ORIGINAL ARTICLE

Effectiveness of Actinomycin D in Treatment of High-risk Hydatidiform Mole Failed with Methotrexate Prophylactic Chemotherapy

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ABSTRACT

Objective: The objective of this study was to assess the effectiveness of actinomycin D (ACT-D) in the treatment of high-risk hydatidiform mole failed with methotrexate (MTX) prophylactic chemotherapy at Tu Du Hospital. **Methodology:** A retrospective cohort study was conducted over 128 medical records which failed MTX prophylactic and full-course chemotherapies against high-risk hydatidiform mole and turned to ACT-D treatment at Tu Du Hospital in the period between August 2011 and December 2012. The study results helped to evaluate the ACT-D effectiveness following MTX chemotherapy failure and find factors related to the effectiveness of ACT-D chemotherapy. **Results:** The successful rate of ACT-D in treatment for high-risk hydatidiform mole patients who failed prophylactic and full-course MTX chemotherapies was 78.91% (95% confidence interval: 0.7–0.85). The successful likelihood of ACT-D chemotherapy in a patient group with low β-human chorionic gonadotropin (h CG) level before ACT-D treatment (<62.75 mIU/mL) was 6.9 times higher than that of patient group with high β-h CG before ACT-D treatment (>787 mIU/mL) (P = 0.012). The successful possibility of ACT-D chemotherapy in a patient group with smaller uterine size before molar evacuation was 4.7 times higher than that of patients with larger uterine size before molar evacuation (P = 0.028). **Conclusion:** ACT-D was effective with the successful rate of 78.91% in treatment for high-risk hydatidiform mole patients who failed prophylactic and full-course MTX treatments without resorting to combination chemotherapy. There were two factors related with treatment results including ACT-D pre-treatment β-h CG level and molar pre-evacuation uterine size.

Key words: Actinomycin D, high-risk hydatidiform mole, prophylactic chemotherapy, single agent chemotherapy with methotrexate

RATIONALE

Hydatidiform mole is a gestational trophoblastic disease histologically characterized by the excessive proliferation of trophoblasts over the development of vascularity, stroma, and collagen leading to the formation of fluid vesicles. Hydatidiform mole epidemiologically accounts for about one over 1500 normal pregnancies in America; this rate is higher at 1:800 in Asia and varies by geographic areas, customs, diet, and heredity. In Vietnam, the rate of hydatidiform mole is quite high at about one over 459 pregnancies. After positive diagnosis, patients will be treated with molar suction and curettage, chemotherapy, or hysterectomy depending on the status of disease. However, about 15% of patients may progress to invasive hydatidiform mole after molar evacuation, and about 4% may turn out to be trophoblastic carcinoma. Although hydatidiform mole is diagnosed and treated quite early nowadays, the potential of post-molar trophoblastic tumor remains a big challenge to treatment. The prevalence of post-molar trophoblastic diseases ranges from 23 over 100,000 pregnancies (in Paraguay) to 1299 over 100,000 pregnancies (in Indonesia).[1] Therefore, the post-molar follow-up and treatment play an important role to increase the rate of success,

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especially in high-risk patient group. Currently, common treatment guideline is using chemotherapy for molar post-evacuation patients with a risk of progressive trophoblastic disease or histopathologic results of invasive hydatidiform mole, trophoblastic carcinoma. Initial chemotherapy is very crucial for single-agent chemotherapy with methotrexate (MTX) or actinomycin D (ACT-D), and single-agent chemotherapy can be applied to 85–95% of cases with low-risk trophoblastic tumors without using combination chemotherapy.[2] ACT-D with positive effectiveness and safety is used at present as the next chemotherapy following MTX failure.[2]

Tu Du is an obstetrics/gynecology specialized hospital (with 2500 patient beds) of the central level providing treatment, training, and research services. The hospital is appointed by the Ministry of Health as the highest level of referral for 32 provinces/towns in Southern Vietnam. Tu Du Hospital is responsible for the treatment and management of most GTN case in Southern Vietnam. Every year, we have roughly 1000 hydatidiform moles and about 150 GTN new cases. At Tu Du Hospital, hydatidiform mole patients are treated with molar suction and curettage, β-human chorionic gonadotropin (β-hCG) monitoring for low-risk patients, and single-agent chemotherapy for high-risk patients; if patients do not respond to single MTX chemotherapy or have a lot of side effects with MTX, the treatment will be turned to single ACT-D chemotherapy regimen. In case patients do still not respond to ACT-D, combination chemotherapy will be applied. Hence, ACT-D plays an important role in single-agent chemotherapy because its failure implies the failure of single-agent chemotherapy resulting in multi-agent application. With that ACT-D role, we conducted the study topic of the effectiveness of ACT-D in the treatment of high-risk hydatidiform mole which failed methotrexate (MTX) prophylactic chemotherapy at Tu Du Hospital. The research question was: How is the effectiveness of ACT-D in treatment for high-risk hydatidiform mole patients who failed MTX prophylactic chemotherapy at Tu Du Hospital?

