

## Comparison of the efficacy of methotrexate and actinomycin D in the treatment of patients with stage I low risk gestational trophoblastic neoplasia (GTN)

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### Abstract

**Background:** Gestational trophoblastic neoplasia (GTN) refers to malignant lesions that arise from abnormal proliferation of placental trophoblast. Even in its metastatic forms GTN is curable with a cure rate of 90-100 %. Currently, methotrexate with or without folic acid, and actinomycin D is recommended for low risk GTN. The aim of this study is to compare the efficacy of methotrexate and actinomycin D as the first-line single chemotherapeutic agents for women with low-risk gestational trophoblastic neoplasia (LR-GTN).

**Methods:** A total of 30 women with LR-GTN were randomized to receive a weekly pulsed dose of 40 mg/m<sup>2</sup> of methotrexate intramuscularly (n=15) or a pulsed intravenous bolus of 1.25 mg/m<sup>2</sup> of actinomycin D every 2 weeks (n=15). An additional cycle was administered as consolidation treatment following normalization of the serum level of beta-human chorionic gonadotropin (<10 IU/L).

**Results:** Complete remission was achieved in 53.3% of patients in the methotrexate group and 86.7% in the actinomycin D group (p<0.04). The mean number of treatment cycles needed to achieve response was lower in the actinomycin D group (4.3 vs. 6.5). The mean duration from beginning of treatment till achieving complete remission was 9.6 weeks for the Act group and 13 weeks for the MTX group.

**Conclusion:** Actinomycin D may be a better option than methotrexate as a first-line chemotherapy agent for patients with LR-GTN but larger multicenter randomized controlled trials should be conducted to establish the most appropriate regimen for these patients.

**Keywords:** Actinomycin D, Methotrexate, Gestational Trophoblastic Disease (GTD).

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### Introduction

Gestational trophoblastic neoplasia (GTN) refers to malignant lesions that arise from abnormal proliferation of placental trophoblast. These groups of diseases have a wide variety and can be divided into 4 groups: 1. Invasive mole, 2. Choriocarcinoma, 3. Placenta Site Trophoblastic Tumor, 4. Epitheloid Trophoblastic Tumor (ETT) (1).

In general, about 15% of patients with complete molar pregnancies develop GTN. The International Federation of Gynecology

and Obstetrics (FIGO) reported the hCG criteria used for the diagnosis of post-molar GTN to include: 1) an hCG level plateau, plus or minus 10 % of baseline recorded over a 3-week duration (days 1,7,14,21); 2) an hCG level rise greater than 10% above baseline recorded over a 2-week duration (days 1,7,14); and 3) persistence of hCG for more than 6 months after molar evacuation (2). The most common symptoms are: irregular vaginal bleeding, uterine sub involution or asymmetric enlargement, and theca lutein cysts (2).

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In the modified World Health Organization (WHO) prognostic scoring system as adapted by FIGO, each stage is divided into high risk and low risk groups. Prognostic factors including (age at diagnosis, preceding pregnancy, interval between preceding and index pregnancy, pretreatment serum level of  $\beta$ -hCG, size of largest tumor whether uterine or metastatic, site of metastases, number of metastases identified, and number of drugs included in previous failed chemotherapy) are scored as 0-4 and then calculated as final score. Patient's final score equal or less than 6 is low risk and a score higher than 6 is high risk. Low risk GTN (LR-GTN) is defined as molar pregnancy with WHO score lower than six. This categorization can be used to predict the patient's response to treatment with a single drug because most of the time low risks cases are treated with only one drug (3).

Despite the inevitability of death in untreated GTN, its treatment with chemotherapy is extremely effective. Therefore, it is the main modality of treatment in patient with GTN.

Even in its metastatic forms, GTN is curable with cure rate of 90-100 % (4).

The first successful treated GTN with Methotrexate (MTX) was reported in 1956. Currently, MTX with or without folic acid, Actinomycin D (Act) recommended for low risk GTN. MTX drug regimens are the most commonly used treatments. This treatment was associated with a 49% to 92.3% improvement (5).

The aim of this study was comparing the therapeutic effects of MTX and Act to find the best available treatment for these patients in south western region of Iran.

### Methods

In this clinical trial the participants included were all patients diagnosed with Stage I Low Risk GTN, referred to a gynecology clinic in Ahvaz, Iran from 2009 to 2011. Each patient was scored according to the WHO system; and low risk group was also determined (Table 1). Written consent was completed by all patients and the study

was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Science.

Thirty participants randomly divided into two groups (each including 15 participants). This study's exclusion criteria were:

1. Previous cancer patients for whom chemotherapy is not possible (with the exception of non-melanoma skin cancer)
2. Patients who had previously received chemotherapy due to GTN.
3. Patients after developing a malignancy were free of disease for less than 5 years.
4. Patients with abnormal liver, renal or hematologic function.

