Original Article

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Quick Response Code:

Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_32_22

Third-line chemotherapy after resistance to Etoposide, Cisplatin-Etoposide, Methotrexate, Actinomycin (EP-EMA) in high risk gestational trophoblastic neoplasia: Experience at the Philippine General Hospital

Julie Ann B. Bolastig-Canson[1], Agnes L. Soriano-Estrella[1]

Abstract:

OBJECTIVE: To describe the experience of the Division of Trophoblastic Diseases of the Philippine General Hospital with the various third-line chemotherapeutic regimens among high-risk gestational trophoblastic neoplasia (GTN) patients who experienced resistance after receiving the etoposide, cisplatin–etoposide, methotrexate, actinomycin (EP-EMA) regimen.

MATERIALS AND METHODS: This was a 17-year descriptive study that included all patients who used various salvage chemotherapy after resistance to EP-EMA as treatment for metastatic, high-risk GTN at the Philippine General Hospital from January 2002 to December 2018. The medical records of eligible patients were retrieved and assessed. All abstracted data were analyzed retrospectively. Descriptive statistics were used to compute for percentages for the various demographic characteristics of the sample population.

RESULTS: From January 2002 to December 2018, a total of 291 patients with metastatic, high-risk gestational GTN were treated at the Philippine General Hospital. Of these, only seven patients received various third-line chemotherapy regimens after resistance to EP-EMA. One patient was excluded due to incomplete data. Among the third-line chemotherapeutic regimens used, 3 patients received paclitaxel/carboplatin, two of whom went into remission while one expired. One patient had vincristine, bleomycin, and cisplatin (VBP) with two adjunctive surgeries in the form of hysterectomy and thoracotomy. She also went into remission. Two patients received paclitaxel–cisplatin/paclitaxel–etoposide (TP/TE) as third line of treatment. The first was shifted back to EP-EMA and eventually developed chemoresistance to EP-EMA and had multiple toxicities. After multidisciplinary conference with the patient and family, they decided to go home and refused further chemotherapy. The other patient had TP/TE followed by bleomycin–etoposide–cisplatin, with adjunctive hysterectomy. Despite multiple cycles of chemotherapy, the disease persisted. She was offered palliative care and the family decided to bring her home. Both patients eventually expired at home.

CONCLUSION: No conclusion can be made about the most effective third line chemotherapy for resistant high-risk GTN because of the limited cases included in this study. An individualized approach is still recommended. Physicians and centers for patients caring for such patients are encouraged to report their experience to improve the management of future patients.

Keywords:

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

[1]*Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines, Manila*

Address for correspondence:
Dr. Julie Ann B. Bolastig-Canson, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines, Taft Avenue, Ermita, Manila 1000 Philippines.
E-mail: lexjul.yoram@gmail.com

Submitted: 04-Mar-2022
Revised: 04-May-2022
Accepted: 17-May-2022
Published: 07-Oct-2022

How to cite this article: Bolastig-Canson JA, Soriano-Estrella AL. Third-line chemotherapy after resistance to Etoposide, Cisplatin-Etoposide, Methotrexate, Actinomycin (EP-EMA) in high risk gestational trophoblastic neoplasia: Experience at the Philippine General Hospital. Philipp J Obstet Gynecol 2022;46:162-70.

Introduction

Gestational trophoblastic diseases (GTDs) are classified clinically into the benign and malignant forms. The hydatidiform moles, complete and partial, as well as the exaggerated placental site and placental nodules are considered the benign forms of GTD, while gestational trophoblastic neoplasia (GTN) is the term now commonly applied to the malignant end of the spectrum of GTDs. It includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These tumors are locally proliferative, have the ability to invade normal tissue, and the potential to metastasize outside of the uterus.[1]

