NEOADJUVANCED CHEMOTHERAPY FOR PATIENTS WITH ADVANCED STAGED EPITHELIAL OVARIAN CANCER

Hoang Bao Nhan[1], Bach Cam An[1], Le Sy Phuong[1], Chau Khac Tu[1], Tran Thi Le Ha[1]

ABSTRACT

Objectives: *To estimate the effects of neoadjuvant chemotherapy in patients with advanced stage ovarian cancer.*

Materials: *31 patients with stage III - IV ovarian cancer who were treated by neoadjuvant chemotherapy in department of Obstetrics and Gynecology of Hue Central Hospital, from January 2009 to December 2013.*

Method: *A perspective study.*

Results: *The median age was 53.8 ± 17.6. 87.1% of patients were staged III when first diagnosed. 19.4% of them responsed to the regimen and 83.9% reached optimal cytoreduction. Rate of recurrence is 25.8% and mean time intervals of recurrence is 8.6 ± 7.2 months.*

Conclusion: *Neoadjuvant chemotherapy is one of the most effective treatments for patients with advanced stage ovarian cancer.*

Key words: *Neoadjuvant chemotherapy, advanced stage ovarian cancer.*

I. INTRODUCTION

Epithelial ovarian cancer (EOC) is one of the most common malignancies in gynecological oncology [4], [11]. In 2008, there were 21.650 patients with EOC who were diagnosed and 15.520 deaths because of the reason. And it is the sixth most common cancer in women worldwide [5].

For many years, especially in the last three decades, there are many advances in diagnose and treatment, but EOC remains the most lethal cancer, the overall survival increases lightly, and the survival after five-years-diagnosed increases from 37% to 45% in a period of 20 years [6].

For patients with EOC, especially in advanced staged disease patients, surgery is the most effective treatment, it is always concerned whenever possible. But in advanced staged EOC women, many of them can not be successfully operated. This makes neoadjuvanced chemotherapy a reasonable treatment [1], [3]. Many researchers reported that, patients who were indicated 2 - 3 cycles of chemotherapy would have higher incidence of successful cytoreductive surgery.

In clinical practice, most of patients with EOC were diagnosed when they had advanced staged disease or bad health status, this makes them unable to be operated primarily. That is the reason we use the regimen of neoadjuvant chemotherapy for these patients.

Objective: To study the effectiveness of neoadjuvant chemotherapy for treatment in patients who were diagnosed epithelial ovarian cancer and staged FIGO III-IV.

II. MATERIALS AND METHOD

2.1. Materials

Including criteria

Patients, who were diagnosed with epithelial

1. Hue Central Hospital

Corresponding author: Hoang Bao Nhan
Email: baonhanob@gmail.com
Received: 30/7/2016
Revised: 9/8/2016 by Pham Nhu Hiep
Accepted: 19/8/2016

ovarian cancer based on pathology, were included consecutively.

Based on laparoscopy, patients of FIGO staged III or IV, and could not reach optimal cytoreductive surgery primarily.

Patients and their relatives agreed to participate in study group.

Excluding criteria

Patients who has a serious health status, thus we could not perform chemotherapy nor surgery.

Contraindications of chemotherapy and surgery.

Patients who did not complete the regimen of neoadjuvant chemotherapy.

2.2. Method

A perspective, un-controled trial.

Our study was performed in three steps.

Step 1: Diagnose and staging of disease.

Patients who were suspected about EOC were indicated to evaluate CA 125 level, and imaging diagnose including pelvis sonography, chest X- ray, and pelvis CT Scan.

Patients were indicated laparocopy first. And at the time of laparoscopy, we took specimens of tissue or fluid of ascites to perform pathology and cytology, and staging the patient, evaluating the capacity of cytoreductive surgery.

Patients who were diagnosed EOC with FIGO stage III - IV and their relatives would be explained the risks, the benefits and steps of neoadjuvant chemotherapy. If they all agreed with the regimen, they would have indicated many tests to prepair for the treatment.