Before starting chemotherapy in each group, in addition to collecting history and physical examination, tests such as: CBC,  $\beta$ -hCG, LDH, SGOT, SGPT, Total bilirubin, Alkaline-Phosphatase, BUN, Creatinine, Thyroid function tests (TFT), chest x-ray (CXR), CT scan or Abdominopelvic sonography were done. Patients were randomly divided into ACT and MTX groups. In the ACT group patients received a dose of  $1.25 \text{ mg/m}^2$ , intravenously, every two weeks and  $\beta$ -hCG levels were checked each week until a negative level was achieved. In the MTX group patients received a dose of  $40 \text{ mg/m}^2$ , intramuscular, each week and  $\beta$ -hCG levels were checked each week until a negative level was achieved. Response to treatment is defined as achieving  $\beta$ -hCG levels less than  $6 \text{ mIU/mL}$  over three consecutive weeks and no response to treatment is defined as less than 10% decrease in  $\beta$ -hCG values in three consecutive weeks or more than 20% rise in  $\beta$ -hCG values over two consecutive weeks. An extra course of chemotherapy as consolidation therapy was considered for each group after achievement of negative  $\beta$ -hCG levels. Failure of response to treatment leads to a change of drug and transfer to the opposite group.

After the first negative  $\beta$ -hCG serum level, it was checked weekly until negative  $\beta$ -hCG levels were maintained for three consecutive weeks and after that it was

Table 1. Characteristics of Methotrexate and Actinomycin D group

|  | Group 1(ACT-D) | Group 2(MTX)     |
|--|----------------|------------------|
| Age (year)                                 | 26.47±6.9      | 26.87±9.6        |
| score                                      | 2.33±1.17      | 2.33±1.34        |
| Number of Gravidity                        | 2.8±2.59       | 2.6±2.16         |
| β-hCG level before treatment               | 33591.7±47853  | 19650.53±39280.2 |
| Chemotherapy cycles for complete remission | 4.33±2.55      | 6.53±3.29        |
| Duration of Treatment (day)                | 67.2±29.2      | 91.67±54.697     |

checked monthly. Complication rates in each group were assessed by a questionnaire at weekly visits. In this questionnaire factors such as mucosal ulcers, inhibition of bone marrow, hepatotoxicity, nausea, vomiting and skin necrosis were assessed and the prevalence of these complications were compared in both groups.

Data analyzed was done using SPSS version 19. Statistical comparison was performed using Chi-square and independent t-tests.  $p < 0.05$  was considered as statistically significant.

## Results

Of 30 participants, one group (15 persons) was treated with Actinomycin D and another group (15 persons) was treated with Methotrexate. Characteristics of two groups are shown in Table 1.

There was no statistical difference between the two groups in terms of age ( $p=1$ ). The disease score in both groups were compared and did not have significant difference ( $p=0.7$ ). There was no statistical difference between the two groups in terms of gravidity ( $p=0.82$ ). There was no statistical difference between the two groups in terms of  $\beta$ -hCG levels prior to treatment ( $p=0.39$ ).

The mean number of courses of chemotherapy to achieve complete remission in the Actinomycin D group was 4.33 courses compared to 6.53 courses in the Methotrexate group. These numbers are statistically different ( $p=0.04$ ) and Actinomycin D group received a less number of courses of chemotherapy.

Average duration of the course of treatment in Actinomycin D group was 67.2 days (9.5 weeks) and 91.67 days (13 weeks) in Methotrexate group. However,

there was no statistical difference in the duration of treatment between the two groups ( $p=0.13$ ).

In terms of response to treatment, in Actinomycin D group 13 participants responded to treatment, two did not respond and then were treated with Methotrexate. One patient responded to Methotrexate, the other did not respond and a multi-drug treatment (including etoposide, methotrexate, Actinomycin D, EMA/CO, cyclophosphamide, vincristine) was used and the patient was treated.

In the Methotrexate group, 8 patients responded to treatment, 7 patients did not respond and were referred for treatment with Actinomycin D, 4 patients responded to treatment but 3 of the 7 patients did not respond to Actinomycin D and were treated with a multi-drug regimen of EMA/CO.

The difference between the responses to treatment was statistically significant ( $p=0.04$ ) and Actinomycin D was more effective. Comparison of response to treatment in two groups is shown in Fig. 1.

