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Low-Dose Induction Chemotherapy for Ultra-High Risk Gestational Trophoblastic Neoplasia With Metastasis to the Brain: A Case Report

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Abstract

Gestational trophoblastic neoplasia (GTN) is uniquely sensitive to chemotherapy. Multi-agent chemotherapy is recommended for high-risk GTN, with the combination of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA-CO) being used the most. Ultra-high-risk patients with a large disease burden are at risk of early death with standard EMA-CO due to tumour lysis-related haemorrhage and clinical deterioration. Low-dose induction chemotherapy with etoposide and cisplatin (EP) is associated with improved outcomes in these patients. This is a case of a woman treated for ultra-high-risk GTN with brain metastasis, managed with low-dose induction etoposide and cisplatin before EMA-CO therapy. She had intracranial bleeding with neurological symptoms after the first treatment cycle, with subsequent complete recovery, in a low-resource hospital.

Categories: Obstetrics/Gynecology
Keywords: ema-co chemotherapy, gestational trophoblastic neoplasia brain metastasis, high risk gestational trophoblastic neoplasia, human chorionic gonadotrophin, ultra-high risk gestational trophoblastic neoplasia

Introduction

Gestational trophoblastic disease (GTD) defines a spectrum of abnormally proliferating trophoblastic tissue [1]. Histologically, it includes the premalignant complete hydatidiform mole and partial hydatidiform mole, as well as the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumour (ETT) [1]. When hydatidiform mole persists, or there is evidence of metastatic disease, it is called gestational trophoblastic neoplasia (GTN) [2]. GTN comprises invasive mole, choriocarcinoma, PSTT and ETT [2]. The risk of malignant transformation is approximately 15% after complete hydatidiform mole and 0.5% to 1% after partial hydatidiform mole [3]. All forms of GTD produce the pregnancy hormone human chorionic gonadotropin (hCG), and thus it is an excellent biomarker of disease progression, response, and subsequent post-treatment surveillance [2]. Post-molar GTN is usually asymptomatic, and it is diagnosed by hCG surveillance when hCG plateaus, rises, or there is a histology showing choriocarcinoma [2]. According to the 2000 FIGO staging and classification, a risk score of ⩽6 is classified as low risk [4]. Stages II and III with risk score ⩾7, and all Stage IV disease are classified as high risk [4]. Among the high-risk group, a subgroup with a score of ⩾13 is classified as ultra-high-risk GTN [2].

Patients with low-risk GTN are treated with one of these single-agent protocols, methotrexate or actinomycin D, with cure rates of almost 100% [2]. Multiple-agent chemotherapy regimens are used to treat high-risk GTN. The most commonly used regimen is EMA-CO, with complete remission rates ranging from 78-91% [3,5]. Treatment is continued until the hCG level has returned to normal and then for a further six consecutive weeks [2]. Monthly hCG titres are monitored for at least 12 months after treatment in high-risk patients due to the risk of late recurrence [2]. Brain metastasis equals FIGO Stage IV and high-risk disease [2]. Gentle induction chemotherapy in ultra-high-risk disease helps reduce early deaths in patients with extensive tumour burden [3].

We present a case of ultra-high-risk GTN with brain metastasis and high disease burden in a young woman. She underwent three consecutive low-dose induction cycles with etoposide and cisplatin chemotherapy before transitioning to EMA-CO. It highlights the delay in presentation, complications of chemotherapy and how financial challenges limit investigations, treatment and follow-up in resource-constrained settings.

Case Presentation

A 26-year-old woman, para two, a housewife from Mutare, Zimbabwe, presented at Parirenyatwa Hospital Accident and Emergency Department with irregular vaginal bleeding, palpitations, shortness of breath, chest pain, dry cough, loss of weight and persistent headache for two months. She had a two-year history of abnormal uterine bleeding following a miscarriage at 10 weeks, for which she did not seek medical care. Her periods became irregular, with amenorrhoea interspersed with prolonged bleeding of varying flow. In those two years, she had been admitted on two occasions with symptomatic anaemia managed with blood

transfusion, as well as two uterine evacuations for suspected incomplete miscarriage at a district hospital. She remained unwell and was eventually referred to a gynaecologist at the provincial hospital, who suspected GTN and transferred her to Parirenyatwa Hospital Gynaecological Oncology Unit. She was HIV-negative with no other chronic illnesses.

