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Factors affecting remission to salvage chemotherapy with Etoposide-Cisplatin/Etoposide-Methotrexate-Actinomycin D (EP-EMA regimen) among chemoresistant high-risk Gestational Trophoblastic Neoplasia patients admitted in a tertiary institution: A 10-year retrospective descriptive study

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Abstract:

BACKGROUND: Approximately 20%–25% of high-risk gestational trophoblastic neoplasia (GTN) patients initially treated with first-line chemotherapy regimen develop resistance to the regimen. The EP-EMA (Etoposide-cisplatin and etoposide, methotrexate and actinomycin D) regimen is the most commonly utilized second-line agent.

OBJECTIVE: This study aimed to identify factors leading to remission using etoposide and cisplatin-etoposide, methotrexate, and Actinomycin D (EP-EMA) as salvage chemotherapy among resistant high-risk GTN.

METHODS: This is a retrospective descriptive study that reviewed the medical records of patients admitted in the section of trophoblastic diseases diagnosed with high-risk GTN from January 2006 to December 2015.

RESULTS: The medical records of 20 patients were retrieved and reviewed. The complete remission rate with EP-EMA is 60% (12/20). The overall survival rate for 1 year is 70% (14/20). Only 20% of the patients went home against advice and did not complete treatment. This regimen reported toxicities ranging from Grade 2–4 myelosuppression and electrolyte imbalance. Forty-five percent had Grade 4 neutropenia and Grade 2 anemia and 20% had Grade 2 thrombocytopenia. Hypokalemia and hypomagnesemia were noted in 8 patients (40%). Although not statistically significant, a trend showed that those in the remission group mostly had Stage III diseases with metastasis only in the lungs, prognostic score of between 7 and 12, and with beta-human chorionic gonadotropin (β-hCG) levels <10,000 mIu/ml at the start of EP-EMA treatment.

CONCLUSION: There is an improved response with EP-EMA chemotherapy across the years in our institution. Factors such as stage of disease, pulmonary metastasis, and low β-hCG at the start EP-EMA chemotherapy denote a possible good response and may contribute to patients' complete remission with EP-EMA chemotherapy. However, further studies with larger patient sample size are recommended to support the latter.

Keywords:

Chemoresistance, EP-EMA, gestational trophoblastic neoplasia, salvage chemotherapy, toxicity

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Introduction

Gestational trophoblastic disease is a spectrum of conditions which arise from the products of conception and threatens the health of reproductive-aged women if not recognized and properly treated.[1] Gestational trophoblastic neoplasia (GTN) represents the malignant component of this spectrum. Included in this group are invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.

Women who are diagnosed with GTN are staged and scored using the FIGO 2000 anatomical staging [Table 1] and scoring system [Table 2].[2] The anatomic staging system determines the extent of the disease while the prognostic scoring system, which classifies the patient as high risk or low risk, predicts the patient's response to chemotherapy.[3]

Once patients are classified to either the low-risk or high-risk group, appropriate management with chemotherapy is initiated to eradicate tumor cells with the goal of achieving cure while having minimal toxicity. Multiple agent chemotherapy consisting of etoposide, methotrexate, Actinomycin D, cyclophosphamide, and vincristine (EMACO) remains the standard treatment for high-risk GTN, with a reported cure rate of 80%–85%.[1] In a local study, the primary remission rate with this regimen was 72%.[4] When using this regimen, methotrexate, D-actinomycin, and etoposide are given on days 1 and 2 while cyclophosphamide and vincristine are given on day 8 of each cycle. Each cycle is given on a weekly interval.

Approximately 20%–25% of high-risk GTN patients initially treated with EMACO develop resistance to the regimen.[5] Among patients with GTN, resistance to chemotherapy or chemoresistance is defined as (1) 3 consecutive serum beta-human chorionic gonadotropin (β-hCG) values showing 2 plateauing values or (2) a rise in β-hCG values in 2 consecutive determinations or (3) appearance of new sites of metastasis while ongoing chemotherapy.[2]

Patients who develop resistance to the EMACO regimen are shifted to platinum-containing regimens as salvage or second-line chemotherapy. The most commonly used regimen is the EMA-EP where the cyclophosphamide and vincristine combination is substituted with cisplatin and etoposide, which are given on day 8 of the cycle.

