REGIMENS OF EM/CO IN TREATMENT OF HISH-RISK GESTATIONAL TROPHOBLASTIC NEOPLASMS

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ABSTRACT

Objectves: *1) To study signs and symptom of high risk gestational trophoblastic neoplasms 2) role of multi-agents chemotherapy in treatment of high-risk patients.*

Methods: *A perspective study.*

Materials: *25 patients who had high-risk gestational trophoblastic neoplasms were treated in department of Obstetrics and Gynecology, Hue central hospital.*

Results: *Mean age of patients was 28.3±7.5, risk-score was 8.6±0.8, number of cycles of chemotherapy was 8.3±3.4, rate of success of the regimen was 96%, only 28% of patients had total hysterectomy, 100% of patients had side-effects, of that the most common was hair-loss. 12 pateints were pregnant after treatment, 41.7% of them reached term pregnancy.*

Conclusion: *Multi-agents chemotherapy with EM/CO regimen is safe and effective in treatment of high-risk gestaional trophoblastic neopalsia.*

Key words: *High-risk gestational trophoblastic neoplasms, EM/CO, pregnancy.*

I. INTRODUCTION

Gestational trophoblastic disease related to pregnancy, can be benign or malignant. These benign forms include partial and complete mole, while gestational trophoblastic neoplasms (GTN) make group of malignancies, those are often consequences of a mole, or even a miscarriage, abortion, malformation or term pregnancy.

GTN are one of the rare human malignancies that are highly curable with chemotherapy even with widespread metastasis. Treatment for GTN, which was recommended by World Health Organization (WHO) in 2002, includes single-, multi-agents chemotherapy, operation, with decision for specific regimen is based on stage and risk-score when diagnosed.

Being treated by recommended regimens, rate of response of high-risk patients is up to 80% with first-line chemotherapy, and more than 90% with second or third line chemotherapy, ever after failed with first-line. Multi-agents chemotherapy is promising for young patients with high-risk GTN when they want to preserve fertility.

The most common and effective multi-agents chemotherapy is EMA/CO (Etoposide, Methotrexate, Actinomycine D/ Cyclophosphamide, Oncovorin). But in clinical practice, we have not had Actinomycine D for a long time: forever but patients must be treated. As a result, we tried to use this regimen without Actinomycine D, regimen of EM/CO (Etoposide, Methotrexate / Cyclophosphamide, Oncovorin), for patients with high-risk GTN in a study with two objectives:

- *To study signs and symptom of high-risk GTN in our department.*

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• *To study effects of EM/CO in treatment of high-risk GTN.*

II. METHODS AND MATERIALS

2.1. Materials

Including criteria

• Patients with GTN.

• Risk-score is higher than 7.

Excluding criteria

• Failure of follow up.

• Phantom βhCG.

2.2. Method: A perspective study.

Estimation of sample-size

• Most important criteria: rate of response of high-risk GTN to multi-agents chemotherapy: 70%.

• α= 0.05; β= 0.1, power= 0.9, m= 0.2.

• Sample size was estimated: $n \geq (1.96/0.2)^2 0.7x0.3$; means: $n \geq 21$

Steps of study

- Estimate risk-score and staging of the disease based on recommendation of FIGO 2002.

- Treat patients with regimens of EM/CO until βhCG is negative in three consecutive weeks.

Before every cycle of chemotherapy, blood count, liver and kidneys function, urine analysis, lung X ray, abdominal sonography, βhCG level test were performed performed. βhCG level of less than 3 mUI/mL is considered negative.

Treatment is considered failure when

• Treatment must be stopped because of complications.

• No response to the regimen.

III. RESULTS

Table 3.1: Characteristics of patients

Characters		n	%
Age (years)		28.3±7.5	
Risk-score		8.6±0.8	
FIGO stage	I	12	48.0
	II	7	28.0
	III	5	20.0
	IV	1	4.0
Antecedent pregnancy	Time intervals	11.3±7.2 months	
	Miscarriage/Abortion	10	40.0
	Mole	14	56.0
	Preterm birth	1	4.0
	Term birth	0	0
Location of metastasis	Lung	8	32.0
	Liver	0	0
	Spleen	0	0
	Brain	1	4.0
	Reproductive system	22	88.0
Previous chemotherapy	One regimen	13	52.0
	Two regimens	3	12.0

Table 3.2: Characteristics of treatment

Characters		n	%
Responsed to first-line chemotherapy		22	88.0
Responsed to second-line chemotherapy		2	8.0
Death		1	4.0
Cycles of chemotherapy		8.3±3.4	
Total hysterectomy		7	28.0
Complications	Bleeding	1	4.0
	Hair-loss	18	72.0
	Digestive system ulcer	11	44.0
	Marrow suppression	3	12.0
	Increase liver enzym	6	24.0

Table 3.3: Outcomes of treament

Outcomes		n	%
Pregnancies after treatment		12	48.0
Recurrence		1	4.0
Time intervals (months)		14.5±3.2	
Outcome of pregnacies after treatment	Miscarriage/Abortion	5	41.7
	Malformation	1	8.3
	Preterm birth	1	8.3
	Term birth	5	41.7

IV. DISCUSSION

According to FIGO recommendation, age is one of factors to estimate risk-score for patients with GTN. Mean age in this study group was 28.3±7.5 years. Similar result was reported by some groups of authors. A study by Priyanka KR in India with 25 high-risk patients found out that mean age was 28.3 years. This study lasted for two-years (from 2012 to 2014), and only patients who were treated with EMA/CO regimen were included [19]. Another study by Hemida REA et al in patients who had resistant GTN also found mean age of them was 28.7 (17-50) years old [8].