On examination, she was alert, pale, wasted, in mild respiratory distress, not jaundiced and with no oedema. Her pupils were equal and reactive to light, and the thyroid gland was not enlarged. Her blood pressure was 89/60 mmHg with a pulse of 92 beats per minute. The chest had equal air entry with mild bilateral diffuse lung crepitations and normal heart sounds. Her abdomen was soft, non-tender, with no hepatosplenomegaly, pelvic-abdominal masses, or ascites. The uterus was bulky, approximately 12 weeks in size. A 6 cm smooth, purplish mass covered the cervix and the anterior vaginal wall. On catheterisation, she drained blood-stained urine. Her weight was 41.6 kg and height 1.62 m, yielding a body surface area (BSA) of 1.40 m^2. Her haemoglobin was 8.1 g/dL (range 11.5-16.0 g/dL), with normal renal and liver function tests, and her serum hCG was 2,985,706 mIU/mL (normal range <5 mIU/mL) (Table *1*).

Parameter	Admission day	Day 1 treatment	Day 8 treatment	Day 15 treatment	Day 22 treatment	Day 32 treatment	Day 46 treatment	Reference range
WBC	8.23	8.18	6.16	6.25	3.72*	8.87	7.86	4-11 × 10^9/L
Neutrophil	2.3	2.0	1.9	1.8	1.4*	2.1	2.6	1.5-7.5 x 10^9/L
Haemoglobin	8.1*	10.1*	9.6*	9.4*	8.0*	8.0*	9.6*	11.5-16.0 g/dL
Platelet count	75*	138*	186	162	140*	158	188	150-400 × 10^9/L
Sodium	137	136	134	134	137	135	134	133-145 mmol/L
Potassium	4.0	3.8	3.7	3.9	3.5	3.8	3.9	3.5-5.3 mmol/L
Urea	2.7	3.0	2.9	3.0	3.8	3.9	3.8	2.5-7.8 mmol/L
Creatinine	78	75	76	80	76	73	77	45-90 µmol/L
Glucose	4.2							3.9-5.5 mmol/L
ALT	27	24	22	26	23	21	22	10-35 U/L
ALP	54	65	54	67	68	71	65	30-130 U/L
Serum hCG	2,985,706*	2,985,706*	2,418,952*	23,194*	7,865*	874*	387*	<5 mIU/mL
RPR	negative							
HIV	negative							

TABLE 1: Laboratory values

Table showing laboratory test results on the day of admission and on the first day of chemotherapy cycles.

* indicates an abnormal value.

WBC: white blood cell; ALT: alanine aminotransferase; ALP: alkaline phosphatase; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; RPR: syphilis rapid plasma reagin

Multiple metastatic lesions were noted on chest X-ray. Pelvic ultrasonography showed a cervical mass with heterogeneous echotexture, measuring 7.7 cm × 6.2 cm, with an extension measuring 5.1 cm × 2.4 cm protruding into the bladder wall. An endometrial mass measuring 6.9 cm × 3.9 cm was seen in the upper segment of the uterus. A computed tomography (CT) scan of the head was requested due to the persistent headache, but the hospital CT machine was not working. She waited four days for her family to raise money to have the CT scan at a private hospital. CT head showed two well-circumscribed brain metastatic lesions (Figure *1*). She was staged as International Federation of Gynaecology and Obstetrics (FIGO) Stage IV. Her FIGO modified WHO risk score was 19 as follows: age 0, antecedent pregnancy 1, interval from index pregnancy 4, pretreatment hCG 4, largest tumour size 2, site of metastasis 4, number of metastases 4, previous failed chemotherapy 0. The score of 19 classified her as ultra-high-risk GTN.

