Durable remission for a woman with refractory choriocarcinoma treated with anti-endoglin monoclonal antibody and bevacizumab: A case from the New England Trophoblastic Disease Center, Brigham and Women’s Hospital and Dana-Farber Cancer Institute

Michael J. Worley Jr. a,b,c*, Kevin M. Elias a,b,c, Neil S. Horowitz a,b,c, Bradley J. Quade d, Ross S. Berkowitz a,b,c

a Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, United States
b Dana-Farber Cancer Institute, Boston, MA, United States
c New England Trophoblastic Disease Center, Boston, MA, United States
d Division of Women’s and Perinatal Pathology, Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, United States

Abstract

A 36-year-old with metastatic and refractory choriocarcinoma following single- and multi-agent chemotherapy and surgical metastectomy experienced a durable remission after receiving therapy with an anti-endoglin monoclonal antibody and bevacizumab. Treatment options and scientific advances in this disease are highlighted.

1. Presentation of case

A 36-year-old G4P1 presented to her primary care provider with a positive urine pregnancy test. Her past medical history was notable for FIGO stage I, WHO risk score of 1 (pretreatment β-hCG <1000 mIU/mL = 1), gestational trophoblastic neoplasia (GTN), seven years prior to the current pregnancy that was treated with single-agent methotrexate (MTX). She underwent a pelvic ultrasound that revealed an empty intrauterine gestational sac with a measurement consistent with a gestational age of 6.1 weeks. Her β-hCG at that time was 7328 mIU/mL. An interval pelvic ultrasound revealed no change to her intrauterine findings. She then underwent a dilation and evacuation for a presumed missed abortion. Pathology revealed secretory endometrium and decidua, but no chorionic villi. One week after surgery, a repeat pelvic ultrasound revealed no change to her intrauterine findings. She then underwent a dilation and evacuation for a presumed missed abortion. Pathology revealed secretory endometrium and decidua, but no chorionic villi. One week after surgery, a repeat pelvic ultrasound revealed a fluid collection within the uterus, in the region of the right cornu. Her β-hCG at that time was 56,569 mIU/mL. Pelvic magnetic resonance imaging (MRI) was obtained and was concerning for an intramural pregnancy. Presuming the diagnosis of an ectopic pregnancy, she received two doses of single-agent MTX (50 mg/m²), with a decline in her β-hCG. One week later, her β-hCG had increased and a repeat pelvic ultrasound revealed a 3.0 × 2.8 × 2.4 cm, complex and cystic mass in the right myometrium. At this point in time, GTN was suspected. Her stage was summarized as FIGO stage I, WHO risk score of 5 (antecedent pregnancy = 1, pretreatment β-hCG 10,000–100,000 mIU/mL = 2, previous failed chemotherapy = 2). She then received two courses of pulsed actinomycin-D. Her β-hCG initially declined, but then began to increase. Metastatic workup at this time included a negative chest x-ray. While computerized axial tomography (CT) imaging may not be used for staging of GTN, a chest CT was obtained and was notable for multiple small pulmonary nodules. Despite her negative chest x-ray, a chest CT was obtained because of the concern for metastatic disease, given the failure to respond to single-agent chemotherapy. Her chemotherapy was then switched to etoposide, MTX, actinomycin-D, cyclophosphamide and vincristine (EMA-CO). She received one cycle of EMA-CO and one week later underwent a total laparoscopic hysterectomy. Pathology showed choriocarcinoma. The decision to proceed with a hysterectomy was made after a thorough discussion with the patient regarding her remaining gross uterine disease that had been resistant to single-agent chemotherapy. Resecting her remaining chemoresistant intrauterine disease was thought to potentially decrease the number of additional cycles of chemotherapy needed to achieve remission. Despite a hysterectomy and two cycles of EMA-CO, her β-hCG increased. At this point the patient was switched to etoposide, MTX, actinomycin-D and cisplatin (EMA-EP). After seven cycles of EMA-EP, her β-hCG normalized. She then went on to receive three additional cycles of EMA-EP for consolidation. After one month of serologic remission, her β-hCG increased and a chest CT revealed multiple new sub-centimeter pulmonary nodules, consistent with recurrent disease. The patient went on to receive multiple salvage chemotherapy regimens, including: paclitaxel and cisplatin alternating with paclitaxel and etoposide (TP/TE), ifosfamide, carboplatin and etoposide (ICE) and high-dose carboplatin and etoposide with autologous stem cell rescue. During treatment with...
salvage chemotherapy, she experienced intermittent increases in her β-hCG and progressive disease on imaging. A positron emission tomography combined with computerized tomography (PET/CT) revealed persistent, bilateral non-FDG-avid pulmonary nodules, as well as a dominant FDG-avid pulmonary nodule located in the right lung. She then underwent thorascopic resection of her active pulmonary disease. Final surgical pathology was consistent with choriocarcinoma. Prior to being treated with postoperative chemotherapy, her β-hCG increased and a chest CT revealed progressive disease in both the right and left lungs. She was then treated with capcitabine. While on treatment, the patient began to experience persistent headaches. This prompted a brain MRI, which revealed two new brain lesions concerning for metastatic disease. These lesions were treated with stereotactic radiation and she was maintained on capcitabine. One month after stereotactic radiotherapy her headaches had resolved, but her β-hCG had increased and a chest CT revealed progression of disease in both lungs. She was then initiated on a single patient treatment protocol with bevacizumab (10 mg/kg) and an anti-endoglin monoclonal antibody (TRC 105). Her β-hCG normalized after four cycles of bevacizumab + TRC 105 and she received four additional cycles for consolidation therapy. At the time of this publication, she has remained off of chemotherapy and in clinical and β-hCG remission for over 28 months.

