

HIGH-DOSE CHEMOTHERAPY COMBINED WITH TARGETED THERAPY SUPPORTED BY PERIPHERAL AUTOLOGOUS STEM CELLS TRANSPLANTATION IN OVARIAN CANCER

Le Sy Phuong¹, Nguyen Duy Thang¹, Chau Khac Tu¹,
Bach Cam An¹, Hoang Bao Nhan¹, Pham Le Diem Hang¹,
Vo Thi Hoai Nam¹, Le Minh Toan¹, Ton That Minh Tri¹

ABSTRACT

Objectives: 1) To study effectiveness of highdose chemotherapy combined with targeted therapy in treatment of late stage and recurrent ovarian cancer. 2) To study effectiveness of peripheral autologous stem cells transplantation in supporting patients after highdose chemotherapy. **Materials:** 11 patients with late stage and recurrent ovarian cancer. **Methods:** a serial-case study. **Results:** Mean age of patients was 49.2 ± 5.2 , 4 patients had two cycles while 7 had one cycle. Mean time of completely normalization of white blood cells was 7.6 ± 0.8 days, platelet was 9.6 ± 2.2 days. Progressive free survival and overall survival were 19.3 ± 5.6 months and 31.0 ± 6.2 months, respectively. **Conclusions:** High-dose chemotherapy combined with targeted is safe and effective in treatment of late stage and recurrent ovarian cancer.

Keywords: high-dose chemotherapy, peripheral autologous stem cells transplatation, epithelial ovarian cancer.

I. INTRODUCTION

Epithelial ovarian cancer (EOC) is one of the most common malignancies in field of gynecological oncology. Patients are often diagnosed in late stage, in other hand, the disease develops rapidly, which makes it difficult to treat the disease and its prediction is often poor [5], [6].

Many researches were made to improve the outcomes of treatment, intraperineal chemotherapy [3], [10], targeted therapy [6], and high-dose chemotherapy, for examples, most of them did not find any improvement as expected, except high-dose chemotherapy [2], [5]. With high-dose chemotherapy, most patients have severe side-effects, or even death [2], [3]. Most common and dangerous side-effect is bone marrow suppression.

To resolve the problem, many treatment like white blood cell stimulation (filgastrim), blood transfusion, antibiotics, and peripheral autologous stem cell transplantation (PASCT) [3].

We performed this study with two objectives:

1. To study effectiveness of highdose chemotherapy combined with targeted therapy in treatment of late stage and recurrent ovarian cancer.
2. To study effectiveness of peripheral autologous stem cells transplantation in supporting patients after highdose chemotherapy.

II. MATERIALS AND METHOD

2.1. Materials

There were 11 patients with late stage and recurrent epithelial ovarian cancer, who were

1. Hue Central Hospital;

Corresponding author: Le Sy Phuong
Email: phuonglesy12@gmail.com
Received: 30/7/2016;
Revised: 9/8/2016 by Pham Nhu Hiep
Accepted: 19/8/2016

High-dose chemotherapy combined with targeted therapy supported by...

treated in Hue Central Hospital, from January 2013 to January 2015.

2.1.1. Included criteria

- FIGO staged III, IV or recurrent epithelial ovarian cancer.

- Age: 18-60.

- Agree to participate in research.

2.1.2. Excluded criteria

- Contraindication with chemotherapy or surgery.

- Concurrent other cancer.

- Do not follow treatment or follow up.

+ For recurrent patients:

- Information about previous treatment is not clear.

- Platinum resistant.

2.1.3. Method of selection:

 consecutive.

2.2. Methode of study

2.2.1. Study designed:

 a seri case study.

Diagnose and cytoreductive surgery

- Patients with primary treatment:

+ Perform sonography, CT scan, CA 125, HE 4.

+ Puncture the acites, with ultrasound guiding, for cytology examination.

+ Laparoscopy for surgical staging, ability of surgery, laparotomy if feasible.

- Recurrent patients: laparoscopy to diagnose and secondary surgery if possible.

