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Review Article

Adult Ovarian Granulosa Cell Tumor: Role of Systemic Chemotherapy and Surgical Treatment

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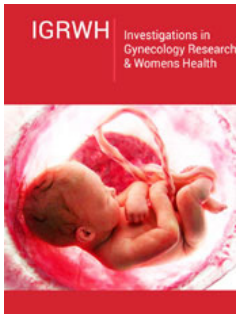

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Abstract

Ovarian granulosa cell tumors (GCT) are rare ovarian neoplasms. The main treatment for GCT is surgical. The volume of operation depends on the stage of the disease and the age of the patient. The possibility of maintaining fertility in patients of reproductive age in the early stages of the disease and the feasibility of lymphadenectomy are discussed. The positive effect of repeated cytoreductive operations for relapse was demonstrated. Role of chemotherapy in the treatment of GCT, due to the rarity of GCT and the late recurrence of the disease, is still not defined. Adjuvant chemotherapy is not shown to protect against relapse in patients with adult type (AGCT). Hormone therapy is considered to be a promising direction for the palliative treatment of AGCT relapses.

Keywords: Granulosa cell tumors; Relapse; Surgical treatment; Fertility-saving treatment; Chemotherapy; Hormone therapy; Aromatase inhibitors

Introduction

Ovarian tumors are a heterogeneous group of tumors, including epithelial and non-epithelial ovarian tumors. Non-epithelial ovarian tumors account for approximately 10% of all ovarian cancers, including malignant germ cell tumors and and sex cord-stromal tumors. Sex cord-stromal tumors consist of a heterogeneous group of neoplasms with diverse clinicopathological features and biological behavior. GCT are rare sex cord-stromal tumors. Their frequency is approximately 3%-5% of all malignant ovarian tumors, and the incidence is from 0.6 to 2.1 cases per 100000 women per year [1]. According to the histological features, GCT are divided into two types: adult and juvenile [2]. Both adult and juvenile types GCT, due to the uncertainty of their malignant potential, until recently, according to the 2003 WHO histological classification, were referred to borderline tumors due to the relatively high 5-and 10-year survival [3]. In the 2014 WHO histological classification, GCOS were divided into borderline, which included the GCT of the juvenile type, and the malignant GCT of the adult type [4].

Despite the definition of AGCT not as borderline, but as low-grade malignant tumors, there are no specific recommendations for the surgical and drug treatment in such patients. This is primarily due to the late recurrence of the disease, requiring long-term follow-up of patients, as well as the rarity of these tumors and conflicting data on prognosis factors.

Surgical treatment

The main treatment is surgery (hysterectomy with bilateral salpingoophorectomy). It was shown significant positive effect of full staging at an early stage and primary treatment in a specialized clinic on the indicator of five-year relapse-free survival [5]. Multivariate analysis of multicenter retrospective study with data on 102 patients with AGCT of an adult type did not find the effect of surgical treatment options on the recurrence rate of the disease [6]. Fertility-saving unilateral salpingooophorectomy is one of the options for surgical treatment in young patients with stage IA [7,8]. Stage of the disease is an independent prognostic factor for the occurrence of a relapse of the disease [9,10]. For advanced disease it is recommended to perform optimal interval cytoreduction after chemotherapy, but lymphodissection is not recommended because according to the authors it did not affect the recurrence rate of the disease, and metastases were not found in histological examination of the removed lymph nodes [5].

Drug treatment

The role of drug treatment in AGCT is under discussion. Increasing of relapse-free survival and time to progression has been reported in high-risk patients receiving adjuvant chemotherapy [11,12]. Other studies have not found a positive effect of chemotherapy on relapse rates, even in the early stages of AGCT [13,14]. In AGCT patients with stage IC, there were no differences in relapse-free survival between patients with or without adjuvant chemotherapy [14]. Adjuvant chemotherapy is not shown to protect against relapse in patients with adult type AGCT [8]. The most widely used first-line adjuvant treatment regimen in patients with AGCT is BEP regimen. Platinum-based chemotherapy is currently used for patients with advanced stages or a recurring disease, with a total response rate of 63% to 80%. Combination chemotherapy with taxes and platinum appears to be a suitable regimen for further research [15]. The gynecological oncology group (GOG) is currently conducting a randomized phase II trial, the results of which are expected in 2024, by comparing the effect of the TC regimen with the BEP regimen on progressive survival in adult GCT patients (ClinicalTrials.gov Identifier NCT01042522). It is expected that the TC regimen may be associated with relatively lower toxicity and similar non-progressive survival compared to the BEP regimen.

Hormone therapy based on progestogens (megestrol) and gonadotropin-releasing hormone agonists [16-18] is considered to be a promising direction for the palliative treatment of GCT relapses. It was also shown promising results of the use of aromatase inhibitors in relapses of AGCT [19,20]. The efficacy of targeted therapy, particularly, mTOR inhibitors and tyrosine kinase inhibitors in the treatment of GCT, is currently being investigated [21,22].

Discussion

GCT are rare low-grade malignant sex cord-stromal tumors with indolent behavior. The etiology of GKO, like most ovarian epithelial tumors, is unknown. GKO of the ovaries are distinguished by their ability to secrete sex steroid hormones (estrogens), and glycoprotein hormone inhibin, which are used in the clinic as tumor markers. So, the majority of patients are diagnosed at early stage [6,23]. The main risk factors of AGCT include nulliparity, fatness, oral contraceptives and family cancer history. The recent studies provided powerful evidences that fork head box protein L2 (FOXL2), PI3K/AKT signaling pathway, TGF-β signaling pathway, Notch signaling pathway and etc. were involved in granulosa cell tumor through influencing cell proliferation and apoptosis [24]. More and more clinical data show that FOXL2 mutation is the main factor in AGCT. So, understanding the FOXL2 regulation mechanism is instrumental to develop new prevention and therapy methods [25]. The main treatment is surgery [6-8]. Most clinicians agree that in patients of a young and young age with stage IA disease can be limited to unilateral adnexectomy with adequate surgical staging, which allows these women to maintain reproductive function [7,8]. At the pre- and postmenopausal age, preference is given to radical surgery in the amount of extirpation of the uterus with appendages and removal of the momentum with mandatory optimal surgical staging [5,6,8,9,15]. Stage of the disease is an independent prognostic factor for the occurrence of a relapse of the disease [9,10]. Adjuvant chemotherapy is not shown to protect against relapse in patients with adult type AGCT [8]. High recurrent rate is the most critical factor for GCT death. At present, the most important problem lies in the early diagnosis and prevention of recurrence. Studies showed that hormones play a critical role in the pathogenesis and treatment of GCT, especially in some ineffective cases for radiotherapy and chemotherapy [24,25]. Targeting drugs for signal pathway in the subsequent chemotherapy can significantly improve the survival rate of patients [21,22,24,25].

Conclusion

There were not found significant difference in the overall and relapse-free survival of patients with ovarian AGCT, depending on the options of surgical and drug treatment they underwent. Additional multicenter randomized trials are needed to clarify the effectiveness of the various options for surgical and drug treatment of adult GCT patients.

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