Study objectives

The objectives of this study were as follows:

- To assess ACT-D effectiveness in the treatment of high-risk hydatidiform mole which failed MTX chemotherapy at Tu Du Hospital.
- To examine ACT-D treatment result-related factors in study subjects.

STUDY METHODOLOGY

Study design

This was a retrospective cohort study.

Target population

High-risk hydatidiform mole patients who failed MTX prophylactic chemotherapy were selected.

Study population

High-risk hydatidiform mole patients who failed MTX treatment and turned to ACT-D at the Tu Du Hospital Department of Oncology were selected for the study.

Sampled population

High-risk hydatidiform mole patients who failed MTX treatment and turned to ACT-D at the Tu Du Hospital during the period of August 2011 – December 2012.

Inclusion criteria

Medical records were clearly identified on:

- High-risk hydatidiform mole patients classified with Goldstein standards 1982.
- Having MTX prophylactic chemotherapy under the medical prescription of the Department of Gynecologic Oncology.
- MTX chemotherapy failure by the conclusion of physicians' consultation at the Department of Gynecologic Oncology.
- ACT-D chemotherapy given after MTX failure.
- Medical records completed after the last ACT-D treatment cycle.

Exclusion criteria

- Medical records did not have all parameters for data collection sheet.
- Patients were qualified for chemotherapy since the beginning: Histopathology was choriocaricinoma, etc.
- Patients did not comply with treatment scheme (return visit not on schedule) or failed full course of treatment.

Sample estimate

Formula of proportion estimate with absolute precision:

$$n = \frac{Z^2_{1-\alpha/2} P(1-P)}{d^2}$$

α=0.05; d: 5%

By the study of Hoekstra AV *et al.*,[3] *P* was 92% or 0.92=>n=113 cases.

Implementation method and data collection

Step 1: Subject screening

- Medical records were sorted out with the diagnosis of high-risk hydatidiform mole, having histopathologic results as hydatidiform mole, MTX prophylactic chemotherapy, and then turning to ACT-D among medical archives during 2012 and the past 4 months of 2011. Patient's name and admission number as well as dates of admission and discharge were obtained from those selected records. Based on those pieces of information, we got access to written medical records at the Archives House of Tu Du Hospital.

- Medical records of hydatidiform mole qualified with inclusion and exclusion criteria were picked out.

Step 2: Grouping

Patients were divided into two groups of ACT-D treatment success and failure to see how the successful rate was. We analyzed factors related to ACT-D treatment failure by grouping.

Step 3: Variable collection

Information from medical records was collected on clinical symptoms and laboratory tests before and after ACT-D treatment. Those pieces of information were coded into variables on data collection sheet for analysis.

Step 4: Data recording on ACT-D chemotherapy and follow-up

- Patients with ACT-D chemotherapy were admitted into hospital for 5 days per each treatment cycle. If no considerable side effects were noted, patients were discharged and had a return visit every 2 weeks. On return visit, patients were checked with clinical examination, β-hCG test and panel test for repeated chemotherapy. Another cycle of chemotherapy was indicated in case treatment criteria were met. In case β-hCG level did not reduce by one log at least or increased, ACT-D treatment was regarded as failure and patients were prescribed combination chemotherapy.
- Regarding adverse effects, the attending physician checked every day and recorded into clinical progress section of medical records for functional and physical symptoms such as mouth ulcer, nausea, vomiting, hair loss, urine and feces, uterus, theca lutein cyst, and metastatic signs. Complete blood count and kidney function tests were also made after chemotherapy cycle finished or when side effects were found.

Description of essential variables

High-risk hydatidiform mole

A nominal variable - was determined when patients were diagnosed of hydatidiform mole plus one of the following criteria (Goldstein 1982):

- Maternal age ≥40 years.
- Blood β-hCG level ≥100,000 mIU/mL.
- Larger-for-date uterus.
- Theca lutein cyst ≥6 cm.
- History of gestational trophoblastic disease.
- Pre-eclampsia, hyperthyroidism, trophoblastic embolism.

