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Clinical characteristics, management, and outcome of gestational trophoblastic neoplasia patients with brain metastasis: A 10-year experience at the Philippine General Hospital

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Abstract:

OBJECTIVE: This study aimed to determine the clinical characteristics, management, and outcome of gestational trophoblastic neoplasia (GTN) patients with brain metastasis.

MATERIALS AND METHODS: This was a 10-year descriptive study that included all patients with brain metastasis from GTN. Patients' sociodemographic and clinicopathological profiles were described. Using Kaplan–Meier survival curve, the survival time was determined.

RESULTS: From January 1, 2010, to December 31, 2019, there were 33 GTN patients with brain metastasis. Four were excluded from the study due to incomplete records. Twenty-nine patients were included in the study. Nineteen (65.51%) patients presented with neurologic symptoms upon diagnosis and one (3.44%) during treatment. All received etoposide, methotrexate, actinomycin, oncovin (EMACO) as first-line treatment. Five (17.24%) patients were given induction chemotherapy with low-dose etoposide–cisplatin. Seventeen (58.62%) patients underwent whole-brain radiation and two (6.89%) were given intrathecal methotrexate. Thirteen patients (44.82%) achieved biochemical remission with EMACO chemotherapy. Four patients (13.79%) had resistance to EMACO and were given Etoposide Cisplatin Etoposide Methotrexate Actinomycin (EP EMA). Four patients (13.79%) underwent an adjunctive hysterectomy. Four patients (13.79%) died during treatment. One patient (3.44%) was unable to continue her chemotherapy because she got pregnant before her first consolidation course. There were eight early deaths (<4 weeks of admission) and hence were excluded in the analysis. Three patients who went into biochemical remission relapsed on the 1st, 2nd, and 3rd months after their last consolidation course, respectively. The median follow-up time was 27 months. After excluding early deaths, the survival rate between 3 and 7 years after treatment is at 61.9%. The mean survival time was 5.43 years. Six surviving patients were contacted. Five (17.24%) of them had resumed their everyday life, and one is currently undergoing chemotherapy.

CONCLUSION: The study was able to document brain metastasis from GTN to be 14.28% (29/203) among metastatic high-risk admissions. The biochemical remission rate from first-line treatment was of 61.90% (13/21) and resistance rate was 19.04% (4/21). Lost to follow up after achieving biochemical remission was a challenge encountered.

Keywords:

Brain metastasis, gestational trophoblastic neoplasia, intrathecal methotrexate, whole-brain radiation

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Introduction

Gestational trophoblastic neoplasia (GTN) is a group of uncommon malignant gynecologic tumors arising from the trophoblast, including invasive mole, choriocarcinoma, and placental site epitheloid trophoblastic tumor.[1] This malignancy group has a remarkable sensitivity to chemotherapy, and the cure rates are almost 100% in the low-risk group and 95% in the high risk with the current chemotherapy regimen.[2,3] However, some conditions make the prognosis of certain GTN patients poor such as those with the far advanced disease at presentation and long interval time from the time antecedent pregnancy.[4] In addition, brain metastasis is regarded as a poor prognostic factor.[5,6] Brain metastasis from GTN is rare, with an incidence of 3% to 21.4%.[5] The survival rates of patients with brain metastasis are significantly reduced to 69.8%–71.1%.[7,8]

Etoposide, methotrexate, actinomycin, oncovin (EMACO) chemotherapy is the first-line treatment for metastatic high-risk GTN patients. In patients with brain metastases, an increase in the methotrexate infusion to 1 g/m^2 will help the drug cross the blood-brain barrier. Some centers use intrathecal methotrexate (MTX) 12.5 mg which is given during the CO part when EMACO is used or with the EP part in the.

Etoposide cisplatin, etoposide, methotrexate, actinomycin (EP/EMA) regimen. Some centers may give whole-brain radiotherapy 3000 cGy in 200 cGy daily fractions concurrent with chemotherapy use, stereotactic or gamma knife radiation to treat existing or residual brain metastases after chemotherapy.[9]

Patients with EMACO resistance are mostly salvaged with paclitaxel and Etoposide, alternating with paclitaxel and cisplatin (TE/TP) or with (EP/EMA). In China, the 5 FU-based floxuridine, actinomycin-D, etoposide vincristine (FAEV) regimen is also an effective salvage treatment. For women who have resistance from EP/EMA or TE/TP, options for treatment will include several other standards or high-dose chemotherapy regimens such as etoposide, ifosfamide, and cisplatin or carboplatin, BEP (bleomycin, etoposide, and cisplatin), 5-fluorouracil, actinomycin-D, FAEV high-dose chemotherapy with autologous bone marrow or stem cell transplant and immunotherapy with pembrolizumab can be offered after failure of salvage chemotherapy.[9]

At present, in our institution, high-dose EMACO with concomitant whole-brain radiation is the protocol being followed. Initial reports of the success of treatment in the Philippine General Hospital showed a remission rate of 35% for patients initially presenting with brain metastasis and 15% for patients who developed brain metastasis during or after initial treatment. There are, however, several factors that contribute to the lower survival rate, which include the inability to give systemic chemotherapy on time and lack of surgical intervention.[10]

Among GTN patients with brain metastasis who present with increased intracranial pressure, craniotomy is indicated for central nervous system (CNS) decompression and stabilization. Isolated nodules resistant to drug treatment are excised and this therapeutic regimen results in primary remission of 65% to 80% of and up to 90% cure.[11]

General objective

To determine the clinical outcome of GTN patients with brain metastasis managed at the Philippine General Hospital from January 1, 2010, to December 31, 2019.

Specific objective

1. To determine the incidence of GTN with brain metastasis patients admitted and managed at the Philippine General Hospital from January 1, 2010 to December 31, 2019
2. To describe the clinical profile of GTN patients with brain metastasis patients in terms of age, antecedent pregnancy, interval months from the index of pregnancy, pretreatment serum beta human chorionic gonadotropin (hCG) (mIU/mL), largest tumor size, site of several metastasis per site previously failed chemotherapy, histopathology diagnosis if applicable, WHO score, International Federation of Gynecology and Obstetrics (FIGO) stage, neurologic symptoms and size and location ofbrain metastasis
3. To determine the different treatment modalities used either high-dose methotrexate with concomitant whole-brain radiation or MTX and utilization of induction chemotherapy
4. To describe the treatment response of the managed patients as to:
   a. Mean number of cycles of the first-line chemotherapy before biochemical remission or resistance
   b. Number of patients who had biochemical remission or resistance to the first-line chemotherapy
   c. Number of patients who had toxicities and adverse reactions encountered during chemotherapy
   d. Number of patients who needed adjunctive procedures
   e. Number of patients who needed salvage chemotherapy
   f. Number of patients who died during and or after treatment
   g. Survival time of the patients included in the study.

