CASE REPORT

Chemo-resistant Gestational Trophoblastic Neoplasia and the Use of Immunotherapy: A Case Report and Review of Literature

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ABSTRACT

This is the first reported case of the use of immunotherapy in chemo-resistant Gestational Trophoblastic Neoplasia (GTN) in the country. A 41-year-old, Gravida 4 Para 3 (3013) with a diagnosis of GTN, Stage III: WHO risk score of 13 (Choriocarcinoma) was initially managed with 10 cycles of multiple agent Etoposide, Methotrexate, Actinomycin D- Cyclophosphomide and Vincristine (EMACO) and 19 cycles of Etoposide, Cisplatin- Etoposide Methotrexate and Actinomycin D (EP-EMA). With continuous rise in beta human chorionic gonadotropin (ßhCG) levels, the patient was referred to a Trophoblastic Disease Center where there was note of tumor progression to the brain. She was started on third-line salvage chemotherapy of Paclitaxel and Carboplatin (PC) with concomitant whole brain irradiation completing three cycles after which chemoresistance was again diagnosed with increasing hCG titers and increase in the number and size of the pulmonary masses which were deemed unresectable. Immunotherapy was started with Pembrolizumab showing a good response with marked fall in ßhCG levels. The onset of immune-related adverse events (irAEs) caused a marked delay in subsequent cycles of immunotherapy. With management of the irAEs, two more cycles of Pembrolizumab with fifty percent dose reduction were given with corresponding drop in ßhCG levels. However, the patient subsequently developed gram-negative septicemia with possible hematologic malignancy and finally succumbed to massive pulmonary embolism. The case highlights the importance of prompt diagnosis and referral to a Trophoblastic Disease Center and the use of immunotherapy in chemo-resistant GTN.

Keywords: gestational trophoblastic neoplasia, choriocarcinoma, chemo-resistance, pembrolizumab, immune-related adverse events

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INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is the malignant end of the spectrum of gestational trophoblastic disease. They are pregnancy-related tumors arising from abnormal placentas and includes the more common invasive mole (IM) and choriocarcinoma (CC) and the rare types of placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). From a dreaded malignancy in the early 1950s to the first remission using methotrexate in metastatic choriocarcinoma in 1956, the developments that followed on diagnosis and management using newer chemotherapeutic agents led to a totally different outlook on GTN. GTN is now considered to be one of the most curable solid tumors in women with cure rates greater than 90% even in the presence of metastases.[1]

But despite the excellent cure rates in GTN, a particular group of high-risk patients, which includes the index patient, follows a different course. These patients develop resistance to first-line multiple agent EMACO or will relapse after remission and will need salvage chemotherapy. Even after

primary salvage chemotherapy, 10-20% of these patients will still fail treatment and will require a multi-modality approach of multiple combination of chemotherapy, surgery, and radiation.[2] With multidrug resistance, a novel treatment in the form of immunotherapy had been used in different centers abroad showing favorable results.

CASE PRESENTATION

A 41-year-old G4P3 (3013) with a working diagnosis of GTN III: 13 (Choriocarcinoma) was referred for EP-EMA chemoresistance. The patient had hypertension (two years ago) and diabetes mellitus (three months ago) managed by oral medications. The family and psycho-social history were non-contributory. The history of the present illness started three years prior to admission when she initially underwent a curettage after a period of amenorrhea of six months. The pregnancy test was positive and transvaginal ultrasound showed a thickened endometrium. The histopathology result was choriocarcinoma with an initial ßhCG of 354,000 mIU/ml. She completed 10 cycles of EMACO chemotherapy, with the last 3 cycles intended to be consolidation courses despite rising serum ßhCG titers noted after the 8th cycle (Figure 1A). With continued hCG elevation, work-up was

