table* for risk of AOF by age and treatment exposures. **Conclusions**: Older age at diagnosis, exposure to high doses of alkylating agents and especially exposure of the ovaries to RT increase the risk of AOF. These results will facilitate patient counseling in the future.

Risk of AOF by age and treatment

Survivors AD>12y vs	Survivors AD≤12y	RR	95%CI
AA score 3	AA score 0	3.9	2.4-6.2*
ORT≥1000cGy	no ORT	326.1	131.1-950.1*
AA score3+ORT ≥1000cGy	AA score0,no ORT	355.3	76.2-2214.6*

*=p<0.0001

References:

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