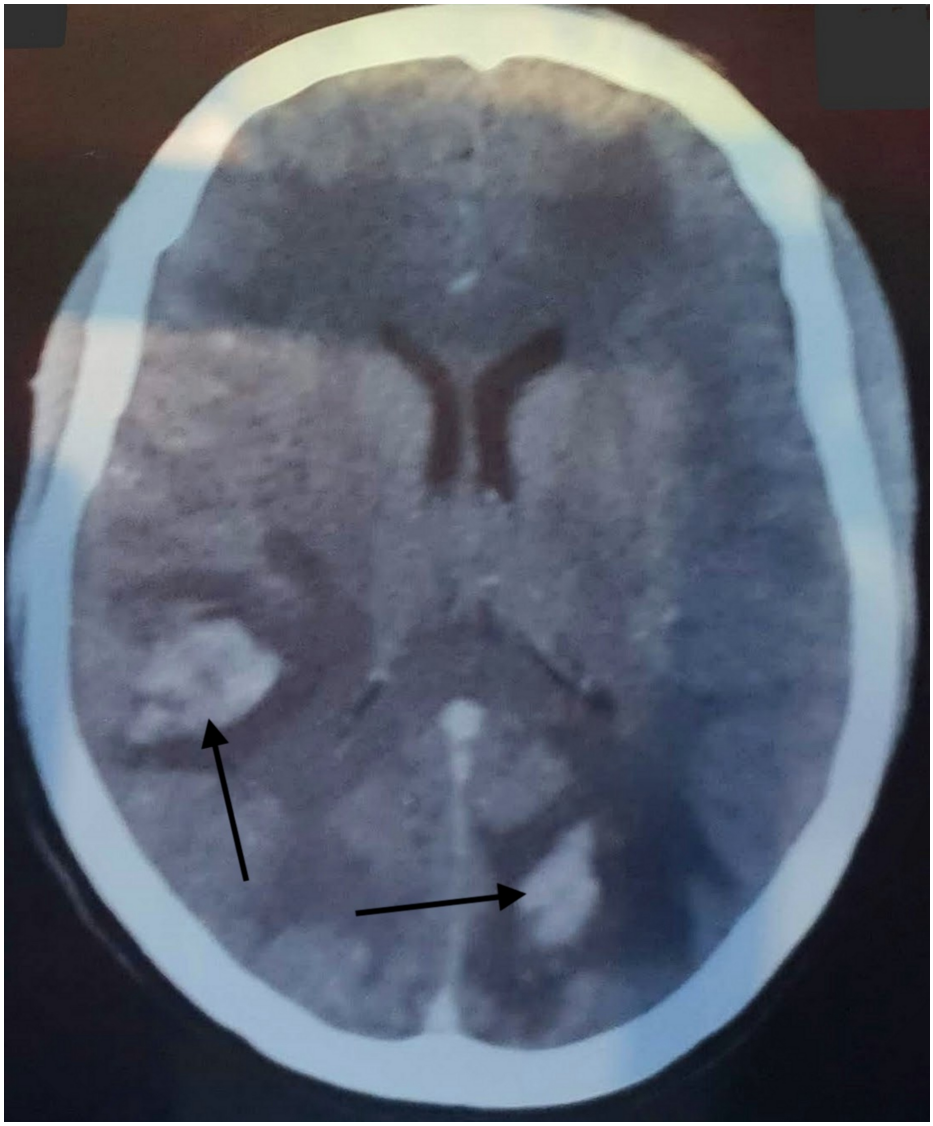


FIGURE 1: Brain CT showing metastatic lesions.

Brain CT shows two hyperdense metastatic lesions (marked by arrows), each surrounded by lower-density oedema.