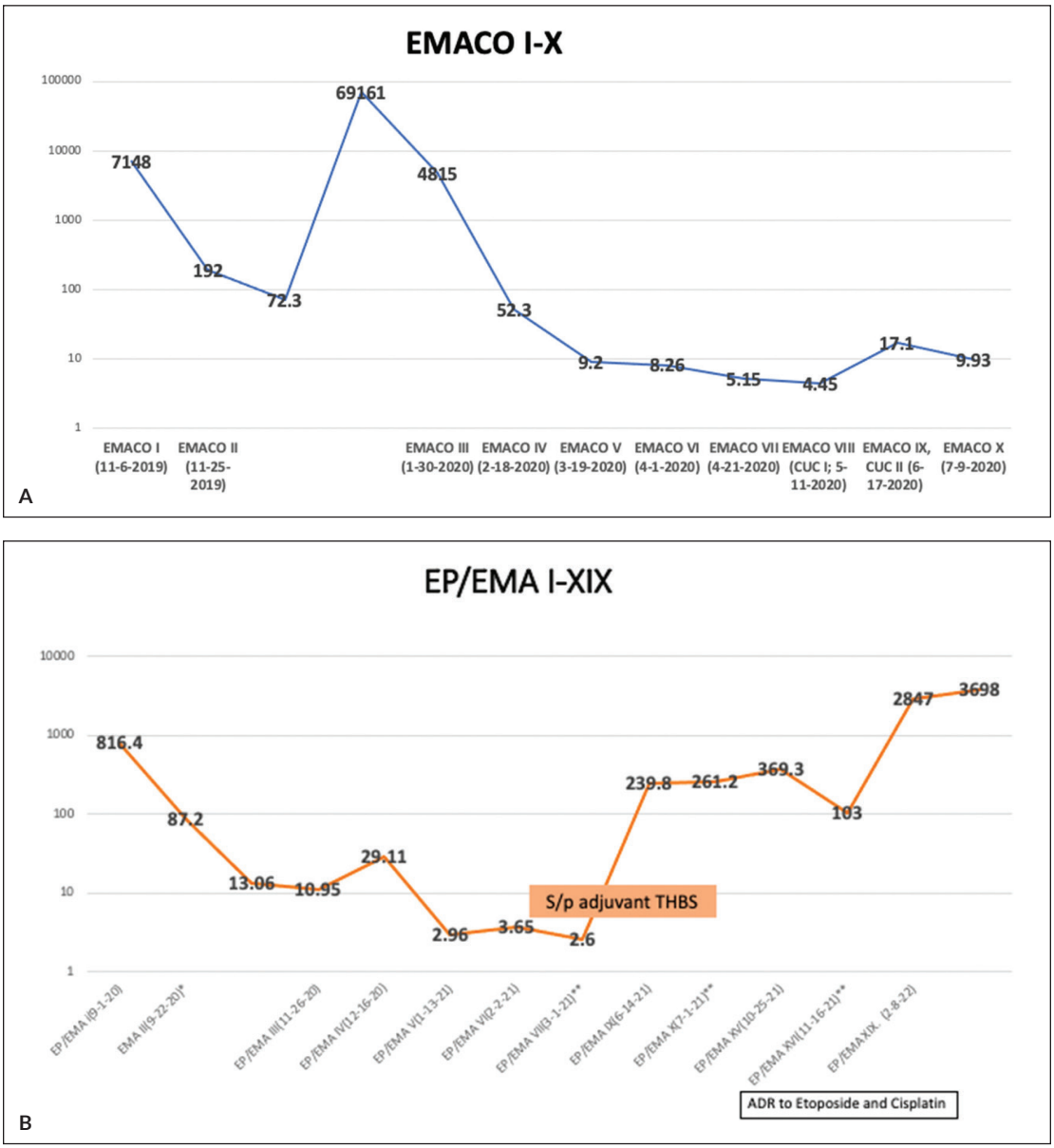

Figure 1. (A) EMACO cycles; **(B)** EP/EMA cycles.

**EP was omitted in the 2nd cycle; **EP/EMA cycles VIII, XI-XIV, XVII-XVIII which were not included in the graph were given in between dates without corresponding hCG titers; adverse drug reaction to etoposide and cisplatin was noted on EP/EMA XVIII and XIX.*

done with a diagnosis of tumor recurrence. She was started on EP/EMA with note of a normal serum ßhCG of 2.96 mIU/ml after her 5th cycle. She underwent total hysterectomy with bilateral salpingectomy showing no evidence of tumor on histopathology. After three consolidation courses, she again had rising serum ßhCG titers. EP/EMA was still continued for another 11 cycles completing 19 cycles with persistently elevated serum ßhCG. There was note of episodes of dyspnea and flushing with Etoposide and Cisplatin on the last 2 cycles of EP/EMA. (Figure 1B)

On admission, the patient was awake, alert, and ambulatory with stable vital signs. The physical examination and pelvic examination findings were unremarkable. A chest x-ray, whole abdominal ultrasound, and a cranial CT scan to complete the metastatic work-up were done. The chest x-ray showed an increase in the number and size of the pulmonary masses and a cerebellar metastatic focus was identified on cranial CT scan consistent with a diagnosis of tumor progression (Figure 2). The creatinine level was elevated at 128 umol/L (CrCl = 69 ml/min) and the ßhCG level was 8,926.84 mIU/ml. The admitting working impression was GTN III:13 (Choriocarcinoma); Tumor progression (Brain and Lungs); EMACO and EP/EMA chemoresistance with adverse drug reaction to Etoposide and Cisplatin; Chronic Kidney Disease, chemotherapy induced.

With a history of adverse reactions to Etoposide and Cisplatin and an elevated creatinine level, the patient was prepared for third-line treatment of Paclitaxel and Carboplatin with 50% dose reduction. Concomitant whole brain irradiation to address the brain metastasis was started with the 1st cycle of Paclitaxel and Carboplatin. Initial adequate response was noted until after the 3rd cycle when ßhCG level rose (Figure 3A). With the focus of resistance identified to be the persistent pulmonary masses, considerations of all possible options of treatment were presented in a multidisciplinary conference with Thoraco-vascular Surgery, Anesthesia, Pulmonology, and Ethics. Based on the multiple foci and the location of the pulmonary lesions, the masses were deemed unresectable and consequent referral to hospice care was discussed.