2. Pathology of gestational trophoblastic neoplasia

The endometrial curettage specimens collected seven years prior to her current illness showed the classical features of complete hydatidiform mole. Numerous hydropic chorionic villi were visible macroscopically. These enlarged villi contained fluid-filled cystic cavities by microscopic examination. The trophoblasts of these cavitated villi had circumferential and frequently exuberant trophoblast hyperplasia. Although the trophoblast atypia in the villi was modest, the implantation site trophoblasts were quite atypical. Such implantation site atypia is frequently found in complete moles. Immunohistochemistry for p57 demonstrated loss of staining in cytotrophoblasts and villous stromal cells, confirming the histological diagnosis of complete mole. Loss of p57 expression in complete mole reflects diandry.

The hysterectomy specimen was notable for a single red-tan, well circumscribed 1.8 cm nodule with a fleshy cut surface bulging out of the right uterine wall. Histologically, the nodule contained a sheet-like proliferation of syncytiotrophoblasts and cytotrophoblasts. As no chorionic villi were present, the diagnosis of choriocarcinoma was made. Extensive necrosis, possibly reflecting chemotherapeutic effect, was present. Lymphovascular invasion by choriocarcinoma also was present microscopically. During her presentation, multiple pulmonary wedge biopsies excised more than 10 well circumscribed nodules ranging in size from 0.5 to 1.6 cm. Like the hysterectomy specimen, each nodule contained expansile proliferations of mononuclear and syncytiotrophoblasts with highly atypical nuclei, as well as abundant...
tumor cell necrosis and recent hemorrhage (Fig. 3D). The discreteness and multiplicity of the choriocarcinomatous nodules support classification as pulmonary metastases.

3. Detailed aspects of the presented case

3.1. Single-agent chemotherapy

When trying to determine initial treatment for patients with GTN, it is critical to assign them an accurate FIGO stage and WHO risk score. As in this case, those with stage I–III disease and a WHO risk score of ≤6, are considered to have low-risk disease because of a high likelihood of cure and low risk of resistance to single-agent therapy. For patients with low-risk disease, treatment with single-agent MTX or actinomycin-D is associated with an excellent prognosis and complete remission in approximately 80–90% of patients [1–5]. However, there is data to suggest that among patients with a WHO risk score of 5–6, only 30% of patients will achieve remission with single-agent chemotherapy, despite being classified as low-risk GTN [6].

As noted in her first episode of GTN, our single-agent of choice for low risk GTN is MTX. There are a variety of treatment schedules for MTX administration, but available data suggests that either 5-day or 8-day MTX is more effective than weekly intramuscular (IM) dosing. Based on our experience at the New England Trophoblastic Disease Center (NETDC), we currently use 8-day MTX with alternating leucovorin every two weeks until the β-hCG is undetected. We then administer three consolidation courses to reduce the risk of relapse [7]. While this is our preference, there is no consensus on what should be the favored primary single-agent treatment. In fact, data from randomized trials do suggest that actinomycin-D may be associated with higher cure rates, with fewer required cycles of treatment to achieve cure. However, treatment related toxicity is often greater when comparing actinomycin-D to MTX [1,4].

