Case report

Retreatment with aromatase inhibitor therapy in the management of granulosa cell tumor

Melissa Schwartz, Gloria S. Huang *

Department of Obstetrics & Gynecology and Women's Health, Division of Gynecologic Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, 1695 Eastchester Road, Suite 601, Bronx, NY 10461, United States

1. Introduction

Granulosa cell tumors (GCTs) represent 3% to 5% of ovarian neoplasms. These tumors arise from the sex-cord stromal cells of the ovary (Colombo et al., 2007). Characteristically, GCTs produce inhibin (Lappöhn et al., 1989) and express aromatase activity promoting estrogen synthesis (Kato et al., 2015). There are two subtypes of GCTs, adult and juvenile, with the former comprising 95% of cases.

Most cases of GCT are diagnosed with stage I disease and have a 10-year survival rate of 60–90% (Lauszus et al., 2001). These tumors may recur years to decades after the initial diagnosis, thus necessitating life-long disease surveillance. Cytotoxic chemotherapy and radiation therapy for women with advanced-stage or recurrent disease have shown limited benefit (Schumer and Cannistra, 2003). A systematic review of GCT cases reported in the literature suggested that most respond to hormonal therapy (van Meurs et al., 2014). However, a multi-institutional retrospective cohort study showed only ~18% objective response rate among patients with measurable adult GCT treated with hormonal therapy (van Meurs et al., 2015). Although data are sparse, in several reported cases aromatase inhibitors have been useful in the management of GCT (Freeman and Modesitt, 2006; Lamm et al., 2014). We present herein a unique case of recurrent GCT that previously progressed on the aromatase inhibitor anastrozole but subsequently

* Corresponding author.
  E-mail address: ghuang@montefiore.org (G.S. Huang).

had a sustained partial response of 24 months duration during retreatment with another aromatase inhibitor letrozole.

2. Case

A 65-year-old (gravida 1, para 1) Caucasian woman presented with her 4th recurrence of GCT in July 2012. Her past medical history was notable for hypothyroidism, hyperlipidemia, and hypertension. She was overweight (Body Mass Index of 27 kg/m^2) and had an excellent performance status (ECOG score = 0).

Treatment history: She had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection and omentectomy in 2003 with a diagnosis of FIGO stage IA GCT of the ovary. Intraoperatively, the ovarian mass was 9 cm diameter and confined to the ovary. No adjuvant treatment was given. In March 2005, an increased serum Inhibin B level detected her first disease recurrence. The patient underwent a tumor debulking surgery involving the lower abdominal wall in April 2005. Post-operatively she transferred her care to our institution and completed adjuvant external beam radiation.

A second recurrence was diagnosed in November 2006 with an elevated serum Inhibin B and an enlarged left para-aortic lymph node; a fine needle aspiration (FNA) of the para-aortic lymph node confirmed GCT. The patient received 4 cycles of bleomycin, etoposide and cisplatin (BEP), completed in February 2007 with resolution of the left para-aortic lymphadenopathy accompanied by normalization of the Inhibin B. In August 2008, a third recurrence was noted after a surveillance CT scan showed an enlarging left para-aortic lymph node to 3.4 × 2.0 cm with concomitant increase in Inhibin B to 126 pg/mL The patient was treated with the aromatase inhibitor anastrozole with rapid normalization of the inhibin B level and after 3 months of treatment, a CT showed a partial response with decrease in para-aortic nodal mass to 1.95 × 1.05 cm. However, a follow-up CT showed disease progression with enlargement of the left para-aortic lymph node in April 2009. Anastrozole was discontinued and the patient went to the operating room in July 2009 for a complete surgical resection of the para-aortic mass. Subsequently, the patient received adjuvant external beam radiation therapy 45 Gy to the para-aortic region. The patient was monitored closely by physical examination, Inhibin B, and surveillance CT scans, and remained disease-free for 3 years.

Present management: At presentation of her 4th recurrence, the Inhibin B level was elevated to 265 pg/mL and a CT scan in July 2012 revealed a new pelvic mass involving the posterior bladder wall. A CT-

guided FNA confirmed recurrent GCT. She received four cycles of carboplatin and Taxol with stable Inhibin B levels. A CT scan following cycle 4 demonstrated a >30% increase tumor diameter of the pelvic mass now measuring $8.0 \times 7.4 \times 6.7$ cm, indicating disease progression on chemotherapy. Chemotherapy was discontinued. The patient declined surgery.