At this point, the patient was well motivated to try other treatment options. Subsequently, the patient was prepared for immunotherapy with Pembrolizumab 200 mg intravenous infusion every 21 days. The benefits and possible adverse reactions were thoroughly explained to the patient and her family. The patient was admitted for the 1st cycle of Pembrolizumab and on day 8 post pembrolizumab, vaginal mucositis, Grade 2, was noted (Figure 4A) managed with Prednisone. There was marked improvement of the ulceration after three days (Figures 4B and C). Hematologic adverse reactions ensued with thrombocytopenia progressing to Grade 3 managed with Prednisone and platelet transfusions. Concomitant leukocytosis to as high as 35 x 10^3/µl was observed attributed to the steroid treatment. The patient was referred to the Hematology service for co-management. Despite the immune-related adverse reactions, adequate response was noted after the 1st cycle of Pembrolizumab with decrease in serum ßhCG levels from Pre-pembrolizumab 1 of 10,612.00 mIU/mL to 99.00 mIU/mL on rest day 27 (Figure 3B).

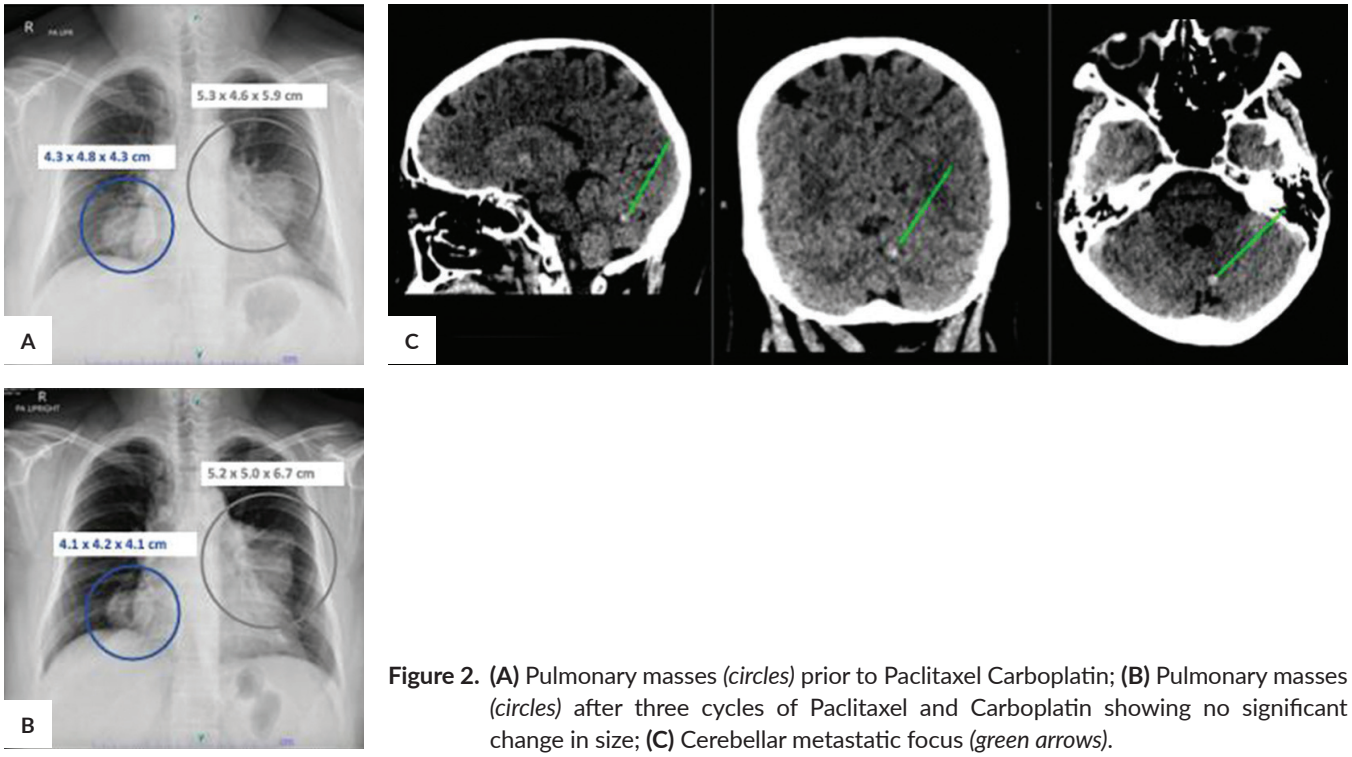

Figure 2. **(A)** Pulmonary masses *(circles)* prior to Paclitaxel Carboplatin; **(B)** Pulmonary masses *(circles)* after three cycles of Paclitaxel and Carboplatin showing no significant change in size; **(C)** Cerebellar metastatic focus *(green arrows)*.