During our patient’s second episode of GTN, she received weekly single-agent MTX (50 mg/m²) at an outside institution prior to referral to the NETDC. This was likely administered given the suggestion of an ectopic pregnancy. Despite an initial decline in her β-hCG, she quickly displayed resistance, with a rise in her β-hCG after her second cycle. Given this, as well as her previous exposure to MTX (and the fact that it was given weekly rather than the preferred multi-day schedule), she was switched to single-agent actinomycin-D. The choice of single-agent actinomycin-D, rather than transitioning to a multi-agent regimen was made to minimize treatment associated toxicity [8]. Currently, the trophoblastic disease center at Charing Cross Hospital is using a single-agent regimen based on the availability of the last available dose of the most recent drug, but MTX or actinomycin-D are either unavailable or not tolerated.

3.2. Multi-agent chemotherapy

At the NETDC, if patients fail to achieve a sustained response or remission after the administration of single-agent MTX or actinomycin-D, multi-agent chemotherapy is the treatment of choice. For the patient presented, we selected EMA-CO as first-line multi-agent chemotherapy. This is also the same regimen we select for primary therapy for women that present with high-risk (i.e. WHO score >6) GTN. This regimen is well tolerated and would expect to provide remission rates of 75–95% for women with low-risk disease that is resistant to single-agent chemotherapy, or as primary treatment for patients with metastatic disease and high-risk scores [6,12,13]. Despite initiating EMA-CO and undergoing a hysterectomy, our patient’s β-hCG continued to rise. Our patient was then switched to EMA-EP, as data would suggest that this regimen would induce remission in approximately 75% of patients resistant to
EMA-CO [7,14]. In our patient, normalization of her β-hCG was achieved after seven cycles of EMA-EP. She then went on to receive three cycles of consolidation chemotherapy. There is a paucity of data to definitively state the appropriate number of consolidation chemotherapy cycles. In the absence of conclusive evidence, three cycles of consolidation chemotherapy was selected, to be consistent with a previous report [7]. Unfortunately, her remission was brief and her β-hCG level began to rise.

3.3. Salvage chemotherapy

In the setting of refractory GTN, there are several alternative chemotherapy regimens (e.g. TP/TE and ICE) and single-agent therapies (e.g. carboplatin and gemcitabine) that have displayed activity [15–17]. There are no randomized data to suggest how to sequence these regimens. Given similar efficacy among available treatment options, we balanced expected toxicities, as well as the anticipated treatment schedule, when selecting salvage chemotherapy for the presented patient. This was particularly important for our patient, as she also had a small child to care for during therapy.

Despite multiple salvage chemotherapy regimens (e.g. EMA-CO, EMA-EP, TP/TE and ICE), our patient had an inadequate response to therapy. With an attempt to achieve sustained remission, high-dose carboplatin and etoposide with autologous stem cell rescue was utilized. At the time of this decision, there was no reported alternative salvage regimen that was more likely to achieve remission. While achieving a brief remission, her β-hCG again increased. After high-dose chemotherapy with stem cell rescue, our patient had persistently diminished bone marrow reserve. This limited the use of other potential chemotherapy regimens. Therefore, she was placed on capcitabine, which is associated with limited hematologic toxicity [18]. Alternative salvage chemotherapy options include: 5-fluorouracil based multi-agent regimens, carboplatin, gemcitabine and pegylated liposomal doxorubicin [19]. Although not available at the time we treated this patient, there is growing data to suggest that the use of immunotherapy check point inhibitors (e.g. pembrolizumab) may have activity in chemotherapy resistant GTN [20] and there is an actively recruiting phase II trial of avelumab being conducted in France (ClinicalTrials.gov NCT03135769).

3.4. The role of surgery for GTN

3.4.1. Hysterectomy

Hysterectomy may contribute to patient outcomes in several situations. Among patients with non-metastatic (Stage 1) GTN, who do not wish to preserve fertility, hysterectomy may be employed as an adjuvant procedure to primary chemotherapy. At the NETDC, 39 patients with stage 1 GTN were treated with hysterectomy and one course of chemotherapy and all attained remission with no further treatment. Chemotherapy is administered due to the substantial risk of occult metastases, such as pulmonary micrometastases. Pulmonary micrometastases are common and despite a normal chest x-ray, chest CT will reveal micrometastases in 40% of patients (as was shown in our case) [21,22]. Hysterectomy may also be useful in controlling complications of disease like bleeding or sepsis or to excise a focus of drug resistant tumor [23–25]. Similar to the management of our patient, hysterectomy may also be helpful in patients with large uterine tumor masses to reduce the tumor burden and allowing for fewer courses of chemotherapy [25]. At the NETDC, hysterectomy was performed in 19 patients for drug resistant tumors and 16 (84%) patients achieved remission [25]. Similarly, hysterectomy was performed in 18 Hungarian patients with chemoresistant uterine GTN and 15 (83%) attained complete remission [26].

