Comparison of the clinical response of high-risk and ultra high-risk gestational trophoblastic neoplasia to etoposide-methotrexate-actinomycin-cyclosphosphamide-vincristine: Experience at the Philippine General Hospital

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ABSTRACT

Background: Recent studies have shown poorer outcomes for patients with prognostic score above 12. Authors have proposed categorizing these patients as ultra high-risk to emphasize the need for a different treatment regimen.

Objectives: This study was conducted to compare the clinical response of high-risk and ultra high-risk Gestational Trophoblastic Neoplasia (GTN) patients who were managed at the Philippine General Hospital, from January 1, 2010 to December 31, 2015, after receiving the EMACO regimen as first line treatment.

Methods: All patients diagnosed with metastatic high-risk GTN who were managed at the Philippine General Hospital from January 1, 2010 to December 31, 2015 and given the EMACO regimen as first-line treatment were included in the study. Patients were divided into high-risk disease or patients with a WHO prognostic score of 7-11 and ultra high-risk disease or patients with WHO prognostic score of 12 and above. Using the Z-test on two proportion, treatment outcome between the two groups were compared.

Results: A total of 57 patients diagnosed with metastatic high-risk GTN were included in the study. Of these, 35 or 61% were classified as high-risk while 22 or 39% were ultra high-risk. The primary remission rate of the high-risk group was 89% compared to 77% for the ultra high-risk group. The difference was not statistically significant (p=0.2542). Out of the 57 patients included in the study, 48 patients achieved remission after being treated with EMACO. An additional 4 patients achieved remission after being shifted to EPEMA due to resistance to the first line agent. All patients were alive after one year of follow-up, giving a one-year survival rate of 91.2%.

Conclusion: The result of this study showed a relatively higher remission rate for high-risk (89%) than ultra high-risk GTN (77%) with EMACO as first line chemotherapy regimen, but statistical analysis revealed no significant difference. This finding suggests that EMACO may still be used as first line regimen for ultra high-risk GTN to attain remission.

Keywords: gestational trophoblastic neoplasia, high-risk, ultra high-risk, EMACO

INTRODUCTION

The diagnosis of Gestational Trophoblastic Neoplasia (GTN) has become less confusing over the years due to the current guidelines that have put clear borders on how to appropriately classify patients. These guidelines were formulated not only to establish diagnosis but more importantly to shed some light on the management of this aggressive but very curable malignant neoplasm.

GTN is a clinical term that denotes a disease state in which there is physical, radiologic and/or biochemical evidence of invasive mole, choriocarcinoma, placental site trophoblastic tumor or epithelioid trophoblastic tumor.[1] It is the malignant component of the spectrum of gestational trophoblastic diseases.

Like any other malignant neoplasm, an accurate staging and classification for GTN is essential in assessing the prognosis and formulating an individualized approach to treatment of patients. As such, in 2000, the International Federation of Gynecology and Obstetrics (FIGO) following the recommendation of its cancer committee, ratified a revised classification system for GTN. What was promulgated was a combined FIGO anatomic staging system (Table 1) with a revised World Health Organization (WHO) prognostic scoring system (Table 2).[2,3] The FIGO anatomic staging system defines the extent of the disease while the WHO prognostic scoring

system predicts the possible resistance of the tumor to single-agent chemotherapy.[4] In the WHO prognostic scoring system, a score below 7 classifies the patient as being low-risk, while patients with a score of 7 or more are considered high-risk.

