Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(5): 106
https://doi.org/10.31083/j.ceog4905106

Original Research

Comparing and Evaluating Five-Day Chemotherapy Agents Actinomycin D and Methotrexate in Low-Risk Post-Molar Gestational Trophoblastic Neoplasia: A Retrospective Analysis

Juan Xu[1,2], Xinmei Wang[2], Pengpeng Qu[2,*]

[1]Clinical College of Central Gynecology and Obstetrics, Tianjin Medical University, 300700 Tianjin, China
[2]Department Gynecologic Oncology, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin Key Laboratory of Human Development and Reproductive, 300700 Tianjin, China
*Correspondence: Drqupp@163.com (Pengpeng Qu)
Academic Editor: Laura Avagliano
Submitted: 16 January 2022 Revised: 23 February 2022 Accepted: 24 February 2022 Published: 7 May 2022

Abstract

Background: Low-risk post-molar gestational trophoblastic neoplasia is sensitive to chemotherapy, but there is no consensus regarding the best treatment regimen for low-risk post-molar gestational trophoblastic neoplasia. This study aimed to assess the efficacy, toxicity and cost-effectiveness of actinomycin D and methotrexate in low-risk post-molar gestational trophoblastic neoplasia. **Methods**: 210 patients with Federation International of Gynecology and Obstetrics(FIGO)-defined low-risk post-molar gestational trophoblastic neoplasia received either a first-line five-day methotrexate intramuscular injection biweekly (MTX group) or a five-day actinomycin D infusion biweekly (Act-D group). Demographic information, disease manifestations, initial treatment plan, treatment-related adverse events, cost-effectiveness and the effects of drugs on ovarian function and quality of sexual life were recorded and retrospectively compared. **Results**: The complete response rates were 72.73% for the Act-D group and 75.41% for the MTX group, with no statistically significant difference. Compared to the Act-D group, the MTX group had a significantly shorter total number of chemotherapy cycles and average hospitalization expenses ($p < 0.05$). There was no severe adverse effect reported for either group, but the Act-D group was associated with significantly higher leukopenia (grade 1 or 2) (59.38% vs. 17.39%). The two regimens had reversible effects on ovarian function and quality of sexual life, but there was no significant difference between the two groups. **Conclusions**: There were similar complete response rates and no severe adverse effect reported for either group, but the total treatment course was shorter and the average hospitalization expenses were lower in the MTX group. Five-day MTX intramuscular biweekly injections remain the treatment of choice for patients with low-risk post-molar gestational trophoblastic neoplasia. Chemotherapy will have a certain impact on ovarian function. Gynecological oncologists should pay attention to the protection of ovarian function in patients with gestational trophoblastic neoplasia during perioperative chemotherapy.

Keywords: low-risk post-molar gestational trophoblastic neoplasia; actinomycin D; methotrexate; cost-effectiveness; ovarian function

1. Introduction

Gestational trophoblastic neoplasia (GTN) arises from the abnormal proliferation of placental trophoblasts, comprising invasive moles, choriocarcinoma, placental site trophoblastic tumors, and epithelioid trophoblastic tumors. Most of these tumors can be cured by chemotherapy without surgery [1]. According to the International Federation of Gynecology and Obstetrics (FIGO) standards, National Comprehensive Cancer Network (NCCN) guidelines diagnose post-molar GTN based on one of the following conditions: (1) the serumβ-HCG plateaus for four consecutive values over three weeks; (2) the serumβ-HCG rises by 10% for three values over two weeks; and (3) the serum β-HCG level was abnormal six months after curettage.

Based on the staging system of FIGO 2000 [2], including the World Health Organization's (WHO) scoring system, patients are divided into low risk (stages I–III, score <7) and high risk (stages II–IV, score ≥ 7) groups, which are predictive of the potential for chemotherapy resistance [3].

According to all guidelines low-risk GTN should be treated with single-agent chemotherapy, either MTX or actinomycin D. However, there is a wide variety of treatment protocols, with differences regarding the route of administration, doses, frequency, and medication used, but there is still lack of sufficient data to strongly support one over another [4–8]. There is no consensus on the best single-agent regimen, and the choice of both the drug and regimen is usually institution-specific [9]. Based on treatment experience and good therapeutic effect, we usually use MTX intramuscular injection for five days biweekly and an endogenous bolus dose of Act-D for five days biweekly. Rare studies have evaluated the use of biweekly five-day MTX and Act-D. This retrospective study compared the results of these regimens, administered as first-line and as total single-agent chemotherapies.