Step 2: Treat patients with step by step: chemotherapy - surgery - chemotherapy.

Included women were indicated protocol with combination of Paclitaxel (Paxus PM 230 mg/m^2) and Carboplatin (Kemocarb AUC 5-6) for three cycles every twenty-one days. After three cycles of chemotherapy, patients were evaluated the responsibility based on RECIST 1.1. Then these patients were performed cytoredutive surgery. At last, they were indicated to have more three cycles of paclitaxel and carboplatin with the same dose of neoadjuvant chemotherapy.

Step 3: Getting information of patients, using SPSS 17.0 for results.

III. RESULTS

3.1. Age and FIGO staging

Table 1: Age and FIGO stage of study group

Age (Mean ± 2SD)	53.8 ± 8.8	
FIGO stage	n	%
FIGO III	27	87.1
FIGO IV	4	12.9
	31	100

3.2. CA 125 level during the treatment

Table 2: CA 125 during the treatment

Cycle	Min	Max	Mean	SD
First	8	2136	387.7	604.6
Second	8	2495	292.6	736.9
Third	6	1622	281	484.3
Fourth	4	1243	215.1	350.9
Fifth	2	1089	163.6	275
Sixth	2	786	80.2	166.3

3.3. Responsibility with neoadjuvant chemotherapy based on RECIST 1.1

Table 3: Responsibility with neoadjuvant chemotherapy based on RECIST 1.1

	n	%
Completely response	3	9.7
Partial response	3	9.7
Stable disease	11	35.4
Progressive disease	7	22.6
Un-evaluable disease	7	22.6

3.4. Cytoreductive surgery and recurrence

Table 4: Cytoreductive surgery and recurrence

		n	%
Residual tumor	≤ 1 cm	26	83.9
	> 1 cm	5	16.1
Recurrence		8	25.8
PFS* (Mean ± 2SD)		8.6 ± 7.2 (months)	

*PFS: Progressive free survival

IV. DISCUSSION

4.1. Age

The mean age of the study group was 58.3 ± 8.8 years old, the maximum and minimum age were 76 and 46, respectively. EOC is most common in menopausal and postmenopausal women [4].

Age is the most important risk factor of EOC, it is defined in many studies, there are about 50% of all EOC patients in United State who were diagnosed at the age above 65. The mean age of diagnosis is 63 years, and the highest incidence is 70-74 year-old-group, and life-time risk is 57/100000 [11].

The predition is worse in older patients because of the worse health status and the risk of wider distance of the disease. Chan JK et al reported that, the overall survival (OS) in older is lower than younger patients [4], [9].

4.2. FIGO stage of EOC

In our study, patients were positive diagnosed and staged based on laparoscopy, which is very popular in many countries, but not performed routinely in Vietnam. The procedure makes it more feasible and easier to get specimens of the tumors, which is helpful for pathology examination. In addition, laparoscopy makes it possible to visualize the abdominal cavity, in which very important to stage the disease, and after three cycles of neoadjuvant chemotherapy the visualization would be meaningful to evaluate the responsibility of the tumor.

The positive diagnose and staging, which maybe done by laparoscopy or laparotomy, is necessary for every cancer, but as demanded above, many of patients can not successful recieve cytoreductive surgery primarily. That is reason why we chose laparoscopy to diagnose and stage patients suspected with EOC. But some authors do not recommend this as routinely, because laparoscopy can make it possible to get exact diagnose and staging, but does not effect the OS and PFS of the EOC patients [5].

Most of the patients in study group had FIGO stage III. In this study, one of the including criteria is staged III or IV of EOC. These are advanced stage of EOC, most of women were diagnosed in these stages. Eventhough there are now many biomarkers which are used for early detection of EOC, but this is really a matter. In a randomized control trial in United State with 78.216 women at the age of 55 - 74 years old who had CA 125 level evaluated combined with vaginal sonography annually difference were found between the study group and the others who had gynecologic examination as usual [1], [6], [8]. And only 35% of EOC in women in United State are detected in early stage [8].