Anjana C et al when devided patients with high-risk GTN into two groups, under and above 40 years old, they reported that 40 of 48 patients in their group were 40 or lesser, while only 8 of them were above 40 [1]. Studies by Maria A et al, Dobson LS also found that most of high-risk GTN patients were younger than 40 years old [3], [14]. Although old maternity is a high-risk factor for GTN, but women do not often want to get pregnant when they reach 4th decade of their life, this makes lower rate of this group of age in patients with high-risk GTN.

Risk-score in our study group was 8.6±0.8. High-risk GTN was determined when patient had FIGO stage of I, II, III with risk-score more than 7, or FIGO stage of IV [17]. Priyanka KR, in a study with high-risk patients who treated by EMA/CO regimen, reported that most of them had risk-score less than 10 [19].

Application of risk-score in classification of GTN is still not uniformed. According to recommendation of FIGO in 2015, this group of diseases is divided

into low-risk and high-risk, which was based on FIGO staged and risk-score [16], [17]. However, some author divided GTN into low, medium and high-risk patients, and based merely on risk-score [19], [20]. This makes differences from center to center in the treatment of these diseases.

FIGO stage is also an important predictive factor of GTN, and its combination with risk-score should be used to predict in all patients with GTN [16], [17]. In our study group, only patients with high-risk disease were included, they also had late stage, rate of FIGO stage III and IV were 20% and 4%, respectively. A study with all stage patients reported that rate of FIGO stage III and IV were 9.7% and 11.3%, respectively [14].

Antecedent pregnancy is also important. 56% of patients in our study had previous mole pregnancy, 40% of them had miscarriage or abortion. GTN often occurs after a mole pregnancy, although it can manifest from any type of antecedent pregnancy [7], that is why authors recommended that, on all kinds of pregnancy should be performed histology examination when terminated [17], [18], [20].

In our group, only 8 patients had metastasis, the rate of lung and brain metastasis was 32% and 4%, respectively. Lung is the most common site of metastasis in patients with GTN [2], [20]. Maria A reported that rate of lung metastasis was as high as 80%. Study by Hemida RAE showed that the rate of lung metastasis was also 75% [14]. Many authors also found the similar rate [9]; Thus, they concluded that, for all patients with GTN, thorax X ray should be performed rutinely [5], [18], [20].

Other site of metastasis is less common than lung, of those, colon is very rare site. Ghaemmaghami F published one case of this site of metastasis, and she was succsessfully treated by surgery and chemotherapy with regimen of EMA/EP [6].

Number of chemotherapy cycles in our study was 8.3±3.4 for each patient. There is no limit in the number of chemotherapy in patients of GTN, the regimen is applied untill negative βhCG level for three consecutive weeks [18], [20].

GTN are the only group of malignancies which are curable even when it is in metastasis phase [4], [8], [20]. Because trophoblastic cells are very sensitive to chemotherapy agents [16], [20]. Only when metastasis come to brain, where drugs can not reach high level, the role of radiation and surgery in these circumstances are limited, treatments are difficult, most of patients with brain metastasis had poor prognostic [9], [10], [13].

Rate of response to first-line chemotherapy in our study was 88%, while to second-line was 8%. Maria A reported a different result when rate of response of patients with high-risk GTN was only 56% (14/25 of patients), however, he divided his patients into low, medium and high-risk group based on risk-score [14], this is difference between the two studies. Moreover, he also indicated procedures like curretage, hyterectomy much less widely than ours. Rate of hyterectomy in study of Maria A was 11.3% (7/62), when this rate in our study was 28%.

WHO recommended that, total hysterectomy should not be perform routinely, and when necessary, it should be delayed until two cycles of chemotherapy had already been taken [4], [9]. Because trophoblastic tumors are perfused by fragile vessels, metastases are often hemorrhagic, and disease is easy to metastase through procedures [18], [20]. Hysterectomy is performed only when patient has severve hemorrage, while preservation of uterus does not effect the treatment [12].

In our study, when being applied with regimen of EM/CO, all of patients had side-effects. Hair-loss was the most common, and others like digestive system ulcer, elevated liver enzyms, marrow suppressive were also met. These are very common for patients with multi-agents chemotherapy [12], [18], [19].

Rate of infertility after treatment in women with GTN is 7%, rate of recurrence is 1/1000-1/100 higher than women in reproductive age [15], a multi-center study with 2,657 patients who had previous chemotherapy, most of them had successful pregnancies after treatment, 76.7% of them reached term pregnancy, only 5.3 preterm birth, 1.3% had still birth, and 14.2% had abortion, only 1.8% of babies had malformation [16]

Question is, how long after chemotherapy patients could get pregnant. Most authors recommended that, patients should wait untill two years after the last chemotherapy [9], [11], there is no strong evidence, however, for this wait. More recently, in 2015, FIGO advised that pregnacy could wait only for 12 months, but again, the level of this recommendation is only C [17].

In this study, there were 12 women who get pregnant after treatment of GTN. We only observed and reported without further attention to other agents which could affect ability to become pregnant as well as fetal growth process due to inadequacy in sample size. Of those, 41.7% reached term pregnancies.

There was one patient who had recurrnce. Most of perspective studies found that, rate of recurrent is 5% in low-risk, and 20% in high-risk patients [9], [11], [15].

V. CONCLUSION

Multi-agents chemotherapy with regimen of EM/CO is safe and effective for patients with high-risk GTN. Total hysterectomy is not common, and with out hysterectomy, women could have a successful pregnancy after treatment of GTN.

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