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Table 1. Characteristics of patients with low-risk post-molar GTN.

Characteristics	All	MTX group (n = 122)	Act-D group (n = 88)	*p*-value
Age (years)	34.91 ± 9.45			
<40	146 (69.52%)	86 (58.90%)	60 (41.10%)	$p = 0.76$
≥40	64 (30.5%)	36 (56.25%)	28 (43.75%)	
Time from previous pregnancy				
<4 months	180 (85.71%)	106 (58.89%)	74 (41.11%)	$p = 0.69$
≥4 months	30 (14.29%)	16 (53.33%)	14 (46.67%)	
Pretreatment β-HCG (mIU/mL)				
<1000	58 (27.6%)	36 (62.07%)	22 (37.93%)	$p = 0.53$
≥1000	152 (72.38%)	86 (56.58%)	66 (43.42%)	
Tumor size (cm)*				
0–3	165 (81.67%)	93 (56.36%)	72 (43.64%)	$p = 0.58$
≥3	37 (18.32%)	23 (62.16%)	14 (37.84%)	
Lung metastasis				
NO	76 (36.19%)	64 (84.21%)	12 (15.79%)	$p < 0.001$
YES	134 (63.81%)	58 (43.28%)	76 (56.72%)	
WHO score				
≤4	196 (93.33%)	116 (59.18%)	80 (40.82%)	$p = 0.27$
5–6	14 (6.67%)	6 (42.86%)	8 (57.14%)	

*Eight cases underwent hysterectomy before chemotherapy.

2. Methods

We conducted a retrospective review of medical records to identify patients with low-risk post-molar GTN between 2010 and 2020 in the department of Gynecologic Oncology, Tianjin Central Hospital of Gynecology Obstetrics, China. We identified a total of 210 patients with available response data.

Pretreatment evaluations included chest X-ray, CT scans of the lung, transvaginal ultrasound, and serum β-HCG. The diagnosis was confirmed according to the 2000 FIGO criteria and FIGO/WHO risk-factor scoring system for GTN [10].

The inclusion criteria were as follows: (1) the previous pregnancy was a hydatidiform mole; (2) the prognosis score of FIGO (2000) was ≤6; (3) the first single-agent chemotherapy was five-day MTX or Act-D; and (3) there was no previous treatment history of other chemotherapies. The exclusion criteria were as follows: (1) patients with other primary malignant tumors; (2) patients with other serious complications which interfered with the chemotherapy strategies; and (3) patients who refused the study protocols or study follow-up.

The MTX regimen consisted of a five-day intramuscular injection (MTX, 0.4 mg/(kg/d) repeated every 14 days. The maximum dose was 25 mg/d). The Act-D regimen consisted of a five-day intravenous injection (Act-D, 0.5 mg; (10–13 ug/kg) repeated every 14 days).

Evaluation criteria for chemotherapy included monitoring serum β-HCG levels every week during chemotherapy. Complete remission (CR) was defined as a normal serum β-HCG level (<5 mIU/mL) for more than six months after the end of treatment. Resistance was defined as a serum β-HCG plateau of ±10% over two weeks or a re-elevation in at least one serum β-HCG level measurement. Relapse was defined as a serum β-HCG re-elevation after three normal weekly tests in the absence of a new pregnancy.

Adverse events were defined and classified according to standardized criteria (Common Terminology Criteria for Adverse Events-CTCAE v4.0). Complete blood cell count, and renal and liver function tests were regularly assessed during chemotherapy. We also assessed the total number of chemotherapy cycles, hospitalization duration, and the cost of hospitalization.

A questionnaire was conducted by telephone to investigate the situation of patients half a year after chemotherapy, including: (1) The menstrual situation of patients, including menstrual cycle, menstrual period and menstrual volume before and after chemotherapy, so as to evaluate ovarian function; (2) sexual life problems mainly include changes in sexual desire, vaginal dryness, sexual life satisfaction and sexual intercourse pain after chemotherapy.