The current recommendation for non-metastatic and low-risk metastatic disease is single-agent chemotherapy either with Methotrexate or Actinomycin. On the other hand, combination chemotherapy is given to metastatic high-risk patients with or without adjunctive treatment. Currently, the EMACO regimen, consisting of Etoposide Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine, is the most commonly used protocol given its high remission rate and tolerable toxicity profile. The primary remission rate of high-risk GTN patients treated with EMACO, as reported by a local study done at the Philippine General Hospital by Cagayan et. al, was 72% with a sustained remission rate of 80% and a five-year survival rate of 86%.[5,6] In a review by Deng et.al in 2013, EMACO was also reported to be the preferred and most widely used first line combination therapy.[7]

Recently, several authors have reported poorer outcomes for patients with a WHO prognostic score of 12 or higher. They proposed that these patients be classified as having ultra high-risk disease to emphasize the difference in prognosis and treatment. Ultra high-risk GTN would refer to any presentation of GTN that might be associated with early death within weeks of starting chemotherapy or poor long term survival. Features of ultra high-risk GTN are indicative of high disease burden at presentation including a FIGO prognostic score of more than 12.[8]

Kong et al in 2017 documented that 65.7% of the ultra high-risk patients achieved complete remission, but, 15.9% of them eventually relapsed.[9] Bolze et al on the other hand, concluded that GTN patients with FIGO score of ≥13 had a higher 5-year mortality rate (38.4%) than that of the high-risk patients (12%).[10] In the same study, ultra high-risk patients were also found to be at higher risk for early death than the high-risk GTN patients.[10] In the Philippines, no study has been done to compare the clinical response of ultra high-risk and high-risk patients to EMACO as first line treatment.

Table 1. FIGO Staging for Gestational Trophoblastic Neoplasia

Stage	Description
I	Disease confined to the uterus
II	Disease extending into the pelvis
III	Disease spread to lungs with or without known genital involvement
IV	All other metastatic sites (liver, kidney, spleen, brain)

OBJECTIVES

The present study was therefore conducted to compare the clinical response of high-risk and ultra high-risk GTN patients after receiving the EMACO regimen as first line treatment among patients who were managed at the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology, Philippine General Hospital, from January 1, 2010 to December 31, 2015.

Specific objectives

1. To determine the over-all remission rate following treatment with EMACO as first line chemotherapy agent.
2. To compare the primary remission rates of high-risk patients (WHO score of 7-11) versus ultra high-risk patients (WHO score of 12 and above) to the EMACO regimen as first line treatment.
3. To determine the one-year survival rate of high-risk patients versus ultra high-risk patients

Table 2. WHO Prognostic Scoring for Gestational Trophoblastic Neoplasia

	0	1	2	4
Age (in years)	< 40	≥ 40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval from antecedent pregnancy to chemotherapy (in months)	< 4	4 - 6	7-12	> 12
hCG (mIU/ml)	$< 10^3$	10^3 - 10^4	10^4 - 10^5	$> 10^5$
Number of metastases	0	1 - 4	5 - 8	> 8
Site of metastases	Lung	Spleen/ Kidney	Gastrointestinal tract	Brain/ Liver
Largest tumour mass (in cm)		3 - 5	> 5	
Previous chemotherapy			Single-agent	Combination

MATERIALS AND METHODS

Study Design:

This is a retrospective cohort study.

Patient population:

All patients diagnosed with metastatic high-risk GTN who were managed at the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology of the Philippine General Hospital from January 1, 2010 to December 31, 2015 and were given the EMACO regimen as first line treatment were included in the study. Patients were then divided into two groups: Group 1 included those with high-risk disease or patients with a WHO prognostic score of 7-11 while group 2 included those with ultra high-risk disease or patients with WHO prognostic score of 12 and above. Patients who were treated with other regimens aside from EMACO as first line treatment, as well as those with incomplete treatment due to non-compliance, and those diagnosed to have placental site trophoblastic tumor or epithelioid trophoblastic tumor were excluded from the study.

Description of the study procedure:

The database of the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology of the Philippine General Hospital from January 1, 2010 to December 31, 2015 were reviewed to identify patients who were eligible for inclusion into the study. Case records of the patients were then retrieved and reviewed. Data regarding the patients' demographic and disease characteristics such as the stage, prognostic score, pretreatment serum BhCG, site and extent of metastases were recorded in a patient data extraction form. Clinical response to treatment was likewise recorded as either remission, shift to a second line agent or death.