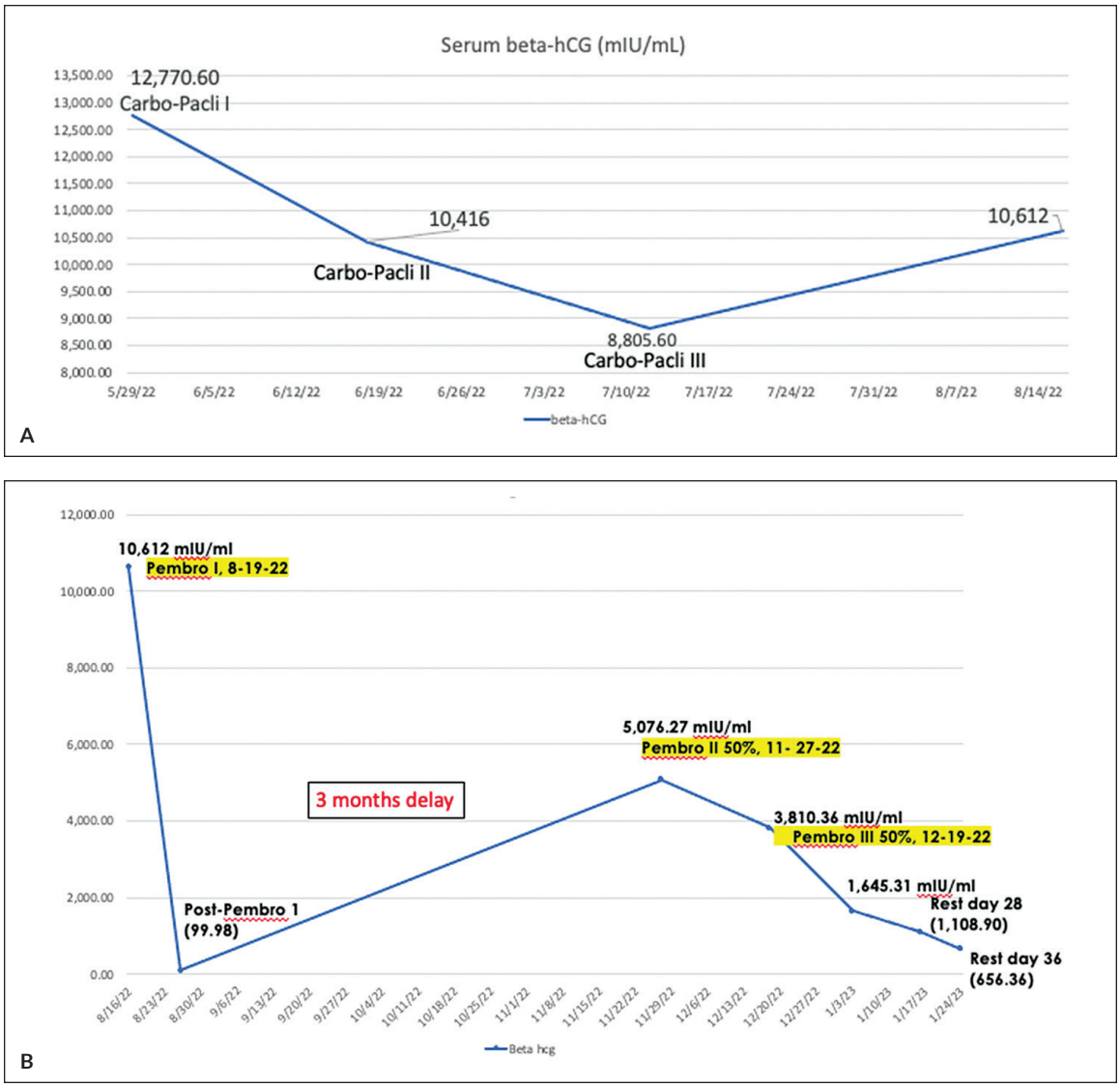

Figure 3. **(A)** hCG regression curve with Paclitaxel Carboplatin; **(B)** hCG regression curve with Pembrolizumab.

In the interim, pancytopenia developed with anemia and leukopenia. Bone marrow aspiration done by the Hematology service was normal. Prednisone was continued and granulocyte colony stimulating factor was given as required. Intravenous immunoglobulin was given once and the patient was started on elthrombopag, a thrombopoietin-receptor agonist. With the marked delay in the second infusion of Pembrolizumab (three months), there was a noted increase in hCG (5,076.27 mIU/ml) associated with a significant increase in the size of pulmonary nodule seen on the left upper lobe both on chest x-ray and chest CT scan. Even with these developments, the outlook of the patient remained positive and hopeful that subsequent doses of Pembrolizumab may be administered.

With improvement in hematologic toxicities to grade 1, a second and third infusion of Pembrolizumab at 50% dose reduction were given on Day 100 and 122 from the first infusion with consequent decrease in the hCG level (1,645.31 mIU/ml). However, there was again worsening of associated hematologic toxicities to grade 3 granulocytopenia and grade 4 thrombocytopenia.