Regarding the side effects of these two drugs the following findings were seen:

1. Two participants in the Methotrexate

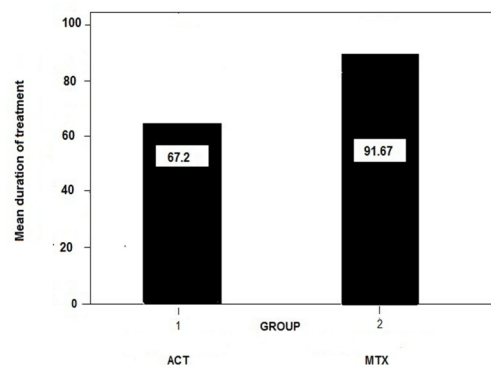


Fig. 1. Comparison of mean duration of treatment in Methotrexate and Actinomycin D group

group experienced nausea and vomiting during treatment.

2. In the Actinomycin D group no cases of mucosal ulcers were seen but one case was seen in the Methotrexate group.

3. One case of elevated liver enzymes was seen in the Methotrexate group.

The rate of complications including mucosal lesions, increased liver enzymes, vomiting and other issues did not have statistically significant differences between the two groups ( $p=1,0.86,0.46$  respectively).

### Discussion

In comparison of the effects of Methotrexate and Actinomycin D to find the best treatment for patients with GTN, the Actinomycin D group received fewer chemotherapy courses to achieve remission and in general it was more effective.

So far different regimes and protocols have been reported for the treatment of low-risk GTD. But the best and most cost efficient protocol with minimal toxicity has not been achieved yet. However, each institution and country, based on their circumstances and their patient's conditions, select the appropriate treatment for their patients. For example, in Brazil the recommended treatment in deprived areas is Methotrexate despite the fact that the efficacy did not differ between Methotrexate and Actinomycin D groups. Additionally, patient satisfaction was higher in the Actinomycin group (15).

In our study, complication rates were not different between the two groups; but in practice, were higher in the Methotrexate group. In three clinical trials, complete remission with MTX pulse therapy was 49-53%, markedly lower than ACT-D pulse treatment which was 69-90% (18-20). In one study, a 5-day regimen of Actinomycin was compared to an 8-day regimen of methotrexate and Folinic acid (MTX-FA) to treat GTD without metastases; complete remission was 100% in the Actinomycin group and 74% in the Methotrexate group (17). In a retrospective

study by Abrao et al, low-risk GTD patients treated with 5-day regimen of ACT-D or MTX and Folinic acid (MTX-FA) or a combination of ACT-D and MTX were analyzed; no significant difference in the recovery rate of the three groups was seen (61.4%, 69% and 79.1% respectively). The side effects in the combination therapy group were 62.5%, in the 5 day ACT-D regimen group were 19% and in the 5 day MTX regimen group were 28.6% ( $p=0.0003$ ) (15).

In a study by Yarny et al., the mean number of chemotherapy courses to achieve complete remission was 4.8 in ACT-D group and 6.8 in the MTX group and the duration of treatment in the ACT-D group was longer (18). In our study the number of courses of chemotherapy in patients treated with Actinomycin D was also less than the other group (4.33 versus 6.53). With this we can conclude that patients are more likely to be satisfied with Actinomycin D. But it should be noted that the duration of the course of treatment in this study was not statistically different between the two groups. In other studies, mean number of chemotherapy courses to achieve complete remission was 4 courses with Actinomycin D (17). In a prospective study by the Gynecology Oncology Group (GOG), ACT-D pulse regime once every two weeks with a remission rate of 73% was compared with MTX regime once every week with a remission rate of 58%. ACT-D pulse regime once every two weeks intravenously was more effective than intramuscular MTX regime once every week (20). In our study the response rate was higher in ACT-D group compared to MTX group (86.6% compared to 53.3%). In one study in Thailand, drugs were given as 5 day doses and again the effectiveness of ACT-D was higher than MTX (17). In Baptista et al. study MTX, ACT-D and etoposide were compared. Remission rate with etoposide was 100%, with ACT-D was 90% and with MTX was 50%. Similar to this study ACT-D was more effective than MTX. They found

mean time intervals between beginning treatment and remission similar in both groups (21).

In a study by Yarandi et al., the most important predictor of treatment response was  $\beta$ -hCG levels before treatment. However, in our study despite equal serum  $\beta$ -hCG levels in both groups, response to treatment was more in the ACT-D group (18).

Finally, given the findings of this study and previous studies, Actinomycin D is a more effective treatment for low-risk GTD. Moreover, because ACT-D has the lowest toxicity levels, it may offer the best option to treat patients with low-risk GTD. More research is needed to determine the most ideal one-drug regimen. Limitation of this study was its sample size. We recommend larger population for future studies.

### Conclusion

Actinomycin D may be a better option than methotrexate as a first-line chemotherapy agent for patients with LR-GTN but larger multicenter randomized controlled trials should be conducted to establish the most appropriate regimen for these patients.

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