Description of outcome measurements:

This study determined the effectiveness of the EMACO regimen as first line treatment for high-risk and ultra high-risk patients based on the following terms:

1. Over-all primary remission rate refers to the number of patients who achieved remission after receiving EMACO regimen over the total number of patients included in the study. In cases of GTN, complete response or remission is defined as three consecutive normal BhCG determinations, with normal value being 0-5 mIU/mL. Persistent radiological abnormalities during or after treatment are not considered evidence of disease as long as the BhCG concentration is normal.
2. Primary remission rate for high-risk patients was computed as the number of patients with WHO prognostic score of 7-11 who achieved remission after receiving EMACO regimen over the total number of high-risk patients.
3. Primary remission rate for ultra high-risk patients was computed as patients with WHO prognostic score of 12 and above who achieved remission after receiving EMACO regimen over the total number of ultra high-risk patients.
4. One year survival rate was computed as the percentage of high-risk and ultra high-risk patients who were treated with EMACO as first line treatment who survived and lived for 1 year after the start of treatment.

Data Analysis

Descriptive measures such as frequency, percentage, mean, median, minimum and maximum were used to describe the profile of the respondents. Chi-square test of independence was used to determine significant difference in the distribution of patients according to stages, pretreatment BhCG level and site of metastasis. Z-test of Two Proportions was applied in determining difference between the remission rates of high-risk and ultra high-risk patients. The software Simplified Statistics for Researchers (SSR Version 1.0) was used to obtain necessary measures for data analysis.

RESULTS

A total of 57 patients diagnosed with metastatic high-risk GTN who were managed at the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology of the Philippine General Hospital from January 1, 2010 to December 31, 2015 and were given EMACO regimen as first-line treatment were included in the study. Of these, 35 or 61% were high-risk patients while 22 or 39% were ultra high-risk. Table 3 shows the summary of patients included in the study.

Clinical profile

Majority of the high-risk patients had an age within the 26-34 year-old bracket, constituting 38.46%. On the other hand, 41.6% of patients in the ultra high-risk group were in the older age range of 35-45 years. This data suggests that patients with an older age tend to have a higher prognostic score at presentation and were likely to be classified as ultra high-risk. In terms of gravidity, most of the high-risk patients had one antecedent pregnancy (31.44%) while most of the ultrahigh-risk patients had at least 4 prior pregnancies.

In both groups, most patients had a serum BhCG in the range of 100,000-500,000 mIU/ml. The average

pretreatment BhCG level of the high-risk GTN patients was 382,603 mIU/ml. The lowest BHCG level was 5,809 mIU/ml and the highest was 1,000,000 mIU/ml. The average serum BhCG for the ultra high-risk group was 525,847 mIU/ml with a range of 1,244 mIU/ml to 2,291,033 mIU/ml. Although the level of BhCG among ultra high-risk patients was numerically higher than the high-risk group, there was no statistically significant difference noted.

The lungs were the most common site of metastasis for both high-risk and ultra high-risk patients. As such, majority of the patients were classified as stage III disease. Other metastatic sites such as brain, liver and gastrointestinal tract were also recorded and were found to be higher in number in ultra high-risk patients (27%) as compared to high-risk GTN patients (5.9%). Table 4 summarizes the demographic and clinical characteristics of the patients included in the study.