Subsequently, the patient had COVID-19 infection, presenting with fever, cough, and hemoptysis. CBC revealed anemia, thrombocytopenia, and granulocytopenia with presence of abnormal forms of stabs, metamyelocytes, myelocytes, promyelocytes, and blasts in the peripheral smear. A consideration of acute myeloid leukemia from previous chemotherapy was considered. Blood culture revealed Gram-negative bacteremia (*Escherichia coli, Klebsiella pneumonia, Acinetobacter baumanii*). She was on oxygen support and intravenous antibiotics with ciprofloxacin and ceftazidime. A whole abdominal CT scan done as part of the workup for Gram-negative bacteremia showed incidental findings of nodules in the liver and masses on the abdominal wall

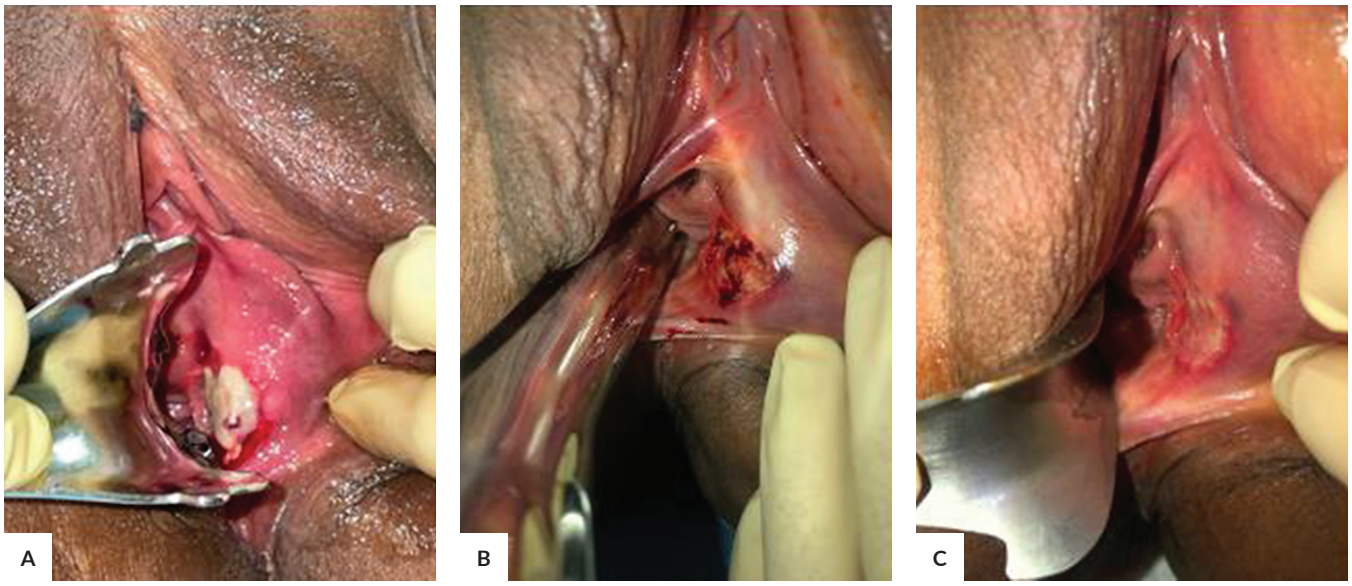

Figure 4. Vaginal mucositis post Pembrolizumab I managed with Prednisone. **(A)** Rest day 8; **(B)** Rest day 10; **(C)** Rest day 11.

and the adnexal region. Despite these, hCG levels showed a decreasing trend (Figure 3B). On hospital day 13, the patient had difficulty of breathing with associated chest pain, tachycardia, and desaturations as low as 71%. The patient refused any additional intervention and eventually expired due to massive pulmonary embolism.

DISCUSSION

Gestational trophoblastic neoplasia remains to be a highly treatable tumor with prompt diagnosis and management. Excellent cure rates in GTN are mainly due to its chemosensitivity and the availability of an excellent tumor marker, beta human chorionic gonadotropin (ßhCG), used not only for initial diagnosis but also to monitor treatment response and detect relapse. Added to this is the development of an optimal classification system used to guide primary chemotherapy and standardize management, the FIGO 2000 Staging System combined with the WHO prognostic scoring system, wherein high risk and ultra high-risk patients with a score of 7 and greater are primarily started on multiple agent chemotherapy.[1]

