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Risk factors for chemoresistance in metastatic high-risk Gestational Trophoblastic Neoplasia

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Abstract:

BACKGROUND: Gestational trophoblastic neoplasia (GTN) is a tumor known to be sensitive to chemotherapy. However, a subset of patients still develop resistance to the primary intensive chemotherapy.

OBJECTIVE: This study aimed to determine the risk factors for multidrug resistance among high-risk metastatic GTN patients at University of the Philippines–Philippine General Hospital from January 2014 to December 2018.

MATERIALS AND METHODS: A case–control study involving 111 high-risk metastatic GTN patients who underwent primary intensive chemotherapy Etoposide Methotrexate Actinomycin Cyclophosphamide Oncovin (EMACO) was done at the Philippine General Hospital from January 2014 to December 2018. The medical records of eligible patients were retrieved and reviewed. A comparison of the profile between patients who achieved remission (controls) and those who exhibited chemoresistance (cases) to the EMACO regimen was done. Stepwise logistic regression analysis and Cox's proportional hazards regression were used to determine the significant risk factors that could predict EMACO chemoresistance among these high-risk patients.

RESULTS: The cases and controls were comparable in terms of their clinicodemographic profiles. Adjusting for confounders, multivariate analysis showed that the number of metastasis, FIGO stage, and World Health Organization (WHO) prognostic scores were all predictors of survival. Using the fitted logistic regression model, the accuracy of predicted death and survival was 85.16%.

CONCLUSION: The pretreatment serum beta-human chorionic gonadotropin level, number of metastasis, tumor size, FIGO stage, and WHO prognostic score were significant predictors of treatment failure. A higher number of metastatic lesions, stage, and WHO prognostic scores indicated poor survival.

Keywords:

Gestational trophoblastic neoplasia, metastatic high risk, multidrug resistance, risk factors

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Introduction

Gestational trophoblastic neoplasia (GTN) is a systemic disease known to be one of the few highly curable malignancies responsive to chemotherapy. It has also a reliable serum tumor marker, beta-human chorionic gonadotropin (β-hCG), that can be used for diagnosis, monitoring response to treatment, and posttreatment surveillance. Thus, early diagnosis and institution of individualized risk-based therapy are paramount for successful treatment outcomes.[1]

The successful treatment of these trophoblastic tumors, except for the placental site and the epithelioid trophoblastic tumors (ETTs), hinges upon the introduction of effective chemotherapeutic drugs that offer excellent cure rates. Currently, the etoposide,

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methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO) regimen is the first-line chemotherapy for high-risk GTN patients worldwide. It is generally well tolerated by patients.[2] Complete response and long-term survival rates were reported to be more than 80% across different trophoblastic disease centers. The reported overall survival rate of high-risk GTN cases after EMACO hovers between 86% and 97.9%.[3,4] A 2006 study done at the Philippine General Hospital demonstrated a primary remission rate of 72% among high-risk patients given EMACO with an 80% remission rate after salvage treatment.[4] Despite a good primary remission rate, approximately 25% of high-risk GTN patients developed resistance to first-line EMACO or relapsed after completion of initial therapy.[5] This subset of EMACO-resistant cases poses a significant problem because very few salvage regimens have been found to be effective after EMACO.

Objectives

The main objective of the study was to determine the risk factors for multidrug resistance among high-risk metastatic GTN patients at University of the Philippines–Philippine General Hospital from January 2014 to December 2018. The secondary outcomes include the prevalence of multidrug resistance, the clinical profile of patients who achieved remission after EMACO and those who developed chemoresistance to the regimen, the clinical profile and outcome of patients given salvage therapy, and the probability of death in GTN patients who developed EMACO resistance using the World Health Organization (WHO) prognostic factors and FIGO anatomic stage.

Materials and Methods

This case–control study was approved by the institution's technical and ethical review boards. Included were all clinically diagnosed GTN cases, as well as histologically confirmed choriocarcinoma and invasive mole, who were classified as high risk with WHO prognostic scores of >7, and with metastatic disease (FIGO anatomic Stages II–IV) who were given the EMACO regimen at the Philippine General Hospital from January 2014 to December 2018. Excluded were patients initially treated outside the institution, those with histopathologic diagnosis of placental site trophoblastic tumor and ETT, and those with double primary malignancies.

