ORIGINAL RESEARCH

DOI: 10.5336/jcog.2021-87522

# Eight-Day Methotrexate/Folinic Acid Regime as Single Agent Chemotherapy for Low-Risk Gestational Trophoblastic Neoplasia: A Retrospective Study

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**ABSTRACT Objective:** To evaluate the 8-day methotrexate (MTX)/folinic acid (FA) as a first-line chemotherapy regimen treatment in terms of complete regression of disease in women with low-risk gestational trophoblastic neoplasia (GTN). **Material and Methods:** All patients with low-risk GTN treated with an 8-day MTX/FA regimen were retrospectively included in the study. International Federation of Obstetrics and Gynecology and the modified World Health Organization Prognostic Scoring System were used to classify the risk of GTN. All women received diagnostic imaging evaluation before starting the treatment. The same MTX/FA regime was used repeating as a two-week cycle until normalization of the beta-human chorionic gonadotropin (ß-HCG), thus monthly ß-HCG follow-up was scheduled for up to 1 year. **Results:** Successful treatment was achieved in 56/66 (84.8%) patients. Nine (13.6%) women had resistance and 1 (1.6%) toxicity. The resistance patients were successfully treated with EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) protocol, whereas the patient who showed toxicity to the MTX/FA regime was successfully treated with actinomycin-D. **Conclusion:** Eight-day MTX/FA regime could be useful in low-risk GTN patients with good security margins. The toxicity rates in this protocol were determined as quite low. All resistance was treated successfully with the EMA-CO protocol.

**Keywords:** Gestational trophoblastic disease; drug therapy; methotrexate

Gestational trophoblastic neoplasia (GTN) is a rare pregnancy-related group of diseases, which include invasive mole, choriocarcinoma, epithelioid trophoblastic tumor, and placental-site trophoblastic tumor, marked by abnormal trophoblastic cell proliferation.[1-3] According to the Modified World Health Organization (WHO) Prognostic Scoring System and the International Federation of Obstetrics and Gynecology (FIGO), GTN is classified as low or high risk. The scoring system includes age, antecedent pregnancy, the interval between pregnancies, pre-treatment beta-human chorionic gonadotropin (ß-HCG) levels, tumor site, tumor size, previous failure of chemotherapy, and the number of metastases.[4] A score of ≤6 identifies the low-risk patients, whereas a score of ≥7 classifies the high-risk group.[5] Due to an intrinsic sensitivity to chemotherapy, GTN is broadly considered an easily treatable malignancy.[6] When diagnosed promptly and treated in reference centers, GTN shows an overall survival rate ranging from 90%, for high-risk, to 100% for low-risk.[7-9] The most common and efficient chemotherapy procedure in low-risk GTN patients is single-agent chemotherapy using methotrexate (MTX), etoposide, or actinomy-

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Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

***Received:*** 13 Dec 2021 ***Received in revised form:*** 06 Feb 2022 ***Accepted:*** 21 Feb 2022 ***Available online:*** 03 Mar 2022

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cin-D (Act-D).[9] In general, the alternative agent is utilized as second-line chemotherapy after the first-line treatment failure, before resorting to multiagent therapy.[10] Despite many protocols having been developed about the use of these agents, there is no consensus on which is the most effective regimen.[11] Some studies have shown Act-D is more effective than MTX, however, the latter is still widely preferred due to the low side-effect profile and the longstanding experience in its use.[12,13] The most common MTX protocol used is the 8-day regimen consisting of MTX and folinic acid (FA).[10] However, there is not a consensus on the prescription, ranging from 1 mg/kg per day to 50 mg/day.[14-16]

This study is a retrospective evaluation of low-risk GTN patients treated at one of the 2 large tertiary referral hospitals serving a large population. We aim to assess the effectiveness in terms of the complete response of MTX 50 mg/day (days 1, 3, 5, 7) and FA 0.1 mg/kg/day (days 2, 4, 6, 8) as a first-line chemotherapy regime for low-risk GTN.

## MATERIAL AND METHODS

### STUDY DESIGN AND DATA COLLECTION

Between 2000 and 2018, all consecutive patients with low-risk GTN were treated at one of these 2 institutions (İstanbul Kanuni Sultan Süleyman Training and Research Hospital, and Diyarbakır Gazi Yaşargil Training and Research Hospital) were retrospectively retrieved and included in the study. University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee approved this retrospective research (date: September 27, 2019, no: 345). We performed this study consistent with the Declaration of Helsinki ethical principles. Information about patients' characteristics, type of treatment, complications, and follow-up was retrieved from the hospital record system and reported in an ad-hoc database respecting privacy.

