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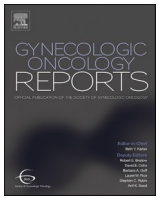

Challenges in treatment of gestational trophoblastic neoplasia in patients with MTHFR mutation: A case report

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1. Introduction

Gestational trophoblastic neoplasia (GTN) encompasses several different pathologies including complete and incomplete molar pregnancies, invasive molar pregnancies, placental-site trophoblastic tumor, gestational choriocarcinoma, and epithelioid trophoblastic tumor (Turgal & Beksac, 2016). GTN arises from the abnormal proliferation of trophoblasts. The World Health Organization (WHO) score is based on several characteristics such as patient's age, antecedent pregnancy, interval since antecedent pregnancy, pre-treatment beta-human chorionic gonadotropin (bHCG) hormone level, site and number of metastases, and failure of prior chemotherapy (Ngan et al., 2018). The WHO defines low-risk disease with a score of less than 7 (Bruce et al., 2021; Ngan et al., 2018).

Low-risk disease is often treated with single-agent treatment, as recommended by the National Comprehensive Cancer Network (NCCN) guidelines and is associated with an overall excellent prognosis with survival rates reaching 100 % (Alazzam et al., 2012). Methotrexate (MTX) and dactinomycin (ActD) are the preferred single-agent therapies with MTX often preferred in clinical practice compared to ActD as it is well-tolerated, effective, and convenient to administer (Alazzam et al., 2012; Li et al., 2018). In 2011 the gynecologic oncology group (GOG) reported that in patients with a WHO score less than 5 ActD was superior to weekly MTX administration (Osborne et al., 2011). Both regimens were also found to be well tolerated in patients with low-risk diseases but were also found to have lower efficacy rates in patients with WHO score of 5 or more and isolated cases of recurrences; therefore, it is recommended that the chemotherapy regimen is tailored to each patient based on other clinical considerations (Li et al., 2018; Osborne et al., 2011).

Methotrexate inhibits dihydrofolate reductase, an enzyme that is crucial in the folate-dependent enzymatic pathway in the nucleic acid synthesis cascade (Urano et al., 2002). The Methylenetetrahydrofolate reductase (MTHFR) is the enzyme responsible for converting the intermediary amino acid homocysteine. The most common genetic polymorphisms in this enzyme are due to deletion mutations with the most common being the C677T allele that leads to a buildup of homocysteine due to decreased enzymatic activity (Urano et al., 2002). The MTHFR C677T allele has a genotypic frequency of 10–25 % and plays a role in activating folic acid and directly inhibiting the action of MTX, leading to decreased efficacy of the medication (Ren and Wang, 2006). A proposed mechanism of treatment toxicity is thought to be from excessive buildup of homocysteine which been implicated in vascular disease, thromboembolisms, and pre-eclampsia (Liew and Gupta, 2015). Several studies reported MTX-related toxicities in patients with the MTHFR allele with rheumatoid arthritis and hematologic malignancies, particularly hepatotoxicity but none have been reported in relation to treating gynecologic malignancies (Ren and Wang, 2006; Aggarwal et al., 2006). It is unknown what proportion of the genotypic mutations lead to changes in the phenotypic changes that impacts treatment response or causes treatment toxicity. We present a case of a patient with post molar pregnancy, in whom an identification of MTHFR C677T mutation led to an alteration of recommended chemotherapy regimen.

2. Description of case

Our patient is a 34-year-old gravida 4, para 1, aborta 2, who presented to her obstetrician for a positive pregnancy test to establish prenatal care. She had a history of recurrent pregnancy loss and work-up revealed an MTHFR C677T mutation. She was found to have a bHCG of 84,853 and a transvaginal ultrasound showed a mass with cystic "grape-like" structures in the endometrial cavity, suspicious for a molar pregnancy. Chest x-ray was normal. The patient subsequently underwent an ultrasound guided dilation and curettage for evacuation of molar pregnancy with final pathology confirming a complete hydatidiform mole. On serial serology testing, the patient was found to have increasing bHCG values starting with a nadir of 1200 and 1917 and 3626, performed one week apart.

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The patient was referred to a gynecologic oncologist for management of post molar GTN. Her WHO score was 2 and she was offered single-agent therapy with either MTX or ActD regimen. Due to the presence of the MTHFR mutation, the patient was counseled regarding decreased efficacy and increased toxicity of MTX therapy based on the literature review of patients with rheumatoid arthritis receiving MTX with MTHFR mutations. After consideration, the patient opted for ActD regimen of 2.4 mg IV. After two cycles of therapy, the patient's bHCG was less than 5 and she received an additional 3 cycles for a total of 5 cycles. The patient has been in surveillance with bHCG levels less than 5 for over six months.

3. Discussion

Methotrexate is used to treat several gynecologic conditions, including ectopic pregnancy and low risk GTN (Bachman & Barnhart, 2012). The absolute contraindications to MTX therapy are chronic liver disease, thrombocytopenia, peptic ulcer disease, renal failure, intrauterine pregnancy, immunodeficiency, and recurrent pregnancy loss. (Bachman & Barnhart, 2012) Currently, there are no guidelines that help guide the decision for MTX therapy in patients harboring somatic or germline MTHFR mutations.

In the work-up for recurrent pregnancy loss, MTHFR mutations are not part of the routine recommended screening as the data linking it to pregnancy loss is limited (Ren & Wang, 2006). Our patient was found to have an MTHFR mutation which played an important role in guiding the management of her GTN. After a literature review, it was noted that MTHFR mutations have altered the efficacy of MTX in rheumatoid arthritis patients. The C667T allele has been associated with decreased efficacy and increased toxicity with MTX administration (Urano et al., 2002; van Ede et al., 2001; Aggarwal et al., 2006). However, there is limited data regarding the MTHFR C667T allele and its significance in the management of GTN. It is unknown whether MTX would have a decreased efficacy or increased toxicity in GTN patients with the C667T allele. Current limited literature recommends an individualized approach to guide management in this patient population.

Based on the current available evidence, the patient was counseled regarding the risks and benefits of MTX therapy and ultimately opted to undergo treatment with ActD. Alternatively, the patient could have been offered a repeat dilation and curettage which can be offered. However, only 40 % of patients in a GOG trial had cure rates without chemotherapy (Osborne et al., 2016). The patient tolerated Act D regimen well and had a complete response to therapy after 2 cycles. Further retrospective studies are needed to assess response to and tolerability of MTX in patients with MTHFR mutation who are undergoing treatment for GTN. The authors conclude that routine testing for MTHFR mutations should not be offered, but reflex testing can be considered if MTX toxicities are suspected. It is recommendation to have a discussion with patients who are undergoing treatment with MTX with known MTHFR mutations and consider an alternative therapy to MTX in treatment of GTN as the risk of toxicities could be morbid when an alternative therapy with ActD is well tolerated.

Author contribution

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Informed Consent:

The authors of the manuscript report that the patient had given consent for the publication of the manuscript and was informed that all the information within the manuscript consisted of deidentified data and has been prepared to be used for academic purposes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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