The data were statistically analyzed by SPSS software (version 22.0, Inc, Chicago, IL, USA). The measurement data were described by mean ± standard deviation and median. The counting data were expressed by percentage. The comparison between groups was performed by chi square test or Fisher exact test, with $p < 0.05$ was statistically significant. Chi square test was used for the comparison between the two groups, and binomial logistic regression analysis was used for multivariate analysis.

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Table 2. Evaluating Act-D and MTX five-day chemotherapy agents in low-risk post-molar GTN.

	MTX	Act-D	*p*-value
CR	75.41% (92/122)	72.73% (64/88)	$p = 0.93$
Chemotherapy cycles for serum β-HCG decreased to normal	3.37 ± 1.37	3.28 ± 1.22	$p = 0.77$
Total number of chemotherapy cycles	5.21 ± 1.69	6.06 ± 1.19	$p = 0.045$
Hospitalization duration (d)	7.03 ± 4.33	7.48 ± 5.02	$p = 0.67$
Average hospitalization expenses (RMB)	3383.36 ± 792.19	5103.44 ± 846.51	$p < 0.001$

Table 3. Comparison of the MTX group and Act-D group in adverse events.

	MTX (n = 92)	Act-D (n = 64)	*p*-value
Leukopenia (grade 1 or 2)	17.39% (16/92)	59.38% (38/ 64)	$p < 0.001$
Gastrointestinal disorders	19.56% (18/92)	21.88% (14/64)	$p = 0.84$
Mucosal ulcer	6.52% (6/92)	6.25% (4/64)	$p = 0.96$
Abnormal liver function	17.39% (16/92)	18.75% (12/64)	$p = 0.88$

3. Results

Of the 210 patients in this study, a total of 122 were treated with MTX and 88 patients were treated with Act-D. The characteristics of the two low-risk post-molar GTD treatment groups are summarized in Table 1. All participants received suction and curettage before chemotherapy for diagnosis and mass removal, and eight patients underwent hysterectomy before chemotherapy.

CR was achieved in 75.41% (92/122) of the MTX group and 72.73% (64/88) of the Act-D group. The difference was not statistically significant. In patients with CR, the average total number of chemotherapy cycles was 5.70 ± 1.69 with MTX and 6.06 ± 1.19 with Act-D.

A total of 54 participants (25.71%) showed resistance to the single-agent chemotherapy, all of them finally achieved a CR after combination chemotherapy (FA/EMA-CO). Forty-nine of 54 patients (90.74%) were treated with FA, and 5 (9.26%) were treated with EMA-CO.

The number of courses required to normalize the β-HCG and the duration of hospitalization was similar between the two groups, with no statistically significant differences. The Act-D group had more hospital expenses (RBM 5103.44 ± 846.51) compared to the MTX group (Renminbi (RBM) 3383.36 ± 792.19). The Act-D group had more total number of chemotherapy cycles than the MTX group, with statistically significant differences (Table 2).

There were no severe adverse effects reported for either group. T Abnormal laboratory tests (leukopenia and abnormal liver function) and gastrointestinal disorders, followed by mucosal ulcer, were the most common adverse events of the two regimens. However, in both regimens, most patients developed only mild (grade 1 or 2) chemotherapy-related toxicity. There was no significant difference in the incidence of abnormal liver function, gastrointestinal disorders, and mucosal ulcers between the two groups ($p > 0.05$). The incidence rate of leukopenia (grade 1 or 2) in the Act-D group was relatively higher than the MTX group ($p < 0.05$) (Table 3).

Chemotherapy had a certain impact on menstrual conditions and sexual life. Of the 210 patients in this study, 8 patients underwent hysterectomy before chemotherapy, and 202 patients with menstrual conditions could be investigated, including 116 cases in MTX group and 86 cases in Act-D group. (1) menstrual cycle: no amenorrhea occurred in both groups; there was no significant difference in menstrual cycle changes between the two groups ($p = 0.6689$); (2) Menstrual period: menstrual period shortening was the main manifestation. The incidence of menstrual period changes in MTX group and Act-D group were 70.69% and 75.58% respectively, with no significant difference ($p = 0.5231$); (3) Menstrual volume: the menstrual volume of most patients decreased. The decreased menstrual volume accounted for 62.93% in MTX group and 68.98% in Act-D group respectively, but there was no significant difference between the two groups ($p = 0.4671$); (4) After chemotherapy, there were some changes in sexual desire, vaginal dryness, sexual life satisfaction and sexual intercourse pain in both groups, but there was no significant difference between the two groups ($p > 0.05$) (Table 4).