The GTN diagnosis was based on an increase of ≥10% in the value of at least three ß-HCG measurements in two consecutive weeks, a steady state of at least 4 ß-HCG values measured in 3 weeks, a ß-HCG value >20,000 IU/L four weeks after uterine evacuation, an increasing ß-HCG 6 months following the uterine evacuation and confirmation of metastasis.[11] The FIGO and the Modified WHO Prognostic Scoring System were utilized to classify the GTN. To determine the patient's score, features such as age, antecedent pregnancy, the period between pregnancies, pre-treatment ß-HCG values, tumor site, tumor size, previous failure of chemotherapy, and the number of metastases were recorded. A chest X-ray was used to diagnose pulmonary metastasis, and magnetic resonance imaging or computed tomography was applied in cases with suspected brain and liver metastases. Complete blood count, platelet count, renal (creatinine), and liver function tests (aspartate aminotransferase, blood bilirubin) were performed after the detailed physical examination performed before MTX chemotherapy and these laboratory tests were repeated at regular intervals during the treatment.

### TREATMENT AND FOLLOW-UP

The MTX/FA 8-day regimen was started as the first single-agent chemotherapy. MTX was administered at 50 mg/day on the 1$^{st}$, 3$^{rd}$, 5$^{th}$, 7$^{th}$ days, and FA at 1 mg/kg/day on the 2$^{nd}$, 4$^{th}$, 6$^{th}$, 8$^{th}$ days of the treatment 24-h following each MTX dosage. This cycle was continued as a two-week cycle until normalization of the values. Once a normal ß-HCG value was obtained, 3 cycles of consolidation dose were given to each patient. Treatment was continued if the ß-HCG value decreased at least 1 log or more, measured in consecutive two-week intervals. After remission was achieved in patients, normal ß-HCG levels were monitored for 4 consecutive weeks, followed by monthly ß-HCG follow-up for up to 1 year. During the one-year follow-up following the treatment, patients were informed about the importance of not getting pregnant and about appropriate contraception methods.

### TREATMENT OF THE RESISTANCE AND TOXICITY CASES

For patients who developed drug toxicity during the MTX/FA treatment, Act-D as a single agent was given. Without regard to the single-agent regime, if the ß-HCG value decreased by less than 1 log, maintained a plateau, or increased again within 2 consecutive weeks, the EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) protocol was started. Hysterectomy was considered for

older patients with no reproductive requirement, and for those who requested surgery. We assessed the treatment toxicity based on the latest National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.[17] Relapse was described as 2 consecutive increased ß-HCG values after the exclusion of a newly formed pregnancy during follow-up.

### STATISTICAL ANALYSES

We performed the statistical analysis with the software SPSS Statistics for Windows version 22 (IBM; Armonk, New York, USA). We performed a descriptive analysis of the records following the completion of the audit. Numerical data were presented as mean±standard deviation or median (range), whereas frequency and percentage were used for categorical data.

## RESULTS

The characteristics of the low-risk GTN cases are shown in Table 1. Fifty-six (84.8%) patients treated with MTX/FA as first-line chemotherapy for low-risk GTN showed complete regression of the disease during the observational period. Nine (13.6%) women presented resistance whereas only 1 (1.6%) showed toxicity (Table 2). The patient who presented toxicity after MTX/FA treatment was treated successfully with Act-D showing no toxicity or resistance (Table 2). The patients who developed resistance during treatment with MTX/FA were successfully treated with the EMA-CO procedure showing no toxicity or resistance (Table 2). To summarise, 84.8% of patients treated with chemotherapy for low-risk GTN were successfully treated with MTX/FA, 1.6% were treated with Act-D, and the remaining 13.6% with EMA-CO procedure (Figure 1). No patient underwent hysterectomy instead of medical therapy after resistance to the chemotherapy was detected.

**TABLE 1:** Patient characteristics.

| | Low-risk GTN (n=66) |
|---|---|
| Age (years)[a] | 30.09±9.53 |
| Parity | 1.78±2.71 |
| Antecedent pregnancy[b] (%) | |
| - Molar | 62 (93.9) |
| - Abortion | 3 (4.5) |
| - Term | 1 (1.6) |
| Metastatic disease, n (%) | 5 (7.57) |
| FIGO score | 1 (1-6) |
| Stage, n (%) | |
| I | 61 (92.4) |
| II | 2 (3.0) |
| III | 4 (4.6) |
| Number of treatment coursesa | |
| - MTX/FA | 3.34±1.15 |
| - EMA-CO | 3.3±0.67 |
| - Act-D | 3 |
| Number of consolidation courses, n (%) | |
| - 3 | 66 (100) |

[a]Data are reported as mean±standard deviation;
[b]Data are reported as median and range; GTN: Gestational trophoblastic neoplasia;
FIGO: International Federation of Obstetrics and Gynecology;
MTX/FA: Methotrexate/folinic acid;
EMA-CO: Etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine;
Act-D: Actinomycin D.