The subjects were identified from the annual ward and admission reports, outpatient department census, and the GTN computer database of the Division of Trophoblastic Diseases, UP-PGH. The medical charts were retrieved from the medical records section. The pertinent information was recorded in the patient data abstraction form.

Cases were EMACO-resistant patients who demonstrated the following conditions while on active treatment: (1) two plateauing values over three consecutive serum β-hCG determinations, (2) an increase in β-hCG level by one log over 6 weeks, (3) rise in two consecutive serum β-hCG levels, or (4) appearance of new site (s) of metastasis.

Controls were high-risk patients who achieved biochemical remission defined as three normal weekly serum β-hCG values (<5.0 miu/ml) after completion of three consolidation courses of the EMACO regimen.

The data were encoded into the Microsoft Excel Spreadsheet. The SAS (1995, SAS Institute Inc.) program was used. Statistical analysis included descriptive statistics, such as measures of central tendency and dispersion, relative frequency, and rate. Univariate analysis for each prognostic factor was done. Multiple logistic regression analysis was performed to determine the significant prognostic factors while controlling for confounders. The Cox's proportional hazards regression was utilized to determine the important prognostic factors for survival. The level for statistical significance was set at the probability value of < 0.05. Results were presented in the respective tables.

Results

There were 131 high-risk metastatic GTN patients admitted at the Philippine General Hospital during the 5-year study period from January 2014 to December 2018. Twenty patients (15.3%) were excluded for various reasons: five patients (5) were on combination regimens (EA, MEA, and EACO) other than EMA-CO, one (1) had a double primary malignancy, three (3) had ETT, five (5) died prior to treatment, four (4) went home against medical advice, and two (2) were lost to follow up.

Remission rate of high-risk metastatic gestational trophoblastic neoplasia

From the 111 eligible patients, 92 (82.9%) achieved remission while 19 patients developed resistance to EMA-CO, giving an overall 5-year primary EMACO resistance rate of 17.12%. Table 1 shows the yearly number of GTN cases treated with EMACO and the outcome of treatment.

The overall 5-year remission rate for high-risk metastatic GTN is 91.9%, after censuring the 11 patients who died prior to treatment, who went home against advice, and who were lost to follow-up. In a worst-case scenario, the 5-year remission rate is 87.2%.

Table 1: High-risk metastatic gestational trophoblastic neoplasia cases given EMA-CO regimen at the Philippine general hospital from 2014 to 2018

Year	Total GTN patients on EMA-CO per year	Number of patients who responded to EMA-CO (controls), *n* (%)	Number of patients who developed resistance to EMA-CO (cases), *n* (%)
2014	23	19 (82.6)	4 (17.4)
2015	24	20 (83.3)	4 (16.7)
2016	26	22 (84.6)	4 (15.4)
2017	22	18 (81.8)	4 (18.2)
2018	16	13 (81.2)	3 (18.8)
Total	111	92 (82.9)	19 (17.1)

GTN=Gestational trophoblastic neoplasia, EMA-CO=Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine

Demographic and clinical profile of gestational trophoblastic neoplasia patients

The overall mean age of patients was 30 (±9.17) years; the youngest was 19 and the oldest was 49 years of age. A higher proportion of older patients were found among cases while controls tend to be younger. The overall mean gravidity and parity were 2.19 (±1.16) and 2.89 (±2.23), respectively. Molar pregnancy was the most common antecedent pregnancy for both groups accounting for 91.1% among controls and 78.9% among cases. There were more nonmolar antecedent pregnancies (21.1%) among cases.

Majority underwent suction curettage consistent with the history of molar pregnancy in 87.4% of patients. Two cases and five controls had dilatation and curettage. Two cases and two controls developed GTN after hysterectomy for molar pregnancy. No surgical intervention prior to EMACO were seen in 5.5% of the patients in the remission group and in 1.1% of patients in the resistance group. (revised phrase). Sixty percent of cases received chemoprophylaxis after a molar pregnancy compared to only 41.5% of controls.