Etoposide, methotrexate, and D-actinomycin etoposide and cisplatin (EMA-EP) has a reported induced remission rate of 76% with or without adjunctive surgery.[6] Bower *et al.* reported that 76% of their patients were successfully treated with EMA-EP alone after developing resistance to the EMACO regimen.[7] In a similar study done in Charing Cross Hospital, the remission rate to EMA-EP was reported at 70%.[8] In a local study done in 2006, the primary remission rate was much lower at 31.6%, with a 1-year overall survival rate of only 32%.[9] In the same study, factors that were identified that influenced complete response included age, duration and stage of disease, and use of adjunctive treatment like brain radiation.

The EMA-EP regimen has also been shown to be well tolerated and moderately toxic in several studies.[10] Some reported toxicities of this regimen include anemia as seen in 21% of cases, leukopenia in 63%, and thrombocytopenia in 40% of cases. It is also associated with hypomagnesemia and liver toxicities in other cases.[11]

In our institution, modification has been done to the EMA-EP regimen by giving the etoposide and cisplatin on the 1st day of the cycle while the etoposide, methotrexate, and Actinomycin D are given on days 7 and 8. Hence, the acronym EP-EMA is shown in Table 3. The use of the EP-EMA regimen as salvage chemotherapy or second-line treatment has been implemented in the past 18 years. This study aimed to identify the factors leading to disease remission following the administration of EP-EMA regimen as salvage chemotherapy. The specific objectives were as follows:

1. To determine the primary remission rate and overall 1-year survival rate of patients treated with salvage chemotherapy in the form of EP-EMA
2. To compare the clinic-demographic profile of patients in terms of age, gravidity, parity, antecedent pregnancy, interval from last pregnancy, stage of the disease, largest tumor size, site of metastases, and baseline serum β-hCG for those who achieved remission with EP-EMA versus those who did not
3. To determine number of patients who had recurrence of the disease after achieving remission with EP-EMA
4. To evaluate hematologic, renal toxicity, hepatic toxicity, and electrolyte imbalance resulting from the use of EP-EMA.

Table 1: International Federation of Gynecology and Obstetrics 2000 anatomic staging

Stage	Definition
Stage I	Disease confined to the uterus
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, and broad ligament)
Stage III	GTN extends to the lungs with or without genital tract involvement
Stage IV	All other metastatic sites

GTN=Gestational trophoblastic neoplasia

Stage

Significance of the study

The findings of this study will allow trophoblastic disease specialists/gynecologic oncologists to identify patients

Table 2: International Federation of Gynecology and Obstetrics 2000 scoring system

Factors	0	1	2	4
Age (years)	<40	>40		
Antecedent pregnancy	Mole	Abortion	Term	
Pregnancy interval (months)	<4	4-6	7-12	>12
-hCG (mIU/ml)	<1000	1000-10,000	10,001-100,000	>100,000
Largest tumor (cm)		3-5	>5	
Site of metastases		Spleen, kidney	GI tract	Liver, brain
Number of metastases		1-4	5-8	>8
Prior chemotherapy			Single	≥2 agent
Total score	Low risk=0-6		High risk=7 and above	

β-hCG=β-human chorionic gonadotropin, GI=Gastrointestinal

Table 3: Etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin regimen

Time	Treatment
Day 1	Etoposide 100 mg/m^2 by IV infusion in 400 ml of saline solution over 1 h
	Cisplatin 80 mg/m^2 IV with prehydration
Day 7	D-actinomycin 500 mcg in 30 ml saline solute × 30 min
	Etoposide 100 mg/m^2 by IV infusion in 400 ml of saline solution over 1 h
	Methotrexate 100 mg/m^2 IV push
	Methotrexate 200 mg/m^2 IV infusion over 12 h
Day 8	D-actinomycin 500 mcg in 30 ml saline solute × 30 min
	Etoposide 100 mg/m^2 by IV infusion in 400 ml of saline solution over 1 h
	Folinic acid 15 mg IM or PO every 12 h for 4 doses beginning 24 h after starting methotrexate

IV=Intravenous route, IM=Intramuscular route, PO=Per orem or oral route

early in the course of their treatment who will develop possible resistance to EMACO and identify patients who will be more responsive to the salvage chemotherapy in the form of EP-EMA. In addition, the results of this study will also aid in managing toxicity earlier and avoid progression or severity of this complication as identified by the results of this study. The study will also encourage general obstetrician-gynecologists to have a high index of suspicion among their patients who are in the reproductive-aged group who manifest with abnormal signs and symptoms following a pregnancy. This will facilitate early diagnosis of the disease and timely intervention and treatment among patients diagnosed with GTN.