Materials and Methods

Study design

This was a descriptive study that was approved by the Institutional Review Board, University of the Philippines Manila Research Ethics Board.

Patient population

Inclusion criteria

This study included all GTN patients who had brain metastasis admitted at the Philippine General Hospital from January 1, 2010 to December 31, 2019.

Exclusion criteria

Patients diagnosed with double primary malignancy, those with a histologic diagnosis of placental site trophoblastic tumor or epithelioid trophoblastic tumor, as well as those with the incomplete clinical record were excluded from the study [Figure 1].

Description of the study procedure

A review of the ward reports of the division of Trophoblastic Diseases of the Department of Obstetrics and Gynecology of the Philippine General Hospital from January 1, 2010, to December 31, 2019, was done to identify GTN patients with brain metastasis. The medical records of eligible patients were retrieved and assessed. Only the data pertinent to the study's specific objectives were abstracted from the medical records and recorded in a patient data form. The following data were extracted:

1. Age
2. Antecedent pregnancy
3. Interval months from the index of pregnancy
4. Pretreatment serum beta hCG (mIU/mL)
5. Largest tumor size
6. Site of number of metastasis
7. Previously failed chemotherapy
8. Histopathology diagnosis, if applicable
9. WHO score
10. FIGO stage
11. Neurologic presentation
12. Administration of high-dose methotrexate with concomitant whole-brain radiation or MTX
13. Number of cycles of the first-line chemotherapy before biochemical remission or resistance
14. Biochemical remission or resistance to the first-line chemotherapy
15. Toxicities and adverse effects encountered during chemotherapy
16. Administration of induction chemotherapy
17. Adjunctive surgery done
18. Need for salvage chemotherapy
19. Identify the salvage chemotherapy used
20. Death or who were lost to follow-up
21. Date of the last consult.

To determine the survival time, date of the diagnosis of the disease, date of first chemotherapy administration and the date of the last recorded consult was obtained. To assess the patient outcome, survivors were contacted through phone or social media in the first half of 2021.

Description of outcome measurements

The primary outcome measure was the survival time which was determined using the Kaplan–Meier survival curve. The biochemical remission rate to first-line chemotherapy was also noted. Biochemical remission is defined as three consecutive normal serum beta hCG levels (≤5 miU/mL). On the other hand, resistance is defined as 2 plateauing values, 1 rising weekly beta hCG titer, or the appearance of new metastasis. Upon completion of chemotherapy, radiographic evidence of residual tumor was not considered evidence of disease as long as the beta hCG level remained <5 mIU/mL. Secondary outcomes included the resistance rate, causes of death, toxicities brought about by administering the various chemotherapeutic regimens, and functional outcomes among patients who have achieved biochemical

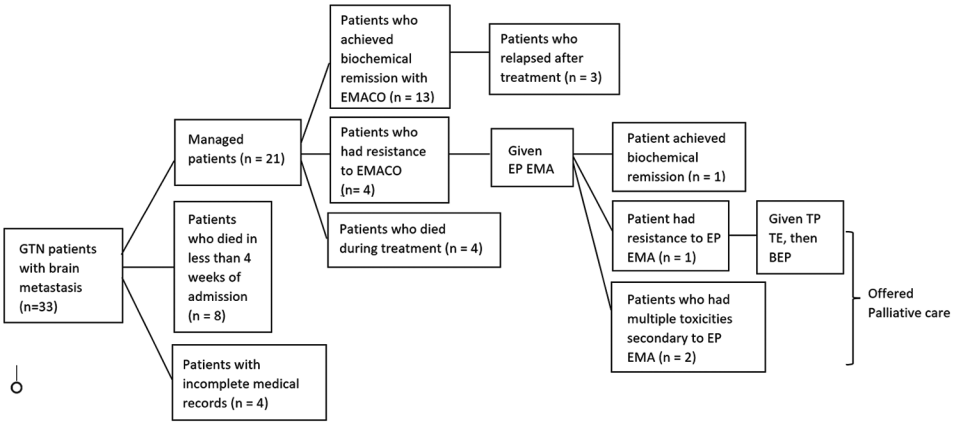

Figure 1: Patient selection, management, and outcome flowchart

remission. Toxicities were categorized using the WHO toxicity scoring system [Table 1].

Data analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the sample population. The survival time was determined using Kaplan–Meier survival curve.

Results

From January 1, 2010, to December 31, 2019, a total of 203 patients with metastatic, high-risk GTN were managed at the division of Trophoblastic Diseases, Department of Obstetrics and Gynecology of the Philippine General Hospital. Of these metastatic high-risk GTN, thirty-three (16.25%) patients had brain metastasis. Among these, four patients were excluded due to incomplete data. There were 29 patients included in the study, 21 of which were managed for at least 1 month, and 8 died in <4 weeks of admission.

Clinical characteristics of gestational trophoblastic neoplasia patients with brain metastasis

Twenty-six patients had a FIGO stage of IV, one patient had a FIGO stage of III who had tumor progression to the brain, and two patients had a FIGO stage of I who had tumor recurrence to the brain. Twenty-six patients had a WHO prognostic score of ≥12, two have ≥7, and one had 3 (A case of tumor recurrence 10 years after remission from her low-risk GTN).

Table 2 shows the clinical characteristics of the 29 patients included in the study. The patients' age ranged from 17 to 52 years old. 79.31% (23/29) were <40 years old, while 20.68% (6/29) were >40 years old. The hydatidiform mole was the antecedent pregnancy in 58.62% (17/29) patients, 34.48% (10/29) for term pregnancy, and 6.89% (2/29) for abortion. The interval from the index pregnancy to the diagnosis of GTN was more than 12 months in 58.62% (17/29) of patients, seven to 12 months in 10.34% (3/29), 4 to 6 months in 17.24% (5/29), and 13.79% (4/29) in <4 months. The pretreatment serum beta hCG in mIU/mL was ≥100,000 in 66.69% (20/29), 10,000 to <100,000 in 27.58% (8/29), and <1,000 in 3.44% (1/29). The largest tumor size was greater or equal than 5 centimeters in 58.62% (17/29), 3–4 centimeters in 31.03% (9/29), and <3 centimeters in 10.34% (3/29). Lung metastasis was observed in 100% of the patients (29/29), liver metastasis in 24.13% (7/29), vaginal metastasis in 17.24% (5/29), kidney metastasis in 17.24% (5/29), splenic metastasis in 10.34% (3/29), vaginal stump metastasis in 6.89% (2/29), and cervix, adrenal, gastrointestinal, and spine metastasis in 3.44% (1/29). 31.03% (9/29) had a number of metastasis

