

Aromatase inhibitors — a viable option for recurrent granulosa cell tumour of ovary: overview and case report

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Abstract

Granulosa cell tumour of the ovary in adults is a rare tumour of low malignant potential affecting middle aged peri or post menopausal patients. These tumours are often diagnosed at an early stage, due to their hormonally active nature. They, however, have unique distinguishing histologic features and behaviour of frequent and late local or systemic relapses. The diagnosis can be challenging with unusual presentations. There is high association of endometrial carcinoma. Surgery is the mainstay of management in early low risk disease, while radiotherapy and systemic platinum based chemotherapy are employed in higher stage with poor prognostic indices. Survival is good in early stage disease. Recurrent, progressive, and treatment refractory disease is not infrequent and poses management challenge. Endocrine manipulation and hormone treatment are employed in few cases with equivocal results, as reported in literature. We present a case of recurrent and treatment refractory GCT in a postmenopausal patient, managed by aromatase inhibitor Anastrozole with reasonable efficacy.

Keywords: Aromatase inhibitors, CA Ovary, Granulosa cell tumour, Anastrozole, Oncology Royal Hospital.

Introduction

Granulosa-theca cell tumours, the sex cord stromal tumours, are rare ovarian tumours also commonly described as granulosa cell tumours (GCTs). GCTs of ovary account for approximately 2-5% of all ovarian tumours and can be further divided into adult (95%) and juvenile (5%) types based on their morphologic and microscopic features.¹⁻⁴ They commonly produce oestrogen, which is often the reason for early diagnosis.¹ The tumours themselves are hormone sensitive with an autocrine and paracrine influence in premenopausal and an endocrine effect from aromatase conversion in postmenopausal patients. Adult GCTs (AGCTs) usually occur in postmenopausal women and have late recurrences (Schumer, Mom, East). GCTs usually have a low malignant potential, yet systemic metastasis is documented.^{3,5,6} The adult variant is more aggressive while the juvenile type (JGCTs) has a better prognosis.¹

Clinical Response (CR) rate is very good in AGCTs and JGCTs due to the early stage at diagnosis.² More than 90% of AGCTs and JGCTs are diagnosed before spread occurs outside the ovary.^{1,7} Five-year survival rates are 90-95% for stage I and 25-50% for advanced-stage.^{1,4} Despite good CR and survival rates AGCTs are well known for late recurrence with a poor outcome, as much as 30 years after primary diagnosis.^{3,5} Morbidity of GCTs primarily is due to endocrine manifestations like endometrial hyperplasia, endometrial carcinoma, and an increased risk for breast cancer.⁶ A multifactorial etiology is proposed based on genetic, autocrine and endocrine factors.^{1,6} The tumour markers of interest in GCTs are inhibin, Müllerian-inhibiting substance (MIS), or antimüllerian hormone (AMH).⁴

Surgery is the mainstay and often a sufficient way of treatment in GCTs. Radiotherapy and systemic chemotherapy in adjuvant settings are used for advanced stage or recurrent disease.^{1,2,4,6} The GCTs are hormone-active tumours, originating from granulosa cells which produce estradiol. Thus, hormonal agents have been evaluated as potential treatments for advanced stage or recurrent adult granulosa cell tumours.^{2,6,7} Recently several published reports have indicated the possible use of hormonal therapy in the management of recurrent chemoresistant or progressive non-responding granulosa-theca cell tumours, including medroxyprogesterone acetate, GnRH agonists, and megestrol (Megace).⁸ Aromatase inhibitor Anastrozole, which inhibit the conversion of androstenedione to estrone, is described recently in the management of GCT patients who previously received surgery and chemotherapy.^{6,7,9} Several patients with recurrent disease demonstrated normalisation of their serum inhibin, decrease in tumour size, and an increase in disease-free survival.⁴ Several authors have recommended aromatase inhibitors as a treatment strategy for recurrent and refractory disease.^{1,7}

We report a case with recurrent metastatic adult granulosa cell tumour in a postmenopausal patient who received multiple treatment modalities, including many lines of systemic chemotherapy and radiotherapy. She was finally started on Anastrozole, with subsequent normalisation of

inhibin B levels and a good radiological and clinical response. She has been maintained and stabilised on this cost-effective treatment for almost 20 months, with an improved quality of life (QoL) from PS of 4 to PS of 2 on WHO scale. The study was carried out with the informed consent of the patient and under the institutional ethical guidelines.

