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Original Article

Comparing and evaluating the efficacy of methotrexate and actinomycin D as first-line single chemotherapy agents in low risk gestational trophoblastic disease

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: The aim of this study was to compare responses to single-agent chemotherapies and evaluate the predictive factors of resistance in low risk (LR) gestational trophoblastic disease (GTD). The chemotherapy agents included methotrexate (MTX) and actinomycin D (ACT-D).
Methods: We conducted a retrospective study of 126 patients with GTD who were treated between 2000 and 2013. A total of 71 patients with LR GTD were treated with MTX (8-day regimen or weekly regimen, n=53) or ACT-D (bi-weekly pulsed regimen or 5-day regimen, n=18). The successful treatment group and the failed treatment group were compared and analyzed to identify prognostic factors.
Results: The complete response rates were 83.3% for ACT-D and 62.2% for MTX, with no statistically significant difference. There was no severe adverse effect reported for either group. Longer interval durations from the index pregnancy (>2 months, p=0.040) and larger tumor size (>3 cm, p=0.020) were more common in non-responders than in responders; these results were statistically significant.
Conclusion: Based on our results, ACT-D may be a better option than MTX as a first-line single chemotherapy agent for LR GTD. The bi-weekly pulsed ACT-D regimen had minimal, or at least the same, toxicities compared with MTX. However, due to the lack of strong supporting evidence, it cannot be conclusively stated that this is the best single agent for first-line chemotherapy in LR GTD patients. Further larger controlled trials will be necessary to establish the best guidelines for GTD treatment.

Keywords: Methotrexate; Dactinomycin; Gestational Trophoblastic Disease; Drug Therapy

INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a group of rare pregnancy-related diseases that arise from the abnormal proliferation of placental trophoblasts. Benign GTD lesions consist of complete and partial hydatidiform mole. Malignant GTD lesions consists of four clinicopathologic entities: 1) invasive mole, 2) choriocarcinoma, 3) placental site

trophoblastic tumor (PSTT), 4) epithelioid trophoblastic tumor (ETT) [1-3]. This subset of malignant lesions is referred to as gestational trophoblastic neoplasia (GTN) and may develop after a molar or non-molar pregnancy. The International Federation of Gynecology and Obstetrics (FIGO) committee has modified the anatomic staging system for GTN, placing more emphasis on prognostic factors. With the prognostic scoring system proposed by the World Health Organization (WHO), patients are divided into low risk (LR, stages I–III, score <7) and high risk (HR, stages II–IV, score ≥7) groups, which are predictive of the potential for chemotherapy resistance [4].

The results of previous studies have shown that both methotrexate (MTX) and actinomycin D (dactinomycin, ACT-D) are safe, effective, and inexpensive chemotherapy agents for LR GTD [2]. However, due to the chemosensitive nature of GTD and its low prevalence, there is no consensus regarding the best single treatment regimen for LR GTD. The risk of recurrence of LR GTD is <5%–10%. If single-agent chemotherapy fails or GTD recurs, then re-score the patient. If still low-risk can safely give either the 5-day same regimen or the other single agent drug. If re-score resulted in high-risk, combination chemotherapy should be used. HR GTD has to be treated with combination chemotherapy because of its low complete response (CR) rate to single-agents. Worldwide, the most commonly used first-line chemotherapy for HR GTD is a combination of etoposide, MTX, ACT-D, cyclophosphamide, and vincristine (EMA-CO) [5]. Adjuvant surgical procedures, in particular hysterectomies and pulmonary resections, are also required for patients with chemoresistant GTD [6].

There is currently no worldwide consensus regarding the best initial chemotherapy for either LR GTD or HR GTD. The choice of treatment regimen depends more on the clinician's own experience of, or preference for, a particular treatment, rather than any evidence regarding the relative efficacy, safety, or convenience of the treatment. This study aimed to compare the treatment outcomes of single-agent chemotherapy regimens in LR GTD and to evaluate predictive factors for treatment failure, in order to reach a definitive conclusion regarding the true comparative effectiveness of these agents.