GTN is diagnosed based on the patient's clinical presentation, supported by imaging studies and beta human chorionic gonadotropin (hCG) titers. Primary treatment remains to be chemotherapy and the choice of treatment protocol is based on the FIGO 2000 Staging System [Table 1] and Modified WHO Prognostic Scoring System [Table 2]. Using the aforementioned classification systems, patients with nonmetastatic or stage I disease as well as those with metastatic, low-risk disease are given single-agent chemotherapy in the form of either methotrexate or actinomycin D. On the other hand, metastatic, high-risk patients are started on multiple agent chemotherapy with the EMACO regimen, composed of etoposide, methotrexate, actinomycin D, cyclophosphamide, and oncovin (vincristine) being the most commonly used.[2] Despite the good response rate to EMACO, a proportion of patients develop resistance and are, therefore, shifted to a second-line chemotherapy. In this case, the EP-EMA regimen, which replaces the Cyclophosphamide and Oncovin component of EMACO with Etoposide and Cisplatin is the most commonly used. Following resistance to EP-EMA, no recommendation is available as to the next chemotherapy regimen that should be used. Succeeding chemotherapy after EP-EMA are mostly based on case reports due to the rarity of the condition. Locally, no study has so far focused on this issue. This study was, therefore, undertaken to describe the institution's experience on the various third-line chemotherapy regimens used after resistance of high-risk GTN patients to the etoposide, cisplatin-EMA (EP-EMA) regimen. The following are the study's objectives:

Table 1: FIGO 2000 anatomic staging for gestational trophoblastic neoplasia

Stage	Description
Stage I	Disease confined to the uterus
Stage II	Disease extends to outside the uterus but confined to the pelvic organs
Stage III	Pulmonary metastasis
Stage IV	Metastasis to other sites

FIGO: International federation of gynecology and obstetrics

Table 2: WHO prognostic score

Prognostic factors	Score			
	0	1	2	4
Age	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Pregnancy interval (months)	<4	4-6	7-12	>12
Beta hCG titer (mIU/mL)	<1000	1000-<10,000	10,000-100,000	>100,000
Size of largest tumor (cm)	<3	3-5	>5	
Site of metastasis		Spleen, kidney	GI tract	Liver, brain
Number of metastasis		1-4	5-8	>8
Prior chemotherapy			Single-agent	≥2 agents

hCG: Human chorionic gonadotropin

General objective

To describe the experience of the Division of Trophoblastic Diseases of the Philippine General Hospital with the various third-line chemotherapeutic regimens among high-risk GTN patients who experienced resistance after receiving the EP-EMA regimen.

Specific objectives

1. To ascertain the incidence of patients who used other salvage chemotherapy after with EP-EMA from January 2002 to June 2018
2. To determine the demographic and clinical profile of patients who presented with resistance with the EP-EMA in terms of age, gravidity, parity, antecedent pregnancy (complete or partial mole, term delivery, abortion/unknown), histology or clinically diagnosed GTN, site of metastasis, number of metastasis, WHO FIGO prognostic score, number and type of previous chemotherapy, previous surgery
3. To enumerate the types of third-line chemotherapy protocols used during the study period
4. To describe the treatment response to third-line chemotherapy protocols in terms of:
   a. Treatment outcome categorized as remission, chemoresistance, or death
   b. Number of chemotherapeutic cycles administered to achieve remission
   c. Toxicities brought about by the third-line chemotherapeutic regimens.

Materials and Methods

Study design

This was a retrospective descriptive study that was approved by the institution's technical and ethical review board.

Patient population

This study included all patients who used third-line chemotherapy after resistance with EP-EMA as treatment for metastatic, high-risk GTN at the Philippine General

Hospital from January 2002-December 2018. Patients diagnosed with nonmetastatic and low-risk GTN, those with histologic diagnosis of placental site trophoblastic tumor or epithelioid trophoblastic tumor, as well as those with incomplete clinical record were not included in the study.

Description of the study procedure

A review of the records of the Section of Trophoblastic Diseases of the Department of Obstetrics and Gynecology of the Philippine General Hospital from January 2002 to December 2018 were done to identify high-risk GTN patients who used other salvage chemotherapy regimens after resistance to EP-EMA. The medical records of eligible patients were then retrieved and assessed. Only the data pertinent to the specific objectives of the study were abstracted from the medical records and recorded in a patient data form. The following data were extracted:

a. Age
b. Gravidity and parity
c. Antecedent pregnancy
d. Interval between the last pregnancy and the diagnosis of GTN
e. Method of arriving at the diagnosis, either by histopathology or by clinical presentation
f. Serum beta hCG at the start of the third-line chemotherapy regimen
g. Number of chemotherapeutic cycles prior to shifting to third-line chemotherapy
h. FIGO stage
i. Number of chemotherapeutic courses needed to achieve remission
j. Duration of treatment delays
k. Dose reductions in percentage
l. Clinical, hematological and biochemical toxicities
m. Performance and timing of surgery
n. Histology, if available
o. Treatment outcome (e.g., remission, resistance or death)
p. Cause of death.