The mean interval from antecedent pregnancy to onset of symptoms was longer among cases with 13.12 (+2.26) months compared to 10.35 (+1.56) months among controls. Both cases and controls have similar pretreatment serum β-hCG levels. As for tumor size, the cases had a bigger mean tumor of 6.27 (+1.03) cm compared to controls of 3.56 (+1.09) cm. Aside from mean tumor size, majority of the cases (89.5%) had tumor sizes of 5 cm or more. In contrast, more than half of the controls had smaller tumor sizes between 3 and 5 cm.

The most common site of metastasis for both groups was the lungs, which was seen in 60.9% of controls and in 57.9% of cases. However, a higher proportion of cases had distant metastases to the brain and/or liver compared to controls. Cases also had a higher mean number of metastatic lesions (7.01 + 2.19) compared to controls (4.95 + 1.87).

Based on the 2000 FIGO anatomical staging, majority of the controls were in Stage III disease, one-fourth were in Stage I, and the rest (13.0%) in Stage IV. For the cases, majority were in Stage III (57.9%) and Stage IV (42.1%). None of the cases had Stage II disease.

There were a higher proportion of controls (73.9%) that had WHO prognostic scores between 7 and 12 compared to cases (42.1%). Conversely, there were more ultra-high-risk (WHO score >12) cases compared to controls (26.1%).

Hysterectomy was the most common adjunctive procedure performed in both groups although more hysterectomies were done among cases (73.7%) compared to controls (51.1%). Four patients in the control group had resection of localized uterine tumor. In addition, two (2) had thoracotomy, four (4) had whole-brain irradiation, and two (2) had intrathecal methotrexate. Among the cases, one-fifth (4) underwent brain irradiation. A third of controls did not get any adjunctive procedure. No adjunctive procedure was done on a case assessed as poor candidate for surgery.

Whenever histopathologic confirmation was feasible, the most common finding for both groups was choriocarcinoma but was higher among cases (63.2%) compared to controls (41.3%). In contrast, a higher proportion of invasive moles were found among controls (14.1%) than among cases (10.5%).

For the controls, the mean number of EMACO cycles prior to remission was 8.0 (+2.2). Among cases, resistance developed around the mean of 6.67 (+1.81) EMACO cycles. The mean time interval between EMA-CO courses was similar for both groups, 13.64 (+0.24) days for controls and 14.02 (+2.11) days for cases. Note, however, that chemotherapy for the controls was almost always given on time (97.8%) with <14-day interval between courses. Almost a third of cases (31.6%) had delays in chemotherapy schedules with 15- and 21-day intervals between courses. Most delays were due to cumulative drug toxicities and intercurrent infections.

Although there were no statistically significant differences in demographic and clinical characteristics between cases and controls, cases tend to be older

and had longer time interval between antecedent pregnancy to onset of symptoms, larger tumor size, more histologically confirmed choriocarcinomas, and more episodes of delayed chemotherapy cycles.

The clinical profile of high-risk metastatic GTN treated with EMACO is presented in Table 2.

Clinical outcome of EMACO-resistant gestational trophoblastic neoplasia patients

Ten patients went into remission after salvage chemotherapy giving a remission rate of 52.6% for this subset of patients. Nine patients (47.4%) responded to the first-line cisplatin-based salvage regimen etoposide-paclitaxel-etoposide-methotrexate-actinomycin (EP-EMA). One patient developed resistance to EP-EMA but responded to the second-line salvage regimen of paclitaxel-carboplatin.

Six patients (31.6%) died during salvage treatment. Five patients died while on EP-EMA. The causes of death were acute respiratory insufficiency (2), septic shock (2), and pulmonary embolism (1), and 2 died due to septic shock. One patient had EP-EMA resistance, underwent salvage hysterectomy, and shifted to TP-TE regimen (paclitaxel-cisplatin/paclitaxel-etoposide), then bleomycin-etoposide-paclitaxel regimen. With the persistence of disease, the patient opted for palliative care and eventually died at home.

Three patients (15.8%) refused further treatment and opted for palliative care.