MATERIALS AND METHODS

We conducted a retrospective review of medical records to identify patients with histologically confirmed GTD who received chemotherapy between 2000 and 2013 in Asan Medical Center, Korea. We identified a total of 126 patients for whom response data were available. Patients with histologically confirmed PSTT or ETT were excluded. For each patient, we collected information on the following: clinical history, physical examination results, laboratory test results (complete blood count, beta human chorionic gonadotropin [β-hCG] levels, liver function test results, and renal function test results), histologic result, chest X-ray results, and computed tomography results. Tumor size had measured by available imaging tools like sonography, computed tomography or magnetic resonance imaging. These patients were scored according to the modified WHO prognostic scoring system and categorized as either LR GTD or HR GTD [7]. Cases of choriocarcinoma with metastasis were regarded as HR GTD, regardless of the WHO prognostic score. Patients in the LR GTD group were treated with a single chemotherapy agent. The MTX regimen consisted of either an 8-day regimen (intramuscular [IM] MTX, 1 mg/kg, on days 1, 3, 5, and 7) with folinic acid rescue (days 2, 4, 6 and 8) or a weekly regimen (IM MTX, 50 mg/m^2). The ACT-D group regimen consisted of either a bi-weekly pulsed intravenous (IV) regimen (ACT-D, 1.25 mg/m^2)

or a 5-day IV regimen (ACT-D, 12 mcg/kg for 5 days, repeated every 14 days). CR was defined a normal β-hCG level (<2 IU/L) for more than 6 months after the end of treatment. Toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events when complications occurred. Assessments were carried out for nausea, mucosal ulcer, hepatotoxicity, bone marrow toxicity, and skin necrosis. If there was a persistent rise (>20%) or plateau (<10% decrease) in β-hCG levels during chemotherapy, salvage treatments were added to the regimen to try to overcome resistance. Disease relapse was defined as a rise in β-hCG levels more than 6 weeks after the completion of treatment. Basic patient characteristics (including WHO prognostic score) were collected for each group. In the single-agent chemotherapy group, patients were subdivided into complete responder and treatment failure groups and baseline characteristics were compared. We obtained institutional review board approval for these studies. Data analysis was executed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U-test, Fisher's exact test, and the independent sample t-test were used for comparison between the groups. A p value <0.05 was considered statistically significant.

RESULTS

Of the 126 patients in this study, 71 patients with LR GTD received single-agent chemotherapy. A total of 53 patients were treated with MTX and 18 patients were treated with ACT-D. The characteristics of the two LR GTD treatment groups are summarized in **Table 1**. All patients were received suction and curettage before chemotherapy for diagnosis and removal of masses. The mean tumor sizes were 3.5 cm (range 1.5–5.5 cm) and 3.2 cm (range 1.2–5.2 cm) in the MTX and ACT-D groups, respectively. Twenty-one (39.6%) patients and 10 (55.5%) patients had pretreatment β-hCG levels of over 100,000 IU/L in the MTX and the ACT-D groups, respectively. Age, gravidity, pretreatment serum β-hCG levels, initial tumor size, and lung metastasis were all similar between the two groups, with no statistically significant differences. The mean follow-up duration after treatment completion was 2.0 years (range 0.2–8.6 years). Serum β-hCG level tests and gynecological exams were carried out during the follow-up period to check for recurrence. CR was achieved in 48 of 71 patients

Table 1. Characteristics of patients with low risk gestational trophoblastic disease

Characteristics	MTX group (n=53)	ACT-D group (n=18)	p value
Age (yr)	30.6±2.1	37.0±4.8	0.840
Gravidity	1.2±0.2	1.1±0.3	0.820
Histology at initial diagnosis			
Invasive H-mole	28 (52.8)	2 (11.1)	
Complete H-mole	14 (26.4)	8 (44.4)	
Partial H-mole	11 (20.8)	8 (44.4)	
Pretreatment β-hCG (IU/L)	228,753±13,294	221,625±16,162	0.600
< 100,000 IU/L	32 (60.4)	8 (44.4)	
> 100,000 IU/L	21 (39.6)	10 (55.6)	
Largest tumor size (cm)	3.5±2.0	3.2±2.0	0.390
Lung metastasis	13 (24.5)	5 (27.8)	0.970
Follow up duration (yr)	2.2±0.5	1.9±0.9	0.980
Response according to regimen			
MTX 8-day regimen	11/16 (68.8)		
MTX weekly regimen	22/37 (59.5)		
ACT-D pulsed regimen		11/13 (84.6)	
ACT-D 5-day regimen		4/5 (80.0)	