Chemotherapy (usual dose)

- Neo-adjuvant chemotherapy for 3-6 cycles for patients who could not reach optimal cytoreductive surgery (Paxus PM 230 mg/m² + Carboplatin AUC 6), and perform interval surgery whenever possible.

- If patients could reach optimal cytoreductive surgery, perform laparotomy immediately and perform 6 cycles of adjuvant chemotherapy thereafter.

Harvesting peripheral autologous stem cell

- At Center of blood transfusion and heamatology.

- Stem cell is stored in -196^o C.

High-dose chemotherapy combined with targeted therapy: Paxus PM300mg/m²+Carboplatin (AUC = 12, 14, 16, 18) + Avastin 7,5mg/m².

Transplant peripheral autologous stem cell

- If bone marrow does not recover properly after 2 weeks, would be performed peripheral autologous stem cell transplantation.

- Follow up until bone marrow recovers properly.

Secondlook surgery: after 6-12 months.

III. RESULTS

Table 3.1: Characters of patients

Characters		(n=11)
	Recurrent	6
	Primary treatment	5
FIGO stage	IIIC	8
	IV	3
Response to first line chemotherapy	Complete	7
	Partial	4
Cytoreductive surgery	Optimal	7
	Suboptimal	4
Age at diagnose TB±SD (min, max)	49.2±5.2 (41-57)	

Table 3.2: Characters at high-dose hemotherapy

Characters		(n=11)
Number of high-dose chemotherapy	One cycle	7
	Two cyckes	4
Time intervals between cycles (days)	44.8±5.7 (38-50)	

Table 3.3: White blood cell, neutrophil, platelete during high-dose chemotherapy

Characters	Mean±SD	min	max	
Nadir of WBC ⁽¹⁾	1.0±0.3	0.5	1.8	x10 ⁹ /L
Nadir of NEU ⁽²⁾	0.3±0.05	0.2	0.4	x10 ⁹ /L

<i>Time period of decreasing WBC</i>	1st cycle	25.8±10.2	15	36	days
	2nd Cycle	24.0±9.1	15	34	days
<i>Nadir of PLT⁽³⁾</i>		15.5±6.4	2	19	x10 ⁹ /L
<i>Time period of decreasing PLT</i>	1st cycle	17.5±1.7	15	18	days
	2nd Cycle	24.0±3.5	21	28	days
<i>Intervals of normalization</i>	WBC	7.6±0.8	9	6	days
	PLT	9.6±2.2	13	7	days

(1): white blood cell, (2): neutrophil, (3): platelete

Table 3.4: Side-effects of high-dose chemotherapy

Grade	BMS ⁽⁴⁾	ELE ⁽⁵⁾	Kidneys			Vomitting, nausea
			failure	Hair-loss	Infection	
Grade 1	0	0	0	0	0	0
Grade 2	0	4	0	0	0	0
Grade 3	0	0	0	11	0	4
Grade 4	11	0	0	0	0	7
Total	11	4	0	11	0	11

(4): bone marrow suppression, (5): elevated liver enzymes.

Table 3.5: Outcomes of treatment

<i>Outcomes</i>	<i>n=11</i>
<i>Recurrence</i>	4
<i>Free disease survival</i>	6
<i>Death</i>	1
<i>Time of follow up (months)</i>	8.5±5.5 (3 - 21)
<i>PFS⁽⁶⁾ (months)</i>	19.3±5.6 (14 - 31)
<i>OS⁽⁷⁾ (months)</i>	31.0±6.2 (14 - 83)

(6): progressive free survival, (7): overall survival

IV. DISCUSSION

4.1. Characteristics of patients

Age at diagnose of patients in our study group was 49.2±5.2 years. Similar results was reported by authors, Patrick JS and colleagues, in a study of 421 patients who were treated by high-dose chemotherapy supported by autologous stem cell transplantation, reported mean age of patients was 48 (18-65) years [1].

There were 7/11 patients who reached optimal cytoreductive surgery, means size of remaining tumor was less than 1 cm. Some authors used 0.5 cm or even 2 cm as their target of optimal surgery [6].