Definition of outcome

Binary variable with two values of success or failure was assessed by Berkowitz and Goldstein's standards (2007):[4]

- ACT-D treatment success: When β-hCG reduced by one log after each ACT-D treatment cycle and gradually moved toward negative, time for β-hCG level toward negative was counted from molar post-evacuation to <6 months later.
- ACT-D treatment failure: When β-hCG did not reduce by one log or increased after ACT-D chemotherapy.

β-hCG

A continuous variable - was determined at Tu Du Hospital by applying Abbott's complete β-hCG testing system. Testing method was immunofluorescence with measuring unit of mIU/mL. Negative value was set <5 mIU/mL. Test results were recorded at different points in time and divided by three percentiles of 25–75% to analyze data and look for relationship.

RESULTS

There were 1374 cases of molar suction and curettage from August 2011 to December 2012, of which 1073 cases (78.09%) were high-risk hydatidiform mole. Among 1073 high-risk hydatidiform moles, 818 cases (76.23%) were applied MTX prophylactic chemotherapy. In 818 cases with prophylactic chemotherapy, there were 156 (19.07%) MTX treatment failures, of which 141 cases (90.38%) went on with ACT-D chemotherapy, six cases (3.85%) quit the treatment, and nine cases (5.77%) received combination chemotherapy. Among 141 ACT-D treatments, we picked out 128 medical records which met study criteria and parameters for research, and the other 13 cases were ruled out due to insufficient information for the study.

Results of ACT-D chemotherapy

ACT-D was effective in the treatment for MTX-failed high-risk hydatidiform mole patients without resorting to combination chemotherapy at a successful rate of 78.91% (95% confidence interval [CI]: 0.7081–0.8561).

Table 1 describes patients' epidemiologic characteristics and high-risk factors in the study. Checking with Chi-square test demonstrated that β-hCG factor before ACT-D treatment had relation with treatment results only.

ACT-D treatment result-related factors

To control confounders and cofactors, multivariate analysis was conducted to find the correlation between factors and ACT-D treatment results.

Table 2 presented the results of multivariate analysis to control confounders. There were two factors associated with ACT-D treatment results including ACT-D pre-treatment β-hCG level and molar pre-evacuation uterine size. Adjusted OR(*) was produced to compare with crude OR for more precision [adjusted OR(*) >crude OR by 10%: 6.9 versus 6.1

Table 1: Study population's characteristics

Factors	Success *n*=101 (%)	Failure *n*=27 (%)	*P* (*)
Epidemiologic			
Age (years)			
≤20	10 (90.91)	1 (9.09)	0.739
21–<35	66 (76.74)	20 (23.26)	
35–<40	13 (81.25)	3 (18.75)	
≥40	12 (80.00)	3 (20.00)	
Locality			
Provinces	86 (78.18)	24 (21.82)	0.619
HCM city	15 (83.33)	3 (16.67)	
Occupation			
Housework	30 (73.17)	11 (26.83)	0.082
Farmer	40 (86.96)	6 (13.04)	
Worker	18 (85.71)	3 (14.29)	
Public employee	7 (53.85)	6 (46.15)	
Business	6 (85.71)	1 (14.29)	
Weight			
≤50 kg	68 (67.33)	33 (32.67)	0.434
>50 kg	16 (59.26)	11 (40.74)	
High risk			
Pre-treatment β-hCG			
<175,364	24 (72.73)	9 (27.27)	0.5
175,364–<932,286	53 (82.81	11 (17.19)	
≥932,286	24 (77.42)	7 (22.58)	
ACT-D pre-treatment β-hCG			
<62.75	29 (90.63)	3 (9.37)	0.013
62.75–787	53 (81.54)	12 (18.46)	
>787	19 (61.29)	12 (38.71)	
Maternal age			
<40	87 (78.38)	24 (21.62)	0.708
≥40	14 (82.35)	3 (17.65)	
Uterine size			
≤gestational age	64 (84.21)	12 (15.79)	0.075
>gestational age	37 (71.15)	15 (28.85)	
Theca lutein cyst			
No	89 (77.39)	26 (22.61)	0.06
Yes	12 (92.31)	1 (7.69)	
Hyperthyroidism			
No	97 (80.16)	24 (19.84)	0.147
Yes	4 (57.14)	3 (42.86)	
Number of MTX cycles			
1	36 (72.00)	14 (28.00)	0.467
2	36 (83.72)	7 (16.28)	

(Contd...)