4. Discussion

The cure rate for low-risk GTN approaches 100%, primarily because of the high sensitivity of GTN to chemotherapy [11–13]. It has been reported that single-agent chemotherapy is the first choice for low-risk GTN [14], and the usual chemotherapy medicines include MTX, Act-D, 5-FU, and VP-16. However, the remission rates of single-agent chemotherapy vary from 50% to 90%. Chemotherapy resistance occurs in 20%–30% of patients with low-risk GTN, who then require salvage chemotherapy or operation [11,15]. Therefore, the effectiveness, risk factors, and resistance associated with single-agent chemotherapy for low-risk GTN have become an important research focus.

Table 4. Menstruation and sexual life after chemotherapy in low-risk post-molar GTN.

Characteristics	MTX group (n = 116)	Act-D group (n = 86)	*p*-value
Menstrual cycle			
Normal	62 (53.45%)	49 (56.98%)	$p = 0.6689$
Abnormal	54 (46.55%)	37 (43.02%)	
Menstrual period			
No change	34 (29.31%)	21 (24.42%)	$p = 0.5231$
Change	82 (70.69%)	65 (75.58%)	
Menstrual volume			
No change	43 (37.07%)	37 (43.02%)	$p = 0.4671$
Change	73 (62.93%)	49 (68.98%)	
Sexual desire change			
No change	68 (58.62%)	45 (52.33%)	$p = 0.3928$
Change	48 (41.38%)	41 (47.67%)	
Vaginal dryness			
NO	61 (52.59%)	44 (51.16%)	$p = 0.8872$
YES	55 (47.41%)	42 (48.84%)	
Sexual satisfaction			
YES	45 (38.79%)	37 (43.02%)	$p = 0.5650$
NO	71 (61.21%)	49 (56.98%)	
Sexual pain			
No	87 (75%)	69 (80.23%)	$p = 0.4018$
YES	29 (25%)	17 (19.77%)	

210 cases were included in this study and divided into MTX group and Act-D group. The results showed that the complete remission rates of Act-D group and MTX group were 72.73% and 75.41% respectively, with no significant difference. Compared with Act-D group, the total chemotherapy cycle and average hospitalization cost in MTX group were significantly shorter ($p < 0.05$). There were no serious adverse reactions in both groups, but the leukopenia (grade 1 or 2) in Act-D group was significantly higher than that in the control group (59.38% vs. 17.39%). The two regimens had reversible effects on ovarian function and quality of sexual life, but there was no significant difference between the two groups.

While both MTX and Act-D are effective first-line drugs for low-risk GTN, there is a lack of consensus on the preferred regimen [4]. There are several different chemotherapy regimens for low-risk GTN, which have produced inconsistent results in non-randomized and retrospective studies [4,9,16,17]. There is currently no worldwide consensus regarding the best initial chemotherapy for GTN. The choice of treatment depends on the clinician's own experience or preference. In our hospital, the five-day MTX and the five-day Act-D protocols are the most commonly used single-drug chemotherapy regimen for low-risk GTN. There is currently rare report comparing the two chemotherapy regimens.

In our study, the total CR rate of single-drug chemotherapy (MTX and Act-D) was 74.29%, the CR rates of the MTX group and Act-D group was 75.41% and 72.73%. Our results regarding the CR rates of the single-agent chemotherapeutics are similar to those of the GOG study and other reports [18,19], which shows that our regimens are effective and feasible. Another randomized trial came to the opposite conclusion, which compared a low dose of MTX (30 mg/m^2) with Act-D and found Act-D to be superior with a complete response rate of 53.3% vs. 69.7%, respectively [20].