Methods

Study design

This is a retrospective descriptive study conducted to identify the factors that affected or led to disease remission following the administration of EP-EMA chemotherapy.

Patient population

All patients diagnosed with high-risk GTN who were initially treated with EMACO chemotherapy but developed resistance and were shifted to EP-EMA as salvage chemotherapy were included in the study. Patients were admitted in the Section of Trophoblastic Diseases, Department of Obstetrics and Gynecology of the Philippine General Hospital, from January 1, 2006, to December 31, 2015, and were able to complete a 1-year follow-up after achieving remission with EP-EMA regimen. Patients with histopathological diagnosis of placental site trophoblastic tumor or epithelioid trophoblastic tumor were excluded from the study.

Description of the study procedure

The weekly ward and annual reports of the section of trophoblastic disease of the Department of Obstetrics and Gynecology of the Philippine General Hospital from January 1, 2006, to December 31, 2015, were reviewed to identify patients who were eligible for inclusion in the study. The medical records of all eligible patients were then retrieved and reviewed. The following clinicodemographic profile of each patient was recorded using the patient data extraction form: gravidity, antecedent pregnancy, interval from the last pregnancy to diagnosis of GTN, pretreatment ß-hCG titer, largest tumor size, FIGO stage, WHO Prognostic Score, ß-hCG prior to EP-EMA, site of metastasis, and performance of adjunctive surgery. The hematologic, renal, and hepatic toxicities were likewise recorded data extraction form based on the WHO toxicity criteria grading system.[12]

Patients were divided into two groups to determine factors that affected treatment outcome. Group 1 included patients who achieved remission with EP-EMA while Group 2 included patients who failed to achieve remission. Patients who were unable to complete treatment or went home against medical advice prior to completion of treatment were included in Group 2.

Description of outcome measures

1. Factors affecting remission were identified
2. The study also determined the efficacy and tolerability of EP-EMA regimen as measured by the following:

a. Primary remission rate, computed as number of patients who developed resistance to EMACO but

achieved remission with EP-EMA regimen over the total number of patients included in the study

b. Overall remission rate, computed as the number of patients who achieved remission with EP-EMA chemotherapy and with a third-line regimen over the total number of patients included in the study
c. Overall 1-year survival rate, determined as the total number of patients who achieved remission with EP-EMA and a third-line regimen who were alive for at least 1 year after treatment over the total number of patients included in the study
d. Toxicity grade is the score obtained from the WHO common toxicity criteria grading system of the different parameters including levels of hemoglobin, white blood cell, platelet count, absolute neutrophil count (ANC), serum creatinine, liver transaminases (SGOT and SGPT), and electrolyte imbalances, particularly hypomagnesemia and hypokalemia.

Statistical analysis

Descriptive statistics including medians and ranges were computed for continuous variables such as age and baseline β-hCG. Qualitative variables were summarized as proportions. To determine the comparability of the group who achieved remission versus who did not achieve remission, two-tailed Fisher's exact test was done. To determine the association of certain factors and outcome of treatment, Chi-square test was applied and level of significance was set at 0.05 with 95% confidence interval.

Results

From the years 2006–2015, the Section of Trophoblastic Diseases of the Department of Obstetrics and Gynecology of the Philippine General Hospital admitted a total of 134 patients who were diagnosed with high-risk GTN. Twenty-one patients (15.7%) were shifted to EP-EMA after developing resistance to EMACO, and all of the patients' records were available for review. One patient was excluded due to a histopathologic diagnosis of epithelioid trophoblastic tumor. Hence, a total of 20 cases formed the patient population of the study [Table 4].

Table 5 is the summary of the demographic characteristics of the 20 patients included in the study. Majority of the patients were in FIGO Stage III (80%) and Stage IV (20%) of the disease. The most common site of metastasis was primarily in the lungs alone as seen in 10 patients (50%). For the prognostic score, 9 patients (45%) had a score between 7 and 12 while 11 patients (55%) had a score of more than 12. Majority (65%) had a β-hCG of more than 100,000 mIU/ml at the time of diagnosis.