Remission Rate

Out of the 57 patients included in the study, 48 went into remission after receiving EMACO as first line agent, giving an over-all primary remission rate of 84%. Thirty-one out of 35 (89%) patients in Group 1 or high-risk group achieved remission. Two (6%) patients died while on EMACO chemotherapy and another two patients (6%) were shifted to second line chemotherapy in the form of EP-EMA, which consists of Etoposide, Cisplatin, Methotrexate and Actinomycin D, because of chemoresistance to EMACO. Of the two patients who were shifted to EP-EMA, one achieved remission

Table 3. Summary of patients who met the inclusion criteria for high-risk and ultrahigh risk

Year	Total Number of Patients	High-Risk		Ultra High-Risk	
		Frequency	Percentage	Frequency	Percentage
2010	15	7	46.6%	8	53.3%
2011	4	4	100.0%	0	0.0%
2012	9	6	66.6%	3	33.3%
2013	11	7	63.6%	4	36.4%
2014	8	8	100.0%	0	0.0%
2015	10	3	30.0%	7	70.0%
Total	57	35	61.4%	22	38.6%

Table 4. Demographic and clinical characteristics of patients

PARAMETERS	HIGH-RISK PATIENTS (n=22)		ULTRA HIGH-RISK PATIENTS (n=22)	
	Frequency	%	Frequency	%
STAGE				
Stage I	0	0	0	0
Stage II	1	2.6	2	9.0
Stage III	32	91.5	14	63.6
Stage IV	2	5.9	6	27.0
PRE-TREATMENT BHCG				
1,000 – < 10,000	2	5.9	4	18.0
10,000 – 100,000	8	22.8	2	9.0
100,000 – < 500,000	17	48.6	9	41.0
> 500,000	8	22.8	7	32.0
SITE OF METASTASIS				
Vagina/parametria	0	0	1	4.5
Lungs	32	91.5	15	68.0
Brain / liver / GI	2	5.9	6	27.0
Others (Bladder)	1	2.6	0	0

while the other one died. For group 2 or the ultra high-risk group, 17 out of 22 patients or 77% attained remission with the first line chemotherapy (EMACO). Two (9%) patients died while on chemotherapy while three (14%) patients were shifted to EP-EMA because of chemoresistance, all of whom eventually achieved remission. The primary remission rate of the high-risk and ultra high-risk groups were not statistically significantly different (p=0.2542).

One-Year Survival Rate

Out of the 57 patients included in the study, 48 patients achieved remission after being treated with EMACO. An additional 4 patients achieved remission after being shifted to EPEMA due to resistance to the first line agent. All patients were alive after one year of follow-up, giving a one-year survival rate of 91.2%.

DISCUSSION

Gestational trophoblastic neoplasia represents less than 1% of gynecologic malignancies. It has a high cure rate if treated early in accordance with well-established guidelines.[11] Recently, studies have reported a remission rate of 100% for low risk non-metastatic GTN and more than 80% for metastatic high risk GTN.[12-14] Such high remission rates may be attributed to three factors, namely (1) tumor is highly chemosensitive, (2) availability of assays that reliably measure BhCG levels, and (3) presence of a risk-based classification system that guides clinicians on the proper chemotherapeutic agent to administer to patients.[1,15-17] This classification system, promulgated in 2000 by the FIGO, combines the FIGO staging system with the revised WHO prognostic scoring system, which stratifies patients as having either low-risk or high-risk disease. Patients with low-risk disease are advised to receive single agent chemotherapy as first line agent in the form of either Methotrexate or Actinomycin. On the other hand, metastatic high-risk patients must receive multi-agent chemotherapy initially in order to improve survival. Among the regimens that have been formulated, the EMACO regimen, is the most widely used, not only because of its high efficacy, but also because of the tolerable toxicities associated with its use.[7] Similar to most institutions worldwide, the Division of Trophoblastic Diseases of the Department of Obstetrics and Gynecology of the Philippine General Hospital administers the EMACO regimen as the first line chemotherapeutic regimen to all metastatic, high-risk GTN patients.

In this study, a total of 57 patients received EMACO as first line treatment for a diagnosis of metastatic high-risk GTN. Primary remission rate was 84% (48 out of 57 patients), which was comparable to the figures reported by Newlands (82%) and Cagayan (80%).[17,18] Five patients developed chemoresistance and were shifted to EP-EMA. Four patients eventually achieved remission after receiving second line chemotherapy, giving a survival rate of 91.2%. Such figures substantiate the high cure rate achieved among patients with GTN provided that chemotherapy is started soon after diagnosis and given on schedule.