3.4.2. Surgery for metastatic disease

Because GTN is highly sensitive to chemotherapy, patients with metastatic disease can often be cured without the need for surgical resection [27]. While considerable progress has been made in the chemotherapy regimens used for GTN, select surgical procedures remain important in treatment. Surgical intervention may be required for life-threatening complications such as hemorrhage, bowel or urinary obstruction, or infection [28–30]. In addition, surgical resection may be utilized to remove extra-uterine tumor that is resistant to chemotherapy [28].

Surgical resection of persistent, viable pulmonary nodules that are resistant to chemotherapy can be curative among highly selected patients. Tomoda et al. evaluated 19 patients with chemoresistant GTN that were treated with surgical resection of pulmonary metastases. Based on their experience, they proposed the following criteria to predict successful pulmonary resection: (1) patient is a good surgical candidate, (2) primary malignancy is controlled, (3) no evidence of other metastatic sites, (4) pulmonary metastasis is limited to one lung and (5) β-hCG level is less than 100 mIU/mL. In their series, complete remission was achieved among 14 of 15 patients (93%) who met all five criteria. In contrast, four patients met less than five criteria and none of these patients achieved complete remission [31]. With respect to our patient, she did not meet the criteria defined by Tomoda et al. for the highest likelihood of remission following surgical resection. However, after multiple chemotherapy regimens failed, with limited therapeutic options remaining, resection of chemoresistant pulmonary lesions was employed to contribute in the effort to achieve remission with additional systemic therapy.

An important point highlighted in the presented case is the use of imaging prior to surgical resection. Radiographic evidence of tumor regression within the lung may be significantly delayed, when compared to β-hCG response to treatment. In addition, nonviable fibrotic nodules may persist after tumor regression for months, years or indefinitely after completing chemotherapy [30,32]. The use of PET/CT may improve the detection of viable tumor prior to surgical resection [33,34]. Following surgical resection, an undetectable β-hCG level within two weeks of resection is highly predictive of a favorable outcome [35–39].

Approximately 8–15% of patients with metastatic GTN will have brain metastases [28,40–46]. These lesions are often highly vascular and develop central necrosis and hemorrhage. Like our patient, most women with brain metastases have clear neurological symptoms including nausea, vomiting, headache, seizures, slurred speech, visual disturbances or hemiparesis [47–51]. In the event of intracranial hemorrhage or increased intracranial pressure, craniotomy can be a life-saving surgical procedure. Craniotherapy is also indicated for the resection of isolated, peripherally located, drug resistant lesions. Evans et al. reported on a series of seven women undergoing craniotomy for metastatic GTN. In this series, 3 of 4 women (75%) achieved complete remission after craniotomy to relieve intracranial pressure. The remaining three women underwent craniotomy for resection of drug resistant lesions and complete remission was achieved in two of these patients (66%). In this series, patients also received whole-brain radiation and concurrent chemotheray [43]. The combination of multi-agent chemotherapy and whole-brain radiation is commonly employed in the United States to treat brain metastases from GTN. Long-term sequelae of whole-brain radiation may include impaired cognition, dementia, gait ataxia and behavioral changes. Stereotactic radiotherapy was utilized for our patient and has the potential to decrease neurotoxicity (compared to whole-brain radiation). Stereotactic radiotherapy allows for precise delivery of a single high-dose fraction of radiation to a small target volume, with a sharp fall-off of the dose to adjacent normal tissues [52]. The presented patient had had no residual neurological deficits after treatment of her brain metastases and the majority of patients treated for brain metastases should expect a similar outcome [27]. It is also important to note that patients with brain metastases may also be treated with chemotherapy without radiation therapy. High-dose MTX and intrathecal MTX have been shown to achieve complete remission in 23 of 27 patients (85%) [53].
3.5. Evaluation of targeted therapy

With standard chemotherapy options exhausted, molecular analysis of our patient’s tumor was obtained. Tumor profiling is available through many institutional and commercial laboratories and may offer insight into potential therapeutic targets. Our patient’s tumor profile revealed no chromosomal rearrangements. Somatic variants in MAP3K1, MUTYH and TP53 were detected. Low copy number gain of chromosome 1q and 1q13-11, including EGFR and 14q, as well as one copy deletion of PANCA on 16q24 were also detected. While molecular analysis of our patient’s tumor failed to reveal alterations that could possibly guide management strategies, recent reports highlight the potential of tumor profiling in the management of GTN.

