การรอดชีวิตของผู้ป่วยมะเร็งรังไข่ที่กลับเป็นซ้ำที่ได้รับการรักษาโดยยาเคมีบำบัดกลุ่ม Second-Line

Survival Outcome in Relapsed Ovarian Cancer Treated with Second-Line Chemotherapy

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Abstract

Objective : To compare survival outcome between relapsed ovarian cancer patients who received second-line chemotherapy and those who had no further chemotherapy treatment.

Methods and Materials : A retrospective review of medical charts with relapsed ovarian cancer treated at King Chulalongkorn Memorial Hospital from 1995-2000 was undertaken. 99 relapsed ovarian cancer patient's charts were identified. 48 of them had second-line chemotherapy (group A) and 51 cohorts were offered no chemotherapy (group B). Initial data after primary treatment being recorded were age, stage, histology and residual tumor. Second data set at time of tumor relapse were presence of ascites, site of metastasis, performance status, attempts of secondary cytoreductive surgery and size of relapsed tumor. Chi square test was used to compare difference between group. Survival curve was constructed by Kaplan Meier method. Log rank and Cox regression were used to prove independent variables.

Results : There was no difference between two groups. Once relapsed, more tumor progression during initial chemotherapy (primary platinum resistance) was found in group A (Group A, 31.2% versus Group B, 7.8%). Secondary cytoreductive surgery remained a single prognostic factor (p=0.016). Median survival time after relapse (SAR) in group A and B was 12 and 3 months respectively (p=0.000). Prolong survival was found in patients treated with second-line chemotherapy.

Conclusion : Second-line chemotherapy prolonged survival in relapsed ovarian cancer. It was more attractive in cases who could be secondarily cytoreduced.

Keywords : relapsed ovarian cancer, second-line chemotherapy, secondary cytoreductive surgery

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บทคัดย่อ

จุดประสงค์ : เพื่อศึกษาเปรียบเทียบการรอดชีวิตของผู้ป่วยมะเร็งรังไข่กลับเป็นซ้ำที่ได้รับการรักษาโดยยาเคมีบำบัดกลุ่ม Second-line กับกลุ่มที่ไม่ได้รับยาเคมีบำบัด

วิธีการศึกษา : เป็นการศึกษาข้อมูลย้อนหลังในผู้ป่วยมะเร็งรังไข่กลับเป็นซ้ำจำนวน 99 รายที่เข้ารับการรักษาในโรงพยาบาลจุฬาลงกรณ์ระหว่างปีพุทธศักราช 2538-2543 โดยมีการรักษาด้วยยาเคมีบำบัดกลุ่ม Second-line ในผู้ป่วยจำนวน 48 ราย (กลุ่ม A)เปรียบเทียบกับกลุ่มที่ไม่ได้รับยาเคมีบำบัดจำนวน 51 ราย (กลุ่ม B) มีการบันทึกข้อมูลของการศึกษาของการรักษาเริ่มแรกในเรื่อง อายุ ระยะของโรค ผลทางพยาธิวิทยา และการคงเหลือของเนื้องอกหลังการผ่าตัดครั้งแรก และข้อมูลหลังการกลับเป็นซ้ำของมะเร็งรังไข่ได้แก่ น้ำในช่องท้อง ตำแหน่งของการกระจาย สภาพของผู้ป่วย การรักษาด้วยการผ่าตัด และขนาดของเนื้องอกหลังจากนั้นเปรียบเทียบข้อมูลสองกลุ่มโดยใช้ X^2 ศึกษาการรอดชีวิตโดยใช้ K aplan Meier method และศึกษาปัจจัยที่มีผลต่อโรคด้วย Log rank and Cox regression

ผลการศึกษา : พบว่าข้อมูลเบื้องต้นก่อนการกลับเป็นซ้ำในกลุ่ม A และกลุ่ม B ไม่แตกต่างกัน แต่หลังมีการกลับเป็นซ้ำ พบว่ามีภาวะดื้อต่อ Platinum พบในกลุ่ม A เท่ากับ 31.2% เปรียบเทียบกับกลุ่ม B เท่ากับ7.8%นอกจากนี้ยังพบว่าการรักษาโดยการผ่าตัดหลังการกลับเป็นซ้ำเป็นปัจจัยเดียวที่มีผลต่อการพยากรณ์ของโรค (p=0.0016) ค่ากลางการรอดชีวิตหลังการกลับเป็นซ้ำในกลุ่ม A มากกว่ากลุ่ม B อย่างมีนัยสำคัญทางสถิติ (12 และ3 เดือนตามลำดับ) (p=0.000)

