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REVIEW

Malignant Ovarian Germ Cell Tumor: Point for General OB-GYN

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Although relatively uncommon compared to epithelial ovarian cancer, malignant ovarian germ cell tumor (MOGCT) is the cancer that most patients could be cured. The evolution of treatment during the past two decades has been one of the true success stories in oncology. Many recent advanced discoveries have arisen from the studies of testicular cancer, which is 10- fold more common than ovarian germ cell tumor.[1] MOGCT account for less than 5% of ovarian cancer.[1] Their significance is greater than their numerical implied incidence because they occur in children and young women during their prime age.[2,3] Contrasting dramatically with epithelial ovarian cancer, which usually occurred in perimenopausal or postmenopausal age. Since management for this cancer is definitely different from epithelial ovarian cancer according to age of the patient and as well as being chemosensitive tumor itself. Fertility function is a major concern for patients. This article is a review of current clinical profiles, practical management and outcomes of patients with MOGCT.

Clinical presentation

The mean age of presentation of MOGCT is 18-22 years.[3,4] Most patients complaint about symptoms of increased abdominal distention not more than a month.[4] Some present with menstrual irregularities. Most of the tumors are solid or solid-cystic in consistency. The mean tumor diameter is 16 cm. Ascitic fluid does not always present. The tumor almost always presents unilaterally except for dysgerminoma that may be bilateral, about 10-15%. A contralateral mature cystic teratoma may be detected in approximately 5-10% of the patients 5 and should be treated with ovarian cystectomy. Moreover, MOGCT frequently presents as stage I disease. Dysgerminoma is the most frequent histological subtype; endodermal sinus tumor is the second most common according to the record of King Chulalongkorn Memorial Hospital.[4]

Pathologic classification

Ovarian germ cell malignancies are believed to originate from primordial germ cells that migrate into the gonadal ridge during the 6th week of embryonic life.[3] Consequently, ovarian germ cell tumors might exhibit a spectrum of histological differentiation that mimics a primitive development of embryo. For example, dysgerminoma appears to descendfrom a relatively undifferentiated cell, whereas yolk sac tumors show malignant change in its cell line committed to extraembryonic differentiation. Immature teratomas are derived from cells predisposed to somatic (embryonic) differentiation and recapitulate tissue from all the three primitive germ cell layers, i.e., ectoderm, endoderm and mesoderm. When considered together, dysgerminoma, yolk sac tumor,

immature teratoma and the mixed germ cell tumor comprise more than 90% of malignant germ cell tumors. Nongestational choriocarcinoma, and polyembryoma rarely manifest as homogeneous entities and comprise the remaining 5-10%.

Table 1. World Health Organization Classification of germ cell tumors

Dysgerminoma
Endodermal sinus tumor
Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Teratomas
Immature
Mature(dermoid)
Monodermal(struma ovarii, carcinoid)
Mixed form
Gonadoblastoma

Tumor markers

Both serum human chorionic gonadotropin and alpha-fetoprotein were identified in the mid-1970. These substances in the serum lead to dramatic improvements in monitoring of patients with these tumors.[6] Table 2 illustrates typical findings in the sera of patients with various histological types.

Table 2. Serum tumor markers in malignant ovarian germ cell tumors

Tumor type	AFP	HCG	LDH
Dysgerminoma	-	+	+
Endodermal sinus tumor	+	-	+
Immature teratoma	+	-	-
Choriocarcinoma	-	+	-
Embryonal carcinoma	+	+	-
Mixed tumor	+	+	-

Other serum tumor markers identified in the serum of some patients with germ cell tumors include lactic dehydrogenase isoenzymes which have been reported to elevate in ovarian dysgerminomas.[7] Elevation of neuron-specific enolase level is observed in patients with immature teratomas and dysgerminomas.[8] Increased level of serum CA 125 is found in some patients with MOGCT.[9] The immunohistochemical of p53 also positive with approximately 50% accuracy in MOGCT, but it seems to have no significant correlation with the prognosis in yolk sac tumor.[10] In general, when patients are being suspicious of having MOGCT, serum human chorionic gonadotropin and alpha-fetoprotein should be measured.

Management of MOGCT

Initial operation: Laparotomy is initially indicated for both the diagnosis and treatment in young patients being suspected of having ovarian tumor. As many as

