Transplantation of frozen thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria

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Objective: To report the single-center results of orthotopic retransplantations of cryopreserved ovarian tissue in cancer survivors and evaluate the validity of commonly accepted procedure limitations.
Design: Prospective cohort study.
Setting: Tertiary university-affiliated assisted reproduction technology (ART) and oncology centers.
Patient(s): Twenty cancer survivors who underwent ovarian transplantation of frozen-thawed ovarian tissue with the aim to conceive.
Intervention(s): Ovarian tissue cryopreservation (OTCP) and transplantation, endocrine monitoring, in vitro fertilization (IVF).
Main Outcome Measure(s): Endocrine profile, IVF, pregnancies, live births.
Result(s): The patient ages at tissue harvesting ranged from 14 to 39 years. Fifteen women had hematologic malignancies, and two had leukemia (chronic myelogenous leukemia and acute myelogenous leukemia). Ten patients were exposed to nonsterilizing chemotherapy before OTCP. After transplantation, the endocrine recovery rate was 93%. Fourteen patients underwent IVF treatments with a fertilization rate of 58%. Sixteen pregnancies were achieved (10 after IVF, 6 spontaneous), resulting in 10 live births, two (twins) after harvesting from the mother at the age of 37. Two pregnancies are currently ongoing. After transplantation, 53% of patients conceived, and 32% delivered at least once. One patient conceived four times. Preharversting chemotherapy exposure was not associated with inferior outcomes. All patients, including two leukemia survivors, remained cancer free.
Conclusion(s): Orthotopic transplantation of thawed ovarian tissue is a highly effective measure to restore fertility in sterilized cancer patients. Chemotherapy exposure before harvesting and age >35 is a realistic option in selected patients. Retransplantation in leukemic patients is possible after application of maximal safety measures. These results have led the national ethical and professional authorities to decide for the first time not to consider OTCP as an experimental modality for fertility preservation.
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Q2 **Key Words:** ■■■

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Ovarian tissue cryopreservation (OTCP) aims to provide a chance for future fertility for young women and prepubertal girls who are at major risk for significant ovarian injury and sterility, most commonly as a result of radiation/chemotherapy induced loss of ovarian follicular reservoir (1). It has been more than a decade since the first reports of live births after OTCP and retransplantation (2, 3), and to date, more than 60 live births have been described by multicenter reports (4, 5), single-center studies (6, 7), and case reports (8–10) from dozens of centers worldwide. Nevertheless, significant heterogeneity exists among different

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groups regarding selection criteria for OTCP, such as age limits for tissue collection and ineligibility due to previous exposure to chemotherapy (11) or specific cancer diagnoses that might preclude retransplantation. Some of these exclusion criteria were adapted into practice long before data on true procedural limitations became available (12). Tissue preparation, freezing and transplantation techniques are also diverse, applied differently worldwide.

A major challenge is estimation of true transplantation success rates in cancer patients. Reports on pregnancies and deliveries are currently compiled from multiple centers, some of which do not conduct complete pretransplantation endocrine monitoring, therefore possibly including transplantations performed in patients who were not sterilized in the first place. To accurately assess fertility outcomes after transplantation of cryopreserved–thawed ovarian tissue we describe here the results of a single-center study of OTCP outcomes. Transplantations were performed using a uniform technique by one team, which consistently performed pre/posttransplantation endocrine monitoring, fertility treatments, and in vitro fertilization (IVF) procedures in all patients. This study provides an accurate evaluation of procedure success rates and allows for a careful clarification of procedure limits and risks.