In light of the patient's prior partial response to anastrozole, another course of hormonal therapy was initiated on January 18, 2013, consisting of the aromatase inhibitor letrozole 2.5 mg by mouth daily. Concurrently, the patient began atorvastatin and an exercise program for management of her hyperlipidemia. After beginning letrozole therapy, her Inhibin B levels consistently declined until becoming undetectable (<10 pg/mL) in December 2013. On physical examination, the pelvic mass was increasingly cystic and compressible by palpation, concordant with CT imaging findings, which after 7 months of therapy decreased solid components of the mass and a slight increase in the pelvic cyst diameter. Follow up CT imaging at 14 and 18 months showed decreasing size of both cystic and solid components of the pelvic mass. In December 2014, the Inhibin B remained undetectable <10 pg/mL, 23 months after initiating letrozole therapy. In January 2015, a CT scan confirmed a sustained partial response to letrozole therapy with a significant reduction in her pelvic mass, now measuring $4.0 \times 2.6 \times 2.5$ cm, 24 months after initiating letrozole therapy.

During month 25 of treatment, the patient developed a detectable Inhibin B level of 16 pg/mL, which increased to 32 pg/mL 6 weeks later. A subsequent CT scan confirmed disease progression after 30 months of letrozole therapy.

3. Discussion

No standard treatment exists for recurrent or advanced GCT. Cytotoxic chemotherapy regimens such as BEP have anti-tumor activity but are associated with significant side effects and tumor responses are usually transient (Brown et al., 2005). Hormonal therapy is often employed in the management of surgically unresectable GCT, due to the limited efficacy and toxicities of chemotherapy.

FOXL2 is required for the normal development of granulosa cells. In >90% of ovarian adult-type GCT, FOXL2 has a specific single point mutation C134W (Shah et al., 2009). Recent studies showed that mutant FOXL2 binds the aromatase promoter and increases its activation to a higher level compared to wildtype FOXL2 (Fleming et al., 2010). Upregulation of aromatase by mutant FOXL2 could be a common event promoting the development and progression of adult GCT. Extrapolating from studies done in hormone receptor positive breast cancer, aromatase inhibition offers potential advantages compared with tamoxifen and other hormonal therapies.

For the treatment of granulosa cell tumors, the data on aromatase inhibitor therapy is sparse, with fewer than 20 evaluable cases reported. The responses to aromatase inhibitor therapy among cases reported in the literature are highly variable. In the current case, the duration of response differed between her initial treatment with anastrozole and her later treatment with letrozole. One possible explanation is the greater reduction in plasma estradiol and estrone sulfate levels in postmenopausal women taking letrozole 2.5 mg once daily compared with anastrozole 1 mg once daily (Dixon et al., 2008). As determined by highly sensitive radioimmunoassay, only 2% of women taking letrozole had a plasma estradiol level ≥3 pmol/L versus 37% of women taking anastrozole. We speculate that the antiestrogen efficacy of aromatase inhibition may also have been further potentiated by the patient's concurrent statin therapy. A primary metabolite of cholesterol, 27-hydroxycholesterol acts as a selective estrogen receptor modulator (SERM) capable of promoting tumor growth in estrogen-receptor-positive breast cancer models (Nelson et al., 2013). Total cholesterol and 27-hydroxycholesterol levels are closely correlated in patients. Inhibition of cholesterol synthesis using the statin atorvastatin reduces 27-hydroxycholesterol and negates the pro-tumorigenic effect of a high-fat diet in animal models of breast cancer. Thus, the concurrent

statin therapy in this patient may have potentiated the efficacy of aromatase inhibition by lowering total cholesterol thereby lowering levels of the endogenous SERM 27-hydroxycholesterol.

To our knowledge, this is the first case report to describe *retreatment* with aromatase inhibitor therapy for the management of GCT. Despite disease progression on her initial aromatase inhibitor, 4 years later retreatment with another aromatase inhibitor resulted in a sustained partial response for 24 months. During this time, the patient enjoyed an excellent quality of life and avoided the morbidity associated with surgery or cytotoxic chemotherapy. We propose that aromatase inhibitor therapy should be considered in the management of recurrent and advanced GCT, even in patients who have progressed on prior hormonal therapy. In addition, combination treatments to increase the efficacy of hormonal therapies should be prioritized for further investigation in the management of this disease.

