Outcome of Recurrent and Persistent Disease of Malignant Ovarian Germ Cell Tumor: A Retrospective Analysis at King Chulalongkorn Memorial Hospital

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Malignant ovarian germ cell tumor has one of the most successful treatment outcomes in gynecological malignancy. More than 80% of the patients can be cured from this rare type of tumor. However, patients with recurrent and persistent disease after primary treatment are still the problem of management. The present study has reviewed the treatment outcome of this cancer in King Chulalongkorn Memorial Hospital during the 12 years period from 1993 to 2004. The overall cases of malignant ovarian germ cell tumor were 71 cases, 8 cases had recurrent disease after primary treatment and all cases received platinum-based chemotherapy for the salvage treatment. All patients in this group received long-term survival with median survival time of 87 months. In patients with persistent disease, 10 cases that resisted to first line adjuvant chemotherapy. Cisplatin and Etoposide regimen was applied as second line treatment, but none of these patients received long term response. The survival outcomes in these 2 groups are significantly different. The overall survival from the treatment of malignant ovarian germ cell tumor in King Chulalongkorn Memorial Hospital was 85.1%. In conclusion, the outcome of treatment in patients with recurrent disease after non-platinum chemotherapy is excellent. Salvage therapy in this group should contain platinum-based regimen. Patients whose disease persisted after platinum-containing regimen had a poor survival outcome.

Keywords: *Malignant ovarian germ cell tumor, Recurrent disease, Persistent disease*

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The incidence of malignant ovarian germ cell tumor is rare, less than 5% of all malignant ovarian tumors (an incidence approximately 1/10th that of testicular cancer[1]) be cured by adjuvant chemotherapy. Since the chemotherapy era has begun, cure rate of malignant ovarian germ cell tumor has dramatically increased because of the new regimens of chemotherapy. In the current period, over 80% of patients reached long term survival[2,3]. However, there is little information in the patients with recurrent and persistent disease. Due to the limited number of patients with malignant ovarian germ cell tumor, current concepts of management in this disease are from the data of testicular cancer, which has many more cases than ovarian germ cell tumor. Randomized control trials could not be done for this cancer. The present study retrieved data from patients with malignant ovarian germ cell tumor in King Chulalongkorn Memorial Hospital. The objective of the present study was to determine the outcome in the patients who had persistent and recurrent disease after primary treatment. The survival outcome and response to salvage therapy were focused.

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Material and Method

From 1993 to 2004, the data was collected from patients who registered in King Chulalongkorn Memorial Hospital including those who were initially treated as well as those who were referred. Patients diagnosed as malignant ovarian germ cell tumor according to WHO classification were included. The data collection was focused in 2 subgroups, recurrent and the persistent diseases. The recurrent group was defined as patients whose disease had recurred more than 6 months after primary treatment and the persistent group was defined as patients who did not respond to induction chemotherapy or had recurrent disease before 6 months after primary treatment. General characteristics, initial stage according to International Federation of Gynecology and Obstetrics (FIGO), cell type, primary operation, adjuvant treatment, time to recurrence, salvage treatment and survival outcome were collected. Survival time was the major outcome to determine. The time to recurrence was the duration from primary treatment to the first detection of recurrent disease. Survival time was defined as duration from primary treatment until patients expired or the last follow up. Three chemotherapy regimens were used in most of the cases. At the time of the present study, platinum based chemotherapy regimen was not applied to all patients.

Vincristine, Actinomycin-D and Cyclophosphamide (VAC) regimen was given as vincristine 1 mg / m^2 on the first day, actinomycin-D 300 microgram/m^2 and cyclophosphamide 150 mg/m^2 from the 1^{st} day to the 5^{th} day every 3 weeks.

Cisplatin, Vinblastine and Bleomycin (PVB) regimen was given as vinblastine 6 mg/m^2 on the first day, bleomycin 10 unit/m^2 in day from the 1^{st} day to the 5^{th} day, and cisplatin 20mg from the 1^{st} day to the 5^{th} day every 3 weeks.

