

Comparison of Two Therapeutic Regimens: Methotrexate-Folinic Acid (8 days) and Weekly Methotrexate in Patients with Low risk Gestational Trophoblastic neoplasia

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Received: 29 April, 2018

Accepted: 17 October, 2018

ARTICLE INFO

Article type:

Original Article

Keywords:

Folic Acid

Gestational Trophoblastic Neoplasia

Methotrexate

Abstract

Background: Methotrexate is used in the treatment of Low-risk Gestational Trophoblastic Neoplasia. The purpose of this study was to compare the therapeutic responses and side effects of two therapeutic methods which were prescribed for patients suffering from Low-risk Gestational Trophoblastic Neoplasia. One method was the *daily use of Methotrexate-Folic Acid* (for 8 days) and the other was the *weekly use of Methotrexate*.

Methods: This study is a randomized double-blind clinical trial which was undertaken on 122 patients suffering from Low-risk Gestational Trophoblastic Neoplasia, who referred to AfzaliPoor Hospital in Kerman City, Iran. The patients were randomly divided into two groups: one group took Methotrexate-Folic Acid daily for a period of 8 days (muscular taking of one milligram/kilogram of Methotrexate in days 1,3,5 and 7; and 0.1 milligram/kilogram of Folic Acid in days 2,4,6 and 8); the other group took the same medication weekly (muscular taking of 30 to 50 milligrams per each square meter of body mass every week).

Results: Findings showed that 95% of the patients effectively responded to the *8-day regimen* and 90% responded to *weekly regimen*. Five percent of the *8-day regimen* group and 10% of the *weekly regimen* group needed a second treatment. This difference was not significant. Concerning the related side effects, only one patient in the *weekly regimen* group experienced nausea and vomiting, and one patient experienced neutropenia; while 4 patients in the *8-day regimen* group experienced nausea and vomiting, one patient had mucositis, 2 patients had conjunctivitis, two patients experienced neutropenia, and one patient had thrombocytopenia.

Conclusions: Considering the related costs, the *8-day regimen* was significantly more economical and affordable than the *weekly regimen*.

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Citation: Honarvar Z, Masoumi M. Comparison of Two Therapeutic Regimens: Methotrexate-Folinic Acid (8 days) and Weekly Methotrexate in Patients with Low risk Gestational Trophoblastic neoplasia. Journal of Kerman University of Medical Sciences, 2018; 25 (6): 462-470.

Introduction

The term "Gestational Trophoblastic disease" covers a wide range of placental diseases including Complete and Partial Hydatidiform Moles, invasive Mole, Pregnancy-induced Choriocarcinoma, and placental site trophoblastic tumor. The disease is divided into two types: metastatic and non-metastatic. Basically, all types of Non-metastatic Gestational Trophoblastic Neoplasia can be treated by chemotherapy. Nowadays, Gestational Trophoblastic Neoplasia is known as the most curable women's cancers (1). Various single-drug regimens with different results and side effects have been applied for non-metastatic patients. Since many years ago, 4 drug types including Methotrexate with/without Folic Acid, ActinomycinD, Etoposide and 5 types of Fluorouracil have been used (1). Methotrexate and ActinomycinD have been the most commonly used drugs for treating Gestational Trophoblastic Neoplasia and have been recommended as the first line drugs for treating Non-metastatic Gestational Trophoblastic Neoplasia (2-6).

In 1987, Hertz et al. published their report of the first successful treatment of Gestational Trophoblastic Neoplasia with Methotrexate. Methotrexate was highly active in creating clinical response in a large number of patients. Nevertheless, as it has been emphasized in the initial studies, the best method for prescribing Methotrexate has not been recognized (7). In the primary studies, Methotrexate venous or oral consumption for a few days resulted in mucositis and bone marrow suppression, while discontinuous administration of

Methotrexate had a better therapeutic effect and less toxicity (8).