80% of women with MOGCT undergo the operation with non-specialized gynecologic oncology center.[5] Probably because of the urgency of the patients' symptoms or the physicians' low suspicions for malignancy. Ideally, a vertical midline incision is preferable in order to obtain adequate exposure and proper surgical staging. A comprehensive staging should be performed with inspection of the entire peritoneal cavity, cytological examination for peritoneal fluid, peritoneal biopsies from area of frequent tumor spread (cul-de-sac, paracolic gutters, diaphragms), infracolic omentectomy and selective lymph node biopsy from the pelvic and para-aortic lymph nodes. But for most patients with MOGCT, unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is appropriate. Scientific support for such an approach, even without any randomized clinical trial, has revealed at least equivalent sustained remission rates that conservative surgery yields compared with radical surgery.[3,11-15] If bilateral ovarian masses are encountered during the surgery, a unilateral salpingo-oophorectomy of the more suspicious side is appropriate. Ovarian cystectomy of the contralateral ovary or bilateral ovarian cystectomy may be an alternative treatment. However, one caveat is that patients with dysgenetic gonads with XY karyotype should undergo bilateral salpingo-oophorectomy. Detailed initial laparotomy, including formal node dissection, seems unlikely to influence long-term survival, but may identify about 14% of dysgerminoma patients in earlier postoperative therapy.[16] In the largest published study, lymph node removal was not required unless there was palpable and abnormality presented at the time of surgery.[17]

A strong recommendation for aggressive primary surgical cytoreduction of MOGCT is still controversy, based on available data particularly regarding extensive lymphadenectomy and intestinal resection. However, obvious gross tumor should be excised or biopsied and surgical effort should focus on safely resecting all gross disease when feasible.

Secondary surgery: The value of secondary cytoreductive surgery in MOGCT is less clear than that of primary cytoreductive surgery. Germ cell tumors are relatively more chemosensitive than epithelial tumors and are more likely to respond to second-line therapy. Therefore, if the patients have an isolated focus of persistent tumor, then surgical extirpation should be considered before changing chemotherapeutic regimens. A number of patients with pure ovarian immature teratomas or mixed germ cell tumors have persistent mature teratoma at the completion of the chemotherapy has been observed.[18,19] Likewise, a persistent retroperitoneal mass representing desmoplastic fibrosis without viable tumor in a patient who received chemotherapy for recurrent ovarian dysgerminoma has been reported. For those with persistent masses, options for their diagnosis and management include surgical intervention, fine-needle aspiration biopsy, or surveillance with serial imaging studies.

Second look laparotomy: Most literatures show that positive findings in second look laparotomy are extremely rare. Gershenson et al. recently reported negative findings in 52 of 53 patients.[20] It seems that in patients with initial rise of serum tumor marker levels reflex the activity of disease. Then second look procedure is not necessary. Second look operation should be limited to patients with advanced disease and initial negative tumor markers or tumors that contain teratoma elements. With more effective chemotherapy and better imaging techniques, the need for second look laparotomy would be further reduced.

Treatment after primary surgery: Over the past three decades, the literatures have examined the result of "conservative surgery" without postoperative treatment in stage IA dysgerminoma.[21,22] Gordon et al. concluded, " there was no statistical difference in survival based on size of tumor I dysgerminoma.[22] Women with surgically staged IA dysgerminoma may be closely followed up without adjuvant chemotherapy, regardless of the size of tumor.[22] According to Norris et al., only one of 14 patients with stage I grade 1 immature teratoma had a recurrence.[19] Most investigators have not recommended adjuvant

therapy in this group of patients.[23]

Radiation

The exquisite radiosensitive of dysgerminoma, like that of seminoma in male, has long been recognized. However, several significant advances in our understanding of this disease should now allow us to devise treatment schemes in which the cure rate are not compromised and fertility is usually preserved. Because of the effectiveness of chemotherapy, nowadays, radiation has very limited role in dysgerminoma. In patients with fertility is not preserved, radiation may be the choice for infradiaphragmatic region. Radiation should be preserved for salvage therapy in dysgerminoma.[16]

Chemotherapy

Non-dysgerminomatous tumors

Beginning in approximately 1970, the VAC regimen (vincristine, actinomycin-D, cyclophosphamide) began to be used for non-dysgerminomatous tumors. After almost two decades of experience with VAC regimen the result shows that this combination produces a high proportion of cure in cases of no gross residual disease (72%).[24] But in patients with unresectable or incompletely resected tumors, the sustained remission rate is less than 50%.[24-26]

When cisplatin was introduced into clinical trial in the late 1970, a combination of vinblastine, bleomycin, and cisplatin (VBP regimen) had documented the efficacy in malignant ovarian germ cell tumor.[25,27] Literatures suggest that excellent results are achieved in stage I disease with VBP regimen, and the results are superior to those with VAC regimen in patients with advance disease. Unfortunately, no randomized clinical trials have been conducted to compare VAC and VBP regimens.