All values are expressed as mean (± standard deviation) or number of patients (%).
MTX, methotrexate; ACT-D, actinomycin D; H-mole, hydatidiform mole; β-hCG, beta human chorionic gonadotropin.

Table 2. Characteristics of patients with low risk gestational trophoblastic disease according to treatment response

Characteristics	Responders (n=48)	Non-responders (n=23)	p value
Age (yr)	32.5±1.7	29.4±1.4	0.380
Interval months from index pregnancy	1.7±0.2	4.0±2.0	0.040
Pretreatment β-hCG (IU/L)	226,421±42,798	228,885±109,848	0.150
Largest tumor size (cm)	30.2±2.6	38.8±3.2	0.020
WHO score	3.9±0.3	3.8±0.3	0.850
Lung metastasis	12 (25.0)	6 (26.1)	0.922

All values are expressed as mean (± standard deviation) or number of patients (%).
WHO, World Health Organization; β-hCG, beta human chorionic gonadotropin.

(67.6%) in the LR GTD group: 33 of 53 patients (62.2%) in the MTX group (11/16 (68.8%) in 8-day regimen and 22/37 (59.5%) in weekly regimen) responded to treatment and 15 of 18 patients (83.3%) in the ACT-D group (11/13 (84.6%) in bi-weekly pulsed regimen and 4/5 (80%) in 5-day regimen) responded to treatment. The difference between groups was not statistically significant. In patients with CR, the average number of cycles was five (range 2 to 10) with MTX and four (range 2 to 9) with ACT-D. A total of 23 patients (32.3%) with LR GTD showed resistance to the single-agent chemotherapy: 20 patients in the MTX group and 3 patients in the ACT-D group. Non-responders were defined as patients who had rising β-hCG levels after the first chemotherapy cycle, or those in whom β-hCG levels plateaued despite receiving three chemotherapy cycles. All single-agent chemotherapy non-responders finally achieved a CR after combination chemotherapy (EMA-CO). Patients with LR GTD were classified as either responders or non-responders, and the following patient characteristics were evaluated: age, interval from index pregnancy, pretreatment serum β-hCG level, largest tumor size, WHO prognostic score, and lung metastasis (**Table 2**). Longer interval duration from the index pregnancy (>2 months, p=0.040) and larger tumor size (>3 cm, p=0.020) were observed more frequently in non-responders than responders; these results were statistically significant. There were no statistically significant differences observed for the WHO prognostic score or the incidence of lung metastasis between responders and non-responders.

DISCUSSION

The first study on MTX was published in 1956 and its use in combination with folinic acid as "rescue" was reported in 1971. The use of ACT-D as a first-line therapy for LR GTD was reported in 1972. The most commonly used chemotherapeutic regimen for MTX is an 8-day regimen with folinic acid rescue, while for ACT-D, it is a bi-weekly pulsed IV regimen. CR rates of 77%–81% have been previously reported with MTX [8,9]. A phase III randomized trial comparing the efficacy of weekly MTX and bi-weekly pulsed ACT-D regimens in the treatment of LR GTN was published by the Gynecologic Oncology Group (GOG) in 2011; the remission rates in 216 randomized patients were 58% and 73% in the MTX and ACT-D arms, respectively [10]. The superior response rate observed with ACT-D was consistent with that observed in other studies that compared ACT-D treatment with 5- or 8-day MTX regimens, which are more commonly used and offer a higher initial remission rate [11,12]. In a Cochrane review, ACT-D treatment was associated with significantly higher primary response rates than MTX treatment [13]. Furthermore, CR is attained with fewer ACT-D chemotherapy cycles (4.8) than MTX cycles (6.8) [14]. Additionally, when pulsed ACT-D was studied as a secondary therapy in MTX-failed LR GTN patients, it showed a CR rate of 75% [15]. Although our results did not show statistically significant differences, a higher response rate was observed in the ACT-D group than in the MTX group (83.3% vs. 62.2%).