Table 1: WHO common toxicity criteria grading

Toxicty	0	1	2	3	4
WBC (cells/mm^2) leukopenia	>4	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
Platelet	Within normal level	75.0 - Normal	50-74.9	25-49.9	<25
Hemoglobin (g/dL)	Within normal level	10 - Normal	8.0-10.0	6.5-7.9	<6.5
Granulocytes/bands (ANC)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<5
Lymphocytes (cell/mm^2)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<5
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	Painful erythema, edema, or ulcers but can eat	Painful erythema, edema, or ulcers and cannot eat	Requires Parenteral and enteral Support
Transaminases (AST, ALT)	Within normal level	<2.5×normal	2.5-5.0×normal	5.1-20×normal	>6.0×normal
Creatinine	Within normal level	< 1.5×normal	1.5-3.0×normal	3.1-6.0×normal	>6.0×normal
Alopecia (hair loss)	None	Mild	Pronounced or total	-	-
Hypomagnesemia (mg/dL)	>1.4	1.2-1.4	0.5-1.1	0.6-0.8	<0.5
Skin	None	Scattered macular of papular eruption or asymptomatic erythema	Scattered macular or widespread eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, popular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis

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

Table 2: Clinical characteristics of the twenty-nine patients included in the study

Characteristic	Number of cases (*n*=29), *n* (%)
Age at diagnosis (years old)	
<40	23 (79.31)
>40	6 (20.68)
Antecedent pregnancy	
Hydatidiform mole	17 (58.62)
Abortion	2 (6.89)
Term	10 (34.48)
Interval after the index pregnancy and the start of treatment (months)	
<4	4 (13.79)
4-6	5 (17.24)
7-12	3 (10.34)
>12	17 (58.6)
Pretreatment serum βhCG (mIU/mL)	
<1000	None
1000-<10,000	1 (3.44)
10,000-<100,000	8 (27.58)
≥100,000	20 (66.69)
Largest tumor size (cm)	
<3	3 (10.34)
3-4	9 (31.03)
≥5	17 (58.62)
Sites of metastasis	
Lungs	29 (100)
Liver	7 (24.13)
Vagina	5 (17.24)
Kidney	5 (17.24)
Spleen	3 (10.34)
Vaginal stump	2 (6.89)
Cervix	1 (3.44)
Adrenal	1 (3.44)
Spine	1 (3.44)
Gastrointestinal	1 (3.44)
Number of metastasis	
1-4	9 (31.03)
5-8	5 (17.24)
>8	14 (48.27)
Previously failed chemotherapy drugs	
1 (methotrexate)	5 (17.24)
Histology	
Choriocarcinoma	3 (10.34)
Invasive mole	1 (3.44)
Neurologic symptoms	
Present	20 (68.96)
Absent	9 (31.03)

βhCG: β-human chorionic gonadotropin

of 1–4, 17.24% (5/29) had 5–8, and 48.27% (14/29) had metastases of more than 8. Previously failed chemotherapy drugs in the form of methotrexate were present in 17.24% (5/29). Nineteen (65.51%) patients had neurological symptoms upon diagnosis, one (3.44%) had neurological symptoms during management, and nine (31.03%) patients had no neurological symptoms.

Fifteen (51.72%) patients had single brain metastasis, four (13.79%) had two, three (10.34) had three, one (3.44%) had 5, and four (13.79%) were reported to have multiple lesions. The location for brain metastasis was known in 27 patients, and 2 were not identifiable due to a massive hemorrhage. The location of the brain metastasis was as follows: parietal ($n = 6$), frontal ($n = 4$), occiput ($n = 3$), temporal ($n = 1$), frontotemporal ($n = 1$), frontoparietal ($n = 1$), frontal and parietal ($n = 3$), cerebral and cerebellar ($n = 1$), parietal and occipital ($n = 2$), parietal, posterior, and occiput ($n = 1$), frontal and medial ($n = 1$), frontoparietal, frontal, and thalamus ($n = 1$), parietal and superior sagittal sinus ($n = 1$), and lateral ventricle ($n = 1$). The size of brain metastasis ranged from 0.2 cm to 4.0 cm.

Management and outcome of gestational trophoblastic neoplasia patients with brain metastasis

Twenty-one patients were managed for at least 1 month and all received EMACO as first-line chemotherapy [Table 3]. Seventeen (58.62%) patients underwent whole-brain radiation and 2 (6.89%) were given MTX. Five (17.24%) patients were given induction chemotherapy with low-dose etoposide–cisplatin. Thirteen patients (44.82%) achieved biochemical remission. The chemotherapy cycles ranged from 6 to 10 cycles before achieving biochemical remission. The most common toxicities from EMACO chemotherapy [Table 4] were infections of 76.19% (16/21), hypokalemia of 66.66% (14/21), and anemia grade 2–4 of 61.90% (13/21). Nine out of nineteen (47.36%) patients who had with neurological symptoms upon diagnosis achieved biochemical remission. One patient who had neurological symptom during the course of treatment was given palliative care. Four out of nine (44.44%) patients who had no neurological symptoms achieved biochemical remission.

Four patients (19.04%) had resistance to EMACO and were given EP EMA as salvage chemotherapy. EMACO chemotherapy cycles ranged from 5 to 15 prior to resistance. One patient (25%) achieved biochemical remission. Three (75%) patients were offered palliative management secondary to multiple chemotherapy-induced toxicities, chronic tubulointerstitial nephritis with persistent febrile neutropenia MASCC 17–23 and chronic kidney disease Stage 3b. Among these, one patient had chemoresistance to EP EMA, TP TE, and BEP. She had multiple toxicities secondary to her treatment. One patient was administered EP EMA due to tumor relapse and eventually achieved biochemical remission.

Four patients (19.04%) underwent an adjunctive hysterectomy. Two (50%) had the histopathological result of choriocarcinoma, 1 (25%) had an invasive mole, and one did not have results since it was done in another hospital.