สรุป : การให้ยาเคมีบำบัดชนิด Second-line ในกลุ่มผู้ป่วยมะเร็งรังไข่ที่กลับเป็นซ้ำสามารถเพิ่มระยะเวลาการรอดชีวิต โดยเฉพาะในกลุ่มที่สามารถทำการผ่าตัดได้

นิยามศัพท์ : มะเร็งรังไข่กลับเป็นซ้ำ, ยาเคมีบำบัดกลุ่ม second line, secondary cytoreductive surgery

Introduction

FIGO staging and volume of post-surgical residual tumor are most important factors that influence survival in patients with ovarian cancer.[1-8] Relapsed disease is more common in advanced stage as compared to early stage (80% versus 20%).[9, 10] When tumor relapsed, it is almost never curable. Resistance to chemotherapy is known to play a major role, lead to failure from cancer cells eradication and eventually let the tumor grow and kill patients. Carboplatin as a single agent or combined with cyclophosphamide is a standard first-line regimen for treatment of ovarian cancer throughout our country. In advanced stage disease, 10-20% of them survive over 5 years. [2, 11] Unfortunately, most of them ultimately relapse and die of disease.

Reinduction with platinum based chemotherapy if they are initially sensitive to platinum is a common approach while others who progress or refractory to platinum often require second-line chemotherapy agent. Over the past decade numerous clinical trials of varied second-line chemotherapy for the treatment of relapsed ovarian cancer have been reported.[12-21] Response rates with these second-line agents in this population ranges from 10-25%.[22, 23] It is unlikely that our patients will have access to most costly commercially available agents. In practice, it is difficult to identify patients in whom the benefits of second-line chemotherapy will be obtained or warrants expenses that incurred during treatment. It is our hypothesis to find out whether these second-line agents when given to patients who resist to platinum will lead to prolongation of patient's survival. A retrospective study was conducted and the survival outcome of relapsed ovarian cancer patients treated with second-line chemotherapy was compared to those cohorts who did not receive any chemotherapy treatment.

Patients and Methods

The medical records of 348 patients who were diagnosed as common epithelial ovarian cancer at King Chulalongkorn Memorial Hospital between 1995 and 2000 were retrieved. All patients were treated with primary cytoreductive surgery followed by platinum-based chemotherapy. Cases of neoadjuvant chemotherapy were excluded. 12 had neoadjuvant chemotherapy. None received paclitaxel as first-line

combination. Patient's charts with tumor relapse were identified and recruited into this study. Age, parity, histological type, FIGO stage, residual disease, onset of recurrence, time of death, treatment after recurrence including type of second-line chemotherapy were recorded as variables. Relapse was verified by either undoubted physical examination, imaging or tumor markers.

Definition of pattern of relapse used in our study was based on Markman's criterion.[24] Defined that platinum-sensitive group were patients who initially responsed to platinum-based chemotherapy and platinum-free interval >6 months. Primary resistance to platinum were patients who progressed during first-line platinum-based chemotherapy or were initially responded to platinum based chemotherapy and platinum-free interval <6 months.Secondary platinum-resistant include patients who responsed to a platinum regimen as primary therapy (at least a partial response) and who did not responsed to a second organoplatinum treatment program and called acquired resistance. Bulky tumor was tumor that large than 2 centimeters by physical examination.

Survival time after relapse (SAR) was defined as time after onset of relapse until time of death or last contact, or until December 2002. A listing of patients who had expired was obtained from the Ministry of Internal Affairs. After receiving a name list of deceased patients who were not on the list to confirm their survival status. In relapsed patients, multimodality of treatments was used. If there was solitary nodule, surgery was indicated. Platinum reinduction were used in platinum sensitive patients while second-line chemotherapy were used in platinum resistant patients. Radiotherapy or anti-cancer hormone were alternatives for relapsed patients who were physically unfit for further chemotherapy or not access to second-line agent

Results

There were 99 patients included in this study. 48 patients received second-line chemotherapy (Group A), 51 patients who relapsed had no chemotherapy (Group B). Patient characteristics at the beginning of primary treatment was well balanced between two groups, $p<0.05$. (Table 1)