There are various methods for prescribing Methotrexate according to the drug dosage, instruction (oral or injection), intervals of drug taking, and adding or not adding Folic Acid in its prescription. To decrease Methotrexate toxicity, Bagshawe and Wilde (1964) for the first time used the *8-day* therapeutic method by intramuscular injection of Methotrexate with a dosage of 1 milligram/kilogram every other day and Folic Acid muscular injection with a dosage of 3.1 grams/kilogram every other day (9). The most common method used in Europe is the simultaneous treatment with Methotrexate and Folic Acid; and in large-scale studies a complete response to such a treatment has been reported to be 69.5-80% and serious toxicity has been reported to be 4-13.6% (10-13).

The other method is Methotrexate *weekly regimen* in which Methotrexate is prescribed as muscular injection with a dosage of 30-50 milligrams/square meter of body area every week (14-15). The Gynecology Oncology Group of USA has distinguished this method as the best among Methotrexate prescription regimens, provided that the effectiveness, toxicity and cost effectiveness of different methods are compared together. The most important disadvantage of this regimen is the long duration of healing period, which lasts for 15-20 weeks in some patients, particularly when it is prescribed for patients suffering from Low-risk Gestational Trophoblastic Neoplasia with metastatic lesions (16).

Although different treatment methods have been applied in different studies, there is no consensus in regard to the best treatment method. Considering that at the referred medical centers, 8-day Methotrexate-Folic Acid regimen is the common method for treating Non-Metastatic Gestational Trophoblastic Neoplasia, this study investigated the percentage of responses to the treatment in patients suffering from Low-risk Gestational Trophoblastic Neoplasia. In addition, researchers compared the two treatment methods (8-day Methotrexate regimen and weekly Methotrexate regimen).

Materials and Methods

This double-blind clinical trial was conducted in Afzali Poor Hospital, Kerman City, Iran in 2014-2016. In the trial process, 120 available patients diagnosed as suffering from Low-risk Gestational Trophoblastic Neoplasia were divided into two groups by the use of random number table. [If sum of the points, obtained based on the FIGO scoring system, was below seven, then Gestational Trophoblastic Neoplasia was considered as a low-risk disease. The following factors were taken into account in this regard. Previous pregnancy, time lapse between previous pregnancy and the present pregnancy, pre-treatment of β -HCG serum level, the biggest tumor size at metastasis area, number of specified metastases, and the number of drugs in previously failed chemotherapy.

A written consent form was prepared and obtained from all patients in order to do tests and start treatment. Furthermore, patients under the study were assured that their personal information in the data-gathering forms will be kept

confidential and the results would be presented as the whole population. This study was initiated after its confirmation by the Ethics Committee of Kerman University of Medical Sciences.

The exclusion criteria were: the histologic result of placental site trophoblastic tumor or Choriocarcinoma, reluctance to take effective birth control pills during the study, existence of any type of metastasis in brain, kidney, GI or liver in high-risk patients with a predictable risk score of 7 or higher, inclination to continue breast-feeding during the study, other aggressive malignancies with a less-than-5- year period free of disease, prohibition to take such drugs due to the treatment of previous cancer and a history of chemotherapy or hysterectomy for previous Gestational Trophoblastic Neoplasia.

Before chemotherapy was started, all patients underwent clinical assessment including history taking and complete physical exam. The β -HCG serum level was measured, complete blood cells (CBC) were counted, and kidney functioning tests (urea, creatinine, electrolytes), liver functioning tests, pelvic and abdomen CT scan and chest radiographic photo were taken. In case of not observing metastasis in the chest photo, lung CT scan was requested. Otherwise, brain CT scan or MRI was done. The uterine curettage was not done in patients before starting the treatment. During and after chemotherapy, β -HCG serum level was measured with the radioimmunoassay method at the hospital. In this study, Methotrexate (made in Celon Labs/India) and Folic Acid (made in

TillomedPharma/Germany) were used for treating the patients.

The first group underwent the *8-day Methotrexate treatment regimen* and the second group underwent the *weekly Methotrexate treatment regimen*. In the *8-day regimen*, Methotrexate was prescribed by injecting a dosage of 1 milligram per each kilogram of body mass in days 1, 3, 5 and 7; and Folic Acid was prescribed by injecting a dosage of 0.1 milligram per each kilogram of body mass 24 hours afterwards.