Table 3: Characteristics, treatment, and outcome of twenty-one patients managed for at least 1 month

Patient number	Age	Antecedent pregnancy	Neurologic symptoms upon diagnosis	Pretreatment hCG (mIU/mL)	WHO	Treatment	Number of brain metastasis	Status/number of consolidation courses
1	35	Mole	None	39,881	12	S/P TAH, BIIAL for GTN with wedge resection of vaginal mass (no histopath result) EMACO VI WBRT	1	Remission 3 CUC
2	21	Term	Right hemiparesis	80,788	13	EMACO VIII WBRT	1	Remission 3 CUC
3	30	Abortion	Dizziness	393,642	14	High-dose EMACO I WBRT EMACO IX	Multiple	Remission 3 CUC
4	24	Mole	Left sided weakness	219,000	17	High-dose EMACO VI WBRT	1	Remission 3 CUC
5	24	Term	Headache	56,240	14	High-dose EMACO I WBRT EMACO VI	5	Remission 3 CUC
6	31	Term	Nausea and vomiting	489,500	19	EMACO X	2	Remission 2 CUC
7	17	Mole	Right hemiparesis	356,684.50	15	EP I High-dose EMACO I with intrathecal methotrexate EMACO II with intrathecal methotrexate EMACO X	1	Remission 3 CUC
8	55	Term	None	714,100	20	High-dose EMACO I WBRT EMACO VIII (with dose reduction on the first consolidation course) Diagnosis of choriocarcinoma after biopsy of the vaginal mass	Multiple	Remission 3 CUC
9	22	Mole	Headache	202,627.19	17	High-dose EMACO I WBRT EMA EMACO III Modified EMACO I EACO V	3	Remission 3 CUC
10	26	Mole	Left hemiparesis	64,785	10	EMACO I WBRT TAH (invasive mole) EMA EACO II Modified EMACO IV	1	Remission 3 CUC
11	52	Mole	None	2,459,673.15	21	EACO XIII WBRT EMACO XI with 25% reduction in actinomycin, etoposide methotrexate	1	Remission 3 CUC Tumor relapse Ongoing treatment
12	32	Mole	Lower extremity Weakness and pain	760,761.17	15	EMACO X High-dose EMACO I EP II EP EMA with high-dose MTX I WBRT EP EMA XI (with dose reduction)	1	Remission 3 CUC Tumor relapse Tumor progression Remission 1 CUC

Contd...

Table 3: Contd...

Patient number	Age	Antecedent pregnancy	Neurologic symptoms upon diagnosis	Pretreatment hCG (mIU/mL)	WHO	Treatment	Number of brain metastasis	Status/number of consolidation courses
13	33	Mole	None	22,781	12	High-dose EMACO I WBRT EMACO XII High-dose EMACO I EMACO V EP EMA V	Multiple	Remission 3 CUC Tumor relapse Remission 3 CUC
14	37	Term	None Had seizure during the course of treatment	200,000	10	EMACO XV TAHBS EP EMA VII with intrathecal methotrexate (renally adjusted) Diagnosis of choriocarcinoma after biopsy of the cervical mass	2	Tumor progression to the brain Palliative
15	18	Term	Headache, vomiting, left hemiparesis	356,648.50	17	High-dose EMACO I WBRT EMACO VI EP EMA VII TP/TE II BEP III TAH (choriocarcinoma)	2	Palliative
16	33	Mole	Loss of consciousness Seizure	49,599.38	16	High-dose EMACO I WBRT EMACO V (with dose reductions) EP EMA VI (renally adjusted)	1	Palliative
17	38	Mole	Decrease in sensorium	175,000	18	EMACO III	Not seen due to hemorrhage	Death during treatment
18	41	Mole	Blurring of vision Headache	>1,125,000	16	EP I High-dose EMA WBRT EMACO II Diagnosis of choriocarcinoma after biopsy of the cervical mass	1	Death during treatment
19	30	Mole	Left hemiparesis	148,316	8	EP I High-dose EMACO I WBRT	2	Death during treatment
20	44	Term	None	1,163,154.64	21	High-dose EMACO I WBRT Day 5 of EMACO II	2	Death During treatment
21	21	Mole	None	>1,125,000	3	MTX VII High-dose EMACO I WBRT EMACO XII	3	Tumor recurrence to the brain, lungs incomplete chemotherapy

hCG: Human chorionic gonadotropin, TAH: Total abdominal hysterectomy, GTN: Gestational trophoblastic neoplasia, EMACO: Etoposide, methotrexate, actinomycin, oncovin, WBRT: Whole-brain radiation therapy, EP: Etoposide cisplatin, BEP: Bleomycin etoposide cisplatin, TP: Paclitaxel-cisplatin, TE: Paclitaxel-etoposide, EMA: Etoposide methotrexate actinomycin, MTX: Methotrexate, S/P: Status post, BIIAL: Bilateral Internal Iliac Artery Ligation, CUC: Clean up course, TAHBS: Total Abdominal Hysterectomy with Bilateral Salpingectomy

Four patients (19.04%) died during treatment. Three of which presented with neurologic symptoms upon diagnosis and all were managed for 2 months. Two patients died of cerebral hemorrhage and two patients died of pulmonary embolism.

One patient (4.76%) was not able to continue her chemotherapy because she got pregnant before her first consolidation course. Her beta hCG level at that time was 1.6 mIU/ml.

There were eight early deaths [Table 5], five among which presented with neurologic symptoms. Among the early deaths, 2 (25%) patients died during the first cycle of chemotherapy, 1 (12.5%) died after two cycles of EP induction chemotherapy and 5 (62.5%) patients died

Table 4: Toxicities/adverse effects of chemotherapy

Chemotherapy used	Toxicity	Cases (%)
EMACO	Infections	17/21 (80.95)
	Hypokalemia	15/21 (71.42)
	Anemia grade 2-4	15/21 (71.42)
	Leukopenia grade 2-4	12/21 (57.14)
	Neutropenia grade 2-4	10/21 (47.61)
	Transaminassemia grade 2-4	7/21 (33.33)
	Febrile neutropenia grade 2-4	5/21 (23.80)
	Granulocytopenia 2-4	6/21 (28.57)
	Stomatitis grade 1-2	5/21 (26.31)
	Hypomagnesemia grade 2-4	4/21 (19.04)
	Hypochloremia	3/21 (14.28)
	Thrombocytopenia	4/21 (19.04)
	Hypocalcemia	2/21 (9.5)
	Hyponatremia	1/21 (4.76)
	Pancytopenia	1/21 (4.76)
	Rash	1/21 (4.76)
	Cutaneous emphysema	1/21 (4.76)
	Bullous fixed drug eruption	1/21 (4.76)
	Sensorineural hearing loss	1/21 (4.76)
EP	Infection	2/4 (50)
	Septic shock	1/4 (25)
	Hypokalemia	1/4 (25)
	Hypomagnesemia	1/4 (25)
	Thrombocytopenia grade 4	1/4 (25)
EP EMA	Leukopenia grade 2-4	5/5 (100)
	Thrombocytopenia grade 2-4	5/5 (100)
	Granulocytopenia grade 2-4	5/5 (100)
	Hypokalemia	5/5 (100)
	Infection	5/5 (100)
	Anemia grade 2	4/5 (80)
	Hypomagnesemia	3/5 (60)
	Pancytopenia	2/5 (40)
	Acute kidney injury	2/5 (40)
	Chronic kidney injury	2/5 (40)
	Febrile neutropenia 4	2/5 (40)
	Hyponatremia	2/5 (40)
	Hypokalemia	2/5 (40)
	Cardiomyopathy	1/5 (20)
	Peripheral nephropathy	1/5 (20)
	Neutropenia grade 4	1/5 (20)
	Transaminassemia	1/5 (20)
	Hyperphosphatemia	1/5 (20)
	Mucositis	1/5 (20)
TP/TE	Hypomagnesemia grade 1	1/1 (100)
	Anemia grade 2	1/1 (100)
	Leukopenia grade 3	1/1 (100)
	Granulocytopenia grade 4	1/1 (100)
BEP	Leukopenia grade 2-3	1/1 (100)
	Granulocytopenia grade 2-4	1/1 (100)
	Anemia grade 2	1/1 (100)
	Thrombocytopenia grade 2	1/1 (100)
	Hypomagnesemia grade 1	1/1 (100)
	Hypokalemia	1/1 (100)
Others		
Whole-brain radiation	Adverse effects	
	Bilateral radiation-induced parotitis	1/17 (5.88)
	Radiation-induced otitis media	1/17 (5.88)
	Optic atrophy	1/17 (5.88)