Description of outcome measurements

The primary outcome of the study was the primary remission rate. The definition of response used in GTN differs from conventional solid tumor criteria since serum beta hCG concentrations correlate accurately with the behavior of the tumor. Complete response or remission is defined as three consecutives normal beta hCG 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 beta hCG concentration is normal. Secondary outcome included the toxicities brought about by the administration of the various third-line chemotherapeutic regimens. Toxicities were categorized using the WHO toxicity scoring system [Table 3].

Data analysis

All the data were encoded and tabulated using the data processing software, Microsoft Excel, which were collated, and checked periodically for consistency and completeness. Descriptive statistics were used to compute for percentages for the various demographic characteristics of the sample population.

Results

From January 2002 to December 2018, a total of 291 patients with metastatic, high-risk GTN were managed at the Section of Trophoblastic Diseases, Department of Obstetrics and Gynecology of the Philippine General Hospital. Of these, 7 patients (2.4%) developed resistance to both EMACO and EP-EMA and were thus given third-line chemotherapy. One patient was excluded due to incomplete data. Of the six patients included in the study, three received paclitaxel/carboplatin combination, one was given VBP, and two received paclitaxel–cisplatin/paclitaxel–etoposide (TP/TE). Table 4 shows the third line of chemotherapy used by the patients.

Clinical and demographic profiles of gestational trophoblastic neoplasia patients

Table 5 shows the demographic and clinical characteristics of the patients included in the study. The patients' age ranged from 17 to 44 years old. Out of the 6 patients, 3 were from 20 to 30 years old. Hydatidiform mole was the antecedent pregnancy of four patients. Eighty-three percent (5/6) had FIGO Stage IV disease on diagnosis. The interval from the index pregnancy to diagnosis of GTN was more than 13 months in 83% (5/6) of patients, and 67% (4/6) of patients had a histopathological diagnosis of Choriocarcinoma.

Response to 3rd line of treatment, adjunctive therapies, and toxicities

All patients included in the study received EMACO as first-line chemotherapy and EP-EMA as second-line chemotherapy. Three patients received the combination of paclitaxel/carboplatin after resistance to EP-EMA. The first case was a 21-year-old, gravida 2 para 0, (0020) who was diagnosed with GTN IV: 13 (choriocarcinoma) with metastasis to the brain. She had a hysterectomy for tumor rupture prior to chemotherapy. She had a hydatidiform mole 3 years prior to the diagnosis of GTN. She underwent whole-brain irradiation, 5 cycles of EMACO and 5 cycles of EP-EMA before receiving to paclitaxel/carboplatin chemotherapy due to resistance. The beta hCG before starting the third-line treatment was 11.93 mIU/mL. She went into remission after four cycles of paclitaxel/carboplatin, inclusive of three consolidation therapies, during which episodes of mild neutropenia were experienced. Total duration of treatment

Table 3: WHO common toxicity criteria grade

	Toxicity				
	0	1	2	3	4
Bone marrow					
WBC (cells/mm^3)	>4	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
Platelet	WNL	75.0-normal	50-74.9	25-49.9	<25.0
Hb (g/dl)	WNL	10-normal	8.0-10.0	6.5-7.9	<6.5
Granulocytes/ bands (cell/mm^3)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Lymphocytes (cells/mm^3)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Gastrointestinal					
Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat 2-5 episodes in 24 h	6-10 episodes in 24 h	>10 episodes in 24 h
Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema or ulcers but can eat	Painful erythema, edema or ulcers and cannot eat	Requires parenteral or enteral support
Liver					
Transaminases (SGOT/SGPT)	WNL	<2.5×N	2.5-5.0×N	5.1-20×N	>20×N
Kidney					
Creatinine	WNL	<1.5×N	1.5-3.0×N	3.1-6.0×N	>6.0×N
Alopecia	No hair loss	Mild hair loss	Pronounced or total hair loss		
Metabolic					
Hypomagnesemia (mg/dl)	>1.4	1.2-1.4	0.9-1.1	0.6-0.8	<0.5
Skin	None	Scattered macular or popular eruption or erythema that is asymptomatic	Scattered macular or popular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, popular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis

WBC: White blood cells, Hb: Hemoglobin, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, WNL: Within normal limits

Table 4: Third-line chemotherapy used

Chemotherapeutic regimens	Number of cases (*n*=6), *n* (%)
Paclitaxel/carboplatin	3 (50)
VBP	1 (17)
TP/TE shifted back to EP-EMA	1 (17)
TP/TE shifted to BEP	1 (17)

VBP: Vincristine, belomycin, and cisplatin, TP/TE: Paclitaxel–cisplatin/ paclitaxel–etoposide, BEP: Bleomycin–etoposide–cisplatin, EP-EMA: Etoposide, cisplatin–etoposide, methotrexate, actinomycin

was 1 year. Unfortunately, she failed to follow up after achieving remission. The second case was a 30-year-old, gravida 4 para 3 (3013), diagnosed with GTN Stage IV: 13 (choriocarcinoma) with metastasis to the brain and liver. She had a hysterectomy for impending tumor rupture prior to chemotherapy. Her antecedent pregnancy 2 years ago prior to diagnosis of GTN was a hydatidiform mole. She underwent whole-brain irradiation, 10 cycles of EMACO and 1 cycle of EP-EMA before receiving paclitaxel/ carboplatin due to resistance. The beta hCG before starting the third-line treatment was 7.14 mIU/mL. She achieved remission after 4 cycles of paclitaxel/carboplatin inclusive of three cycles of consolidation therapy. She had 1-year duration of treatment with mild neutropenia. She was also lost to follow-up after treatment.

The third case was a 44-year-old, gravida 8 para 5 (5035), diagnosed with GTN Stage IV: 14, with metastasis to the lungs and pancreas. She had hysterectomy for complete hydatidiform mole 4 years before the diagnosis of GTN. She had 4 cycles of EMACO and shifted to EP-EMA due to resistance. However, after the 5th cycle of EP-EMA, an increase of beta hCG was noted; thus, she underwent left posterolateral thoracotomy, left pneumonectomy with en bloc resection of the 8th and 9th rib, and chest tube insertion on the left. Histopathology showed multiple foreign body granulomas with areas of hemorrhage, chronic granulomatous inflammation with caseation necrosis, and Langhans-type giant cell reaction consistent with tuberculous etiology. EP-EMA was continued for one more cycle, but beta hCG continued to increased. Third-line chemotherapy in the form of paclitaxel/carboplatin was then started. The beta HCG levels prior to starting of the 3rd line chemotherapy was 40,650 mIU/mL. She received three cycles of paclitaxel/carboplatin chemotherapy, during which she encountered multiple toxicities like anemia, neutropenia, thrombocytopenia, pneumonia, and intra-abdominal abscess. The patient expired due to sepsis after 25 months of treatment. Her beta hCG prior to death was 43,520 mIU/mL.

One patient received VBP after resistance to EP-EMA. She was a 29-year-old, gravida 4 para 2 (2022) with a diagnosis of GTN Stage III: 13 (choriocarcinoma)

Table 5: Clinical and demographic profiles of gestational trophoblastic neoplasia patients

	Variables	Number of Cases (*n*=6)	Percentage (%)
Age (year old)	<15	0	0
	16-20	1	17
	20-30	3	50
	31-40	0	0
	41-45	2	33
	>46	0	0
Gravidity	G1	1	17
	G2	1	17
	G3	0	0
	G4	3	50
	>G5	1	17
Parity	Nullipara	1	16.67
	P1	1	16.67
	P2	2	33
	P3	1	16.67
	P4	0	0
	>P5	1	16.67
Antecedent pregnancy	Hydatidiform mole (unspecified)	3	50
	Complete mole	1	16.67
	Partial mole	0	0
	Term delivery	1	16.67
	Abortion/ectopic	1	16.67
Figo stage	II: High risk	0	0
	III: High risk	1	17
	IV	5	83
Interval from index pregnancy to diagnosis of GTN	< 4 months	1	17
	4-7 months	0	0
	7–13 months	0	0
	>13 months	5	83
Histology	Invasive mole	0	0
	Choriocarcinoma	4	67
	Clinically diagnosed GTN	2	33
Serum beta HCG prior 3rd line of chemotherapy	<1000 mIU/mL	4	67
	1000-10,000 mIU/mL	0	0
	10,000-100,000 mIU/mL	2	33
	>100,000 mIU/mL	0	0
Number of chemotherapeutic cycle with EMACO prior to EP-EMA	1-2	1	17
	3-4	2	33
	>5	3	50
Number of chemotherapeutic cycle with EP-EMA prior to 3rd line	1-2	1	17
	3-4	0	0
	>5	5	83