A total of 14 patients (70%) underwent adjunctive surgery during the course of their treatment (11 – hysterectomy, 2 – thoracotomy, and 1 – salpingectomy). Five patients (25%) did not undergo any adjunctive surgery. One patient (5%) underwent hysterectomy prior to the diagnosis of GTN. All surgeries were performed prior to the institution of EP-EMA.

Assessment of response to EP-EMA

A total of 92 cycles of EP-EMA chemotherapy were given to the 20 patients included in this report. The number of EP-EMA cycles given per patient varied. The median number of cycles was 5–6 (range: 1–7 cycles).

A total of 12 of the 20 patients achieved complete remission giving a primary remission rate of 60%. Four patients (20%) developed resistance to EP-EMA and were shifted to third-line regimen, but only 3 (15%) eventually went into remission using a third-line chemotherapy (2 carboplatin-paclitaxel regimen and 1 VBP regimen), giving an overall remission rate of 75%. One of the 4 patients shifted to a third-line regimen had persistently rising β-hCG despite adjunctive surgery and chemotherapy. She eventually succumbed to hospital-acquired infection. Four patients (20%) went home against medical advice and were not able to complete treatment.

Table 6 shows the summary of the course of treatment using EP-EMA. Among the patients who went into remission with EP-EMA, 7 patients (58%) were given 3 consolidation therapies, 4 patients (33%) had 2 consolidation therapies, and 1 patient (8%) received only 1 additional cycle due to toxicity.

Of the 12 patients who went into remission with EP-EMA, one patient was readmitted and died after EP-EMA treatment. The patient was treated with EP-EMA chemotherapy for 7 cycles for tumor relapse after receiving 8 cycles of EMACO chemotherapy. She presented with decreased sensorium from an intracranial hemorrhage from a tumoral bleed from GTN brain metastasis 4 months post EP-EMA treatment. She eventually succumbed to complications of multiple organ dysfunctions. Of the 4 patients shifted to a third-line chemotherapy, one patient did not achieve remission and eventually died of sepsis. The remaining 14 patients who achieved remission with EP-EMA and a third-line regimen were alive at least 1 year following treatment giving a one-year survival rate of 70%.

Delay in treatment was reported in 39 cycles (42%). The average days of delay is 14 (range: 2-98 days). Treatment delay were due to toxicities or delay in the procurement of chemotherapeutic drugs.

Assessment of toxicity

Table 7 summarizes the toxicities encountered by the patients while being treated with EP-EMA. Anemia

Table 4: Clinical characteristics of patients included in the study

Patient number	FIGO stage	WHO score	Site of metastasis	Number of EMACO cycles	Reason for shifting to EP-EMA	β-hCG at start of EP-EMA	Number of cycles using EP-EMA	Outcome
1	III	13	Lungs	2	Rise	11,404.75	7	Remission third line+
2	IV	17	Lung, brain	5	Plateauing	14.4	5	Remission to third line**
3	IV	13	Lungs, liver, brain	5	Plateauing	8.62	1	Remission to third line**
4	III	11	Lungs	9	Plateauing	15.5	5	Remission
5	III	13	Lungs, vagina	10	Rise	1,382.1	4	HAA
6	III	13	Lungs, vagina	5	Rise	1,100	4	Remission
7	III	11	Lungs, bladder, vagina	9	Rise	72.3	1	HAA
8	III	13	Lungs	5	Plateauing	20.35	5	Remission
9	IV	14	Lungs, liver	3	plateauing	11.08	4	Remission
10	III	14	Lungs	6	Plateauing	17.18	5	Remission
11	III	14	Lungs, vagina	5	Plateauing	9.07	1	HAA
12	III	9	Lungs	2	Rise	208.1	3	Remission
13	III	9	Lungs	7	Rise	176.5	7	Remission
14	IV	14	Lungs, pancreas	5	Rise	525.1	6	Shifted to third line++
15	III	7	Lungs	4	Rise	431.40	7	Remission
16	III	14	Lungs	7	Rise	2,252	7	Remission
17	IV	11	Lungs, GI	8	Relapse	2,870	7	Remission 2 months*
18	III	12	Lungs, vaginal stump	6	Relapse	116.6	5	Remission
19	III	7	Lungs	7	Plateauing	23.04	1	HAA
20	III	11	Lungs	5	Rise	917.60	7	Remission