Table 1. Patient characteristics at initial treatment

Characteristics	Treatment		P value[1]
	Second-line chemotherapy	No-treatment	
Age			
<40	2	7	0.098
≥40	46	44	
Parity			
Nulliparous	22	20	0.506
Multiparous	26	31	
Stage			
Early	7	7	0.903
Advanced	41	44	
Type			
Clear cell	3	9	0.082
Others	45	42	
Residual tumor size			
Less than 2 cm	7	15	0.076
Larger than 2 cm.	41	36	

[1] Using Chi-square test

Median age was 50 years (27-74 years). 12 cases (12.12%) were clear cell carcinoma. 22 cases (22.2%) were optimally debulked. 14 patients underwent attempts of secondary cytoreductive surgery. (9 in arm A and 5 in arm B) Median survival time after relapse in secondary cytoreductive group was longer (11 versus 5 months, p=0.016). (Table2, Figure 1) At time of relapse, more tumor progression during initial chemotherapy (primary platinum resistance) were found in arm A.(Group a, 31.2% versus Group B, 7.8%, p<0.003). (Table 3) Median survival time in group A and group B was 12 and 3 months respectively, p=0.000 (Figure2). Secondary cytoreductive surgery was found to be a single prognostic factor. (p=0.016)

Table 2 Survival differentiation estimated by Log-rank test

Factors	N	Median(months)	P value[1]
Initial stage			
Early	12	3.4	0.985
Advanced	79	6.00	
Perfomance status			
Zubrod=0	15	11.0	0.064
Zubrod=1	51	5.5	
Zubrod=2	25	3.0	
Ascites			
Yes	52	4.0	0.1051
No	39	7.6	
Secondary surgery			
Yes	14	11.0	0.016
No	77	5.0	
Bulky tumor			
Yes	30	6.0	0.071
No	61	5.5	
Metastases			
Abdomen	73	6.0	0.677
Distant	18	5.0	
Platinum resistance			
Primary	16	6.0	0.870
Acquired	75	5.2	
Treatment			
Second-line drugs	47	11.9	0.000
No-treatment	44	2.7	

[1] Using Log rank test

Table 3. Patient characteristics at time of relapse

Variable factors	Second-line chemotherapy	No-treatment	P value[1]
Initial stage			
Early	7	7	0.903
Advanced	41	44	
Platinum resistance			
Primary	15	4	0.003
Acquired	33	47	
Performance status			
Zubrod=0	12	6	0.169
Zubrod=1	26	29	
Zubrod=2	10	16	
Ascites			
Yes	25	32	0.283
No	23	19	
Secondary surgery			
Yes	9	5	0.202
No	39	46	
Bulky tumor			
Yes	15	17	0.825
No	33	34	
Metastases			
Distant	40	41	0.705
Abdomen	8	10	

[1]Using Chi-square tests

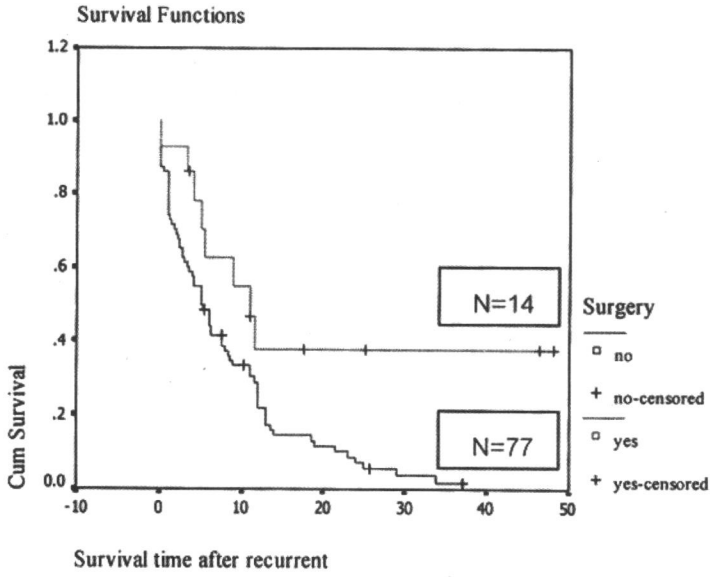

Figure 1 Comparison of survival time after relapse between surgical treatment group

