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Childhood malignant ovarian germ cell tumors: a single institution experience

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Summary

Purpose of investigation: This study aimed to analyze the clinical characteristics and outcome of children with malignant ovarian germ cell tumors (MOGCTs), and to investigate the therapeutic strategy. *Materials and Methods:* All patients with MOGCTs in a single institution during the period January 2001 to December 2012 were analyzed according to the characteristics of patients, treatment, and outcome. *Results:* Eight-nine patients with MOGCTs had a median age 9.5 (range, 0-15) years. Abdominal pain and abdominal distension were the most frequent clinical presentations. Elevated AFP was observed in 78 cases (87.6%). Eighty-seven patients received surgery plus chemotherapy. The surgical procedures consisted of salpingo-oophorectomy plus omentectomy (n=39), salpingo-oophorectomy (n=39), and oophorectomy (n=11). Five patients died: three from disease, one from leukopenic sepsis, and one from disseminated varicella. The overall five-year survival rate was 95.5% for all patients, 100% for Stage I, 96.2% for Stage II, 95% for Stage III, 91.7% for Stage IV, and 71.4% for relapse patients, respectively. Forty-one out of 49 patients in puberty or reproductive age had regular menstrual cycles. Six patients had menostaxis, and two patients required psychological input during the follow up period. Two patients delivered healthy infants without congenital defects. *Conclusion:* The prognosis of malignant ovarian germ cell tumor is favorable. Surgery combined with platinum-based chemotherapy can improve curative efficacy and survival. Further investigation of novel and high-dose chemotherapic regimens is needed for the patients with relapsed tumors. Sex hormone replacement therapy is not necessary for most patients receiving fertility-preserving surgery.

Key words: Pediatrics; Malignant ovarian germ cell tumor (MOGCT); Chemotherapy; Survival rate.

Introduction

Ovarian tumors are rare tumors in pediatric population which make up about 1% of all pediatric cancers [1]. Malignant ovarian germ cell tumors (MOGCTs) comprises approximately 5% of all ovarian malignancies [2, 3]. MOGCTs are highly chemosensitive with a high curability rate. Surgery with adjuvant chemotherapy is the mainstay of treatment. Currently, cure rates for patients with early-stage patients approach 100%, and even in advanced-stage disease, the cure rates reach approximately 75% with a combined strategy consist of surgery and the bleomycin/etoposide/cisplatin (PEB) regimen [4]. The aim of this study was to review the clinical features, management, and outcome in a series from a single institution over a 12-year period. It is the authors' goal that their information may help guide the evaluation and surgical management of future children with MOGCTs.

Materials and Methods

With the IRB approval, the medical records of 89 patients with malignant ovarian tumors evaluated and treated in the present institution from 2001 to 2012 were analyzed. Every patient was diagnosed by surgery or puncture biopsy and pathology. Clinical records including demographics, stage at diagnosis, type of surgery, chemotherapy regimens, serum tumor marker levels, menstrual functions, fertility, and outcome were collected from medical or surgical charts and pathology reports. Clinical staging was according to the Children's Oncology Group staging, a modification of the FIGO (International Federation of Gynecology and Obstetrics staging for ovarian tumors) classification [5]. This classification defines Stage I as a tumor limited to the ovary, Stage II as a tumor with pelvic extension, microscopic residual or positive lymph nodes < two cm, Stage III as a tumor with gross residual or biopsy only, contiguous visceral involvement, lymph nodes with malignant metastatic nodules > two cm, and Stage IV as a tumor with distant metastases, including liver. Histological typing of tumors followed the WHO classification. Immature teratomas were graded according to the Norris classification [6].

Results

Median age at presentation was three years (mean age: 5.6 years, range from neonatal to 15 years). Past medical histories and family histories were unremarkable. Ninety percent of the patients were from rural areas, with most of them having upper lower or lower socioeconomic status. The parents of one-third of the patients were illiterate.

