ORIGINAL ARTICLE: FERTILITY PRESERVATION

Ovarian stimulation in young adult cancer survivors on targeted cancer therapies

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Objective: To describe a clinical approach to and outcomes of IVF in reproductive-aged cancer survivors receiving targeted cancer therapies.
Design: Case report.
Setting: Academic fertility preservation program.
Patient(s): The first case is of a female patient with metastatic lung cancer receiving long-term crizotinib, an anaplastic lymphoma Q2 kinase inhibitor. The second case is of a female patient with metastatic colon cancer receiving long-term denosumab, a RANKL antibody. Both patients presented desiring fertility.
Intervention(s): In vitro fertilization.
Main Outcome Measure(s): Live birth and embryo banking.
Result(s): The potential impact of targeted therapy on oocytes and pregnancy was investigated via literature review and pharmaceutical company inquiries. After oncologic, fertility, and psychological counseling, both survivors underwent ovarian stimulation, IVF, and preimplantation genetic screening. One couple achieved live births of dizygotic twins via gestational surrogacy. The second couple froze one euploid blastocyst for future fertility. Both survivors are stable from their cancer standpoints.
Conclusion(s): Successful fertility treatments are possible in the context of exposure to crizotinib and denosumab. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Crizotinib, denosumab, fertility preservation, ovarian stimulation, targeted cancer treatment

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There are more than 400,000 reproductive-aged women in the United States who have been diagnosed with cancer (1). These young adult cancer survivors (YA survivors) want to raise families and prefer biologic children over adoption and gamete donation (2). Most YA survivors do not undergo fertility preservation before cancer therapy and face infertility and shortened reproductive windows after gonadotoxic treatments such as alkylating chemotherapy or pelvic radiation (3, 4).

In the era of precision medicine, there is increased molecular profiling and use of targeted cancer therapies that block cancer growth by interfering with specific molecules. Accordingly, there is the emergence of reproductive-aged cancer survivors who are receiving long-term targeted cancer therapies when seeking fertility and pregnancy. In contrast to chemotherapy and radiation, fewer data and no professional society guidelines are available on the impact of targeted cancer therapies on both fertility potential and pregnancy. In this context, reproductive and oncology specialists are asked to counsel and manage YA survivors desiring fertility.

We describe strategies for facilitating fertility and parenthood in two couples in which the female partners were receiving targeted cancer therapy. The female partner of the first couple is a young woman with metastatic lung cancer taking long-term crizotinib, an anaplastic lymphoma kinase (ALK) in- Q3 hibitor. The female partner of the second couple is a young woman with metastatic colorectal cancer taking long-term denosumab, an RANKL antibody. We show that successful fertility treatment of these medically complex patients occurred with a multidisciplinary approach, careful evaluation of impact on maternal and offspring health, and thorough counseling.

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MATERIALS AND METHODS AND RESULTS

Informed consent was obtained from patients for this report. The institutional review board of University of California, San Diego indicated that a report of two cases did not require specific institutional review board review.

Case 1

The patient was a 36-year-old gravida 0 lung cancer survivor. At age 33 years she and her husband had experienced primary infertility of 3 years when she was diagnosed with stage IV ALK mutant non-small cell lung cancer. Before her cancer diagnosis she underwent fertility treatments at outside institutions that included clomiphene citrate with and without IUI, gonadotropins with IUI, and one IVF cycle without achieving pregnancy. In her first IVF cycle, 18 oocytes were retrieved, and five cleavage-stage embryos of poor morphologic quality were obtained. Two ETs, one fresh and one frozen, did not result in pregnancy.

At age 33 years she experienced voice changes. Left vocal cord paralysis was found, and imaging studies showed a left upper lobe lung mass, mediastinal adenopathy, pleural-based nodules, and brain metastases. A pleural biopsy showed moderately differentiated lung adenocarcinoma. Molecular testing of the tumor showed that it was KRAS wild type, EGF receptor wild type, and ALK fused. The patient did not undergo fertility preservation counseling before cranial radiation and first-line chemotherapy with cisplatin and pemetrexed owing to urgency of therapy initiation. Upon progression she was enrolled in the PROFILE 1007 clinical trial and began oral crizotinib (Xalkori, Pfizer) therapy. She had a dramatic radiographic response and planned long-term crizotinib therapy.