BEP: Bleomycin etoposide cisplatin, TP: Paclitaxel-cisplatin, TE: Paclitaxel-etoposide, EP: Etoposide cisplatin, EMA: Etoposide methotrexate actinomycin, EMACO: Etoposide, methotrexate, actinomycin, oncovin

before the institution of chemotherapy. The causes of early deaths were cerebral hemorrhage in seven (87.5%) patients and gastro intestinal hemorrhage in one (1.25%) patient.

Patient follow-up after treatment/discharge

One patient was admitted 11 months after biochemical remission due to seizure. Beta hCG, as well as transvaginal ultrasound, were unremarkable. Cranial computed tomography (CT) scan results showed encephalomalic changes in bilateral frontal lobes. The patient was referred to neurology and was managed as a case of acute symptomatic seizure, probably postgliotic. She was discharged improved and remained asymptomatic with normal beta hCG levels up to her last consult.

Among the patients who achieved biochemical remission with EMACO, three relapsed on the first, second, and third months after their last consolidation course [Table 6]. The patient who relapsed on the 1st month after the last consolidation course had residual focus of metastasis documented radiographically as minimally enhancing focus in the subcortical region of the right occipital lobe is measuring 0.5 cm × 0.6 cm × 0.6 cm, pelvic mass adjacent to the bifurcation of the right common iliac vessels measuring approximately 4.8 cm × 1.9 cm × 2.6 cm, splenic mass measuring 1.5 cm × 1.2 cm × 1.2 cm, left adrenal mass measuring 4.4 cm × 1.6 cm × 1.5 cm, and multiple varisized lung nodules with the largest size of 1.7 cm × 1.5 cm × 1.6 cm. She is currently undergoing chemotherapy with EMACO with a 25% reduction of etoposide, methotrexate, and actinomycin and is responding adequately. The patient who relapsed on the 2nd month after the last consolidation course had residual pulmonary mass at the right middle lung field measuring 3.1 cm × 3.0 cm and a sacral focus from S1 to S3. She was given EMACO with high-dose methotrexate. After the treatment, she was lost to follow-up for 5 months. Upon readmission, there was progression to the brain, kidneys, and mediastinum. She was given two cycles of EP induction chemotherapy, EP EMA with high-dose methotrexate with concomitant whole-brain radiation, and ten subsequent EP EMA cycles one among which was a consolidation course. The patient achieved remission.

Table 5: Clinical characteristics of the eight patients who died in less than 4 weeks of admission

Patient number	Age	WHO score	Antecedent pregnancy	Interval after index pregnancy (months)	Pretreatment serum βhCG (mIU/ml)	Site of metastasis	Chemotherapy	Cause of death
1	29	16	Abortion	5	360,377	Brain Lungs	Not done	Intracerebral hemorrhage
2	54	21	Mole	3	256,872	Brain Lungs	Not done	Intracerebral hemorrhage
3	50	13	Term	48	467,878	Brain Lungs Liver Gastroin-testinal	Day 1 of high-dose EMACO Day 1 of WBRT	Intracranial hemorrhage
4	31	17	Term	12	198,000	Brain Kidney	Not done	Intracranial hemorrhage
5	39	20	Mole	48	1,475,301	Brain Lungs Vaginal stump Kidney	S/P EP II	Intracranial hemorrhage
6	36	13	Mole	72	57,714.79	Brain Lungs Liver	Day 6 of high-dose EMACO	Massive GI bleeding
7	26	17	Mole	72	55,727.18	Brain Lungs	Not done	Brainstem herniation
8	38	17	Term	11	463,081.97	Brain Lungs Vagina Liver	Not done	Massive upper GI bleeding

EMACO: Etoposide, methotrexate, actinomycin, oncovin, WBRT: Whole-brain radiation therapy, EP: Etoposide cisplatin, GI: Gastrointestinal, βhCG: Beta-human chorionic gonadotropin, S/P: Status post

The decision to give only one consolidation course was due to multiple chemotherapy toxicities despite reduced chemotherapy doses and chemotherapy-induced chronic kidney disease. She, however, had a residual pulmonary mass at the right lateral segment of the middle lobe measuring 7 cm × 6.8 cm × 6 cm for which she was advised CT scan guided aspiration biopsy, but was unable to comply. Two months after the last chemotherapy course, the patient's serum beta hCG was 5,318.69 mIU/mL. The patient refused further treatment. Another serum beta hCG was obtained 1 month after and was 28,532.90 mIU/mL. This was the last recorded consult of the patient. Upon contacting the patient's sister, the previously advised CT scan-guided aspiration biopsy of her residual pulmonary mass was not carried out and no further medical intervention was done. The patient died at home 8 months after her last chemotherapy cycle. The patient who relapsed on the 3rd month after the last consolidation course had residual metastasis documented radiographically as a 1 cm × 1.1 cm hyperdense enhancing nodule is seen in the right parietal lobe and a fairly defined lung mass in the anterior segment of the right lower lobe measuring 5.2 cm × 4.5 cm × 5 cm. She was initially given EMACO with high-dose methotrexate and four subsequent cycles of EMACO. She had chemotherapy resistance and was administered five cycles EP EMA, three among which were consolidation courses. She eventually achieved biochemical remission. The patient was lost to follow-up after treatment.