Etoposide and Cisplatin (EP) regimen was given as etoposide 100mg/m^2 and cisplatin 20 mg for 5 days every 3weeks.

The data was analyzed by using the SPSS program version 11.1. Descriptive statistical analyses were used. Survival distributions were estimated using the Kaplan-Meier method.

Results

There were 71 patients diagnosed as malignant ovarian germ cell tumor. Among these, 8 patients (11.3%) had recurrent diseases after initial treatment but two refused further treatment, thus the data was analyzed based on the remaining 6 patients. In the persistent group, there were 10 patients (14.1%) who resisted to primary chemotherapy and 9 were available for analysis since one was lost to follow up. Finally, there was a total of 18 (25.3%) patients who had recurrent and persistent disease after initial treatment, but the analysis was based on 15 patients as shown in Table 1.

Patient characteristics

Recurrent group

Mean age in the recurrent group was 18.3 years (range 13-28 years). Histological diagnoses were immature teratoma in 2 cases, dysgerminoma in 2 cases and endodermal sinus tumor (EST) in 2 cases. There was only one patient who received primary treatment at King Chulalongkorn Memorial Hospital, the other 5 patients were referred to King Chulalongkorn Memorial Hospital for further treatment after recurrent disease was diagnosed. The initial staging was stage I in 4 cases, complete staging could not be made in 3 of these cases but operative findings were apparently stage I. The other 2 cases were stage IIIb. After primary surgery, four patients did not receive adjuvant treatment due to the cell type of dysgerminoma and immature teratoma stage I. One patient was diagnosed as EST stage I but no chemotherapy was given.

Concerning primary chemotherapy, 2 cases of stage IIIb received combination chemotherapy, VAC regimen. Median time to recurrence was 18.5 months (mean 23.5 months, range 6-68 months). For salvage therapy, all patients received platinum-based chemotherapy (PVB), 4 patients in this group received salvage surgery combined with chemotherapy.

Table 1. Overall patients of recurrent and persistent disease of malignant ovarian germ cell tumor

	Number (%)
Overall cases of malignant ovarian germ cell tumor	71 (100)
Recurrent of after primary treatment	8 (11.3)*
Persistent disease after 1^{st} line Chemotherapy	10 (14.1)**
Overall cases of recurrent and persistent disease	18 (25.3)***

* Refused further treatment 2 cases
** Loss follows up 1 case
*** Available for analyzed 15 cases

All patients are still alive without disease with median survival time 87 months (mean 93.8 months, range 60-140 months), the characteristics of this group are defined in Table 2 and survival time is demonstrated in Diagram 1.

Persistent group

All of the 9 patients in this group had a mean age of 28.3 years (range 9-47 years). The most common histologic cell type was endodermal sinus tumor (4 cases of EST, 1 case of choriocarcinoma, 1 case of dygermi-

Table 2. Characteristics of recurrent disease

	Age	Primary surgery	Histology	Stage	Adj Px	Time to recurrent	Salvage Px	Outcome	Condition
1.	22	Lt SO	Immature Teratoma	I?	NO	6 mo	Sx + PVB	NED 84 mo	Alive
2.	15	Rt SO	Dysgerm	IIIb	VAC	19 mo	Sx + PVB	NED 60 mo	Alive
3.	13	Rt SO	Dysgerm	I?	NO	24 mo	Sx + PVB	NED 84 mo	Alive
4.	17	Rt SO	Immature Teratoma	Ia	NO	18 mo	Sx + PVB	NED 90 mo	Alive
5.	15	Lt SO	EST	I?	NO	6 mo	PVB	NED 140 mo	Alive
6.	28	Rt SO	EST	IIIb	VAC	68 mo	PVB	NED 105 mo	Alive