She was transfused two units of packed cells and her post-transfusion haemoglobin count was 10.1 g/dL. The tumour board multidisciplinary team (MDT) discussion recommendation was to commence low-dose induction chemotherapy consisting of etoposide 100 mg/m² and cisplatin 20 mg/m² intravenously on cycle days 1 and 2, repeated every seven days for three consecutive cycles before starting EMA-CO. Modified EMA-CO chemotherapy incorporating high-dose methotrexate 1 g/m² for cerebral metastases was recommended. Based on a BSA of 1.40 m², she received etoposide 140 mg diluted in 200 mL of normal saline and cisplatin 28 mg diluted in 200 mL of normal saline, each administered intravenously over 30 minutes on D1 and D2 of treatment. She developed severe headache on D3 with unequal pupils and left upper-limb paresis. At this time, the hospital CT machine had been repaired, and a repeat CT scan of the brain showed intracerebral haemorrhage. Neurosurgeons were consulted and started her on dexamethasone and mannitol to reduce intracranial pressure and carbamazepine as prophylaxis against seizures. The headache started to improve on D5. Physiotherapy was started, with slight improvement in left upper limb weakness being noticed on D8. The second and third cycles proceeded as planned with the same dosage of EP given on D8, D9 and D15, D16 respectively, with no further deterioration. Physiotherapy continued, and hemiparesis had improved markedly by D22 when she returned for EMA-CO.

On day 22, when she was due to start EMA-CO, she developed chemotherapy-induced neutropenia and the cycle had to be deferred. She was treated with subcutaneous filgrastim, a granulocyte colony-stimulating factor (G-CSF), at 5 µg/kg/day from day 25 for 6 days before neutrophil recovery. Her weight improved from 41.6 kg to 44.1 kg, giving a new BSA of 1.44 m². EMA-CO chemotherapy incorporating high-dose methotrexate was started on day 32, 10 days later than scheduled. The regimen consisted of methotrexate

1,440 mg (1 g/m²) administered as a 24-hour intravenous infusion on cycle day 1, etoposide 144 mg (100 mg/m²) and actinomycin D 0.5 mg intravenously on cycle days 1 and 2, with folinic acid rescue on cycle days 2 and 3. Cyclophosphamide 864 mg (600 mg/m²) and vincristine 1.44 mg (1 mg/m²) were administered intravenously on cycle day 8. The treatment cycle was repeated every 14 days. Filgrastim was continued throughout the cycle. She tolerated it well with no further CNS deterioration, pulmonary compromise or any obvious adverse response. The second EMA-CO cycle began on day 46 as scheduled, and she developed severe mucositis on day 48. This was managed conservatively with regular saline mouth rinses, analgesia, and supportive hydration, without stopping the cycle.

Weekly hCG levels since starting EP chemotherapy fell from 2,985,706 mIU/mL to 874 mIU/mL over four weeks before starting EMA-CO (Table *2*). The vaginal metastatic lesion fell out spontaneously and haematuria cleared during the second cycle of EMA-CO. The headaches and other central nervous system (CNS) symptoms resolved. All the chemotherapy drugs except methotrexate were sourced privately using the patient's own money for the low-dose induction and first four EMA-CO cycles, with one cycle being delayed by four days. From the fifth cycle, chemotherapy availability from the hospital pharmacy improved for all the drugs except actinomycin D, which she continued to buy. We had to proceed with some EMA-CO cycles without testing hCG when she had no money. On day 134, the patient's hCG normalised, and she received an EMA-CO cycle followed by a further five cycles, completing a total of six EMA-CO consolidation cycles. Her hCG remained normal in the following 24 months post-chemotherapy, although it could not be measured every month. During this time, she was on the combined oral contraceptive pill. An ultrasound performed after completion of chemotherapy showed a normal pelvis. She recovered completely without neurological sequelae and was subsequently discharged.