The other regimen was the *weekly Methotrexate regimen*, which prescribes Methotrexate as weekly muscular injection with a dosage of 30-50 milligrams per each square meter of the body area (15, 16). Treatment of the weekly type continues until β -HCG serum level is not distinguished (below 5 mU/mL); and in some medical centers a few additional periods are prescribed as Consolidation Therapy. The treatment usually continues for 2-3 weeks in these centers after β -HCG serum level gets normal but in this study we continued therapy only until B-HCG serum level was not distinguished.

Response to treatment occurred when β -HCG serum level got below 5 mU/mL, and it was called "non-response to treatment" or "treatment failure" when one of the following appeared: 1) β -HCG serum level dropped less than 10% during 3 consecutive weeks; 2) β -HCG serum level increased above 13% during 2 consecutive weeks; and 3) The emergence of Metastasis.

After treatment, follow-ups were done for all patients by measuring their β -HCG serum level within the first week and continued for three consecutive weeks with negative BHCG and then it was done monthly for the duration of one year. It was called "Response to Treatment" when β -HCG serum level remained below 5 mU/mL for 3 consecutive weeks after medication was taken.

In this study, "response to treatment" was taken as the primary consequence; and "drug side effects" as the secondary consequence. Random selection of the patients and assessment of the consequences were done by the administrator. In this study, the patients and the ward nurse did not know anything about the treatment type. The collected data were statistically analyzed by using descriptive statistics (e.g. mean \pm standard deviation) as well as inferential statistics. Data were analyzed by SPSS version 16. For the purpose of comparing the mean between the two groups, T-Test was applied for independent variables and Mann Whitney U test was used for nonparametric data. In order to compare qualitative variables between the two groups, chi-square test or accurate Fisher test were applied accordingly. P-value<0.05 was considered as statistically significant.

Results

Among the patients (n=120) suffering from Gestational Trophoblastic Neoplasia, 60 patients received the 8-day Methotrexate treatment and 62 patients received the weekly Methotrexate treatment. These two groups did not have any significant differences regarding age, weight, height, disease

duration, time lapse from previous pregnancy, tumor size, number of metastasis, disease stage, and the type of previous pregnancy. However, there was a significant difference concerning β -HCG serum level (8-day regimen: 46931.23,

and weekly regimen: 110259.58, p-value=0.019) and drug dosage (8-day regimen: 387.86 milligram, and weekly regimen: 478.86 milligram, p-value=0.012) (Table 1).

Table 1. Effects of two treatments (weekly regimen and 8-day regimen) on evaluated variables

	Weekly regimen		8-day regimen		P-value
	Mean	SD	Mean	SD	
Age	30.43	9.01	20.40	8.79	0.524
Weight	64.46	13.59	65.87	13.01	0.561
Height	164.70	9.68	164.83	7.99	0.931
Disease Period Duration	5.95	1.96	5.50	2.57	0.282
β -HCG	46931.23	860.40	110259.58	981.54	0.019
Drug Dosage	387.86	149.49	478.86	233.49	0.012
	Frequency	Percentage	Frequency	Percentage	P-value
Previous Pregnancy					
Molar	54	90	53	85.5	0.749
Abortion	4	6.7	6	9.7	
Term	2	3.3	3	4.8	
Interval Since Previous Pregnancy (Month)					
Below 4 Months	40	66.7	42	71	0.201
4-7 Months	18	30	13	21	
7-12 Months	1	1.7	5	8.1	
Above 12 Months	1	1.7	0	0	
Tumor Size					
Less than 3 cm	38	63.3	38	64.5	0.572
3-5 cm	21	35	19	30.6	
5 cm and more	1	1.7	3	4.8	
Number of Metastases					
Fewer than 1	51	85	53	88.4	0.23
1-3	9	15	7	11.6	
stage of Disease					
1	50	83.3	49	82.3	0.791
2	4	6.7	6	9.7	
3	6	10	5	8.1	