4.3. CA 125 level during the treatment

There are now many methods to follow up patients during treatment, but the most common is CA 125 level. And in this study, we used it for every cycle of chemotherapy. And after 3 cycles of neoadjuvant chemotherapy, CT scan is combined to evaluate the responsibility of the tumor with the treatment.

During the treatment, the mean CA 125 level was decreased. In a study, it was reported that CA 125 level after three cycles of chemotherapy is the most statically, if CA 125 in this time less than 10 UI/ml, the survival rate after 5 years would be more than 50% [7]. And the role of CA 125 after three cycles of chemotherapy was again confirmed, false positive was, however, as high as 19%. This study also concluded that, although the change of CA 125 level could predict the responsibility of the disease, but it could not be used to guide the clinicians [6]. Hence, although CA 125 level decreases after each cycle of chemotherapy, the treatment should be continued without any concerning about CA 125 level. If clinical signs are stable while CA 125 level increases, the treatment should be changed. But

when the clinical status unchange and CA 125 level decrease, the protocol should be continued.

Based on CA 125 level following, a study in Roswell Park Cancer Centre, with the protocol of primary cytoreduction, they reported that the rate of complete response was 30% eventhough there were 13% of these patients had remaining tumour larger than 2 cm, and the PFS after three years was as high as 29% [10].

Acording to a study of Muazzam IA et al, the rate of biochemistry response was 94.1% in patients who were treated by neoadjuvant chemotherapy, which is higher than patients who were treated by primary cytoreduction combined with adjuvant chemotherapy, the difference, however is not statistically significant (94.1% vs 84.7%, p = 0.564) [8].

4.4. Responsibility of tumours base on RECIST 1.1

The evaluation of responsibility for every disease during treatment is very important, especially for cancers, it guides clinicians the best way not only for continuously treatment but for future. Hence, in 1981 WHO recommended the criterias to evaluate the responsibility during treatment, but these were difficult and not accurate. And in 2000, the RECIST (Response Evaluation Criteria In Solid Tumor) was fisrt published [3], [12].

According to RECIST, there were 6 patients (19.4%) in our study who responsed to the regimen, including 3 patients (9.7%) who got completely response. But there were 7 (22.6%) of them had un-evaluable disease. To evaluate the responsibility of cancer based on RECIST, we have to get the accurately diameter of the tumors, but with these patients we could not, because the cancer expanded to the abdominal cavity, which made it impossible to calculate the tumors size exactly.

4.5. Cytoreductive surgery next to neoadjuvant chemotherapy

After three cycles of neoadjuvant chemotherapy, we performed cytoreductive surgery for our patients. There were 83.9% of these patients had optimal cytoreduction, which means < 1 cm residual tumour.

Many studies in all over the world have confirmed the role of optimal cytoreductive surgery in treatment for advanced stage ovarian cancer. When compared with the group of sub-optimal cytoreduction, patients with optimal reduction had statically improvement in OS. And then, others confirmed the role of optimal reduction in improving the PFS in patients with advanced stage ovarian cancer [4], [5].

In EOC patients, surgery is the first treatment which should be indicated immediately when possible [11]. Until now, however, there is not a study that compared the difference between chemotherapy and surgery independently. So this makes it difficult to evaluate the role of these methods in the treatment of EOC.

Primarily cytoreduction is difficult for many patients who have advanced stage of EOC because of many reasons, including health status when first diagnosed, or advanced disease itself made it dangerous for performing surgery or event death. But based on a reporter, it also depends on the experiences of surgeons. The mortality rate of patients with advanced stage EOC also depends on surgeons [7], [9].

The Cochrane library reviewed a randomized controlled trial with 718 patients who had FIGO IIIc and IV stage EOC, and reported that neoadjuvant chemotherapy lowered the rate of adverse complications during surgery (i.e. bleeding, embolism, and infection). And group of patients who were treated with neoadjuvant chemotherapy had higher rate of optimal cytoreduction (80.6% vs 41.6%). This protocol, however, did not improve the PFS and OS statically. But according to the reporter, this study classified many patients who had advanced stage with the tumours that were too large that clinicians could not performed successfully cytoreduction into the group of neoadjuvant chemotherapy, this influenced the results of the study.