Day of treatment	hCG level mIU/mL (normal <5 mIU/mL)	Low dose induction cycle	EMA-CO cycle	Treatment given	Notes
D1	2985706	1		EP	Intracerebral haemorrhage with neurological symptoms.
D8	2418952	2		EP	
D15	23194	3		EP	
D22	7,865				Neutropenia EMA-CO deferred.
D25				Filgrastim	3-day delay before starting treatment.
D32	874		1	EMA-CO	10-day delay to start according to protocol.
D46	387		2	EMA-CO	Severe mucositis. Vaginal metastasis fell off. Haematuria cleared.
D60			3	EMA-CO	No money for HCG.
D78	78		4	EMA-CO	Cycle start delayed by 4 days due to finances.
D92			5	EMA-CO	No money for hCG.
D106	24		6	EMA-CO	
D120			7	EMA-CO	No money for hCG.
D134	4		8	EMA-CO	
D148			9	EMA-CO	No money for hCG.
D162	3		10	EMA-CO	
D176			11	EMA-CO	No money for hCG.
D190			12	EMA-CO	No money for hCG.
D204	2		13	EMA-CO	Last EMA-CO cycle.

TABLE 2: Timeline of serum HCG, induction EP and EMA-CO cycles.

Timeline of serum HCG, induction EP and EMA-CO cycles with associated clinical outcomes.

hCG: human chorionic gonadotropin; EP: etoposide and cisplatin; EMA-CO: etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine; D: day.

Discussion

GTN occurs after a molar pregnancy in 60% of cases, after miscarriages in 30% of cases and after normal pregnancy or ectopic pregnancies in the remaining 10% of patients [6]. In our patient, it was not possible to accurately assign the antecedent pregnancy since she did not seek medical treatment initially. GTN often metastasises via the haematogenous route to the lungs (80%), vagina (30%) and to the brain or liver (10%) [7]. Patients with cerebral metastases may present with seizures, headaches, or hemiparesis. In our case, she presented with severe headache, and metastasis was noted in the brain, vagina, lungs, and possibly the bladder.

EMA-CO chemotherapy is well-tolerated, highly effective and is the most common treatment choice for high-risk GTN cases [2]. An increase in the methotrexate infusion to 1 g/m^2 in modified EMA-CO or EMA-EP helps the drug cross the blood-brain barrier in patients with brain metastases [2]. Intrathecal methotrexate 12.5 mg may also be given at the time of CO when EMA-CO is used or with the EP in the EP-EMA regimen [2]. Remission and response to treatment are assessed using hCG monitoring [2]. Ultra-high-risk patients as well as those with liver, brain, or extensive metastases do poorly when treated with first-line multiple-agent chemotherapy at the beginning [8]. Starting with EMA-CO or EMA-EP in massive disease may cause sudden tumour collapse, with severe bleeding, metabolic acidosis, myelosuppression, septicaemia, and multiple organ failure, any or all of which can result in early death [8].

A retrospective study by Alifrangis et al. of the Charing Cross GTN database demonstrated improved

outcomes in patients with high-risk gestational trophoblastic neoplasia following the introduction of induction low-dose etoposide and cisplatin (EP) before EMA-CO chemotherapy [3]. Among 140 high-risk patients, 33 with extensive disease received induction EP, and the overall early mortality (<4 weeks) rate decreased from 7.2% in the historical cohort to 0.7% in the later cohort [3]. Of the 33 patients who had induction chemotherapy, 15 (45%) were ultra-high risk and 10 (30%) had brain metastasis [3]. Our patient's disease severity matched those in the study, and she received a comparable induction regimen consisting of etoposide 100 mg/m² and cisplatin 20 mg/m² on cycle days 1 and 2, repeated weekly for three cycles [3]. The rationale for this approach is that a more gradual reduction in tumour volume reduces the risk of significant haemorrhage in critical organs in patients with high-volume disease [3]. Despite the low-dose induction approach, she developed intracranial bleeding with neurological deterioration but recovered while receiving the subsequent induction cycles. This highlights the potential for serious neurological complications in patients with extensive metastatic disease despite induction chemotherapy. Theoretically, in our patient, if EMA-CO had been given upfront, the intracranial haemorrhage might have been more serious with a high likelihood of early death. In the event of a significant intracranial bleed, emergency craniotomy may be indicated to stabilise the patient, followed by critical care support throughout the active phase of treatment [9]. Neurosurgeons were involved in our case and felt this was not needed.