SO = Salpingo-oophorectomy, Dysgerm = Dysgerminoma, EST = Endodermal Sinus Tumor, NED = No Evidence of Disease

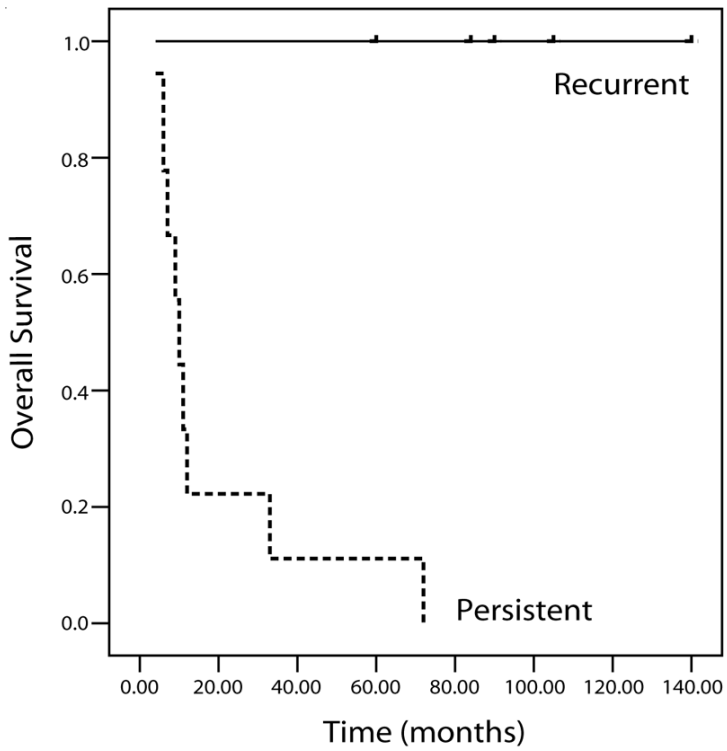

Diagram 1. Survival distribution in the recurrent group and persistent group

noma, 1 case of immature teratoma and 2 cases of mixed germ cell tumor). Only 3 patients were initially treated at King Chulalongkorn Memorial Hospital, the other 6 patients were referred to the hospital for further treatment. Two patients were initially stage I, 3 cases were stage II and 4 cases were diagnosed as stage III. The adjuvant chemotherapy after primary surgery was PVB regimen in 7 cases. The other 2 cases received VAC regimen. Most of the patients who resisted to PVB regimen received etoposide and cisplatin regimen for second line chemotherapy. Not all of these patients could receive long-term response. The 2 patients who resisted to primary VAC regimen received PVB regimen for salvage chemotherapy but showed no benefit from this treatment. All patients received short term survival and died from the disease. Median survival in this group was 10 months (mean 18.2 months, range 4-72 months). The characteristics of this group are defined in Table 3 and survival time was demonstrated in Diagram 1.

Discussion

The information from the literatures concerning salvage therapy for patients with malignant ovarian germ cell tumor with persistent or recurrent tumor is very limited. With proper adjuvant chemotherapy, the overall response rate for malignant ovarian germ cell tumor ranged from 80 to more than 90%[3-5]. In the present report, the incidence of recurrent and persistent disease was 25.3%. If the authors excluded the recurrent group, the overall response to the treatment of malignant ovarian germ cell tumor in King Chulalongkorn Memorial Hospital was 85.1% because all the patients in this group received long-term survival. The present response rate is lower than that of other series. This can be explained by the chemotherapy regimens which were used. At the time of the present study, VAC regimen was used in the patients with optimal or completely resected disease. Platinum-based chemotherapy was applied to the patients with suboptimal surgery and non-dysgerminomatous disease.