Conflict of interest statement

The authors do not have any conflicts of interest.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

Brown, J., Shvartsman, H.S., Deavers, M.T., Ramondetta, L.M., Burke, T.W., Munsell, M.F., et al., 2005. The activity of taxanes compared with bleomycin, etoposide, and cisplatin in the treatment of sex cord-stromal ovarian tumors. Gynecol. Oncol. 97, 489–496. http://dx.doi.org/10.1016/j.ygyno.2005.01.011.

Colombo, N., Parma, G., Zanagnolo, V., Insinga, A., 2007. Management of ovarian stromal cell tumors. J. Clin. Oncol. 25, 2944–2951. http://dx.doi.org/10.1200/JCO.2007.11.1005.

Dixon, J.M., Renshaw, L, Young, O., Murray, J., Macaskill, E.J., McHugh, M., et al., 2008. Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer. J. Clin. Oncol. 26, 1671–1676. http://dx.doi.org/10.1200/JCO.2007.13.9279.

Fleming, N.I., Knower, K.C., Lazarus, K.A., Fuller, P.J., Simpson, E.R., Clyne, C.D., 2010. Aromatase is a direct target of FOXL2: C134W in granulosa cell tumors via a single highly conserved binding site in the ovarian specific promoter. PLoS One 5, e14389. http://dx.doi.org/10.1371/journal.pone.0014389.

Freeman, S.A., Modesitt, S.C., 2006. Anastrozole therapy in recurrent ovarian adult granulosa cell tumors: a report of 2 cases. Gynecol. Oncol. 103, 755–758. http://dx.doi.org/10.1016/j.ygyno.2006.06.022.

Kato, N., Uchigasaki, S., Fukase, M., Kurose, A., 2015. Expression of P450 aromatase in granulosa cell tumors and sertoli-stromal cell tumors of the ovary: which cells are responsible for estrogenesis? Int. J. Gynecol. Pathol. 1. http://dx.doi.org/10.1097/PGP.0000000000000210.

Lamm, W., Schiefer, A., Nöbauer, I.M., Horvat, R., Speiser, P., Köstler, W.J., 2014. Aromatase inhibitor therapy as effective rescue in a patient with tamoxifen-refractory metastatic granulosa cell tumor of the ovary. J. Clin. Oncol. http://dx.doi.org/10.1200/JCO.2013.49.5952 (JCO.2013.49.5952).

Lappöhn, R.E., Burger, H.G., Bouma, J., Bangah, M., Krans, M., De Bruijn, H.W.A., 1989. Inhibin as a marker for granulosa-cell tumors. N. Engl. J. Med. 321, 790–793. http://dx.doi.org/10.1056/NEJM198909213211204.

Lauszus, F.F., Petersen, A.C., Greisen, J., Jakobsen, A., 2001. *Granulosa* cell tumor of the ovary: a population-based study of 37 women with stage I disease. Gynecol. Oncol. 81, 456–460. http://dx.doi.org/10.1006/gyno.2001.6183.

Nelson, E.R., Wardell, S.E., Jasper, J.S., Park, S., Suchindran, S., Howe, M.K., et al., 2013. 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science 342, 1094–1098. http://dx.doi.org/10.1126/science.1241908.

Schumer, S.T., Cannistra, S.A., 2003. *Granulosa* cell tumor of the ovary. J. Clin. Oncol. 21, 1180–1189.

Shah, S.P., Köbel, M., Senz, J., Morin, R.D., Clarke, B.A., Wiegand, K.C., et al., 2009. Mutation of FOXL2 in granulosa-cell tumors of the ovary. N. Engl. J. Med. 360, 2719–2729. http://dx.doi.org/10.1056/NEJMoa0902542.

van Meurs, H.S., van Lonkhuijzen, L.R.C.W., Limpens, J., van der Velden, J., Buist, M.R., 2014. Hormone therapy in ovarian granulosa cell tumors: a systematic review. Gynecol. Oncol. 134, 196–205. http://dx.doi.org/10.1016/j.ygyno.2014.03.573.

van Meurs, H.S., van der Velden, J., Buist, M.R., van Driel, W.J., Kenter, G.G., van Lonkhuijzen, L.R.C.W., 2015. Evaluation of response to hormone therapy in patients with measurable adult granulosa cell tumors of the ovary. Sobs http://dx.doi.org/10.1111/aogs.12720 (n/a–n/a).