MATERIALS AND METHODS

Patients

From January 2004 to March 2015, 20 cancer patients who had stored ovarian tissue before sterilizing chemotherapy underwent autotransplantation in our center to restore fertility and conceive. The patients' ages at the time of cryopreservation were between 14 and 39 years (mean 28.8 years). Fifteen patients had hematologic malignancies and an additional five from solid tumors (Table 1). Ten patients had been treated with nonsterilizing chemotherapy before tissue harvesting. In patient no. 8, ovarian tissue was harvested during a surgery of large abdominal tumor removal and after several chemotherapy cycles. In the remaining nine patients, OTCP was performed when switching to second-line protocols was required due to disease refractoriness (patients no. 2, 3, and 20) or a later relapse (patients no. 1, 4, 6, 14, 16, and 19). In seven of nine cases, collection of tissue was performed before second-line therapy had begun. Two of nine patients (patients no. 1 and 19) underwent chemotherapy cycles right before OTCP took place. Patient no. 1 required immediate salvage therapy on relapse due to poor medical condition incompatible with general anesthesia, and patient no. 19 underwent OTCP after completing second-line chemotherapy when the

TABLE 1

Patient characteristics and pre/posttransplantation endocrine profiles.

				Age (y)		Ovarian function before Tx			Ovarian function after Tx		
Patient	Diagnosis	Pre-OTCP chemotherapy[a]	No. of children	OTCP	Tx	Menses	FSH (mIU/mL)	E^2 (pmol/L)	Menses[b]	FSH (mIU/mL)	E^2 (pmol/L)
No previous chemotherapy											
5	CML	–	0	19	27	No	116.4	<37	Yes (6M)	7.2	147
5′[c]	CML	–	0	21	28	No	44	174	Yes (4M)	100	360
7	Hodgkin's	–	0	19	35	No	87	<100	Yes	12.4	107
9	Breast cancer	–	1	37	45	Yes	8.4	100	Yes	5.7	177
10	NHL	–	0	39	41	No	99	<100	Yes (1M)	96	<100
11	Hodgkin's	–	0	32	36	No	54.6	<73.4	Yes	27.6	126
12	Breast cancer	–	0	33	38	Yes	4.8	858	Yes	6.8	380
13	NHL	–	1	34	42	No	30	100	Yes (6M)	26.4	<100
15	Hodgkin's	–	0	37	40	No	41.8	137	Yes	7.8	645
17	Breast cancer	–	0	37	45	Yes	6.8	232	Yes	14	<185
18	Ewing's sarcoma	–	0	24	28	No	107	<70	Yes	24.3	<100
Previous chemotherapy											
1	NHL	VACOP_B, MINE/ESHAP	1	30	32	No	100	<70	Yes	7	342
2	NHL	VACOP_BX6	1	38	42	No	120	<100	Yes	11	220
3	Hodgkin's	ABVDX4	1	31	36	Yes	10.3	380	Yes	9.5	99
4	Hodgkin's	ABVDX6	1	24	27	No	81	<70	Yes	12.2	<73.4
6	Hodgkin's	ABVD	0	23	26	No	60.7	146	Yes	13.8	<73.4
8	Ewing's sarcoma	VCAIE	0	14	21	No	60	69	No	94	<100
14	Hodgkin's	ABVDX6	0	29	32	No	108	70	Yes	27	288
16	Hodgkin's	ABVDX6	0	32	36	No	33.1	99	Yes	16	95
19	Hodgkin's	ABVDX5, MOPPX1	0	23	28	No	68	70	Yes	44	134
20	AML	Doxoroubicin + ARA-C	0	19	31	No	37	180	Yes	29	70

Note: AML = acute myeloid leukemia; CML = chronic myelogenous leukemia; E_2 = estradiol; FSH = follicle-stimulating hormone; NHL = non-Hodgkin's lymphoma; OTCP = ovarian tissue cryopreservation; Tx = transplantation.

[a] VACOP_B = etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; MINE/ESHAP = mesna, ifosfamide, mitoxantrone, etoposide/etoposide, methylprednisolone, high-dose cytarabine, cisplatin; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; MOPP = mechlorethamine, vincristine, procarbazine, vincristine; VCAIE = vincristine, cyclophosphamide, arabinosidecytosine, idrarubucin.

[b] Numbers in brackets represent duration of menses in case menses ceased during follow-up observation.

[c] Results after the second transplantation.

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