However, drug resistance remains to be a major problem in the management course of GTN. A delay in first-line chemotherapy due to several factors, one of which is misdiagnosis, may cause genetic tumor alterations in choriocarcinoma leading to anti-tumor treatment tolerance.[3] Several studies had been conducted regarding predictors for chemoresistance which include, number and site of metastasis, incomplete previous treatment, tumor age of more than 12 months, large tumor size, high pretreatment hCG of greater than 100,000 mIU/ml, high FIGO stage, and an ultra high-risk score.[4-6] The risk factors for chemoresistance initially present in the index patient included a tumor age of three years, a pre-treatment hCG of more than 300,000 mIU/ml, and an ultra high-risk score of 13. In the initial institution managing the index patient, EMACO was started completing 10 cycles and was subsequently shifted to EP-EMA with the diagnosis of chemo-resistance. The following problems were identified in the course of treatment: (1) repeated delays in chemotherapy cycles; (2) timing of adjunctive surgery; (3) continuous institution of multiple cycles of chemotherapy despite chemoresistance with increasing hCG levels. Consequently, during the patient's admission in the trophoblastic disease center, repeat metastatic work-up showed tumor progression with note of a cerebellar metastatic focus on cranial CT scan and increase in the number and size of the pulmonary lesions.

Third-line Salvage Treatment

A review of literature showed no universally accepted evidence-based guidelines for salvage treatment in high-risk GTN. In the 2016 Cochrane review on chemotherapy for resistant or recurrent GTN, no randomized controlled trials (RCTs) were found. Reported comparable cure rates with these salvage therapies of 60-75% were based only on case series and these good results were mostly associated with adjunctive treatments of surgery and radiotherapy. Thus, no conclusions regarding the most effective and least toxic combination can be drawn. In addition, it was noted that salvage therapy is more likely to fail in heavily pre-treated patients, similar to the index case.[7]

In the Division of Trophoblastic Diseases, University of the Philippines-Philippine General Hospital, the primary salvage treatment after EMACO chemoresistance is EP-EMA. Review of data since 2002 in the institution showed that no conclusion can be made as to the most effective third-line combination chemotherapy for resistant high-risk

GTN due to a limited number of patients undergoing the treatment. The combination used were Cisplatin, Vinblastine, and Bleomycin (PVB), Bleomycin, Etoposide, and Cisplatin (BEP), Paclitaxel Cisplatin/Paclitaxel Etoposide (TP/TE), and Paclitaxel Carboplatin (PC). The most promising result was seen with the Paclitaxel Carboplatin combination with two out of three patients achieving remission.[8] Based on problems of initial reported adverse reactions to Etoposide and Cisplatin and elevated levels of creatinine, the index patient was started on Paclitaxel and Carboplatin with concurrent whole brain irradiation. With subsequent chemoresistance after the third cycle of Paclitaxel Carboplatin, the treatment options left included high dose chemotherapy with autologous peripheral stem cell support and immunotherapy, both of which were not yet tried locally. High dose chemotherapy with autologous peripheral stem cell support is tedious and will require a long duration of hospitalization associated with significant toxicities. Considering the multiple toxicities from previous treatments, the index patient was prepared to start immunotherapy with Pembrolizumab, an immune checkpoint inhibitor.

Immunotherapy

Immunotherapy is different from chemotherapy as it exerts action on the body's immune system rather than the tumor cells. Recent reports show that immunotherapy may be effective in the treatment of GTN using immune checkpoint pathways involving programmed cell death protein 1 (PD-1) receptors expressed on the surface of cytotoxic T cells and its ligand, programmed cell death ligand1 (PDL-1). The interaction between PDL-1 present in the placenta and PD-1 receptors plays a crucial role in feto-maternal tolerance in normal pregnancy. This mechanism also applies to GTN being cancers derived from the placenta and found to express PDL-1 protecting the cancer from attack by the immune system. Recent studies have reported varying degrees of significant expression of PD-L1 in the different subtypes of GTN independent of FIGO score, chemoresistance or poor clinical outcome.[9] In this regard, focus is now on immune checkpoint inhibitors (ICIs) particularly anti PDL-1 and anti PD-1 as an effective treatment for chemo-resistant and relapsed GTN.

Pembrolizumab, an anti PD-1 checkpoint inhibitor, has been reported to have favorable outcomes in cases of heavily pre-treated chemo-resistant GTN. There were three different case reports of patients with choriocarcinoma who received 3-6 different salvage treatment drug combinations who achieved complete response after 3-10 cycles of Pembrolizumab.[10-12] For intermediate trophoblastic tumors (ITT), the patients presented by Choi, one PSTT and one ETT, were the first reported cases of these type of tumors managed using Pembrolizumab in Asia. The PSTT patient had a complete response after 13 cycles of Pembrolizumab and the ETT patient achieved only a partial response after 15 cycles.[13] Ghorani reported on four cases of chemoresistant GTN treated with Pembrolizumab given every three weeks with three patients (2 CC; 1 PSTT) achieving remission even after 5 – 24 months. One patient with mixed PSTT and ETT had disease progression and died after five cycles of Pembrolizumab.[14]

How will you determine favorable response to Pembrolizumab? All the patients reported in the GTN Pembrolizumab case studies including those patients with partial responses and the patient who failed to respond, showed strong expression of PDL-1. The only difference noted for the non-responder in the report by Ghorani was a negative assay of human leukocyte antigen G or HLA-G with absent tumor infiltrating lymphocytes.[14] HLA-G contributes also to the maintenance of gestational tolerance through T cell suppression. Upregulated tumor expression of HLA-G by the three responders in the group suggested that this molecule maybe a significant test of response to immunotherapy compared to PDL-1 which has been reported to always be positive in GTN in different degrees. However, further studies are needed in this regard. For the index patient, we did not test anymore for PDL-1 expression as management with Pembrolizumab then was the last resort. Test for PDL-1 is available locally in the Department of Pathology, College of Medicine, University of the Philippines Manila and outside laboratories as well. For HLA-G test, the specimen has to be sent abroad.