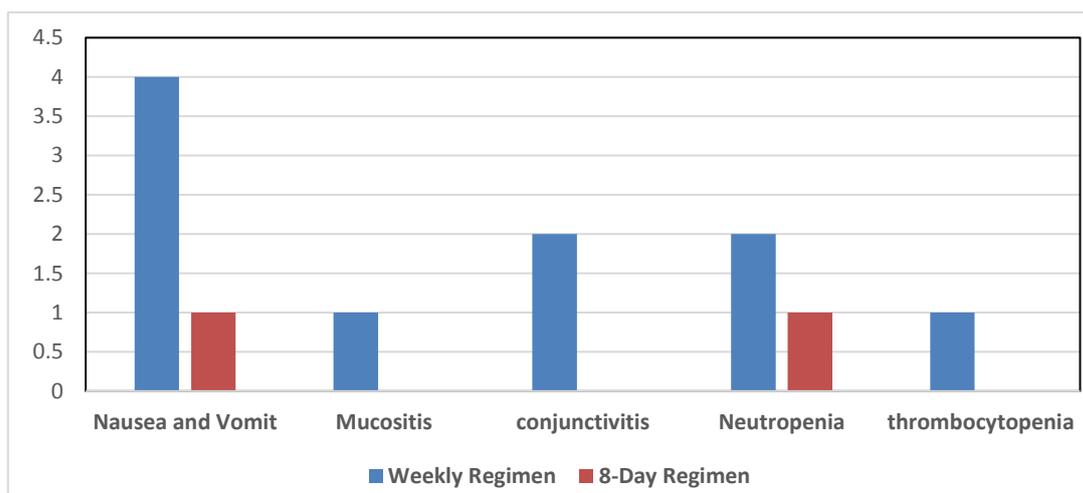


Diagram 1. Frequency of Side Effects in the Two Groups under Study

Regarding the side effects, in the *weekly treatment regimen* group only one patient experienced nausea and vomiting and one patient experienced neutropenia. But in the *8-day treatment regimen* group, 4 patients experienced nausea and vomiting, 1 patient had mucositis, 2 patients experienced conjunctivitis, 2 patients had neutropenia, and 1 patient was with thrombocytopenia. Fifty seven patients (95%) responded to the *8-day treatment regimen* and 54 patients (90%) responded to the *weekly treatment regimen*. Three patients in the *8-day treatment regimen* group (5%) and 6 patients in the *weekly treatment regimen* group (10%) needed the second line multiple drug treatment. Based on the statistical analysis, this difference was not statistically significant.

Last but not least, the average of costs in the *8-day treatment regimen* was 426,236IR with a standard deviation of 1,872.03; while the average of costs in the *weekly treatment regimen* was 534,498.9IR with a standard deviation of 2,876.41. This significant difference between the two regimens (0.12) indicates that the cost of treatment and the cost of hospitalization in the *8-day treatment regimen* group

was much more economical and affordable in comparison to the *weekly treatment regimen* (In order to estimate the costs, the sum of drug prices was used and the expenses of hospitalization was calculated).

Discussion

Several treatment regimens have been reported as the first-line single-drug therapy for Low-risk Gestational Trophoblastic Neoplasia, but due to the arguments regarding the effectiveness, toxicity, and ease of medication, choosing the best treatment regimen is still under question. The effectiveness of single-drug chemotherapy for treating Low-risk Gestational Trophoblastic Neoplasia has been reported in several studies. (17)

The recovering of patients suffering from Low-risk Gestational Trophoblastic Neoplasia was reported to be 74-76% in the study done by Homesley et al. (6). This rate was reported to be 99-100% in the study conducted by Wong et al. (16), and 91.30% in the study done by Alici et al. (18).

In our study, we compared the two treatment methods of Methotrexate with Folic Acid: *8-day* and *weekly*. The *8-day regimen* of Methotrexate with Folic Acid for the treatment of Low-Risk Gestational Trophoblastic Neoplasia is the most common treatment regimen around the world. It is also considered as the preferred treatment regimen at our oncology Center.

Bagshawe et al. investigated the muscular injection of 50 milligrams of Methotrexate in days 1, 3, 5 and 7, and 6 milligrams of Folic Acid in days 2, 4, 6 and 8 every other week. This treatment regimen led to 80% recovery, little toxicity, lack of carcinogenicity, lack of interference with possibility of the next pregnancy, and was recommended as the selective method (11).