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The most frequent primary symptom was abdominal pain, either acute, chronic, or both was reported in 75 patients (84.2%). The second most frequent symptom, major abdominal distension by the abdominal or pelvic mass, was noted in 46 patients (51.7%), associated with pain in 27, and painless in 19; however it was the primary sign in only eight cases. Other symptoms and signs included nausea and vomiting, constipation, urinary symptoms, and fever. Three patients presented as ovarian torsion. Precocious and menstrual disorders were also observed. In four infants, the tumor was found prenatally and was asymptomatic after birth; surgery was performed within two months after their birth. Immature teratoma was diagnosed in four patients; the remaining one patient had a yolk sac tumor (YST). In two patients the ovarian tumor was an incidental finding during investigations for an unrelated pathology (both of them consulted for pneumonia). The duration of symptoms ranged from two hours to two years.

Alpha-feto-protein (AFP) levels were elevated in 78 patients, 65 with pure yolk sac tumors, five with malignant teratoma, four with immature teratoma (Gr II and III), two with embryonal carcinoma, two with mixed teratoma, and were normal in all others. Beta human chorionic gonadotropin ((β-hCG) and AFP levels were both elevated in the patients with embryonal carcinoma.

According to the Children's Oncology Group staging system, five patients with immature teratomas and 19 patient with a malignant tumor were classified as Stage I, 26 as Stage II, 20 as Stage III, and 12 patient with lung metastases (seven), liver metastasis (three), peritoneal metastasis (two) as Stage IV disease (Table 2). Relapse disease was confirmed in the remaining seven patients, two of which relapsing three months from ending platinum-based chemotherapy.

Tumors were found in the left side in 49 cases, in the right side in 40 cases, and no bilateral tumors were found. Regarding the tumor size, the average diameter was 9.5 cm (ranged from 2.5−21 cm). In the operative findings, the average amount of ascites was 120 ml (range 0−3,500 ml). The histologic diagnosis of the 89 tumors is summarized in Table 1. YST were the commonest tumors (n=70), followed by immature teratoma (n=7), malignant teratoma (n=6), mixed teratoma (n=2), embryonal carcinoma (n=2), and dysgerminoma (n=2).

For patients with immature teratoma (grade I) (n=2), surgery and follow-up was the only treatment; the other 87 patients received surgery plus chemotherapy, and no patient received radiotherapy. Four patients with acute symptomatology had undergone emergency surgery: three for torsion of the tumor and one for apparent tumor rupture. The others had been operated upon selectively. Stage III and IV patients had biopsy first, either puncture or surgery, when the diagnosis was confirmed, neoadjuvant chemotherapy was given for two to four courses, then followed by surgery, and chemotherapy was also given after surgery.

Table 1. — *Histopathologic diagnosis in 89 patients.*

Histology	Number of patients
Pure YST	70 (78.8%)
Immature teratoma	7 (7.9%)
Grade I	2
Grade II	2
Grade III	3
Malignant teratoma	6 (6.7%)
Embryonal carcinoma	2 (2.2%)
Mixed teratoma	2 (2.2%)
YST + dysgerminoma	1
YST + embryonal carcinoma	1
Dysgerminoma	2 (2.2%)
Total	89 (100%)

Table 2. — *Stage and outcome of 89 patients.*

Stage	N	EFS (%)	OS (%)
I	24	95.7%	100%
II	26	88.5%	96.2%
III	20	80%	95%
IV	12	58.3%	91.7%
Relapse	7	57.1%	71.4%

EFS: event-free survival; OS: overall survival.

In consideration of reproductive issue, hysterectomy and contralateral salpingo-oophorectomy were not performed in the present institution. The procedures consisted of salpingo-oophorectomy plus omentectomy (n=39), salpingo-oophorectomy (n=39), oophorectomy (n=11). The contralateral ovary was always inspected and palpated very carefully in every patient; seven patients were suspected to have a malignant tumor and biopsy of contralateral ovary was made, meanwhile, no one had tumor. Ascites were sent for cytologic analysis when present.