Griffiths is the first author who studied the role of cytoreductive surgery in patients with late stage of EOC. He divided patients into two groups based on size of remaining tumor, patients with less than 1cm and others with larger than 1 cm. He found out that patients with less than 1 cm of remaining tumor had longer overall servival (40-50 vs 25-38 months). He concluded that, remaining tumor after surgery is the most important factor in predicting the survival of patients with late stage of EOC [6], [9].

4.2. High-dose chemotherapy and side-effects

High-dose chemotherapy is defined when the dose of chemo-agents is three times higher than

High-dose chemotherapy combined with targeted therapy supported by...

usual [2], [12]. We used carboplatin AUC 12 at first cycle and then AUC 14, 16, 18 if patients had good tolerance with regimen. According to Doroshow JH and Synold T, when dose of platinum is increased, effect of cell suppression will increase rapidly [7]. And with newer generation of paclitaxel, when higher dose is indicated, cell killing effect is increased [5].

Many researches reported good outcomes when treated patients by high-dose chemotherapy [2]. Legros M and his colleagues, when followed up for 81.5 months in patients with high-dose chemotherapy, the rate of five-year-survival was 59.5%, and rate of patients with progressive free survival after five years was 23.6%, he reported only one patient died during treatment because of acute heart failure [11]. Moebus V, with 76 patients with the same regimen, but followed up in only 38 months, found that patients with high-dose chemotherapy had longer survival than patients without high-dose (29.6 vs 20.5 months), side-effects, however, were more common [9], [13].

Total number of chemotherapy in our study was 15/11 cycles, 4 patients were performed two cycles of high-dose chemotherapy. The four patients did not have any severe side-effects during previous cycle. A study of Bengala C and his colleagues in 91 patients with EOC, who were treated by high-dose chemotherapy supported by autologous stem cell showed that, found 26 of them had more than two cycles of high-dose [1].

Study of Salerno MG with 55 patients, who were treated by high-dose chemotherapy because of EOC found that 100% of patients had grade 4 bone marrow suppression, other most common side effects was nausea and vomiting [15]. In our group, 100% of patients had bone marrow suppression, nausea and vomiting, 4 patients had elevated liver enzymes, while no patient had abnormal kidneys function.

Side-effects in bone marrow are common and severe, or even death when using high-dose chemotherapy [2], [12]. To resolve these side-effects, clinical physician must have good knowledge, experiences and the most important is, that it must be treated by many expertises. In our study, we

performed high-dose treatment in the Center of Blood transfusion and Hematology, where blood and blood products are always be ready to be used.

100% of patients had neutropenia. When WBC is less than $3 \times 10^9/L$ and/or NEU less than $1 \times 10^9/L$, risk of infection is very high. And when this happens, we indicated filgrastim, blood or blood products transfusion. We only perform PASCT only when bone marrow dose not recovere properly after one week of supporting treatment.

4.3. Targeted therapy in treatment of EOC

The duplication, penetration and metastasis of cancer cells always need vascularisation, in which Vascular Endothelium Growth Factor (VEGF) and its receptors are the most important factors. Study of Paley and colleagues showed that level of VEGF receptor is important to predict the overall survival of patients with EOC. And for late stage disease, high level of VEGF is a sign of progressive in near future [14].

Study GOG 218 with 1873 patients, who were treated by regimen of paclitaxel-carboplatin with or without bevacizumab found that, the bevacizumab arm had statistical longer PFS. Similar result was also found in studies ICON-7 and GOG 213 [6].

The application of targeted therapy may lead to good results, but also side-effects, especially when combined with high-dose chemotherapy [14]. Our study did not find any case of intestine perforation or hypertension.

4.4. Outcomes of treatment

Until now, there were four patients had recurrence, one of them was detected during second-look laparoscopy. She had all elevated markers (CA 125, HE 4). This patient had FIGO staged IV at diagnosing, liver and lung metastasis, failed of cytoreductive surgery after three cycles of neo-adjuvant chemotherapy, she only reached sub-optimal cytoreductive surgery after six cycles of chemotherapy.