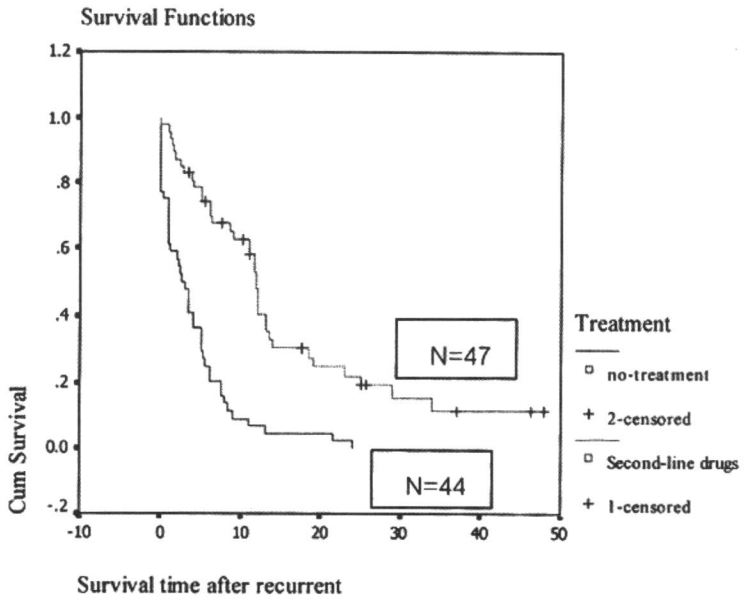

Figure 2 Comparison of survival time after relapse between second-line drugs group and no treatment group

Discussion

Management of relapsed ovarian cancer is controversial and numerous agents That were active in the second-line setting have been identified. Patients with relapses more than 6 months after the completion of their initial therapy can be considered potentially platinum-sensitive and repeated sensitivity to platinum either alone or in combination has been reported.[23, 25-27] For patients with progressive disease within 6 months of therapy, platinum reinduction is fruitless and being considered platinum refractory or resistant.In this setting, palliation is the major goal and single agent therapy is most commonly used.

Initial first-line chemotherapy regimen in our study patients was carboplatin combined with cyclophosphamide or carboplatin alone.[28-30] None of them received paclitaxel as first-line combination. When tumors were refractory or resisted to platinum, paclitaxel was most common used as second-line agent.[31, 32] Liposomal doxorubicin, topotecan, gemcitabine were ostly used as third-line with exceptions.

Brief duration of response, as well as the failure to induce complete response after numerous trials with varied second-line chemotherapy are considered major deadlock in treatment of relapsed ovarian cancer. Conclusion was made that it had been little change in duration of response or survival over the years 1980-1997.[33]

Patient's variables were well balanced between these two groups and is the strength of our study. Secondary cytoreductive surgery was found to influence survival outcome in relapsing ovarian cancer. If tumor was less biological virulence and responded more to chemotherapy, surgery was always helpful no matter when second-line chemotherapy was given (prior to or after surgery).

Survival advantage in patients treated with second-line agents found in our study is interesting. Though median survival time was only 11.9 months difference between the two groups, it is still meaningful that our health policy maker could not ignore this benefit of second-line chemotherapy and universal implementation is to be undertaken. However, huge amount of drug cost will definitely

cast problem to whole nation fiscal policy embracing health care system. Though more patients with primary platinum resistance were found in arm A, prolonged survival was still seen. This finding indirectly indicated a benefit in this patient group whom low response rate is generally obtained after any second-line agents. Since this study was merely an observational study, those cohorts who refused or did not get any chemotherapy might have bulky tumor or medically ill or compromised and succumbed. Bias from physician discretion was well aware and might lead to flaw this study outcome. It is noteworthy that quality of life was not analyzed and integrated in our paper. We admitted that there is no current widely used Thai version-questionnaire form that is generally accepted. It will be of great benefit if data concerning quality of life after treatment with chemotherapy is applied and implemented during patient counseling prior to any treatment decision. Treatment expense should not be overlooked since most of these patients are indigent and poor.

Prolongation of survival when treated with second-line chemotherapy is to be strongly considered compared to cost that incurred during treatment. In addition, quality of life and intangible loss during treatment may outweigh slight survival difference that derives from the second-line treatment. We have to bear in mind all these factors prior to initiation of any expensive treatment in these patients who are poor prognosis.Further collaboration from multicenter trial is strongly needed to direct Health plan policy maker to revise a practical guideline for second-line treatment in these patients setting.

Conclusion

Second-line chemotherapy prolonged survival in relapsed ovarian cancer. It was more attractive in cases who could be secondarily cytoreduced.

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