Recently, authors have reported a poorer outcome for patients with a WHO prognostic score of 12 or more.[10,19] These recent reports have led some experts to propose the addition of an ultra high-risk classification for patients with a score of at least 12 in the WHO prognostic scoring system to emphasize the difference in the prognosis and the probable need for a different first line chemotherapeutic agent.

Shen et al in 2018 reported that the remission rate for ultra high-risk GTN patients treated with EMACO as first line treatment was 67% (16 out of 24 patients).[20] Kong, on the other hand, reported a remission rate of 65.7%.[9] The site of metastases of those patients who developed resistance were the lungs and gastrointestinal tract. The BhCG level was <500,000 mIU/mL. Boltze et al at the French Center for Trophoblastic Diseases showed a 5-year mortality rate of 38.4% among GTN patients with a score of more than 13 compared to only 12% among those with lower prognostic scores. Those who had a score of more than 13 accounted for 52% of deaths in their entire cohort.

In order to improve survival in this subset of patients, experts have recommended variations in the chemotherapeutic regimen that should be given. Some suggest combination chemotherapy in the form of EP-EMA as the primary treatment for ultra high-risk patients. Such was mentioned in the article by Cyriac et.al in 2011, wherein 66.7% of patients had a complete clinical response with the administration of EP-EMA, while progressive disease occurred in 33.3% of patients treated. None of the patients relapsed. This translated to an overall survival rate of 66.7% in the primary setting.[21] In 2012, Osborne et al reported that the use of EMACO regimen resulted in a lower remission rate compared to EP-EMA when it was administered as first line treatment for ultra high-risk patients.[22]

Other experts have proposed the administration of induction chemotherapy, which consists of Etoposide and Cisplatin given on days 1 and 2 of the regimen and repeated weekly for 1-3 weeks before starting standard chemotherapy. This practice was shown to be beneficial for ultra high-risk patients with extensive lung metastasis and/or brain or liver involvement.[23] However, in a recent multi-study analysis done by Li et al, which included 17

studies encompassing 256 patients with FIGO score of at least 12, EMACO, EP-EMA, and FAEV (composed of floxuridine, actinomycin-D, etoposide and vincristine) yielded comparable complete response rates in the first line setting.[24]

In the current study, remission rate of patients with a prognostic score of 7-11 (high-risk disease) was compared to the remission of patients with a score of 12 or more (ultra high-risk disease). Results showed that the remission rate of ultra high-risk patients to EMACO was 77% (17 out of 22), which was higher than the figures reported by other authors. Moreover, the remission rate was not significantly different from the remission rate observed among patients with high-risk disease.

CONCLUSION

The result of this study showed a relatively higher remission rate for high-risk (89%) than ultra high-risk GTN (77%) with EMACO as first line chemotherapy regimen, but statistical analysis revealed no significant difference. This finding suggests that EMACO remains to be a good first line chemotherapy for both high-risk and ultra high-risk GTN to attain remission.

Chemoresistance was observed in both the high-risk (6%) and ultra high-risk group (14%) and majority of the patients subsequently attained remission with salvage chemotherapy in the form of EP-EMA. In our institution, EP-EMA has been used as the second line of treatment for high-risk and ultra high-risk GTN. It has never been used as a first line treatment in our institution due to the good response to EMACO even among those with ultra high-risk disease.

This study also showed that regardless of the pretreatment BhCG level, site of metastasis and stage of both groups, EMACO showed a promising remission rate. Other studies have reported that brain, liver and GI tract, as site of metastases, have the poorest prognosis. However, with the result of this study, EMACO remains to be the regimen of choice for both high risk and ultrahigh risk GTN in our institution with the addition of an adjunctive therapy if indicated. ■

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