One of the patients who was given palliative therapy came in as an emergency room death 7 months after administering her last chemotherapy. Upon contacting their relatives, the two other patients who were offered palliative therapy died at home 3 and 9 months respectively after their last chemotherapy cycle.

One patient was unable to continue her chemotherapy because she got pregnant before her first consolidation course. She is currently at her 35–36 weeks age of gestation. Serum beta hCG was obtained in her 32 2/7 weeks and was 3,067 mIU/mL, acceptable for her gestation age.

Six patients were contacted and 5 (83.33%) have resumed their normal everyday life. One delivered 4 months after her last consolidation course. Delivery was unremarkable, and histopathology of her placenta showed no diagnostic abnormality. One patient resumed employment, one is a homemaker, one resumed education and is in senior high school, one is currently undergoing chemotherapy, and the last patient had prenatal consults at the high-risk maternal clinic in the institution.

The median follow-up was 27 months. Mortality was observed within the 1st 3.1 years. No more death

Table 6: Survival time of the twenty-one managed patients

Patient number	Date of diagnosis of diseases	Date of first chemotherapy cycle/date of last chemotherapy cycle	Outcome	Date of the last consultation	Follow-up after treatment	Survival time (months)
1	September 23, 2009	October 14-24, 2009 March 1-8, 2010	Remission	Lost to follow-up after treatment	Lost to follow-up	Unknown
2	May 17, 2012	May 25, 2012-June 1, 2012 October 2-9, 2012	Remission	April 7, 2021	Delivered via NSD-2016 Histopath of placenta No diagnostic Abnormality recognized Homemaker	107
3	February 11, 2015	February 18-25, 2015 July 6-10, 2015	Remission	February 3, 2021	Resumed employment as a beautician	72
4	October 13, 2015	October 20-27, 2015 January 18-25, 2016	Remission	February 10, 2020	Lost to follow-up	52
5	February 13, 2016	March 1-10, 2016 May 31, 2016-June 7, 2016	Remission	June 10, 2019	Lost to follow-up	40
6	January 11, 2017	January 18-25, 2017 June 26, 2017-July 3, 2017	Remission	April 7, 2021	Homemaker	51
7	March 20, 2018	March 28-29, 2018 October 15-24, 2018	Remission	February 3, 2021	Resumed schooling Grade 12	35
8	March 10, 2017	March 14-21, 2017 September 5-8, 2017	Remission	June 17, 2019	Lost to follow-up	27
9	December 14, 2015	December 18-25, 2015 July 2-9, 2016	Remission	July 13, 2016	Lost to follow-up	7
10	September 15, 2015	September 21-28, 2015 April 20-27, 2016	Remission	January 13, 2020	Lost to follow-up	50
11	May 11, 2019	May 24-25, 2019 October 29-11, 2020	Remission Relapsed 1 month after the last consolidation course	June 30, 2021	Ongoing treatment	25
12	February 18, 2016	February 21-28, 2016 February 12-19, 2018	Remission: Relapsed 2 months after the last consolidation course Remission: Relapsed 2 months after the last consolidation course	May 16, 2018 βhCG=28,532.90 April 18, 2018 βhCG=5318.69	Death - October 29, 2018	32
13	January 5, 2017	April 30, 2017-May 7, 2017 October 3-10, 2018	Remission: Relapsed 3 months after the last consolidation course Remission	October 22, 2018	Lost to follow-up	19
14	March 27, 2017	April 21-28, 2017 August 6, 19-20, 2019	Palliative	September 28, 2019	Death - May 8, 2020	37
15	September 11, 2017	September 26, 2017-October 3, 2017 December 6-13, 2018	Palliative	March 26, 2019	Death - April 19, 2019	19
16	December 28, 2018	January 4-11, 2019 July 24-31, 2019	Palliative	ER death - February 5, 2020	Not applicable	13
17	July 11, 2017	August 7-14, 2021 September 11-18, 2017	Death - September 26, 2017	Not applicable	Not applicable	2
18	February 7, 2018	February 12-13, 2018 May 3-10, 2018	Death - May 14, 2018	Not applicable	Not applicable	2
19	May 26, 2018	May 28-May 29, 2018	Death - August 12, 2018	Not applicable	Not applicable	2.5
20	January 06, 2019	January 26, 2019-February 2, 2019	Death - February 20, 2019	Not applicable	Not applicable	1.5
21	May 22, 2018	May 29, 2018-June 2, 2018 March 17-24, 2020	Incomplete chemotherapy (consolidation courses were not given due to her pregnancy)	June 24, 2021	December 6, 2020 - Informed trophoblastic disease division of her pregnancy	37

βhCG: Beta-human chorionic gonadotropin, NSD: Normal spontaneous delivery, ER: Emergency room

Table 7: Survival function using Kaplan–Meier survival curve

Survival table					
Time (years)	Status	Cumulative proportion surviving at the time		Number of cumulative events	Number of remaining cases
		Estimate	SE		
0.125	1	0.952	0.046	1	20
0.167	1	0	0	2	19
0.167	1	0.857	0.076	3	18
0.208	1	0.81	0.086	4	17
0.333	0	0	0	4	16
0.583	0	0	0	4	15
1.083	1	0.756	0.095	5	14
1.583	1	0.702	0.103	6	13
1.583	0	0	0	6	12
2.083	0	0	0	6	11
2.25	0	0	0	6	10
2.667	1	0.631	0.114	7	9
2.917	0	0	0	7	8
3.083	1	0.553	0.124	8	7
3.083	0	0	0	8	6
3.333	0	0	0	8	5
4.167	0	0	0	8	4
4.25	0	0	0	8	3
4.333	0	0	0	8	2
6	0	0	0	8	1
8.917	0	0	0	8	0

Means and medians for survival time							
Mean				Median			
Estimate	SE	95% CI		Estimate	SE	95% CI	
		Lower bound	Upper bound			Lower bound	Upper bound
5.533	0.919	3.732	7.333	0	0	0	0

Estimation is limited to the largest survival time if it is censored. SE: Standard error, CI: Confidence interval

occurred after 3.1 years. The analysis showed that the mean survival time was 5.43 years with a lower bound of 3.7 years and an upper bound of 7.3 years. After excluding early deaths, the survival rate between 3 and 7 years after treatment was at 61.9% [Figure 2]. The longest survival time was 8.9 years [Table 7].