+Remission with VBP regimen, ++Shifted to carboplatin-paclitaxel but no remission, **Remission with carboplatin-paclitaxel regimen, *Died after 2 months from remission. FIGO=International Federation of Gynecology and Obstetrics, EP-EMA=Etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin, EMA-CO=Etoposide, methotrexate, actinomycin D cyclophosphamide and vincristine, β-hCG=β-human chorionic gonadotropin, GI=Gastrointestinal, VBP=Vincristine, bleomycin, and cisplatinum, HAA=Home against advise

was reported in 80% of patients while leukopenia and thrombocytopenia were encountered in 6 patients and 10 patients (50%), respectively. Neutropenia (decrease in ANC) was noted in 15 patients (75%) with toxicities ranging from Grade 1–4, with Grade 4 toxicity as the most reported in 45% of patients.

Electrolyte imbalances such as hypokalemia and hypomagnesemia were also encountered among patients treated with EP-EMA. Liver and renal toxicities were not common. Grade 1 liver toxicity was reported by 1 patient (5%) while Grade 1 renal toxicity was encountered by 2 patients (10%) only.

Comparison of factors between the remission group and the no remission group

Table 8 shows the comparison between the remission group and the no remission group. The remission group consisted of those who went into remission after treatment with EP-EMA (n = 12) while the no remission group is composed of those who were shifted to third-line regimen (n = 4) and those who went home against advice (n = 4).

There was no observable significant difference between the remission group and the no remission group in terms of gravidity, antecedent pregnancy, interval months from antecedent pregnancy, tumor size, and whether adjunctive surgery was done or not.

Although no significant difference was noted in the two groups with regard to FIGO staging and β-hCG levels prior to starting EP-EMA, results showed a trend toward a lower FIGO stage and β-hCG level among those who achieved remission. In addition, those with metastasis limited to the lungs and prognostic score <12 were mostly noted in the remission group.

Discussion

Gestational trophoblastic neoplasms are highly sensitive to chemotherapy. Low-risk metastatic and nonmetastatic diseases respond well to single-agent chemotherapy with reported complete remission rate from 80% to 88%.[11,13] On the other hand, high-risk metastatic diseases are treated with combination chemotherapy in the form of EMACO. The EMACO regimen was developed in 1979 in Charing Cross Gestational Trophoblastic Disease Center with reported complete remission rate ranging from 69% to 86%.[4,14-16] More recent studies, however, have shown remission rates as high as 97.3 and 100% among patients with high-risk Stage III and Stage II GTN, respectively.[11,17]

Despite its high remission rate, about 20%–25% of patients develop resistance to EMACO chemotherapy.[3,5,6] In addition, approximately one-third will not have permanent remission or will experience relapse.[5,14] Hence, there is a need for salvage

Table 5: Clinicodemographic profile of patients treated with etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin

Characteristics	Frequency (*n*=20), *n* (%)
Age (years), mean (range)	32.15 (20-43)
Gravidity	
1	3 (15)
2	4 (20)
3	1 (5)
≥4	12 (60)
Antecedent pregnancy	
Hydatidiform mole	14 (70)
Abortion	1 (5)
Term	5 (25)
Pregnancy interval (months)	
<4	2 (10)
4-6	3 (15)
7-12	1 (5)
>12	14 (70)
Pretreatment β-hCG (mIu/mL)	
<1000	0
1000-<10,000	4 (20)
10,000-100,000	3 (15)
>100,000	13 (65)
Largest tumor size (cm)	
<3	3 (15)
3-5	0
>5	15 (75)
Missing data	2 (10)
Site of metastasis	
Lungs	10 (50)
Lungs + brain/liver	3 (15)
Lungs + vagina, bladder	5 (25)
Lungs + pancreas, GI	2 (10)
FIGO staging of disease	
I	0
II	0
III	16 (80)
IV	4 (20)
WHO prognostic score	
High risk (score 7-12)	9 (45)
Ultra high risk (>13)	11 (55)
Adjunctive surgery done	
Yes	14 (70)
No	5 (25)
Prior to GTN	1 (5)