Table 1: *(Continued)*

Factors	Success *n*=101 (%)	Failure *n*=27 (%)	*P* (*)
Epidemiologic			
3	22 (84.61)	4 (15.39)	
≥4	7 (77.78)	2 (22.22)	

(*) Chi-square test, β-hCG: Human chorionic gonadotropin, MTX: Methotrexate, ACT-D: Actinomycin D

Table 2: Multivariate analysis of correlation between factors and ACT-D treatment results

Factors	Success *n*=101 (%)	Failure *n*=27 (%)	OR (*)	*P* (*)
MTX pre-treatment β-hCG				
<175,364	24 (72.73)	9 (27.27)	1	
175,364–<932,286	53 (82.81)	11 (17.19)	0.98	0.985
≥932,286	24 (77.42)	7 (22.58)	2.73	0.253
ACT-D pre-treatment β-hCG				
<62.75	29 (90.63)	3 (9.38)	1	
62.75–787	53 (81.54)	12 (18.46)	1.95	0.375
>787	19 (61.29)	12 (38.71)	6.9	0.012
Occupation				
Housework	30 (73.17)	11 (26.83)	1	
Farmer	40 (86.96)	6 (13.04)	0.36	0.123
Worker	18 (85.71)	3 (14.29)	0.42	0.298
Public employee	7 (53.85)	6 (46.15)	1.45	0.666
Business	6 (85.71)	1 (14.29)	0.45	0.532
Uterine size				
≤gestational age	64 (84.21)	12 (15.79)	1	
>gestational age	37 (71.15)	15 (28.85)	4.71	0.028
Blood groups				
O	38 (80.85)	9 (19.15)	1	
A	22 (88.00)	3 (12.00)	0.74	0.737
B	34(70.83)	14 (29.17)	2.53	0.122
AB	7 (87.50)	1 (12.50)	0.41	0.498
Theca lutein cyst				
No	89 (77.39)	26 (22.61)	1	
Yes	12 (92.31)	1 (7.69)	0.27	0.311
Hyperthyroidism				
No	97 (80.17)	24 (19.83)	1	
Yes	4 (57.14)	3 (42.86)	4.66	0.139

(*): Multivariate logistic

for ACT-D pre-treatment β-hCG level, and 4.71 versus 2.16 for pre-evacuation uterine size].

DISCUSSION

After failure of MTX prophylactic chemotherapy, the rate of success for ACT-D chemotherapy was 78.91% (95% CI: 0.7081–0.8561). This result is comparable to that 75.7% of Kang's study (2010)[5] and 75% of Lurain *et al*.[6] However, it is lower than that 92% of Hoekstra's study (2008) possibly due to sampling method and interval between β-hCG tests in which his sample size was smaller and β-hCG tests were made every week against every 2 weeks in our study.

The possibility of ACT-D treatment success in patient group with low β-hCG level before ATC-D chemotherapy (<62.75 mIU/mL in our study) was 6.9 times higher than in patient group with high β-hCG level (>787 mIU/mL in our study) (P = 0.012).This finding is comparable to Chen's study (2004)[7] and McGrath's study (2010)[8]. The possibility of ACT-D treatment success in patient group with uterine size comparable to or smaller than gestational age was 4.7 times higher than in patient group with larger for date uterus (P = 0.028). Therefore, when providing ACT-D treatment for MTX-failed high-risk post-molar patients, it should be paid attention to ACT-D pre-treatment β-hCG level and pre-treatment uterine size against gestational age to counsel patients on treatment effectiveness.

We noted only 1.56% of cases with mouth ulcer and 7.03% with anemia. Those conditions were mild or moderate; no cases needed specialized treatment or chemotherapy interruption. Hence, the adverse effects of ACT-D treatment at Tu Du Hospital were acceptable.

The study data showed that the treatment path should be clearly defined with a transfer from single MTX chemotherapy to ACT-D agent before turning to multiagent chemotherapy. Hospitals which provide the treatment of gestational trophoblastic diseases should have a plan to prepare ACT-D for better treatment services.

In future, it is possible to conduct the following study to find factors related to single MTX chemotherapy failure and factors related to multiagent chemotherapy effectiveness after the failure of single agents such as MTX and ACT-D.

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How to cite this article: Tuan VM, Anh VDB. Effectiveness of Actinomycin D in Treatment of High-risk Hydatidiform Mole Failed with Methotrexate Prophylactic Chemotherapy. J Clin Res Oncol 2019;2(1):1-6.