with metastasis only to the lungs. She had a molar pregnancy 7 years prior to the diagnosis of GTN, for which she underwent suction curettage and received chemoprophylaxis with Methotrexate. She had 2 cycles of EMACO chemotherapy, then encountered resistance thus, total abdominal hysterectomy was done as an adjunctive surgery. Histopathology result was adenomyosis, proliferative endometrium and chronic cervicitis with focal squamous metaplasia. There was no evidence of gestational trophoblastic neoplasia. She then had seven cycles of EP-EMA, but again encountered chemoresistance. Her beta hCG at this point was 3,109.25 mIU/mL. Thoracotomy with wedge resection of the right pulmonary mass was done, which revealed Choriocarcinoma. A week after the operation, beta hCG went down to 264.9 mIU/mL. Fifteen days postsurgery, she was started with VBP, but it was discontinued after 2 days due to multiple toxicities such as electrolyte imbalance, stomatitis, myelosuppression, febrile neutropenia, and ileus. At this point, it was decided not to continue the chemotherapy. She was discharged with beta hCG level of 4.6 mIU/mL. Strict beta hCG monitoring was done and she remained in remission for 2 years after discharge after which she was lost to follow-up.

Two patients had TP/TE as their 3rd line of chemotherapy after resistance to EP-EMA. The first patient was a 44 year old, gravida 4 para 2 (2022), with clinical diagnosis of GTN Stage IV: 17 with metastasis to the lung, left kidney and spleen. On presentation, 4 years after an abortion, she was initially diagnosed as a case of ruptured ectopic pregnancy. She underwent an emergency exploratory laparotomy with bilateral salpingectomy, evacuation of hematoma, ligation of bleeders, and repair of the common iliac vein. The histopathology report of both tubes revealed chronic salpingitis. Her serum beta hCG prior to the operation was 174, 300 mIU/mL, which went up to 219, 000 mIU/mL 3 days after. Metastatic workup for GTN was done and EMACO was started 1 week postsurgery. After 3 cycles of EMACO, she had chemoresistance and was shifted to EP-EMA. Again, resistance was noted after six cycles. Her beta hCG prior to 3rd line of treatment was 54.12 mIU/mL, TP/TE was given for 2 cycles and chemoresistance was again noted. At this time patient had severe hematologic and renal toxicities. Her treatment was reviewed and it was decided to shift back to EP-EMA because the chemotherapy then was reduced to 20% and were not given on time due to toxicities. The beta hCG level was 182.58 mIU/mL prior starting again with EP-EMA. Additional 4 cycles were given, and the last dose was renally adjusted due to renal toxicity. Despite multiple chemotherapies, her beta hCG levels continued to elevate with increased severity of her toxicities. The patient and family decided to go home after a multidisciplinary conference and refused further chemotherapy. She was discharged after 16 months of treatment with beta hCG levels 339,766.95 mIU/mL. She died at home, 2 weeks after going home against medical advice.

The other patient who received TP/TE was a 17-year-old, gravida 1 para 1 (1001) with a diagnosis of GTN Stage IV: 17 (choriocarcinoma) with metastasis to the lungs and brain. She presented with left hemiparesis secondary to intracranial bleed either from bleeding tumor implants or ruptured aneurysm. She had a normal vaginal delivery 3 months prior to the diagnosis of GTN. Her beta hCG levels prior to chemotherapy was 356,684.50 mIU/mL. First cycle of EMACO was with high-dose methotrexate with concurrent whole-brain radiation therapy for 10 days. After 6 cycles of EMACO, she had chemoresistance and was shifted to EP-EMA. However, after seven cycles of EP-EMA, resistance was again noted. At this time, she had multiple toxicities such as hematologic abnormalities and electrolyte imbalances. She had infections and was diagnosed with Major Depressive Disorder with Psychotic Feature. Her beta hCG prior to third-line treatment was 75.19 mIU/mL. She received 2 cycles of TP/TE, but again developed resistance. A fourth line chemotherapy in the form of bleomycin–etoposide–cisplatin (BEP) was given. Serum beta hCG prior to BEP was 303.28 mIU/mL. After the 1st cycle of BEP, there was an increase in the level of beta hCG to 919.01 mIU/mL. Thus, total abdominal hysterectomy was done. Histopathology revealed Choriocarcinoma. Her beta hCG before surgery was 899.33 mIU/mL, then 12 days post operation it decreased to 385.29 mIU/mL. Her 2nd cycle of BEP was only started 42 days postsurgery due to multiple complications. Initially the beta hCG level decreased until after 3rd cycle of BEP, when an increased levels of beta hCG, the highest was noted to be 3,011.31 mIU/mL. This time, it was decided not to pursue with the chemotherapy due to multiple toxicities. Patient and her family were offered palliative care, and they decided to bring the patient home against medical advice after 24 months of treatment. Her last beta hCG was 53, 342.97 mIU/mL. She died at home after a month from discharge.