**TABLE 2:** Treatment outcome of the chemotherapy regimens.

| | Low-risk GTN |
|---|---|
| Methotrexate/folinic acid, n (%) | |
| Success | **56 (84.8%)** |
| Resistance | **9 (13.6%)** |
| Toxicity | **1 (1.6%)** |
| Actinomycin-D, n (%) | |
| Success | **1 (100%)** |
| Resistance | - |
| Toxicity | - |
| EMA-CO protocol, n (%) | |
| Success | **9 (100%)** |
| Resistance | - |
| Toxicity | - |

GTN: Gestational trophoblastic neoplasia;
EMA-CO: Etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine.

## DISCUSSION

Low-risk GTN is a very rare pregnancy-related group of diseases characterized by a high sensitivity to chemotherapy and a cure rate of approximately close to 100%.[18,19] In our report, the cure rate was consistent with the literature. Several single-agent chemotherapy procedures are used throughout the world since there are no consistent pieces of evidence in the literature regarding the treatment of choice.[6-8] Furthermore, there is also not a common agreement

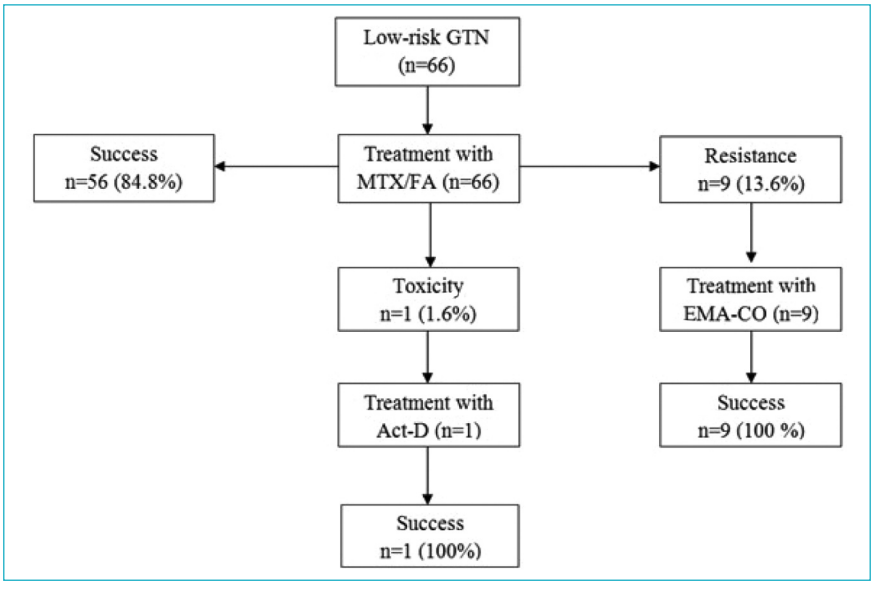


**FIGURE 1:** Treatment results of low-risk GTN cases treated with chemotherapy. GTN: Gestational trophoblastic neoplasia; MTX/FA: Methotrexate/folinic acid; Act-D: Actinomycin-D; EMA-CO: Etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine.

concerning the best administration, the follow-up, and the management of complications, including the not-responsive and recurrent case management. Consecutively, different protocols were postulated and are currently adopted based on the personal experience or preference of each center. In our study, the cure, resistance, and toxicity rates of the 8-day MTX/FA protocol were 84.8%, 13.6%, and 1.6%, respectively. In a comparative analysis of two different MTX/FA regimens, Mangili et al. reported a relapse rate of 4% and a resistance rate of 25%, showing no difference between the 2 groups. They also gathered some representative studies on MTX/FA regimens confirming a similar trend of these rates.[11] However, when the distribution of resistance and toxicity rates was considered, a wide range of values was noted, ranging from 7.3% to 43% and from 2.6% to 4.9% respectively. The differences in terms of resistance and toxicity rates might be ascribed to the inhomogeneity of the reported cases due to the nature of the studies (mainly not randomized control studies, retrospective or case series) and the different regimes adopted.[14,16,20-23] In our report, the toxicity rate was acceptably low (1.6%) and the patient was successfully managed with Act-D. In the current study, the resistance was determined as 13.6% of all the patients subjected to the 8-day MTX/FA procedure, in line with the most representative studies reported in the literature.[7,22] When first-line chemotherapy with single-agent fail, multi-agent chemotherapy can be initiated to obtain a complete remission.[24,25] The EMA-CO protocol has been widely used as multi-agent chemotherapy in The New England Trophoblastic Disease Center for many years and is considered the treatment of choice.[23] For this reason, the 9 (13.6%) patients who developed resistance were treated successfully with the EMA-CO protocol. Complete remission was achieved in all patients with no regard for the treatment administered proving the regime's safety.

## CONCLUSION

The results of this research demonstrated that the 8-day MTX/FA protocol, MTX 50 mg/day, and FA at 1 mg/kg/day, could be used as first-line single-agent chemotherapy in low-risk GTN patients with safe, showing a successful response rate and a very low toxicity rate. Furthermore, all patients who developed resistance were treated successfully with multi-agent (EMA-CO) chemotherapy achieving in all patients a complete response.

### *Source of Finance*

*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.*

### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

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