Postoperatively, one patient developed a wound infection and three mechanical small intestinal obstructions by adhesions, which subsided with conservative measures. Based on the disease stage, patients underwent protocol treatment with surgery and platinum-based chemotherapy. Among patients who received postoperative chemotherapy, 47 patients were treated with 20 U/m^2/d bleomycin on days 1, 8, and 15; 100 mg/m^2/d etoposide on days 1 to 3; and 20 mg/m^2/d cisplatin on days 1 to 5 (PEB regimen) every 21 days. The other 42 patients were treated with 100 mg/m^2/d carboplatin on days 1 to 5, 1.5 mg/m^2/d vinblastine on days 1 and 7, and 15 mg/m^2/d bleomycin on days 1 and 7 (10 CVB regimen) every 21 days. Duration of postoperative chemotherapy varied between two and four cycles depending on tumor marker response and residual mass after initial surgery.

The side-effects of PEB/CVB regimen during chemotherapy were tolerable. Twenty-eight patients had

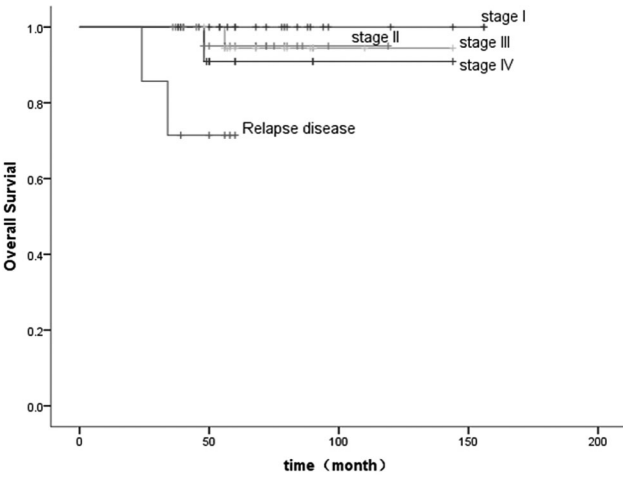

Figure 1. — *The overall survival rate of 89 patients with MOGCTs.*

Grade II to III blood/bone marrow toxicity based on NCIC Common Toxicity Criteria Grading System. No critical infection and hemorrhagic tendency were observed except for one patient that died from leukopenic sepsis. One girl had transient elevation of serum transaminase, one had an abnormal renal function, and one had pulmonary fibrosis observed at follow up, but there were no hearing impairments.

Median time to follow up was five (range 3-14) years. In the current period, five patients had died (three from disease, one from leukopenic sepsis, and one from disseminated varicella after all chemotherapy finished). The five-year event-free survival and overall survival was 92.1% and 95.5%, respectively. The five-year overall survival was 100% for Stage I, 96.3% for Stage II, 95% for Stage III, 91.7% for Stage IV, and 71.4% for relapse patients (Figure 1).

There were no recurrences in patients with malignant tumors. All patients are on long-term follow-up with monitoring of endocrine function and fertility. Forty-one out of 49 patients in puberty or reproductive age have regular menstrual cycles. Six patients had menostaxis and two patients required psychological input during the follow up period. Two patients attempted conception, both of whom delivered healthy infants without congenital defects.

Discussion

MOGCTs are rare in childhood and there are no specific symptoms which indicate this disease. It is reported that most common symptom of MOGCTs was abdominal pain, which was present in 92% of patients, followed by abdominal distension (47.5%), other symptoms including fever, ovarian torsion, menstrual disorder, and urinary symptoms [7, 8] In the present study, the incidence of abdominal pain and abdominal distension was 84.2% and 81.7%, respectively, which was similar to literature report. However, patients presented with acute abdominal pain and signs of peritonitis that can be difficult to distinguish from acute appendicitis. Distinguishing patients with ovarian torsion, acute appendicitis or other surgical lesion may be challenging for pediatric surgeon. It is important to perform imaging tests and laboratory examinations to improve the accuracy of the diagnosis.