Neoadjuvant chemotherapy decreases the size of tumours, so it makes it easier to be removed completely, and higher rate of optimal cytoreduction, but when this is unaffordable, the surgeons could remove as much as possible the tumour. That is

reason why neoadjuvant chemotherapy makes it higher rate of optimal cytoreduction and decreases the size of remaining tumour after surgery.

In our study, there were no death during surgery. This protocol can decrease the rate of death during surgery compared with pimary surgery. Because our study is not controlled, we could not compare the death rate between the two groups as others.

4.6. Recurrence after treatment

Untill now, we have had 8 patients (25.8%) in our group who had recurrence, mean time intervals of recurrence was 8.6 ± 7.2 months. However, the following time of ours was too short, and for future, this rate will get higher and higher.

In women with advanced stage EOC, the rate of recurrence is as high as 75%, and this rate is higher and higher when prolonged the following period. When recurrence happens, cytoreductive surgery is the only treatment which improving the OS and PFS. The mean of OS would be improved as long as three months when increase 10% of optimal cytoreduction in group of recurrent disease [5].

V. CONCLUSION

Neoadjuvant chemotherapy plays an impotant role in treatment for patients with advanced stage of epithelial ovarian cancer.

REFERRENCES

1. Bhoola S, William J. Hoskins (2006) Diagnosis and Management of Epithelial Ovarian Cancer, Obstet Gynecol, 107:1399 - 1410.
2. Chappuis PO, Goffin J, Wong N, Perret C, Ghadirian P, Tonin PN, Foulkes WD (2002) A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer, J Med Genet, 39:608–610
3. Deo SVS, Hemant G, Shukla NK, Raina V, Lalit K, Srinivas G (2006) Neoadjuvant chemotherapy followed by surgical cytoreduction in advanced epithelial ovarian cancer, Indian Journal of Cancer, 43(3):117-121.
4. Fleming GF, Ronnett BM, Seidman J, Zaino RJ, Rubin SC (2009) Epithelial ovarian cancer, Principles and Practice of Gynecologic Oncology, 764-835.
5. Holstein SA, Hohl RJ (2008) Chemotherapy of Gynecology cancers, Chemotherapy source book, The 4th edition, 448-463.
6. Kikkawa F, Nawa A, Ino K, Shibata K, Kajiyama H, Nomura S (2006) Advances in treatment of epithelial ovarian cancer, Nagoya J. Med. Sci, 68:19 – 26.
7. Le T, Faught W, Hopkins L, (2008) The Importance of CA125 Normalization During Neoadjuvant Chemotherapy Followed by Planned Delayed Surgical Debulking in Patients With Epithelial Ovarian Cancer, J Obstet Gynaecol Can, 30(8): 665–670.
8. Muazzam IA, Rizvi F, Sidique MK, Syed AA, Azfar M, Zahid KF (2010) Neoadjuvant chemotherapy in ovarian cancer, Ann. Pak. Inst. Med. Sci. 6(2): 85-90.
9. Ramirez I, Chon HS, Apte SM (2011) The role of surgery in the management of epithelial ovarian cancer, Cancer Control, 8(18):22-30.
10. Robinson WR, Barnett G, MD, Rogers AS (2008) Neoadjuvant chemotherapy prior to intraperitoneal chemotherapy in women with advanced ovarian cancer, Community oncology, 5:376-380.
11. Schorge JO, Miller DS (2008) Epithelial ovarian cancer, Williams Gynecology, Chapter 35.
12. Vergote I, Trope CG, Amant F, Ehlen T, Reed NS, Casado A (2011) Neoadjuvant Chemotherapy Is the Better Treatment Option in Some Patients With Stage IIIc to IV Ovarian Cancer, Journal of Clinical oncology, 29(31):4076-4078.