Immune-related Adverse Events

Based on the hCG trends, the index patient responded very well to Pembrolizumab. From an hCG level of 10,000 mIU/ml pre-Pembrolizumab, hCG dropped to as low as 99.98 mIU/ml 27 days from the initial infusion. However, the onset of immune-related adverse events deter subsequent cycles. Immune-related adverse events (irAEs) are a unique set of toxicities related to immunotherapy with a different underlying mechanism compared to conventional cytotoxic therapy. The enhancement of systemic T-cell activity by ICIs causes a loss of immune tolerance not only in the tumor but in various organs as well resulting in irAEs. In general, they occur quite early mostly within weeks to three months after the initiation of immune checkpoint blockers. Similar to any form of adverse reaction, early recognition and management are vital to avoid significant morbidity or even death. Cutaneous toxicities like rash and pruritis are the most common affecting 71.5% of patients. Endocrine manifestations are reported in about 40% of treated individuals with thyroid dysfunctions being the most common. Serious toxicities are colitis, pneumonitis, cardiac, and neurologic toxicities.[15]

Review of literature showed that the vaginal ulcerations seen in the index patient is a rare occurrence. The first and only reported case in literature was in 2021 from the Cancer Institute of New Jersey in a 67-year-old patient with chemoresistant uterine serous carcinoma. The lesions described were more extensive, Grade 3, compared to

the index patient and seen after her second cycle of immunotherapy. Improvement in one month was noted after intake of Prednisone.[16] The vaginal ulcerations in the index patient was noted on Day 8 post treatment and improved after three days with the use of Prednisone (Figure 3).

The hematologic side effects seen in the index patient became a major problem and caused the marked delay in the continuation of Pembrolizumab. Hematologic immune-related adverse events are reported to be rare but if encountered, the recommended treatment based on the Clinical Practice Guideline of the European Society of Medical Oncology (ESMO) include high dose corticosteroids and immunosuppressive drugs if needed.[17] In the Clinical Practice Guideline of the American Society of Clinical Oncology (ASCO), the initial hematologic manifestation in the index patient of thrombocytopenia was also reported to be uncommon occurring in 8% of patients for all grades and 4.3% for grades 3 and 4.[18] Diagnostic work-up in the form of blood studies and bone marrow evaluation are recommended to determine etiologies other than that secondary to immunotherapy.

Re-challenge and Dosing

The plan of giving a second dose of Pembrolizumab in the index patient raised a concern considering the immune-related adverse events of initial mucositis and pancytopenia. An observational cross-sectional pharmacovigilance study conducted in France with the primary objective of determining the rate of recurrence of initial irAEs after an ICI rechallenge showed that adverse reactions of colitis, hepatitis, and pneumonitis had higher recurrence rates compared with other immune-related adverse events. Based on this study, for the adverse events seen in the index patient, mucositis is more likely to recur compared to the hematological problems (OR 1.66 for mucositis and 1.06 for hematological adverse events). Overall, the recurrence rate of the same immune-related adverse event that prompted discontinuation of ICI therapy was 28.8% after patients received a rechallenge with the same ICI. The authors concluded that with appropriate monitoring and immediate management with recurrence of irAEs, resumption of ICI could be considered for select patients especially those in whom there was noted progression of the disease after discontinuing the ICI as in the index patient.[19]

Another treatment concern was the reduced dose of 50% for the succeeding Pembrolizumab infusions. Based on the pharmacologic information of Pembrolizumab, a fixed dose is given at 200 mg IV infusion every three weeks with no advice regarding dose reduction. Rather, there are studies evaluating the efficacy of various strategies in relation to decreasing drug toxicities such as increasing the interval between treatment. However, studies on weight-based dosing in Pembrolizumab of 2 mg/kg or 10 mg/kg showed similar results on efficacy of the drug.[20] This would mean that dose reductions may be done safely without affecting good response. Although not in GTN, there were studies on modified dosing for Pembrolizumab in Taiwan[21] and Singapore[22], both Asian countries with patients of similar built to Filipinos. The studies showed that a modified dose of 100 mg every three weeks closely approximating the weight-based computation of 2 mg/kg provided the same efficacy looking on progression free survival and overall survival in patients with non-small cell lung cancer providing considerable cost savings to the patient and the health system. The only reported modified dose in GTN was a case report presented from the University of Miami in a chemoresistant choriocarcinoma patient who presented with transaminitis after two cycles of Pembrolizumab 200 mg. After resolution of transaminitis, four more cycles of Pembrolizumab at 100 mg was given to the patient achieving a complete response.[23]