FIGO=International Federation of Gynecology and Obstetrics, β-hCG=β-human chorionic gonadotropin, GI=Gastrointestinal, GTN=Gestational trophoblastic neoplasia

Table 6: Treatment with etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin chemotherapy

	Frequency (%)
Baseline β-hCG at the start of EP-EMA, mean mIu/ml (range)	1087.27 (8.62-11,404)
β-hCG prior to EP-EMA	
<50	8 (40)
51-100	1 (5)
101-500	5 (25)
1-1000	1 (5)
1000-10,000	4 (20)
>10,000	1 (5)
Number of cleanup courses (*n*=12)	
1	1 (8.3)
2	4 (33.3)
3	7 (58.3)
Treatment delay	
2nd cycle (*n*=15, MD=1)	7 (10.1 days) (47)
3rd cycle (*n*=15, MD=1)	10 (22.5 days) (67)
4th cycle (*n*=13, MD=2)	8 (9.5 days) (61)
5th cycle (*n*=11, MD=2)	9 (5.6 days) (82)
6th cycle (*n*=6 MD=2)	3 (24.7 days) (50)
7th cycle (*n*=6, MD=2)	2 (8 days) (33)

EP-EMA=Etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin, β-hCG=β-human chorionic gonadotropin, MD= Mean days

chemotherapy. In such cases, various salvage regimens have been proposed, of which EMA-EP or EP-EMA is the most commonly used regimen.[5] This regimen is the salvage chemotherapy used in our institution for EMACO-resistant high-risk GTN patients.

The results of our study showed that the complete remission rate achieved with EP-EMA was at 60% (12 of 20 patients). This is lower compared to that reported by other institutions. In a study conducted by Bower *et al*. in 1997 and Newlands *et al*. in 2007, EMA-EP was reported to induce remission with or without surgery in 75%–76% of patients.[7,18] Almost the same remission rate of 80% was noted by Lurain *et al*. in 2006.[15] In a more recent study conducted by the same researchers, EP-EMA was noted to achieve remission in 82% of patients.[19] The marked difference in the remission rate achieved in this study compared to those reported in literature may be due to the delays in the institution of chemotherapy. Delays in treatment were commonly due to lack of funds in procuring the medications needed for treatment. In addition, correction of toxicities with blood transfusion for anemia, administration of granulocyte-colony-stimulating factor for neutropenia, and oral and intravenous correction of electrolyte imbalance also took time in the management of these patients.

In a local study conducted by Estrella and Quiño in 2006, complete remission rate with EP-EMA was noted at 31.6%.[9] The results of our study showed a higher remission rate. This can be attributed to a lesser number of patients who went home against medical advice, which accounted for only 20% of the total number of patients treated with EP-EMA compared to the previous study which had a 42% dropout rate. In addition, the higher overall survival rate of 70% was also noted in our study due to a lower number of patients who were not able to complete treatment.

Table 7: Toxicities encountered with etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin chemotherapy