GTN with brain metastasis has lower rates of remission with standard EMA-CO or EMA-EP compared to that without [2]. Enhanced intravenous dose (1 g/m2) of methotrexate in EMA-CO alone or combined with intrathecal methotrexate in EMA-CO or EMA-EP is associated with an 85% survival rate [9]. We gave our patient high-dose methotrexate to increase drug concentration in the cerebrospinal fluid (CSF). The intrathecal route was avoided after the bleed with neurological symptoms to avoid complications of lumbar puncture with raised intracranial pressure. High methotrexate doses are also associated with increased side effects such as oral mucositis, myelosuppression, nephrotoxicity, hepatotoxicity and neurotoxicity [8]. Treatment delay or dose reduction may be required due to side effects but is associated with less than optimal outcomes [10]. Myelosuppression-associated neutropenia can cause systemic infection and neutropenic sepsis, a leading cause of morbidity and mortality in cancer patients. Granulocyte colony-stimulating factors (G-CSF), which stimulate production of new neutrophils, can be used to prevent or treat this [10]. We had to delay starting the first EMA-CO cycle due to neutropenia and used the G-CSF filgrastim to raise the neutrophil count. We used it for treatment of neutropenia and when she had mucositis, but not prophylactically because of the financial burden this would cause to the patient.

Patients with resistance to EMA-CO are mostly salvaged with paclitaxel and etoposide alternating with paclitaxel and cisplatin (TE/TP) or with EMA-EP [2]. Radiotherapy has a limited role in GTN except in the treatment of brain metastasis, and its efficacy compared with intrathecal methotrexate is controversial [2]. Emerging data have shown complete response rates of 70% with the pembrolizumab immunotherapy agent, either alone or in combination with chemotherapy where there is resistance to EMA-EP or TE/TP [2]. Due to the rarity of ultra-high-risk GTN with brain metastasis, further clinical studies are still needed to establish the safety, effectiveness and long-term outcomes of the available treatment protocols. Patients on treatment are advised not to become pregnant during treatment and the follow-up period [2]. Our patient was on the combined oral contraceptive pill during treatment and follow-up. EMA-CO regimen may induce menopause three years earlier, but fertility is not affected, and 83% of women became pregnant after methotrexate or the EMA-CO regimen was given [6].

In this case, the patient's FIGO score of 19 made her ultra-high risk, and she faced the risk of early death from tumour lysis-related haemorrhage and clinical deterioration [2]. Low-dose induction EP was therefore recommended for three consecutive cycles before transitioning to the standard EMA-CO regimen [3]. She was not spared from treatment-related intracranial bleeding, but she responded well to the treatment. Serum hCG levels rapidly decreased before commencing EMA-CO, with subsequent complete recovery at the end of treatment. The long treatment protocol, with medication and investigations not available in our low-resource hospital, placed a heavy financial burden on our patient, who did not have private medical insurance. Health practitioners working in district hospitals and primary health care should have a high index of suspicion for GTD and GTN where repeated miscarriages are reported with no histology, and refer to a higher level of care sooner to prevent women presenting late with advanced disease.

Conclusions

Ultra-high-risk GTN with brain metastasis carries a significant risk of mortality from massive tumour lysis-induced haemorrhage at the beginning of standard combination EMA-CO chemotherapy. This case of stage IV, ultra-high-risk disease demonstrated a favourable outcome following low-dose induction with etoposide and cisplatin for three cycles prior to standard EMA-CO chemotherapy, despite the development of intracranial haemorrhage. Additionally, it highlights how limited access to investigations and treatment in low-resource hospitals negatively impacts women's health.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mercy Gaza, Chipo Gwanzura

Acquisition, analysis, or interpretation of data: Mercy Gaza, Chipo Gwanzura

Drafting of the manuscript: Mercy Gaza, Chipo Gwanzura

Critical review of the manuscript for important intellectual content: Mercy Gaza, Chipo Gwanzura

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