In an evaluation of eight cases of gestational choriocarcinoma, Mello et al. revealed five cases with loss of 9q33.1 [54]. Loss of 9q33.1 encompasses nine genes, including TRIM32, which is thought to be a tumor suppressor gene. TRIM32 directly interacts and ubiquinates X-linked inhibitor of apoptosis (XIAP), leading to proteasome-mediated degradation [55]. XIAP is a well-known cancer therapeutic target and down-regulation of this protein may influence chemosensitivity [56]. Also in the report by Mello et al., in silico functional interaction analysis suggested involvement of the PTEN and PI3K-Akt pathways in gestational choriocarcinoma [54]. Further supporting this concept, a recent study displayed a novel targeted therapy for choriocarcinoma directed at the PI3K-Akt pathway [57]. Based on epidemiologic and case-control studies suggesting chemotherapeutic properties of the flavonoid apigenin, Lim et al. treated choriocarcinoma cell lines with this novel agent. Choriocarcinoma cell lines treated with apigenin displayed reduced viability and migratory properties, increased apoptosis, and suppressed mitochondrial membrane potential. In addition, choriocarcinoma cell lines treated with a combination of apigenin and inhibitors of ERK1/2 and PI3K/AKT pathways revealed synergistic anti-proliferative effects [57].

3.6. Rationale for anti-endoglin therapy

Studying chemoresistance in gestational choriocarcinoma has been limited due to the lack of appropriate experimental models. In our laboratory, we have created a model system for studying mechanisms of chemoresistance in GTN using the established human choriocarcinoma cell line JEG-3. We generated a series of syngeneic JEG-3 chemoresistant clones through serial exposure to progressively higher concentrations of MTX [58,59]. These clones were then profiled using gene expression arrays to identify possible mechanisms of chemoresistance and targets for therapy. Among the upregulated genes associated with chemoresistance, we identified endoglin, a co-receptor of the TGF-β family, which modulates signaling between the TGF-β and ALK5 (Fig. 4) [60]. Endoglin is essential for vascular modeling and is increased in the placenta with a normal placenta cell line (NP). Endoglin expression increases further in JEG-3 and JAR sections from a resected lung metastasis from our patient and confirmed the presence of endoglin in her tumor cells (Fig. 6). From these results, we speculated that our patient might respond to endoglin-targeted therapy. After four cycles of bevacizumab + TRC 105, her β-hCG normalized. She then received four additional cycles for consolidation therapy. Surveillance has included monthly β-hCG values. She was also placed on leuprolide to suppress pituitary gland production of hCG and luteinizing hormone (LH), to reduce the risk of misinterpreting low levels of hCG production as evidence of trophoblastic hCG and tumor relapse [73]. She has remained off chemotherapy and in remission for over 28 months. Of equal importance, she is free of any significant treatment related side-effects.

4. Summary

The management of patients with refractory GTN can be extremely challenging and ideally should be concentrated to trophoblastic disease centers to achieve optimal outcome. Remission may require administration of multiple chemotherapy regimens. In addition, metastatic chemoresistant lesions may require a multidisciplinary approach to effectively eradicate sanctuaries of chemoresistance through surgical resection or irradiation. Ongoing investigations into the mechanism of chemoresistance will expand our knowledge of refractory GTN and as seen in our patient, may provide opportunities for targeted therapy.

Conflict of interest statement

We declare that there are no direct conflicts of interest associated with this manuscript, except the following:

- Dr. Elias reports that TRC 105 was provided by TRACON Pharmaceuticals and discloses travel reimbursement by TRACON Pharmaceuticals to present this work internally.

Fig. 4. In the presence of TGF-β, endoglin (ENG) promotes the association of TGF-β receptor II (TβRII) with the ALK5 homodimer. In the presence of the alternate ligand BMP9, endoglin recruits TβRII to the ALK1/5 heterodimer.

Fig. 5. Endoglin expression is higher in the choriocarcinoma cell lines JEG-3 and JAR compared to a normal placenta cell line (NP). Endoglin expression increases further after exposure to methotrexate (+).
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