Of the 19 patients, only the aforementioned patient underwent salvage hysterectomy. Salvage hysterectomy was contemplated in three patients with chemoresistance but was not done since they were poor surgical candidates. These patients eventually died during the course of the salvage chemotherapy. (revised phrase). Table 3 presents the outcomes of patients who developed EMA-CO resistance (cases).

Risk factors for EMACO resistance

The clinical parameters found to be statistically significant by univariate analysis included pretreatment serum β-hCG of >100,000 miu/ml, number of metastases of more than eight (8) lesions, largest tumor size >5 cm, FIGO Stage 4, and WHO prognostic score of more than 12. Using the stepwise–Cox proportional hazards regression analysis to predict survival, the number of metastasis, WHO prognostic score, and the FIGO stage were risk factors found to be significant for survival presented in Table 4. Increasing the number of metastasis by one (1) resulted to a corresponding increase in the risk ratio by 1.50. The number of metastasis was the most significant factor among all other WHO prognostic factors for predicting resistance to EMACO and survival.

Interestingly, the other clinical parameters that were found to be statistically insignificant yet demonstrated a trend toward a dose–response relationship included interval between antecedent pregnancy and onset of symptoms >13 months and histopathologically proven choriocarcinoma (63.2% of cases) vis-à-vis invasive mole and clinical GTN.

Table 5 presents the performance result of the fitted logistic regression model in the prediction of death and survival at 85.16%. The expected number of deaths and survivors from the logistic regression model approximated that of the observed number of deaths and survivors in the study.

Discussion

GTN is known to be extremely sensitive to chemotherapy. Effective combinations of antineoplastic drugs have led to excellent cure rates even in advanced stages of disease. However, approximately 25% of high-risk GTN patients will develop chemoresistance during treatment.[6] When this happens, the path for cure becomes narrow as options for an effective salvage chemotherapy protocol are limited. Therefore, the problem of chemoresistance in high-risk metastatic GTN remains a major challenge in the management of this malignancy.

Identification of risk factors for EMACO resistance is crucial in the management of GTN patients. Several studies have been conducted to evaluate the clinical significance of these risk factors in relation to treatment failure but showed conflicting results.[7-12]

This study demonstrated that EMACO resistance is associated with an ultra-high WHO risk score of >12, metastatic lesions numbering more than 8 counts, and disseminated disease (FIGO Stage IV). Although these three prognostic factors are interrelated, tumor burden seemed to be most important in the interplay of these factors. Seung and Seog have shown that metastases to two or more organs and tumor age >12 months were predictors of treatment failure and poor prognosis.[13]

Serum β-hCG is a reliable indicator of tumor load. Fülöp *et al*. observed a 10% treatment failure rate when the pretreatment serum β-hCG was $<10^5$ miu/ml. The treatment failure rate significantly rose to 38.5% when the pretreatment serum β-hCG was $>10^5$ miu/ml.[14] However, this study did not find the markedly elevated pretreatment serum β-hCG as an independent risk factor for EMACO resistance because both cases and controls had approximate high levels of pretreatment β-hCG.

Table 2: The demographic and clinical characteristics of cases and controls (*n*=111)