Toxicity criteria	Number of events (*n*=20), *n* (%)
Hemoglobin (g/dL)	
Grade 0 (normal)	4 (20)
Grade 1 (10-normal)	3 (15)
Grade 2 (8.0-10.0)	9 (45)
Grade 3 (6.5-7.9)	4 (20)
Grade 4 (<6.5)	0
WBC (cells/mm^3)	
Grade 0 (>4)	14 (70)
Grade 1 (3.0-3.9)	0
Grade 2 (2.0-2.9)	2 (10)
Grade 3 (1.0-1.9)	4 (20)
Grade 4 (<1.0)	0
Platelet	
Grade 0 (normal)	10 (50)
Grade 1 (75.0-normal)	1 (5)
Grade 2 (50-74.9)	4 (20)
Grade 3 (25-49.9)	3 (15)
Grade 4 (<25)	2 (10)
ANC (g/dL)	
Grade 0 (>2.0)	5 (25)
Grade 1 (1.5-1.9)	4 (20)
Grade 2 (1.0-1.4)	0
Grade 3 (0.5-0.9)	2 (10)
Grade 4 (<0.5)	9 (45)
Hypokalemia (meq/L)	
Grade 0 (≥3.5)	6 (30)
Grade 1 (3.0-3.4)	4 (20)
Grade 2 (2.5-2.9)	2 (10)
Grade 3 (2.0-2.4)	1 (5)
Grade 4 (<2.0)	1 (5)
Missing data	6 (30)
Hypomagnesemia (mg/dL)	
Grade 0 (≥1.4)	6 (30)
Grade 1 (1.4-1.2)	1 (5)
Grade 2 (1.1-0.9)	3 (15)
Grade 3 (1.0-0.6)	1 (5)
Grade 4 (<0.5)	3 (15)
Missing data	6 (30)
Creatinine	
Grade 0 (normal)	12 (60)
Grade 1 (<2.5 × normal)	2 (10)
Grade 2 (2.5-5.0 × normal)	0
Grade 3 (5.1-20.0 × normal)	0
Grade 4 (>20 × normal)	0
Missing data	6 (30)
AST	
Grade 0 (normal)	14 (70)
Grade 1 (<2.5 × normal)	0
Grade 2 (2.5-5.0 × normal)	0
Grade 3 (5.1-20.0 × normal)	0
Grade 4 (>20 × normal)	0
Missing data	6 (30)
ALT	
Grade 0 (normal)	13 (65)
Grade 1 (<2.5 × normal)	1 (5)
Grade 2 (2.5-5.0 × normal)	0
Grade 3 (5.1-20.0 × normal)	0
Grade 4 (>20 × normal)	0
Missing data	6 (30)

WBC=White blood cell, ANC=Absolute neutrophil count, AST=Aspartate transaminase, ALT=Alanine aminotransferase

Although comparison between the remission and no remission groups yielded no significant difference, the study showed a trend toward remission being achieved by patients with Stage III diseases (83%) and with metastasis only to the lungs (75%) compared to those with Stage IV diseases (38%). In addition, 58% of those who went into remission had a prognostic score <13. This results support the recommendation by some authorities to add an ultra-high-risk classification in the FIGO prognostic scoring system, wherein, those with a score of 13 or more have been shown to exhibit poor response to first-line treatment, higher frequency of developing resistance to both EMACO and maybe even to salvage chemotherapy with EP-EMA.[3,20] Patients with Stage IV disease have been shown to have lower response rate ranging up to 80% compared to patients with Stage II and III high risk.[17]

In a study conducted by Powles *et al.* in patients with relapsed and chemorefractory GTN, factors such as metastatic disease, nonpulmonary sites of metastasis, nonmolar pregnancies, and slow hCG-doubling time were considered poor prognostic factors.[21] In the current study, those with Stage III diseases and with lungs as the only site of metastasis showed complete remission to salvage chemotherapy despite relapse or resistance to EMACO. In addition, those with pretreatment β-hCG of <10,000 prior to EP-EMA achieved remission. The same results were also noted in the local study done by Quiño and Soriano-Estrella, supporting the importance of early seeking behavior among patients in order to catch the disease early and to institute treatment promptly. Furthermore, the study of Quiño and Soriano-Estrella identified factors such as age, duration and stage of the disease, and adjuvant radiation treatment as good prognostic factors.[9] These factors were not shown to be statistically significant in our study.

The main adverse effect of EP-EMA reported in our study was neutropenia, with 45% of patients experiencing Grade 4 toxicity. Anemia was also a common adverse effect but less severe, with 45% of patients experiencing Grade 3 anemia. Thrombocytopenia was also reported in 10 patients (50%). Our study supports other literatures that have reported bone myelosuppression manifested

Table 8: Comparison between remission and no remission with etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin regimen