Discussion

The study documented brain metastasis in GTN to be 14.28% (29/203), consistent with that (3%–21.4%) of previous reports in Peking Union Hospital and higher (10.44%) with that of the French Trophoblastic Disease Reference Centre. Brain metastases of GTN are highly vascular lesions, with a propensity for acute intralesional hemorrhage resulting in neurologic deterioration and early death in the course of treatment.[5,8,7] Since the study included patients from the recent past 10 years, it was only able to document the proportion of patients surviving between 3 and 7 years after treatment which was at 61.9% large-scale studies on the other hand would document the 5-year survival rate. French Trophoblastic Disease Reference Centre and Peking Union Medical College Hospital have a 5 year survival rate of 69.8% and 71.1% respectively.[7,8] In a study however conducted at the Charing Cross Hospital 85% of its population were considered long term survivors.[11]

In the study, 47.36% (9/19) of patients who presented with neurologic symptoms upon diagnosis of diseases eventually achieved biochemical remission and 15.78% (3/19) died during treatment. One (5.26%) patient who presented with neurologic symptoms later in the course of treatment was offered palliative care. Four out of nine (44.44%) patients who had no neurological symptoms achieved biochemical remission. A previous study conducted in our institution reported remission in 35% (6/17) among GTN patients who had CNS symptoms on presentation and 15% (2/13) among those who developed lesions during chemotherapy or who had relapsed after initial complete or partial remission.[10] One patient presented with seizure 11 months after chemotherapy and was managed as an acute symptomatic seizure, probably postgliotic. Similarly, in a study including whole-brain radiotherapy interventions, 4 cases of hemianopia, 2 cases of hemiparesis, 2 cases of epilepsy, and an unspecified number of episodes of amnesia, headache, aphasia, and cognitive deficits, were reported.[7]

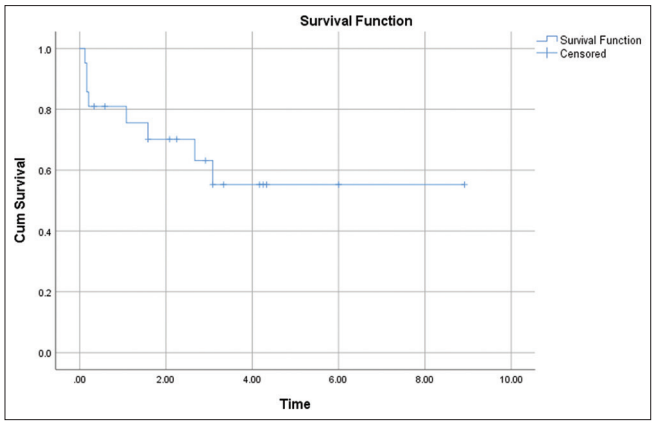

Figure 2: Kaplan-Meier survival curve

EMACO was used as the first-line chemotherapy among the patients studied. Thirteen patients achieved biochemical remission with EMACO chemotherapy documenting a biochemical remission rate of 61.90% (13/21). Four patients had resistance to EMACO documenting a resistance rate of 19.04% (4/21). In a study done by Shen *et al*., the EMACO regimen resulted in a complete remission rate of 67% (16/24) and the resistance rate was 33% (8/24) among ultra-high-risk patients.[12] In the study, the most common toxicities from EMACO chemotherapy were infections of 80.95% (17/21), hypokalemia of 71.42% (15/21), and anemia grade 2-4 of 71.24% (15/21). In the same study done by Shen *et al*., toxicities from EMACO chemotherapy were iii-iv degree neutropenia of 21.6% (36/167), anemia of 96.4% (161/167), and alopecia of 60.5% (101/167).

Five patients were given EP EMA wherein 40% (2/5) had biochemical remission and 20% (1/5) had resistance. She was given TP/TE followed by BEP from which she all had resistance. 60% (3/5) were offered palliative treatment secondary to the chemotherapy toxicities. EP-EMA regimen is the most commonly used salvage chemotherapy for patients who have chemoresistance with EMA-CO. Three studies documented EP-EMA use among metastatic high-risk GTN patients who had relapse/resistance with initial EMACO chemotherapy. Newlands *et al*. Documented a complete response rate of 75% (9/12) and an overall survival rate of 88% (30/34).[13] Mao *et al*. documented a complete response rate of 66.6% (12/18), including 82% (9/11) resistant patients and 43% (3/7) relapsed patients.[14] Lu *et al*. documented a complete response rate of 84.6% (11/13) in which 5 patients who had adjuvant surgery/brain irradiation. In all studies, myelosuppression was an observed side effect.[15] Following resistance to EP-EMA, no available studies recommend the following chemotherapy regimen that should be used. At present, pembrolizumab is a potential treatment option among drug-resistant GTN patients. It is monoclonal antibody that inhibits programmed cell death protein 1, which functions as a checkpoint protein to regulate various immune cells, including T cells, with potential antitumor activity.[16] Ghorani *et al*. reported response to pembrolizumab in 3 of the four patients drug-resistant GTN patients.[9]

Five (17.24%) patients received EP induction chemotherapy. One patient had multiple lung masses with the largest measuring 4 cm × 4 cm in the left apical region, single mass in segment VIII of the liver measuring 4.6 cm × 3.6 cm × 3.1 cm, and subcentimeter enhancing nodules are seen in both upper parietal lobes at the junction of the gray and white matter upon diagnosis. The next patient had tumor progression to the left high parietal region of the brain measuring 4 cm × 4.2 cm × 4.5 cm, mediastinum in the right mid to lower lung field measuring 7.5 cm × 7.5 cm, splenorenal region mass measuring 9 cm × 6 cm × 6.9 cm, and a pulmonary nodule on the mid lung field measuring 1.5 cm × 1.3 cm. Both achieved biochemical remission. The third patient had a mass in the left occipital lobe measuring 3.4 cm × 2.5 cm × 3.1 cm, innumerable subcentimeter nodules scattered diffusely throughout both lungs with the largest of which measured approximately 1.8 cm, a single mass at the segment II of the liver measuring 0.9 cm × 1.5 cm × 1.6 cm, a hypodense focus is noted in the spleen extending from the hilum extending into the splenic capsule and vaginal canal mass that measured 7.3 cm × 6.9 cm × 6.3 cm upon diagnosis. She expired after one cycle of EP induction chemotherapy and two cycles of EMACO chemotherapy with concurrent whole-brain radiation in the first cycle. The fourth patient had 10.2 cm × 9.5 cm lung mass seen at the right upper lobe and a cortical/subcortical right frontoparietal junction measuring 3.2 cm × 3.1 cm × 2.7 cm. She expired after one cycle of EP induction chemotherapy and one cycle of high-dose EMACO chemotherapy with concurrent whole-brain radiation. The last patient had parenchymal lesion in the left frontal lobe with approximate volume of 2.9 cc × 5.2 cc and kidney mass of 4 cm in size. She expired after two cycles of EP induction chemotherapy. All five patients presented with a high volume of disease in the critical organs, which could be at risk of hemorrhage when the full dose of EMACO chemotherapy is administered. Low-dose induction EP chemotherapy consists of etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2, repeating weekly for one to two cycles before commencing EMA/CO. This has been used since 1994 with the rationale for a more gradual reduction in tumor volume reduces the risk of significant hemorrhage in critical organs in patients with high-volume disease. Alifrangis documented the reduction or early deaths to 0.7% (n = 1; 95% confidence interval [CI], 0.1% to 3.7%) compared with 7.2% (n = 11 of 151 patients; 95% CI, 4.1%

to 12.6%) among high-risk patients whom induction chemotherapy was not administered.[17]