PFS in our group was 19.3 ± 5.6 months (95%CI: 15.5 - 23.0), OS was 31.0 ± 6.2 months (95%CI: 17.1 - 44.9). These outcomes are promised for patients with late staged EOC.

In 2003, Parmar in a study with recurrence EOC,

who were treated by regimen of platinum-paclitaxel, reported that PSF and OS were only 13 months and 29 months, respectively [8]. And even worse outcomes when they were treated by other regimens [6], [8]. Chan S and colleagues also reported that the mean period of survival after recurrence was only 12 months [4].

V. CONCLUSION

- High-dose chemotherapy is safe and effective in treatment of late stage or recurrent EOC.
- Peripheral autologous stem cell transplantation is an effective procedure when patients have severe bone marrow suppression.

REFERENCES

1. Bengala C, Guarneri V, Ledermann J, Rosti G, Wandt H, et al (2005) High-dose chemotherapy with autologous haemopoietic support for advanced ovarian cancer in first complete remission: retrospective analysis from the Solid Tumour Registry of the European Group for Blood and Marrow Transplantation (EBMT), *Bone Marrow Transplantation*, 36: 25-31.
2. Bensinger WI (2004) High-dose Preparatory Regimens, *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*, 4th Edition, 316-332.
3. Castonguay V, Wilson MK, Diaz-Padilla ID, Wang L, Oza AM (2015) Estimation of Expectedness: Predictive Accuracy of Standard Therapy Outcomes in Randomized Phase 3 Studies in Epithelial Ovarian Cancer, *Cancer*, 121: 413-422.
4. Chan S, Griffin M, Stewarty J, Gregoryzx K, Hughesk A, et al (2007) Modern Chemotherapy Management of Recurrent Ovarian Cancer: A Multicentre Study, *Clinical Oncology* 19: 129-134.
5. Chase DM, Gibson SJ, Monk BJ, Tewari KS (2013) Updates on Anti-Cancer Therapy in Ovarian Cancer, *Chemotherapy*, 2(1): 109-117.
6. Chobanian N, Dietrich CS (2008) Ovarian cancer, *Surg Clin North Am*, 88(2): 285-299.
7. Doroshow JH, Synold T (2007) Pharmacologic Basis for High-Dose Chemotherapy, *Thomas' Hematopoietic Cell Transplantation*, Third Edition, 130-157.
8. Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R (2015) Optimal primary surgical treatment for advanced epithelial ovarian cancer (Review), *Cochrane Database of Systematic Reviews*, CD007565.
9. Gabra H, Blagden S (2012) Epithelial Ovarian Cancer, *Dewhurst's Textbook of Obstetrics & Gynaecology*, Eighth Edition, 760-775.
10. Jaaback K, Johnson N, Lawrie TA (2016) Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer (Review), *Cochrane Database of Systematic Reviews*, CD005340.
11. Legros M, Dauplat J, Fleury J et al (1997) High-Dose Chemotherapy With Hematopoietic Rescue in Patients With Stage III to IV Ovarian Cancer: Long-Term Results, *J Clin Oncol* 15: 1302-1308.
12. Levin KL, Hryniuk WM (1987) Dose Intensity Analysis of Chemotherapy Regimens in Ovarian Carcinoma, *J Clin Oncol*, 5: 756-767.
13. Möbus V, Wandt H, Frickhofen N, Bengala C, Champion K, et al (2007) Phase III Trial of High-Dose Sequential Chemotherapy With Peripheral Blood Stem Cell Support Compared With Standard Dose Chemotherapy for First-Line Treatment of Advanced Ovarian Cancer: Intergroup Trial of the AGO-Ovar/AIO and EBMT, *J Clin Oncol*, 25: 4187-4193.
14. Rauh-Hain JA, Del Carmen MG (2013) Recurrent Epithelial Ovarian Cancer: An Update on Treatment, *Cancer Network*, 1-10.
15. Salerno MG, Ferrandina G, Greggi S, Pierelli L, Menichella G, et al (2001) High-dose chemotherapy as a consolidation approach in advanced ovarian cancer: long-term results, *Bone Marrow Transplantation*, 27: 1017-1025.