Characteristic	Remission (*n*=12), *n* (%)	No remission (*n*=8), *n* (%)	*P*
Gravidity			
1	2 (17)	1 (12.5)	0.829 (NS)
2	2 (17)	2 (25)	
3	1 (8.3)	0	
≥4	7 (58.3)	5 (62.5)	
Antecedent pregnancy			
Hydatidiform mole	7 (58.3)	7 (88)	0.353
Abortion	1 (8.3)	0	
Term	4 (33.3)	1 (22)	
Pregnancy interval (months)			
<4	2 (17)	0	0.402 (NS)
4-6	2 (17)	1 (12.5)	
7-12	0	1 (12.5)	
>12	8 (67)	6 (75)	
Pretreatment β-hCG (mIu/mL)			
<1000	0	0	0.267 (NS)
1000-<10,000	2 (17)	1 (12.5)	
10,000-100,000	3 (25)	0	
>100,000	7 (58)	7 (87.5)	
Largest tumor size (cm)			
<3	3 (25)	0	0.245 (NS)
3-5	0	0	
>5	8 (67	7 (87.5)	
Missing data	1 (8)	1 (12.5)	
FIGO staging of disease			
I	0	0	0.255 (NS)
II	0	0	
III	11 (92)	5 (62.5)	
IV	1 (8)	3 (37.5)	
WHO prognostic score			
7-12	7 (58)	2 (25)	0.197
>12	5 (42)	6 (75)	
β-hCG prior to EP-EMA			
<50	4 (33)	4 (50)	0.264 (NS)
51-100	0	1 (12.5)	
101-500	5 (42)	0	
1-1000	0	1 (12.5)	
1000-10,000	3 (25)	1 (12.5)	
>10,000	0	1 (12.5)	
Site of metastasis			
Lungs	8 (67)	2 (25)	0.324 (NS)
Lungs + brain/liver	2 (17)	3 (37.5)	
Lungs + vagina, bladder	1 (8)	1 (12.5)	
Lungs + pancreas, GI	1 (8)	2 (25)	
Adjunctive surgery done			
Yes	8 (67)	7 (87.5)	0.607 (NS)
No	4 (33)	1 (12.5)	

NS=Nonsignificant, β-hCG=β-human chorionic gonadotropin, GI=Gastrointestinal, EP-EMA=Etoposide and cisplatin-etoposide, methotrexate, and D-actinomycin, FIGO=International Federation of Gynecology and Obstetrics

as neutropenia, thrombocytopenia, and anemia as the most frequently reported toxicities ranging from 20% to as high as 68%.[10,11,22] In a study conducted by Han *et al*. in 2012, they attributed the higher reported rates of toxicities with the use of EP-EMA to exposure of patients to other chemotherapy before shifted to salvage or second line chemotherapy in the form of EP-EMA. Hence, exposure to several EMACO cycles has a cumulative effect on myelosuppression once patients are shifted to the salvage treatment.[22] In contrast,

when EP-EMA was used as first-line chemotherapy for high-risk GTN, Grade 3–4 anemia, leukopenia, and thrombocytopenia were observed in just 3%, 12%, and 3% of patients, respectively.[10]

Aside from myelosuppression, another adverse effect reported was electrolyte imbalance in the form of hypokalemia and hypomagnesemia. In our study, this was reported in 58% of the patients. Severity ranged from Grade 1–4; most common are Grade 1 hypokalemia and Grade 2 and 4 hypomagnesemia. Electrolyte disturbance is commonly associated with the use of platinum-containing chemotherapeutic agents, particularly with cisplatin.[23] The most commonly associated electrolyte imbalance brought about by cisplatin is low magnesium or hypomagnesemia.[24,25] This is primarily attributed to renal magnesium wasting and/or reduced intestinal absorption.[25] On the other hand, low potassium tends to coexist with low magnesium since magnesium is a cofactor of ATP. When hypomagnesemia due to cisplatin is noted, cells also loose potassium because of failure of sodium-potassium pumps that are dependent to magnesium to close potassium channels.[23]

Adjunctive surgery in the form of hysterectomy is beneficial in patients with bulky uterine masses because it reduces the tumor load. Thoracotomy can also be done for lung masses that persist despite intensive chemotherapy. In our study, most patients had adjunctive surgery done, but performance of surgery failed to show any significant effect on achieving remission with EP-EMA. This may be because most of those who underwent surgery were operated on prior to institution of EP-EMA.

Conclusion

This study showed that response to etoposide and cisplatin-etoposide, methotrexate, and actinomycin D (EP-EMA) as salvage chemotherapy has improved in the past decade. Even though it did not show a statistical significance due to a limited number of patients, a trend in the study identified early stage of disease, limited site of metastasis to the lungs, WHO prognostic score of between 7 and 12, and low β-hCG level at the start of EP-EMA treatment as probable factors that may lead to complete remission among patients with EMACO-resistant high-risk GTN treated with EP-EMA. Patients that are classified as ultra high risk (score or 13 or more) and/or those with Stage IV disease may have poorer response even with salvage chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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