At age 36 years the patient and her partner were referred to our fertility clinic to discuss pregnancy in the context of long-term crizotinib therapy. She reported regular menstrual cycles. Her family history and additional medication use were noncontributory. Her FSH was 7.5 IU/L, E_2 was 24 pg/mL, and antimüllerian hormone was 4.2 ng/mL. The patient's partner was 34 years old with a normal semen analysis and no significant medical problems, exposures, or family history. A literature search was performed on the effect of crizotinib on oocytes, embryos, and pregnancy. Because of the lack of published studies on the effect of crizotinib exposure on gametes and pregnancy, we contacted Pfizer pharmaceuticals and discussed these questions with their toxicologist and pharmacist.

The couple underwent extensive counseling by medical oncology, reproductive endocrinology, and psychology to consider the following: her limited lifespan; risks of cancer progression off crizotinib before and during ovarian stimulation; unknown risks of crizotinib exposure on oocyte and embryo; known fetotoxic effects of crizotinib; and underlying infertility with poor fertility treatment outcomes before cancer. They were counseled on adoption or surrogacy with oocyte donation, but they strongly wished to have a biologic child. After several months of information gathering, counseling, and care coordination, the couple decided to pursue autologous ovarian stimulation, preimplantation genetic screening (PGS), and pregnancy via gestational surrogacy.

For IVF, we held crizotinib starting 16 days before ovarian stimulation to account for the half-lives of crizotinib and its main active metabolite and ending the day after oocyte retrieval. Calculations were based on the half-life of the parent compound (42 hours) and secondary metabolites. The total number of days off of crizotinib was 31. Pretreated with oral contraceptives, the patient underwent a GnRH antagonist protocol with flexible gonadotropin dosing using 250 IU of recombinant FSH (Follistim, Merck & Co.) and 150 IU of hMG (Menopur, Ferring Fertility) as the starting dose. After 13 days of stimulation, ovulation was triggered at a peak E_2 level of 4,830 pg/mL using 4 mg of leuprolide and 1,500 IU of purified hCG. Seventeen eggs were retrieved and noted to have thickened zona, significant granularity, and vacuoles. Fourteen mature eggs underwent intracytoplasmic sperm injection (ICSI), seven poor-quality cleavage-stage embryos between two and seven cells were observed on day 3, and no blastocysts developed after extended culture. No transfer was performed. The patient had no interval disease progression.

Six weeks after this failed cycle, the couple requested a final IVF attempt. Her crizotinib was held again for 31 days as described above. She underwent a GnRH antagonist protocol using fixed-dose ovarian stimulation with hMG 150 IU and clomiphene citrate 100 mg daily. After 14 days of stimulation her peak E_2 was 5,367 pg/mL, and ovulation was triggered using the same regimen as above. Eight oocytes were retrieved and noted to have less granularity and no vacuoles, seven mature eggs underwent ICSI, five cleavage-stage embryos were observed on day 3, and four blastocysts developed and were biopsied for PGS via array comparative genomic hybridization. Two euploid embryos were identified. Because of two prior failed IVF cycles, the decision was made to transfer both embryos (4AB, 4AB) to the gestational surrogate in a frozen embryo transfer cycle. A dichorionic twin intrauterine pregnancy was achieved. At 36 weeks a baby boy (weight 3,175 g) and baby girl (weight 2,948 g) were delivered via cesarean section for malpresentation. The baby girl was observed in the neonatal intensive care unit for 4 days. No gross dysmorphology has been observed in the children, now 2 years old.

The patient continues on crizotinib to this day. She is doing well from her cancer standpoint. She is now receiving a second generation ALK inhibitor and has survived 7 years since her cancer diagnosis.

Case 2

The patient was a 33-year-old gravida 0 colorectal cancer survivor. She had no significant past medical history until she was diagnosed with stage IV colorectal cancer at age 31 years. Because of bowel habit changes, she underwent a sigmoidoscopy that revealed a large sigmoid colon mass. Further imaging scans showed pulmonary, hepatic, lymph node, and bone metastases. She had negative germline testing for familial cancer risk. The patient did not undergo fertility preservation counseling before undergoing chemotherapy with FOLFOX and bevacizumab. She showed good response in liver, retroperitoneal, and bone disease after chemotherapy.