Consequently, in the index patient, after the third reduced dose of Pembrolizumab, there was onset of a moderate COVID-19 infection with Gram-negative bacteremia. With worsening of the blood picture showing bicytopenia and appearance of abnormal immature blasts and myelocytes in the peripheral smear, Acute Myelogenous Leukemia was considered. The patient was heavily pre-treated with combination chemotherapy containing leukemogenic drugs of Etoposide, Cyclophosphamide, and Cisplatin. In the study on the risk of second tumors in GTN patients in Charing Cross, an increased risk of second malignancy was seen in patients receiving multiple cycles of combination chemotherapy. The risk was significantly related to the number of cycles, highest in those who received more than 13 cycles. The six patients in the study who developed leukemia were previously treated with combination chemotherapy including alkylating agents and with significant exposure to Etoposide (five of the six patients dying of the disease). Other cancers with apparent increased risk in the study included oral and pharyngeal cancers, melanoma, and meningioma.[24] The index patient received 10 cycles of EMACO and 19 cycles of EPEMA.

The index patient eventually had Gram-negative septicemia with a whole abdominal CT scan incidentally showing multiple sites of tumor progression in the liver, the adnexal area, and the subcutaneous tissue. However, hCG levels showed further regression (Figure 2). Would this be related to the hematologic malignancy or a manifestation of mixed GTN, choriocarcinoma with the development of intermediate trophoblastic tumors like ETT? In such cases, the evident tumor seen is not reflective of the hCG levels. There have been case reports of GTN patients with initial biopsy results of choriocarcinoma initially treated with combination chemotherapy but with subsequent chemoresistance. Subsequent adjunctive metastasectomy showed histopathology consistent with the diagnosis of an ITT. The theory could be that previous chemotherapy eliminated the more primitive cytotrophoblasts allowing differentiation to intermediate trophoblasts like implantation site or chorionic type intermediate trophoblasts.[25]

Present and Future Directions of Immunotherapy in GTN

Although GTN is not included in the FDA-approved indications of Pembrolizumab, it has been incorporated in recent publications regarding GTN treatment. Immune checkpoint inhibitors are already included in the National Comprehensive Cancer Network (NCCN) Treatment Guidelines of 2019 for chemoresistant high-risk GTN and intermediate trophoblastic tumors.[26] It is also part of the salvage therapies in the most recent FIGO GTN Cancer Report of 2021 and included in several publications dealing with novel treatments of chemoresistant GTN.[27]

There are still several unanswered questions that needed to be addressed by further studies. These include the following: (1) When do you consider giving ICI in GTN?; (2) Can it be given initially in intermediate trophoblastic tumors or as a second- or third-line treatment as what is being done now?; (3) What will be the predictors of response?; (4) How many consolidation courses should be given?; (4)What are the long term effects on fertility knowing that the mechanism of action can affect fetal immune tolerance and subsequent fetal loss? Further studies aim to resolve these questions.

There are ongoing trials on ICI in GTN. The Trophimmun Phase 2 trial is on the use of avelumab, an anti PDL-1 ICI, in low risk GTN patients resistant to Methotrexate. Initial results showed a 53.3% complete response. Cohort 2 was on high risk GTN but was stopped due to poor results.[28] There is also an ongoing Phase 2 trial on the use of Pembrolizumab in chemoresistant GTN[29] and on-going trials of immune checkpoint inhibitors in combination with chemotherapy. TROPHAMET is a trial using avelumab combined with Methotrexate and another trial by NRG Oncology using Pembrolizumab and Actinomycin D for GTN patients with a risk score of 5-6, previously intermediate risk patients wherein 60% in this group exhibit resistance to first-line single agent chemotherapy.[30] The CAP-01 trial is a single-arm phase 2 study on Camrelizumab, another anti PD-1 ICI similar to Pembrolizumab in combination with Apatinib, a vascular endothelial growth factor receptor inhibitor.[31]

CONCLUSION

With the reported strong PDL-1 expression in GTN and the favorable results in case reports of Pembrolizumab in heavily pre-treated chemoresitant GTN, immune checkpoint inhibitors particularly anti PD-1 and anti PDL-1 can be a novel treatment for chemoresistant GTN. This is the first time that immunotherapy was used in the country. Consequently, succeeding cases of chemoresistant GTN eventually managed with immunotherapy may be reported locally. For the index patient, even though the use of Pembrolizumab yielded an adequate response, immune-related adverse events prevented regular institution of the drug. The results of the ongoing trials that aim to address and provide a protocol that can be followed using this treatment modality will largely benefit chemoresistant GTN patients that would otherwise be referred to hospice care.

Statement of Authorship

The author certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The author declared no conflicts of interest.

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