In the study, one patient was given only one consolidation course due to multiple chemotherapy toxicities despite reduced EP EMA chemotherapy doses and chemotherapy-induced chronic kidney disease. Consolidation chemotherapy consists of an additional three cycles for high-risk GTN given after the normal BhCG value (0–5 mIU/mL) is reached. This ensures complete eradication of all viable trophoblastic cells and minimize the risk for relapse.[18] The patient in the study relapsed 2 months after her consolidation course. She refused further treatment and eventually died.

Whole-brain irradiation gives the advantage of preventing intracranial bleeding and potentiating the effect of chemotherapy. In the study, seventeen patients were administered whole-brain radiation, eleven (64.70%) of which achieved biochemical remission. Five surviving patients who had brain radiation were contacted and reported to have no neurologic deficits. Studies that documented combined whole-brain radiotherapy with multidrug chemotherapy have reported survival rates of up to 75%. In comparison, systemic chemotherapy combined with intrathecal MTX has reported a patient survival rate between 71.5% and 85%.[7] MTX was administered in two patients. One (50%) achieved biochemical remission while one (50%) was offered palliative management. Three patients had adverse effects with radiotherapy in the study which were bilateral radiation-induced parotitis, radiation-induced otitis media, and optic atrophy.

Surgery is adjunctive in the management of GTN. It decreases the tumor load thereby decreasing the chemotherapy cycles that is needed to achieve biochemical remission. In the study, four patients underwent an adjunctive hysterectomy, two (50%) achieved biochemical remission, and two were offered palliative treatment. Indications of hysterectomy in GTN management are uterine rupture, vaginal bleeding, and resistance. Cagayan and Magallanes documented a 98.4% survival rate among 129 hysterectomies patients during GTN management.[19] Among GTN patients with brain metastasis who present with increased intracranial pressure, craniotomy is indicated for CNS decompression and stabilization. Isolated nodules resistant to drug treatment are excised, and this therapeutic regimen results in primary remission of 65% to 80% and up to 90% cure.[20]

There was note of residual tumors among the patients who had tumor relapse after the completion of chemotherapy. In a study done by Yang *et al.* among 187 patients who had biochemical remission, 155 (82.0%) had normal beta-hCG titer but with residual tumor in the lung or other organs. Among them, six patients with choriocarcinoma experienced progression of the disease after treatment.[21] Powles *et al*. however documented in a study that radiological abnormalities at the end of treatment are of no prognostic significance if the patient's β HCG levels remain normal, and excision of these lesions does not therefore seem reasonable.[22]

Five out of six (83.33%) contacted patients were documented to have resumed their everyday life. Gavanier reported sequelae in 11 of the 12 (92%) surviving patients; however, nine (75%) had resumed a normal life.[7] This positive functional outcome was also found in a study in the UK that observed that most of the patients involved had a usual quality of life several months after the end of treatment.[23]

One patient delivered 4 months after her last consolidation course. Delivery was unremarkable, and her baby did not have any congenital anomalies or malformation. Histopathological report of her placenta showed no diagnostic abnormality. One patient was not able to complete her chemotherapy cycles because she got pregnant before her first consolidation course. Tranoulis *et al*. had a meta-analysis evaluating reproductive and obstetrical outcomes after administration of chemotherapy among patients with GTN. The study concluded that nearly 90% of patients desiring future fertility after chemotherapy for gestational trophoblastic disease were able to conceive. In addition, adverse pregnancy outcomes were similar to that in the general population. Multi-agent chemotherapy does not seemingly increase the malformation rate.[24] The placenta is submitted for histopathology, and beta hCG is obtained 6 weeks postpartum among GTN patients who delivered because of the possibility of intraplacental choriocarcinoma. It is a rare form of GTN where in most cases were identified in the third trimester (n = 52; 84%) among asymptomatic women (n = 31; 50%) and with the macroscopically normal placenta in 29% (18/62).[25] Up to the time this paper was written, there were no reported pregnancy outcomes among GTN patients with incomplete chemotherapy.

Conclusion

The study was able to document 33 (16.25%) patients with brain metastasis out of 203 metastatic high-risk GTN from January 1, 2010, to December 31, 2019. A total of 29 patients were included. Twenty-one patients were managed for at least 1 month and eight died in <1 month of admission. Thirteen patients (44.82%) achieved biochemical remission with EMACO chemotherapy. Four patients (13.79%) had resistance to EMACO and were given EP EMA. One patient was administered EP

EMA due to tumor relapse. Four patients (13.79%) died during treatment and one patient (3.44%) was unable to continue her chemotherapy because she got pregnant before her first consolidation course. Three patients relapsed after biochemical remission. One achieved biochemical remission after treatment, one is currently on chemotherapy, and one died after refusing further treatment. After excluding early deaths, the survival rate between 3 and 7 years after treatment is at 61.9%. The mean survival time is 5.43 years.

Limitation of the study

Seven out of twelve patients who achieved biochemical remission were lost to follow-up. Documenting sustained remission or death among these patients could have eliminated bias making the study more valid. The study included patients from the recent past 10 years and hence was only able to document the proportion of patients surviving between 3 and 7 years after treatment. The study population was relatively small ($N = 29$) from the tertiary hospital chosen. Consequently, findings are not generalizable to GTN patients with brain metastasis across the country. Lastly, the study was purely descriptive and did not correlate the WHO prognostic factors with the outcome of the patients managed.

Recommendation

A stronger means of patient tracking after biochemical remission is recommended. For patients residing in provinces far from the National Capital Region, they may be referred to the nearest institution equipped with a trophoblastic specialist and a laboratory with serum beta hCG to increase the compliance of follow-up and beta hCG monitoring after achieving biochemical remission. Linkages among the different institutions are encouraged for proper referral. In the absence of a specialist in the area, telehealth in the institution is recommended.

In future studies, it is recommended that a longer time frame may be used to be able to include more patients and calculate for the 5 years survival rate among all patients who achieved biochemical remission. Similarly, correlation of the WHO prognostic factors and outcome of management can make the study more useful and relevant.

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Conflicts of interest

There are no conflicts of interest.

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