The present authors also noticed that, most parents of the patients are illiterate (1/3 of the patients) and from rural areas (> 90%) with a low socioeconomic status. Higher stage of presentation may be owing to late presentation to the doctor or delayed referral to the tertiary care center, which is an important and notable characteristic of children with malignant tumors in developing countries [9-11].

Tumor markers are a significant factor for management, prognosis, and follow-up of MOGCTs. AFP may be elevated in patients with teratomas and it is invariably elevated in yolk sac tumors [12]. Germinoma may present with either positive β-hCG, a marker associated with choriocarcinoma, or CA-125, which is associated with epithelial tumors. In the current study, 87.6% patients presented with elevated levels of AFP, and 92.9% YST patients had abnormal AFP level within the normal range after treatment at follow-up, which supported AFP as an important monitor index at follow up.

Surgical excision has a central role in the management of MOGCTs. Surgery provides valuable information for staging. Because MOGCTs often occur in girls and young women, preservation of ovarian function and fertility is an important goal of treatment. As already reported, GCTs are highly chemosensitive, and platinum-based chemotherapy has revolutionized the overall prognosis of all patients with germ cell tumors, radical ovarian excision, and hysterectomy were not routinely performed in the present institution. In the present authors' experience, unilateral salpingo-oophorectomy or even ovarian-sparing tumorectomy (mainly in localized disease with normal AFP level) is often sufficient. In the current study, the overall survival of MOGCTs was not inferior to previous studies. As bilateral ovarian involvement is rare in children, in this study, none was found to have bilateral involvement. In the present authors' opinion, if the contralateral ovary appears normal, biopsy is not necessary and may contribute to adhesion formation. Although it is not clear to what extent oophorectomy affects the fertility of these patients, the pregnancy rates appear to be the same as that of general population when patients undergo follow-up longitudinally [13]; a single ovary does not imply a reduced fertility potential to conceive. Therefore, the present authors suggest to preserve uterus and contralateral ovarian whenever safe and feasible. However, more work is needed to shed more light on the fertility potential of patients with MOGCTs after sur-

gery.

Chemotherapy plays an important role in MOGCTs treatment and outcome. Immature teratomas Grade II and III, although not truly malignant, have been treated as malignant in the present authors' department. There is no recurrence of immature teratomas in this study, and the overall survival rate was 100%. All of them are alive, aged 7-22 years now, and are between three and 12 years of age post-diagnosis.

Overall survival for MOGCTs was 95.5% in this study; it was lower than literatures reports which were between 97-100% [14, 15]. Lower overall survival rate could be partially explained by the number of patients with advanced disease and relapse disease. The application of platinum-based agents in pediatric chemotherapy regimens has improved survival significantly in children with MOGCTs. The six-year overall survival rate with the PEB protocol has been 95.1% for Stage I, 93.8% for Stage II, 97.35% for Stage III, and 93.9% for Stage IV disease [16]. In the present series, PEB and PVB regimens were both used, and the overall survival rate was no statistical significant differences between the two regimens.

Although dysgerminoma is very sensitive to radiation, patients will lose their ovarian function after radiation. In the present authors' opinion, radiation should be avoided due to the effectiveness of chemotherapy.

The management of recurrent tumor remains an open issue. Patients relapsing within two months of ending platinum-based chemotherapy are considered resistant and have a poor outcome, whereas 30-40% of girls with later relapses could be salvaged [17]. The present data confirmed the unsatisfactory results: 28.6% relapsed patients died of their disease, despite retrieval chemotherapy was given.

The present study has some limitations. Because of the retrospective nature of the study, there was incomplete information in some patients and some patients were lost to follow up after five years. Furthermore, the small number of patients attempting conception precludes the identification of fertility function in the present patients.

Conclusion

MOGCTs are uncommon in children and are highly chemosensitive with a high curability rate. With accurate staging, complete resection, and adjuvant chemotherapy, patients should be expected to have excellent survival rates with maintenance of normal reproductive function after platinum-based chemotherapy. Additional research is warranted in patients with relapsed disease.

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