Subsequently, etoposide-containing regimen shows excellent efficacy in germ cell tumors.[28,29] Combination of bleomycin, etoposide and cisplatin (BEP regimen) reveals equal efficacy but less toxicity in patients with testicular cancer.[30] More recent reports of experience with BEP regimen in ovarian germ cell tumors have been very positive. About 90% of the patients treated by three to four cycles of BEP regimen receive sustained remission.[17,31] According to treatment study in testicular cancer, randomized trial with BEP compare to EP (etoposide and cisplatin) regimen in minimal- or moderate-stage patients demonstrates an inferior outcome for those who are treated without the addition of bleomycin.[32, 33]

Dysgerminoma

Chemotherapy has replaced radiation as the postoperative treatment of choice in dysgerminoma. In a report of GOG's experience, it was revealed that 19 of 20 patients with incompletely resected dysgerminomas treated with either VBP or BEP regimen were disease-free (median follow-up of 26 months).[34] Surveying the entire experience treating dysgerminoma with BEP, it appears that 3 cycles of this regimen are adequate, with the exception of patients with advanced visceral metastasis where longer therapy may be indicated.[2]

Table 3. Commonly used chemotherapy regimens in malignant ovarian germ cell tumors

The VAC regimen (repeated at 28 day intervals):
Vincristine 1.5 mg/m2 (maximum 2 mg) IV day 1 and 15
Actinomycin D 350 mcg/m2 IV day 1-5
Cyclophosphamide 150 mg/m2 IV day 1-5
The VBP regimen (repeated at 21 day intervals):
Vinblastine 12 mg/m2 IV day 1
Bleomycin 20 U/m2 (maximum 30 U) IV weekly on day 1
Cisplatin 20 mg/m2 IV day 1-5

The BEP regimen (repeated at 21 day intervals):
Bleomycin 30 U IV weekly on day 1
Etoposide 100 mg/m2 IV day 1-5
Cisplatin 20 mg/m2 IV day 1-5

Salvage therapy

The most useful information about salvage therapy for patients with germ cell tumors come from the literatures on testicular cancer. For the purpose of appropriate therapy selection, it is important to distinguish between platinum-resistant and platinum-sensitive tumors. There are few reports regarding patients who did not respond to non cisplatin-containing regimens, mostly VAC, and subsequently received VBP or etoposide-containing regimens as salvalge therapy.[25,26,35,36]

Platinum-sensitive patients were defined in women who relapse more than 6-8 weeks after completion of platinum-based chemotherapy.[1] Currently, the most popular salvage regimen includes ifosfamide, cisplatin and either etoposide or vinblastine. About 30% of the patients respond to such regimens.[37]

Platinum-resistant patients: Generally, the group of patients has a poor outcome. Investigation salvage therapy with phase II agents or high-dose chemotherapy is the possible option. In the trial of refractory germ cell tumor treated with high-dose carboplatin plus etoposide-based chemotherapy and autologous bone marrow rescue, complete response was 52% but one patient died of treatment.[38] Maintenance chemotherapy with daily oral etoposide after salvage therapy has also been suggested. Cooper et al. noted that 74% of patients remained disease-free with median follow-up of 36 months. Thus, potentially active salvage therapy may be available in selected cases.

Long-term sequelae

Fertility function: Several studies demonstrated that reproductive capacity basically was unaffected after MOGCT chemotherapy.[3, 11, 12, 15] The true reproductive potential in any of these studies was difficult to ascertain because of the small numbers and relatively short duration of follow-up of patients. But the rate of documented infertility among the number of patients attempting conception was 5-10%, which corresponds to the background incidence rate of infertility in the normal population.

The risk of congenital malformations in the offspring of patients treated with chemotherapy also has been concerned. The risk is highest if chemotherapy is administered during the first trimester of pregnancy, especially when antimetabolites and alkylating agents are used. Chemotherapy administration during the second and third trimesters generally is not associated with an increase in fetal anomaly, although, to our knowledge, the number of patients studied to date is relatively small. In reports in which VAC, VBP combination chemotherapy regimens were used in MOGCT, none showed an increase in the risk of congenital malformations.

Current studies demonstrate that conservative surgery with appropriate addition postoperative treatment is the procedure of choice in young patients with MOGCT.

Secondary malignancy: Long-term complication of chemotherapy, mainly an increased risk of myelodysplasia and leukemia after BEP regimen, continues to be a potential hazard. The increased risk appears to be related to etoposide alone because similar secondary neoplasia is not detected in patients treated with VBP regimen. In addition, the risk of leukemia appears to be dose-related with the highest risk in patients who receive a cumulative dose of etoposide greater than 2000 mg/m^2.[39] The incidence of secondary leukemia in women with MOGCT and treated with BEP is less than 2%. Using a case-control study design, drugs were ranked according to their leukemogenicity.[40] This study demonstrated that increased risk of leukemia associates with combination of doxorubicin and cisplatin.

Conclusion

The evolution in the management of malignant ovarian germ cell tumor has led the dramatic outcome of this disease, compared to epithelial ovarian cancer. Clinicians should be aware for this cancer when young woman presents with rapid progression of ovarian tumor. Preoperative tumor marker detection may be useful in many cases. Complete surgical staging may not be helpful in patients who are still in childbearing age. Preservation of reproductive function during operation is favorable even in advanced stage of cancer. Postoperative chemotherapy with platinum-based regimen continues to be the standard for adjuvant and induction therapy, but patients should be under the monitor of the specialized physicians. Salvage therapy remains a challenge and currently a variety of standards. In the future, combination of treatments may result in long-term survival.

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