Characteristic	Controls (*n*=92) remission, *n* (%)	Cases (*n*=19) chemoresistance, *n* (%)	*P*
Age (years)			
<40	82 (89.1)	9 (47.4)	0.89
≥40	10 (10.9)	10 (52.6)	
Gravidity			
G1	24 (26.1)	4 (21.1)	0.72
G2-G4	56 (60.9)	10 (52.6)	
G5 and above	12 (13.0)	5 (26.3)	
Parity			
Nullipara	5 (5.4)	0	0.67
Primipara	17 (16.8)	7 (87.0)	
Multipara	70 (77.8)	12 (13.0)	
Antecedent pregnancy			
Mole	82 (89.1)	15 (78.9)	0.96
Term	5 (5.4)	2 (10.5)	
Abortion	5 (5.4)	2 (10.5)	
Interval from antecedent pregnancy to symptoms (months)			
<4	16 (17.4)	1 (5.3)	0.71
4-<7	18 (19.6)	2 (10.5)	
7-<13	28 (30.4)	2 (10.5)	
>13	30 (32.6)	14 (73.7)	
Pretreatment serum βhCG (mIU/ml)			
$<10^3$	1 (1.1)	0	0.24
10^3-$<10^4$	1 (1.1)	0	
10^4-$<10^5$	3 (3.3)	3 (15.8)	
$>10^5$	87 (94.6)	16 (84.2)	
Largest tumor size (cm)			
<3	17 (18.5)	1 (5.3)	0.65
3-<5	49 (53.3)	1 (5.3)	
>5	26 (28.2)	17 (89.5)	
Site of metastasis			
Vagina/vulva	13 (14.1)	0	0.25
Adnexa	6 (6.5)	0	
Parametria	5 (5.4)	0	
Lungs	56 (60.9)	11 (57.9)	
Spleen	1 (5.3)	1 (5.3)	
Kidney	1 (5.3)	0	
Gastrointestinal	0	0	
Liver	4 (4.3)	2 (10.5)	
Brain	6 (6.5)	5 (26.3)	
Number of metastasis			
1-4	32 (34.8)	2 (10.5)	0.74
5-8	43 (46.7)	6 (31.6)	
>8	17 (18.5)	11 (57.9)	
Previous failed intensive chemotherapy			
Single drug	34 (37.0)	9 (47.4)	0.20
>2 drugs	0	0	
No prior chemotherapy	58 (63.0)	10 (52.6)	
Intervention prior to chemotherapy			
No intervention	5 (5.4)	2 (10.5)	0.68
Suction curettage	80 (87.0)	13 (68.4)	
Dilatation and curettage	5 (5.4)	2 (10.5)	
TAHBS/TAHBSO	2 (2.2)	2 (10.5)	
Adjunctive procedures			

Contd...

Table 2: Contd...

Characteristic	Controls (*n*=92) remission, *n* (%)	Cases (*n*=19) chemoresistance, *n* (%)	*P*
Hysterectomy	47 (51.1)	14 (73.7)	0.22
Resection of localized uterine tumor	4 (4.3)	0	
Uterine artery ligation	0	0	
Internal iliac artery ligation	0	0	
Thoracotomy	2 (2.2)	0	
Whole-brain irradiation	4 (4.3)	4 (21.1)	
Intrathecal methotrexate	2 (2.2)	0	
No surgical procedure	33 (35.9)	1 (5.3)	
Histopathology			
Invasive mole	13 (14.1)	2 (10.5)	0.72
Choriocarcinoma	38 (41.3)	12 (63.2)	
Clinical diagnosis	41 (44.6)	5 (26.3)	
WHO prognostic score			
7-12	68 (73.9)	8 (42.1)	0.83
>12	24 (26.1)	11 (57.9)	
Stage			
II	24 (26.1)	0	0.45
III	56 (60.9)	11 (57.9)	
IV	12 (13.0)	8 (42.1)	
Chemotherapeutic cycles prior to EMACO remission or resistance			
<6	10 (10.9)	9 (47.4)	0.68
>6	82 (89.1)	10 (52.6)	
Interval between EMACO chemotherapeutic cycles (days)			
<14	90 (97.8)	13 (68.4)	0.21
15-21	2 (2.2)	6 (31.6)	
>21	0	0	

TAHBSO=Total abdominal hysterectomy with bilateral salpingo-oophorectomy, TAHBSO=TAHBS oophorectomy, EMA-CO=Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine, WHO=World Health Organization, β-hCG=β-human chorionic gonadotropin

Table 3: Outcome of emaco-resistant high-risk metastatic gtn patients (n=19)

Outcome	Frequency	Percent
Remission after the first line salvage chemotherapy (EP-EMA) and survived	9	47.4
Remission after the second line salvage chemotherapy (PC) and survived	1	5.3
Chemoresistance after third line salvage chemotherapy and died	1	5.3
Died while on the course of second line chemotherapy	5	26.3
Opted for palliative care	3	15.8

Gestational trophoblastic neoplasms are unique in the sense that clinical features in the patient are as important as the anatomic stage of disease. For this reason, the WHO prognostic score has remained a valuable guide in the choice of first-line chemotherapy. DuBeshter *et al*. reported that the WHO prognostic scoring system was more reliable than the other traditional high-risk factors for the prediction of chemoresistance.[15] Their report concluded that an ultra-high-risk prognostic score of >12 was associated with treatment failure, and this study supported their finding.