In a study by Khan et al., They injected 50 milligrams of Methotrexate muscularly to 250 Low-Risk patients in days 1, 3, 5 and 7, and 7.5 milligrams of Folic Acid orally in days 2, 4, 6 and 8. This study implies the response to treatment without the relapse of the disease in 180 patients (72%) and grades 3 and 4 of toxicity in 10 patients (12).

In a similar line, Hoffman et al. reported that after muscle administration of Methotrexate at an amount of 40 milligrams per each square meter of body area and its weekly increase up to maximum 60 milligrams, 60% of the patients were recovered completely in 8 weeks (19).

In the study conducted by Goldstein et al. findings showed that among patients under treatment with intravenous Methotrexate method every other week, 94% of them recovered completely (20). In this study, response to the *8-day regimen* was observed in 95% of the patients and the response to the *weekly regimen* was 90%. The remaining patients needed the second line multiple drug treatment.

In another study done by Smith et al. using the 5-day Methotrexate method every other week, findings showed that 12% of the patients required a drug shift to Actinomycin D (21). In our study, 5% of the patients in the *8-day regimen* group and 10% of them in the *weekly regimen* group required a change of treatment.

By the same token, drug dosage in the *weekly regimen* group was more than the *8-day regimen* group. This difference between the two groups was statistically significant. That was because β -HCG decrease in *weekly regimen* was once less than its decrease in *8-day regimen*; and due to absence of appropriate response, the drug was inevitably increased almost one and a half times at shorter and repetitious intervals.

We also observed that nausea and vomiting were the most common side effects which were noticed in 4 cases in the 8-day regimen group and 1 case from the weekly regimen group. It is important to mention that few side effects were observed in our study. This is in line with the study done by Gillani et al. (22). Many studies have been conducted concerning a lack of difference between the two regimens (the *8-day* and *weekly*). These studies are mentioned below.

A meta-analysis conducted by Alazzan et al (2012) showed that Actinomycin D results more to the patient's absolute cure than Methotrexate does; moreover, the percentage of Methotrexate failure is more than that of Actinomycin D. Evidence shows that the 8-day and weekly Methotrexate treatment regimens have the same therapeutic effects (4).

Shah and Barroilhetin (2012) compared the *8-day Methotrexate*, *weekly Methotrexate* and *Actinomycin D* regimens and concluded that the *8-day Methotrexate*

regimen was the cheapest regimen (as in our study) and *Actinomycin D* regimen was the second cheapest (4,867 USD and 6,111 USD respectively), and *weekly Methotrexate regimen* was the most expensive regimen (as in our study) (9,089 USD as per each treatment course). In addition, all three methods had similar therapeutic effects (23).

In another study by Alazzam and Tidy on 126 patients in 2009, findings showed that *Actinomycin D* regimen had no advantage over *weekly* and *8-day* *Methotrexate* regimens; or the *8-day Methotrexate regimen* had no advantage over the *weekly regimen* in decreasing the toxicity of chemotherapy or increasing response to the primary treatment. Also, by adding *Actinomycin D* to *Methotrexate* regimen can result in a significant increase in the toxicity of chemotherapy without a significant increase in the response to treatment (4).

Effectiveness of *weekly* *Methotrexate* injection as the first-line treatment in patients suffering from Low-risk Gestational

Trophoblastic Neoplasia is the same as the *8-day* *Methotrexate* regimen. This regimen has fewer side effects and requires fewer patient visits. Accordingly, it is recommended that by equipping required medical and training facilities, correctly follow up of the patients by health care providers, the timely diagnosis of the onset of malignancy in such patients, appropriate treatment can be initiated as soon as possible in order to prevent future consequences of the disease. It is difficult to compare the results of treatment on patients suffering from Low-risk Gestational *Trophoblastic Neoplasia* with each other as the treatment groups are heterogeneous and the treatment methods are diverse. Due to homogeneous patients in the two treatment groups chosen in this study, it is of more potency than other studies. More comprehensive studies with a large number of patients seem necessary to be done in order to choose the best treatment method.

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