The most common adverse event was myelosuppression, which usually represented mild or moderate leukopenia. In our study, there was no severe adverse effect reported for either group, but the Act-D group was associated with significantly higher mild myelosuppression (59.38% vs. 17.39%). While grade 1 and 2 toxicities did not necessitate a change in treatment, they can affect the patients' quality of life. Other adverse events, including liver damage, gastrointestinal reactions, and mucosal ulcers, were also mild and could be relieved after symptomatic treatments. No patient changed their chemotherapy strategy because of severe adverse events. This may be partially because a part of our quality and safety measures involved encouraging our patients to call whenever they had any questions or concerns about their treatment and contacting them weekly about treatment-related adverse effects. Nonetheless, most of our patients experienced only mild chemotherapy-related toxicity with both regimens, as reported by others [21,22].

We also analyzed other factors involved in different treatment options, such as chemotherapy cycles for serum levels of-HCG that decreased to normal, the average total number of chemotherapy cycles, duration of hospitalization, and average hospitalization expenses. We conclude that compared to the Act-D group, the MTX group had a significantly shorter total treatment course of treatment and lower average hospitalization expenses ($p < 0.05$). This finding may be related to regional differences, but it can provide a basis for treatment options in China.

Chemotherapy has a certain impact on ovarian function. For GTN patients, most of them have not completed childbirth or have requirements for reproduction, therefore, we should pay attention to the effect of drugs on ovarian function at the same time of treatment. In this study, 69.52% were younger than 40 years old, of which 27.5% were 22–29 years old, therefore, it is particularly important to choose chemotherapy regimen which has little impact on ovarian function.

This study was conducted by telephone follow-up after chemotherapy. It was found that the effect of chemotherapy on ovarian function was mainly manifested in different degrees of menstrual volume reduction and menstrual cycle disorder during and after chemotherapy, but this menstrual change was reversible. Most patients could return to normal menstruation within 1 year after chemotherapy. However,

this study only investigated menstruation by means of questionnaires to assess ovarian function. Further clinical data are needed to confirm this study.

GTN patients are mostly in the sexually active stage, and the problem of sexual function deserves attention. Chemotherapy can temporarily inhibit or permanently affect ovarian function to a certain extent, lead to the decrease of estrogen level in the body, and cause vaginal dryness and other symptoms. This study also confirmed that the two groups had a certain impact on the quality of sexual life after chemotherapy, but there was no significant difference in sexual desire, vaginal dryness, sexual life satisfaction and sexual pain between the two groups. This may be related to the small sample size of this study, which needs to be increased for further research.

Our study has several limitations. It was a retrospective, single center, non-randomized, cohort study of two regimens, which may not reflect the outcomes in the Chinese general population. We are working with other centers to expand the sample size to continue our research. In addition, this study is a retrospective questionnaire survey, which still needs a large sample size, prospective and long follow-up clinical observational study to further explore the effects of different chemotherapy regimens and cumulative doses on patients' ovarian function and quality of life.

GTN is a gynecological malignant tumor related to pregnancy. Gynecological oncologists should not only pay attention to the curative effect of treatment, but also pay attention to the changes of patients' ovarian function, sexual function, emotion and psychology, so as to ensure that patients will not cause psychological fear and trauma while treating diseases. Because this is a single center retrospective study, the results can only reflect local practice and can not be generalized.

5. Conclusions

In conclusion, there were similar complete response rates and no severe adverse effect reported for Five-day MTX and Act-D, but the total treatment course was shorter and the average hospitalization expenses were lower in the MTX group. Five-day MTX intramuscular biweekly injections remain the treatment of choice for patients with low-risk post-molar gestational trophoblastic neoplasia. Chemotherapy will have a certain impact on ovarian function. Gynecological oncologists should pay attention to the protection of ovarian function in patients with gestational trophoblastic neoplasia during perioperative chemotherapy.

Author contributions

JX and XW—conception and design; PQ—administrative support; PQ—provision of study materials or patients; JX—collection and assembly of data; JX and XW—data analysis and interpretation; all authors, manuscript writing and final approval of manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Tianjin Central Hospital of Gynecology Obstetrics (NO.: KY081) and individual consent for this retrospective analysis was waived. Written informed consent for publication was obtained from all participants.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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