However, in the clinic, MTX is still the most commonly used primary modality for the treatment of patients with LR GTD. This is due to concerns about the potential significant side effects associated with the 5-day ACT-D regimen. The most common side effects of the MTX regimen include nausea, vomiting, hematologic toxicities, mucositis, and conjunctivitis, whereas the 5-day ACT-D regimen is associated with a higher prevalence of alopecia and nausea. Furthermore, in the end, all LR GTD patients achieved remission regardless of their initial response [16]. As a result, most centers use ACT-D as a second-line treatment choice for non-responders or for patients who experience toxicities associated with MTX treatment. However, a GOG study [10] and the above mentioned Cochrane review [13] suggested that the bi-weekly pulsed ACT-D regimen had fewer, or at least same toxicities than the MTX regimen. They also found that there was no significant difference in toxicities between the two groups although the data used in the study were too heterogeneous to be conclusive. In our study, no severe adverse effects (SAEs) were observed in either group. Most of the side effects in the ACT-D group were mild side effects, such as fatigue or gastrointestinal problems, and there was no incidence of alopecia.

We identified the predictors of resistance to single-agent treatment in LR GTD by comparing characteristics of the successful treatment group with those of the failed treatment group. Well known predictors of resistance to single-agent chemotherapy in LR GTD include non-molar antecedent pregnancy, choriocarcinoma in pathology, high pretreatment β-hCG levels, and the WHO prognostic score [17,18]. However, our results showed that a larger tumor size (>3 cm) and a longer duration from the index pregnancy (>2 months) were associated with resistance to single-agent chemotherapy. There were no statistically significant differences in pretreatment β-hCG levels, WHO prognostic scores, or incidence of lung metastasis between the successful and failed treatment groups. These predictors could be affected by different inclusion criteria. Choriocarcinoma tends to be more resistant to chemotherapy than post-molar GTD. In our study, choriocarcinoma patients with an LR score demonstrated a CR of 50%. This is lower than the average response rate of the LR GTD group (63.3%). The choriocarcinoma cases with metastatic LR disease were regarded as HR GTD cases in this study. Combination chemotherapy should be considered as a first-line treatment choice for choriocarcinoma patients with metastatic LR disease.

In our study, each single-agent group involved different treatment regimens, and this could be considered a weakness of this study. The different doses and administration schedules may have affected the response rates and the incidence of side effects. However, our results on the response rates of the single-agent chemotherapeutics are similar to those of the GOG study and there were no SAEs with any of the regimens.

This study reviewed a large number of cases covering a 10-year period; considering the rarity of GTD, this can be considered a particular strength of this study. Our study identified tumor size and duration from index pregnancy as predictors of resistance to single-agent chemotherapy in patients with LR GTD.

Various chemotherapy regimens are used as first-line treatments in patients with LR GTD. However, there is no worldwide consensus regarding the best initial chemotherapy for patients with LR GTD. The chemosensitive nature of LR GTD makes it more difficult to choose the best one-drug regimen. Our study showed a better response rate with ACT-D than with MTX in LR GTD, although this was not a statistically significant difference. Compared with MTX, ACT-D may be the better option as a first-line single chemotherapy agent for

LR GTD. Concerns regarding the potential significant side effects associated ACT-D can be addressed by using a bi-weekly pulsed ACT-D regimen, which shows minimal toxicity. However, a definitive conclusion cannot be made, due to the lack of strong supporting evidence. Further larger controlled trials will be necessary to establish comprehensive guidelines for GTN treatment. Finally, combination chemotherapy should be considered as an initial treatment choice for choriocarcinoma patients with metastatic LR disease due to the lower CR rate associated with a single-agent chemotherapy in these patients.

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