Table 3. Characteristics of patients with persistent disease

	Age	Primary surgery	Histology	Stage	Adj Px	Salvage Px	Survival time	Condition
1.	18	TAH c BSO	EST	Ic	PVB	EP, Paclitaxel	33 mo	Dead from the disease
2.	47	TAH c BSO	Choriocarcinoma	IIc	PVB	EP, radiation	11 mo	Dead from the disease
3.	39	TAH c BSO	Dysgerm	IIc	PVB	EP	12 mo	Dead from the disease
4.	9	Rt SO	EST + Immature	Ic	VAC	PVB	7 mo	Dead from the disease
5.	33	TAH c BSO	EST	IIIc	VAC	PVB + Sx	10 mo	Dead from the disease
6.	7	TAH c BSO	Immature Teratoma	IIIc	PVB	EP (incomplete Rx)	72 mo	Dead from the disease
7.	23	Rt SO	EST	IIc	PVB	EP	4 mo	Dead from the disease
8.	19	Rt SO	EST + Chorio	IIIc	PVB	EP	6 mo	Dead from the disease
9.	30	TAH c BSO	EST	IIIa	PVB	BE	9 mo	Dead from the disease

BE = Bleomycin and Etoposide

BEP regimen, which is the standard first line adjuvant chemotherapy in the current period[2,3] was not available at the time of the present study. Many reports classified patients into platinum-sensitive and platinum-resistant groups[6]. However, non-platinum regimen was still used in the present study, thus the present study defined patients as recurrent and persistent groups.

From the literatures[1,6-9], stage Ia dysgerminoma and immature teratoma stage Ia grade I can be observed without post operative treatment. In the present study, three patients with stage Ia dysgerminoma and immature teratoma did not receive adjuvant chemotherapy. All these 3 cases have recurrent diseases. This may reflect the inaccuracy of surgical staging data because these 3 cases received primary surgery from other hospitals. However, after salvage treatment these patients gained long-term survival from platinum-based chemotherapy with or without surgery. Gershenson et al[10] reported the success of salvage treatment by PVB regimen after failed VAC. Two patients with recurrent disease in the present study received VAC regimen as first line chemotherapy, and responded to platinum based chemotherapy as the second line treatment. According to many studies[11,12], platinum containing regimen was recommended for first line treatment. Median time to recurrence was 18.5 months (mean 23.5 months, range 6-68 months). In the present study, the authors agreed to treat patients with recurrent disease after non-platinum regimen by platinum-combination regimen.

On the other hand, patients with persistent disease had a poor survival outcome. Most of the patients were treated with platinum-combination regimen for first line chemotherapy. The EP regimen in the present study was used for second line chemotherapy from which no patient received long-term benefit. Bleomycin may possibly be required in this regimen because at least two studies have demonstrated the efficacy of BEP (Bleomycin, Etoposide and Cisplatin) better than EP in testicular germ cell tumor[13,14]. Whereas 30-40% of persistent diseases could be salvaged[15-17], all the patients in the present series died after treatment. This reflected the ineffective salvage treatment in patients with persistent disease. The management of patients with platinum-resistant tumor remains a problem. The most useful information about salvage therapy for patients with platinum-resistant comes from the literature on testicular cancer. Reasonable treatment options include either high-dose chemotherapy or phase II drugs[16,18-20]. The studies of high-dose chemotherapy plus autologous bone marrow rescue showed durable complete response of 20-30%[18,19]. However, approximately 20% of patients died of therapy-related complications.

In conclusion, the outcome of treatment in patients with recurrent disease after non-platinum chemotherapy is excellent. Salvage therapy in this group should contain platinum-combination regimen. Patients whose disease persisted after platinum-containing regimen had a poor survival outcome, the etoposide and platinum regimen seemed to have no long term benefit for this group. Salvage therapy with high-dose regimen or other trial regimens should be considered.