Case Report

A 52-year-old female was diagnosed in 1983 to have granulosa cell tumour of the ovary after having a laparotomy, right salpingo-oophorectomy, omentectomy and left ovarian biopsy. She did not receive any adjuvant treatment at that time, and staging information is also not available for review. She was kept under follow-up.

She had local recurrence in September 1995. A re-exploration was done and she underwent excision of right stump of infundible pelvic ligament and Left ovarian biopsy. Histopathology evaluation confirmed recurrent granulosa cell tumour. She was again on follow-up without any adjuvant treatment, as the patient did not agree to it after a complete resection with no evidence of gross macroscopic or microscopic disease. In May 1998 she was again explored due to lower abdominal and pelvic symptoms with left salpingo-oophorectomy and omentectomy. She received external beam radiotherapy to the pelvis as 45Gy/25fractions till July 1998 with a boost to para-aortic lymph nodes of 5Gy/3fractions.

She had a third recurrence in 2004 and was treated with systemic chemotherapy (3 cycles of Bleomycin, Etoposide, and Cisplatin). She had a grade ¾ toxicity and subsequently shifted to Carboplatin/Etoposide for another 2 cycles.

She was then under regular follow-up. There were no co morbid associated diseases and her laboratory investigations were within acceptable range. A follow-up CT scan in January 2008 showed progressive disease (massive

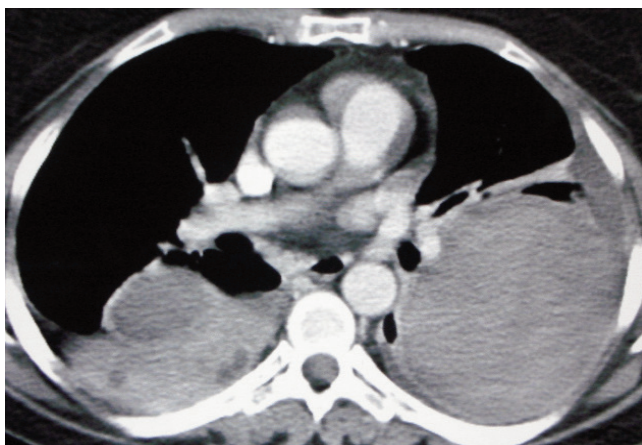


Figure-1: Chest CT scan with IV contrast showing bilateral enhancing pleural-based masses, with areas of cystic necrosis denoting pleural metastases.

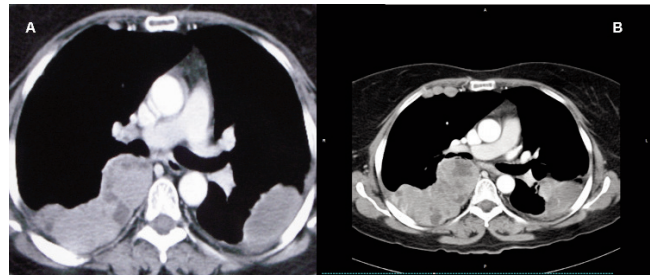


Figure-2: (a) Chest CT scan with IV contrast performed 7 months after the first CT scan, showing significant interval regression in the dimensions of the heterogeneously enhancing pleural-based masses. (b) Chest CT scan with IV contrast performed 20 months after starting the therapy, showing no significant changes compared with previous scans, confirming the "stable disease" status.

right pleural effusion, right lower zone pleural thickening/mass of 5cm, right diaphragmatic mass continuous with pleural thickening, left para esophageal/para aortic mass 5 cm in diameter in lower mediastinum, left lower lobe lung mass of 3cm, a 0.9cm low-density right hepatic lobe lesion). She was started on second line systemic chemotherapy as Taxol/Carboplatin. She had hypersensitivity reaction with the first dose and shifted to Liposomal Doxorubicine/Carboplatin. After 2 cycles the chemotherapy was stopped due to poor tolerance and profound toxicity (myelosuppression, deranged renal functions, severe asthenia). She was then on regular follow-up with symptomatic best-support care.

She was offered to start hormonal treatment by Anastrozole (aromatase inhibitor), in April 2008, but she did not agree. During this follow up period she needed frequent hospitalisation and repeated pleural tapping for recurrent pleural effusion. A repeat CT-scan done in February 2009 showed further disease progression (Figure-1). At this stage she agreed to oral hormonal treatment and started Anastrozole 1 mg daily.