This study demonstrated that FIGO stage is an independent risk factor for EMACO resistance, with the odds of developing chemoresistance greater when the patient has a higher FIGO anatomic stage. The Fülöp *et al*.'s study showed that metastases confined to the pelvis (Stage II) and to the lungs (Stage III) were associated with an EMACO-resistance rate of 12%. This contrasts with a higher 50% resistance in the presence of distant metastasis (Stage IV).[14]

Results of this study revealed a broad range of predicted probabilities of survival and death of high-risk GTN patients treated with EMACO. This suggests that some prognostic factors contained within the WHO scoring system are not very precise in predicting outcomes. However, despite the wide range of predicted probabilities of survival and death, the number of metastases, FIGO Stage, and WHO prognostic score were still statistically significant in the prediction of chemoresistance and death in high-risk GTN patients.

Conclusion and Recommendations

This study found a significant association between the development of EMACO resistance to metastatic lesions

Table 4: Stepwise-cox proportional hazards regression of risk factors in high risk metastatic gtn patients treated with emaco in philippine general hospital from 2014-2018

Risk Factor	Parameter estimate	*P* value Risk ratio	Risk ratio	95% CIF risk ratio
Number of metastasis	0.456	0.0392	1.50	1.23-2.65
WHO Prognostic Score	0.234	0.0389	1.28	1.13-2.78
FIGO Stage	0.356	0.0401	1.88	1.04-1.94

Table 5: Performance of fitted logistic regression model in the prediction of death and survival in in metastatic high risk gtn patients treated with emaco in philippine general hospital from 2014-2018

Actual Number of Deaths 9	Correctly Predicted Number of Deaths 7	Wrongly Predicted Number. of Deaths 2	Total Percentage of Correct Classification 85.16%
Actual Number of Survivors 102	Correctly Predicted Number of Survivors 100	Wrongly Predicted Number. of Survivors 2	

of more than 8 counts, FIGO Stages III and IV, and WHO ultra-high-risk score of more than 12. Additionally, cases tend to be older with longer time interval between antecedent pregnancy to onset of symptoms, larger tumor size, more histologically confirmed choriocarcinomas, and more episodes of delayed chemotherapy cycles.

When diagnosed in the early stages of disease, the tumor tends to be localized and is more responsive to chemotherapy. As the disease advances, the older tumor is hematogenously disseminated to organs not accessible to other treatment modalities, as well as the development of resistant clones. It cannot be overstated that early diagnosis with prompt and appropriate treatment is crucial to the successful treatment of GTN.

In addition, the term adjunctive treatment referring to modalities such as surgery and arterial embolization may lead to a delay in the application of these methods. A renewed attitude toward early surgical extirpation of resectable primary or metastatic lesions deserves consideration to reduce tumor load without forestalling the need for intensive chemotherapy, especially in far-advanced disease. Indeed, a more recent study by Kong demonstrated that surgical intervention is beneficial for ultra-high-risk patients (respiratory rate = 0.336, 95% confidence interval = 0.177,0.641).[16] An earlier study on salvage surgery by Lenhman showed that patients with chemorefractory GTN may benefit from salvage surgery in order to decrease the tumor burden and to eliminate isolated drug-resistant lesions.[17]

Conventionally, the EMACO regimen has been the first-line intensive chemotherapy protocol for high-risk metastatic GTN. However, patients who present with overwhelming disease in the presence of histologically confirmed choriocarcinoma may be given a cisplatin-based intensive regimen at the outset. This could be a subject open to further studies.

Finally, state-of-the-art genomic studies of the cases may provide the key to individualizing treatment, reduce the incidence of chemoresistance, and improve survival of GTN patients with advanced disease.

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Conflicts of interest
There are no conflicts of interest.

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