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ผลการรอดชีวิตของผู้ป่วยมะเร็งรังไข่ชนิด Germ cell tumor ในกลุ่มที่กลับเป็นซ้ำและกลุ่มที่ดื้อต่อการรักษาด้วยยาเคมีบำบัด ในโรงพยาบาลจุฬาลงกรณ์

เรืองศักดิ์ เลิศขจรสุข, ธาริณี แม่นชนะ, วิชัย เติมรุ่งเรืองเลิศ, อภิชัย วสุรัตน์, ตุลย์ สิทธิสมวงศ์, พงษ์เกษม วรเศรษฐสิน, นครินทร์ ศิริทรัพย์, นิพนธ์ เขมะเพชร, ดำรง ตรีสุโกศล

วัตถุประสงค์: *เพื่อศึกษาผลการรักษาในผู้ป่วยมะเร็งรังไข่ชนิด Germ cell tumor กลุ่มที่กลับเป็นซ้ำและกลุ่มที่ดื้อต่อการรักษา*

วัสดุและวิธีการ: *ได้ศึกษาข้อมูลของผู้ป่วยมะเร็งรังไข่กลุ่ม Germ cell tumor ที่กลับเป็นซ้ำและกลุ่มที่ดื้อต่อการรักษาด้วยยาเคมีบำบัด ในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ปี พ.ศ. 2536 - พ.ศ. 2547 รวมระยะเวลา 12 ปี*

ผลการศึกษา: *ในจำนวนผู้ป่วยกลุ่มมะเร็งรังไข่ชนิด Germ cell tumor ทั้งหมด 71 ราย มีผู้ป่วยที่กลับเป็นซ้ำ 8 ราย คิดเป็นร้อยละ 11.3 ผู้ป่วยกลุ่มที่ดื้อยาเคมีบำบัด 10 ราย คิดเป็นร้อยละ 14.1 การวิเคราะห์สามารถทำได้ในผู้ป่วย 15 รายในผู้ป่วยทั้งสองกลุ่ม กลุ่มผู้ป่วยที่กลับเป็นซ้ำพบว่าชนิดของเซลล์มะเร็งเป็น Immature teratoma, Dysgerminoma และ Endodermal sinus tumor การรักษาปฐมภูมิคือได้รับการผ่าตัดเอาก้อนมะเร็งออก และตรวจติดตามหรือให้ยาเคมีบำบัดกลุ่ม Non platinum-based เมื่อกลับเป็นซ้ำผู้ป่วยได้รับยาเคมีบำบัดกลุ่ม Platinum-based ซึ่งทุกรายตอบสนองต่อการรักษาและยังมีชีวิตอยู่โดยมีค่า Median survival time 87 เดือน ส่วนกลุ่มที่ดื้อยาพบว่าชนิดของเซลล์มะเร็งเป็น Endodermal sinus tumor, Choriocarcinoma, Dysgerminoma, Immature teratoma และ Mixed germ cell การรักษาปฐมภูมิคือการผ่าตัดและให้ยาเคมีบำบัดซึ่งส่วนใหญ่ได้รับยากลุ่ม Platinum-based การรักษาในกลุ่มที่ดื้อยาพบว่าผู้ป่วยส่วนใหญ่ได้รับยาเคมีบำบัด Cisplatin และ Etoposide เป็น Second line ผู้ป่วยทุกรายในกลุ่มนี้เสียชีวิต โดยมี Median survival time 10 เดือน*

สรุป: *อัตราการรอดชีวิตของผู้ป่วยมะเร็งรังไข่ชนิด Germ cell tumor ในกลุ่มที่กลับเป็นซ้ำอยู่ในเกณฑ์ดีมาก โดยสามารถรักษาได้ด้วยยาเคมีบำบัดกลุ่ม Platinum based ส่วนในกลุ่มที่ดื้อยาพบว่าผลการรักษาไม่ดี ผู้ป่วยกลุ่มนี้เสียชีวิตทุกรายโดยมีค่าเฉลี่ยของระยะเวลาการรอดชีวิตที่ 10 เดือน*