Table 6 shows the summary of toxicities encountered during treatment. All third line of chemotherapy used had hematologic toxicities.

Discussion

Before the mid-1950's the prognosis of patients with GTN particularly choriocarcinoma, was dismal. Hertz, in the late 1940s, demonstrated that fetal tissues required a large amount of folic acid and could be inhibited by the antifolic compound methotrexate, but it was not until 1956 that Li and associates reported the first complete and sustained remission in a patient with metastatic choriocarcinoma by using methotrexate. Since that report, considerable amount of knowledge and experience has been gained regarding the management of this disease.[1] Today, GTN is recognized as the most curable gynecologic malignancy due to the following reasons: Identification of the hCG as a reliable tumor marker for GTN coupled with availability of quantitative assays for hCG levels, sensitivity of this malignancy to various chemotherapeutic agents, and identification of high-risk factors in the disease process, which allows individualization of treatment. The aggressive use of multiple treatment modalities, using single or multiple-agent chemotherapy regimens, combined with radiation and/or surgery in selected cases have brought about very high remission and survival rates.[1]

Chemotherapy remains to be the primary treatment for GTN, particularly among those with choriocarcinoma or invasive mole. First-line chemotherapy for nonmetastatic and metastatic, low-risk disease is either methotrexate or actinomycin, while EMACO is the most commonly used first-line regimen for metastatic, high-risk disease. Response to treatment is based on serial serum beta hCG determinations. Assessment of response to treatment include the following:[2]

Table 6: Toxicities

Chemotherapy used	Number of patients	Toxicity	Cases	Percentage (%)
Paclitaxel/carboplatin	3	Neutropenia grade 2	2	67
		Anemia grade 2	1	33
		Thrombocytopenia grade 2	1	33
		Infections	1	33
Vincristine, Bleomycin and Cisplatin (VBP)	1	Stomatitis grade 2	1	33
		Febrile neutropenia	1	100
		Hypomagnesemia grade 4	1	100
		Hypokalemia	1	100
		Ileus secondary to hypokalemia	1	100
Paclitaxel-Cisplatin/ Paclitaxel-Etoposide (TP/TE)	2	Anemia Grade 2	2	100
		Neutropenia	2	100
		Granulocytopenia grade 3	2	100
		Hypomagnesemia grade 2-3	2	100
Bleomycin- Etoposide- Cisplatin (BEP)	1	Anemia Grade 2	1	100
		Leukopenia Grade 3	1	100
		Thrombocytopenia Grade 2	1	100
		Granulocytopenia grade 4	1	100
		Hypomagnesemia Grade 1	1	100
		Hypokalemia	1	100

1. Adequate response: One log fall, or >50% fall from the baseline
2. Partial response: <50% fall from baseline
3. Plateau: <10% fall or rise from baseline
4. Biochemical remission: 3 consecutive normal serum beta hCG levels (≤5 mIU/mL)
5. Resistance: 2 plateauing values, 1 rising weekly βhCG titer or appearance of new metastasis.