At regular follow-up and evaluation over 20 months now, she had very good subjective and objective clinical response, described as under:

- She is under regular monthly follow-up in the clinic, and she did not require any hospital admission in the period except once in May 2009 for vomiting and diarrhoea which was promptly treated. Her performance status improved to PS2 on WHO, which was 4 initially at the start of the treatment.

- Inhibin B test result in January 2008 was 3350 ng/l; in November 2009 (after starting Anastrozole) it declined to 2073 ng/l, and in June 2010 it further declined to 878 ng/l.

- A repeated CT scan in November 2009 showed significant regression of the left pleural based mass from 6.6x4.1cm to 4.9x3.9cm.

- Follow up CT scan done in June 2010 showed no

major changes and qualified for "stable disease" status (Figure-2a).

- The patient continued on Anastrozole, tolerated medicine for more than 20 months with no significant adverse events. Bone marrow density was reported normal.

- During the latest follow-up in the clinic in November 2010, the patient maintained the same PS2 WHO scale. A repeated scan in November 2010 after about 20 months of treatment again, revealed no changes (Figure-2b).

Discussion

Adult granulosa cell tumour (AGCT) of the ovary is recently reported as 0.6-3.0% of ovarian tumours, and 70% of sex cord tumours with a median age of 50-54 years at diagnosis.^{1,4,10} It is often a hormone-secretory and endocrine-active tumour, which produces sex steroids like estrogens with their subsequent effects on target tissues.^{2,7} This gives them distinguished presenting clinical features like postmenopausal bleeding, menorrhagia, or metrorrhagia.¹⁰ Less commonly they can be androgenic with virilising effects.

These usually present as abdominal, pelvic mass, abdomino-pelvic mass, or even as occult primary in up to 10%.¹⁰ Diagnosis often is a clinical challenge. They are vascular tumour, sometimes presenting as acute abdomen mimicking ectopic pregnancy.¹ Pelvic examination and ultrasonography are the prime tools of diagnosis. Surgery provides a definite tissue diagnosis, enable staging, and can be an R0 re-section or optimum cytoreduction.

Microscopically these are large cystic tumours made up of granulosa cells in varying combination with sex cord component cells. GCT displays a variety of histologic patterns, including micro follicular, trabecular, insular, and diffuse variants, although a mixture of these patterns is often found. Call-Exner bodies are characteristic of GCT and appear in 30% to 60% of cases. These tumours on IHC are non-specifically positive for CAM 5.2, AE1/AE3, CD10, S100, WT-1, smooth muscle actin and desmin. They are negative for CK7 and EMA.¹⁰ Many genetic aberrations are found in GCTs like trisomy 12, trisomy 14, and monosomy 22.^{1,3}

Due to symptomatic early presentation, survival is good, but in the high-risk group, local relapse is frequent. Prognostic risk factors identified are age, late stage at presentation, T status, high mitotic index, and tumour rupture.⁴

Post-operative adjuvant treatment in high-risk group after optimal R0 surgery is not evaluated prospectively due to rarity of tumours.^{1-3,6} There are reports of better disease free

survival (DFS) and time to progression (TTP) in high-risk patients with adjuvant chemotherapy and/or radiotherapy.¹ An adjuvant treatment by radiotherapy or platinum-based systemic polycychemotherapy is suggested in stages beyond stage I intermediate risk. Recurrent disease is usually managed by interval debulking, systemic chemotherapy or hormonal treatment.¹ A prolonged surveillance by clinical and serologic (Estradiol, Inhibin) evaluation is mandatory to high relapse rate even after prolonged time interval.^{4,6}

The hormonal agents used in recurrent disease are GnRH analogues, Megestrol acetate, Leuprolide, and, more recently, Aromatase inhibitors.^{1-4,6-8} Aromatase inhibitors have consistently shown tumouricidal activity in vitro (in granulosa cell lines) and in vivo experimental systems.⁷ To date, there are very few cases reported in literature of GCTs being treated with Aromatase inhibitors.^{6,7}

Conclusion

Reported cases have shown significant impact of Aromatase inhibitor (Anastrozole) in recurrent, progressive, treatment refractory GCT. This translates into partial response to stable disease, improved QoL, cost effectiveness, better tolerability and good patient compliance. It is likely to give better DFS and TTP, but its impact on overall survival need further long term studies with a much bigger study population to draw statistically significant results.

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