Despite treatment with primary combination chemotherapy, 17%–30% of women with metastatic, high-risk GTN will manifest resistance to chemotherapy. In such cases, second-line chemotherapy with or without adjuvant resection of resistant foci offer eventual cure.[3]

Based on the study by Singhal *et al*., the WHO risk score and presence of metastatic disease predict the probability of developing chemotherapy resistance and disease relapse. Risk of chemotherapy resistance was higher in women with intermediate-risk score (5–6), and risk of relapse was more in those with ultra-high-risk score (≥13).[4]

The EP-EMA regimen, which substitutes etoposide and cisplatin for cyclophosphamide and vincristine in the EMA-CO regimen is the most commonly reported second-line chemotherapy regimen. The reported remission rate after salvage chemotherapy often in conjunction with surgery ranges from 75% to as high as 85% with a survival rate of 61%.[5,6] Associated toxicities are myelosuppression and hepatotoxicity resulting to treatment delays.[4,5,7-9]

Paclitaxel, the first taxane in clinical trials, is active against a broad range of cancers that are generally considered to be refractory to conventional chemotherapy. Its activity against choriocarcinoma cells was first demonstrated in 1995 by two *in vitro* studies. Data of these two studies suggest the high sensitivity of choriocarcinoma cells to Paclitaxel and clinical trials in chemotherapy-refractory patients was advised.[9-11] Since then, a handful of case reports have been published documenting the possible use of paclitaxel either alone or in combination with other agents in the treatment of highly resistant GTN.[9,12-15] In these case reports, sustained remission was achieved. Combination with carboplatin was based on evidence showing antineoplastic synergism between the two agents. Dose and schedule used were based on that used for ovarian CA.

Out of the three patients who received the combination of Paclitaxel and Carboplatin in our study, two patients were able to achieve remission. They were aged 21 and 30 years old, both were diagnosed with choriocarcinoma with metastasis to the brain, both underwent whole-brain irradiation and total abdominal hysterectomy for tumor rupture and impending tumor rupture. The beta HCG levels were as low as 7.14 mIU/mL and 11.93 mIU/mL prior to 3rd line of treatment, and underwent 4 cycles of paclitaxel and carboplatin chemotherapy to achieve remission. The treatment duration was only a year with mild toxicity of neutropenia.

The combination of cisplatin, vinblastine, and bleomycin (PVB) has been used in the past to induce remissions in some patients with resistant high-risk GTN. Gordon *et al*. studied eleven patients who were treated with PVB combination chemotherapy after failure of conventional triple-agent therapy with methotrexate, dactinomycin, and cyclophosphamide for GTD. Of

ten evaluated patients, five (50%) achieved negative titers. Sustained remission was achieved in only two patients (20%). Major hematologic toxicities and two deaths due to sepsis occurred in this group of patients. Although this combination exhibits activity, its clinical use in the treatment of refractory trophoblastic disease is limited.[16,17] In our study, one patient used vincristine instead of vinblastine which are both vinca alkaloids. She was given cisplatin, vincristine, and bleomycin after resistance to EP-EMA, but was not able to complete the regimen due to multiple toxicities.

A study by Wang *et al*. evaluated the efficacy and toxicity of paclitaxel and cisplatin alternating with paclitaxel and etoposide doublet regimen (TP/TE) for salvage of patients with high-risk GTN who had failed chemotherapy and treatment-induced toxicity from previous chemotherapy mostly from EMACO and EP/EMA. Results were promising with an overall survival of 70% for patients who had previous failed chemotherapy and 75% for those with prior toxicities. The TP/TE regimen was well tolerated, with only one patient discontinuing therapy because of toxic effects. The conclusion of the study was that TP/TE was an effective, well-tolerated, salvage treatment for relapsed patients who are heavily pretreated for GTN.[6,17] However, in this study, TP/TE was unable to induce remission in the two patients who were given the regimen. Multiple toxicities were likewise encountered with its use.

In a study of Lurain *et al*., the BEP protocol, which employs bleomycin, etoposide, and cisplatin, was currently their first choice for treating patients with high-risk GTN resistant to EMA-CO/EMA-EP. In their study, BEP regimen induced complete response in about 74% of persistent/relapsed high-risk GTN.[18] However, in our study, BEP was only given after resistance to TP/TE with poor outcome.

Conclusion and Recommendation

No conclusion can be made about the most effective third line chemotherapy for resistant high-risk GTN because of the limited cases included in this study. However, the use of paclitaxel/carboplatin showed promising result, since two of the three patients given this regimen went into remission.

In the treatment of patients with GTN, particularly those with highly resistant disease, an individualized approached should still be observed. Clinicians and centers caring for such patients should report their experience to shed light on the proper management and care of future patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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