RESEARCH COMMUNICATION

# Resistant Gestational Trophoblastic Neoplasia Patients Treated with 5-Fluouracil plus Actinomycin D

**Manatsawee Manopunya, Prapaporn Suprasert**

## Abstract

**A combination of 5-fluorouracil plus actinomycin D (5FU plus Act D) is the regimen that has been commonly administered to Chinese and Japanese gestational trophoblastic neoplasia patients as the first or second line of treatment with an excellent outcome. However, the efficacy of this regimen in a salvage setting was unclear. To evaluate the efficacy and safety of the 5 FU plus Act D regimen utilized in this condition, all GTN patients resistant to at least three previous chemotherapy regimens who received the 5 FU plus Act D regimen between August 2009 and January 2011 at Chiang Mai University Hospital were reviewed. There were five cases who met the criteria. Four of those patients were in FIGO stage III to IV with a WHO scoring of more than 12. The median number of cycles for each patient was two and only one case achieved remission while four of the cases were unresponsive. The toxicity was evaluated in 12 cycles. Common complications were uncomplicated myelosuppression and mucositis. In conclusion, this regimen revealed modest efficacy in a salvage setting with manageable toxicity.**

**Keywords:** Gestational trophoblastic neoplasia - 5 fluorouracil - actinomycin D salvage treatment

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## Introduction

Gestational trophoblastic neoplasia (GTN) is one of the most curable gynecologic cancers due to its high sensitivity to various chemotherapeutic regimens. Patients whose World Health Organization (WHO) scores are equal to or greater than seven were defined as a high risk group and are recommended for treatment with a chemotherapy combination such as EMA/CO (Etopside, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristin) regimen with a response rate of over 70%.

Patients resistant to the EMA/CO regimen may be treated by modifying this regimen by substituting cisplatin and etoposide (EMA/EP) on day eight (Bower et al., 1997). However, in patients who fail with EMA/EP, durable responses are infrequent. Efforts continue to identify new agents or new combinations effective in treating resistant disease. Matsui et al. (2002) reported that 5-fluorouracil (5-FU) in combination with Actinomycin D (Act D) induced remission in nine of eleven (82%) patients who were resistant to the first line regimen with acceptable toxicity. Nevertheless, this regimen is not utilized worldwide in many countries, especially in Thailand ,and the efficacy with recurrence after receiving multiple chemotherapy regimens is unclear. We conducted this retrospective review to identify the efficacy and toxicity of the 5-FU and Act D combination of chemotherapy regimen used in patients with heavily pretreated GTN.

## Materials and Methods

Following approval by Research Ethics Committee, the medical records of the patients with chemo-refractory GTN who received at least three previous chemotherapy regimens and treated with 5-FU plus Act D between August 2009 and January 2011 at Chiang Mai University Hospital were reviewed.

The clinical data such as stage, initial treatment, investigation results, the types and number of previous chemotherapy regimens were recorded. A history of any operation and histological proof of GTN were also noted. Blood exams including the complete blood count, liver function test, renal function test, and Beta-hCG were evaluated before starting chemotherapy in each cycle. The following imaging procedures: chest radiography, liver ultrasonography, pelvic ultrasonography and computerized –tomography (CT –scan) of the suspected organ were in each case performed when clinically indicated.

The chemotherapy protocol consisted of intravenous 5-FU 1000 mg/m2 plus Act D 0.5 mg/m2 given daily for five days every 21 days until disease progression. In cases with remission that was defined as serum β-hCG levels below the 5 IU/L, at least two more cycles of 5FU plus Act D regimen were added. The toxicities were evaluated and classified by a modification of the WHO toxicity criteria (Miller et al., 1981).

*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand *For correspondence: manatsawee.m@hotmail.com*

**Table 1. Characteristics of Patients with Chemorefractory GTN**

| Age in years | FIGO 2000 stage | Risk group at time of diagnosis | Previous treatment before receiving FA | No. of cycles |
|---|---|---|---|---|
| Type of GTN: *Postmolar GTN* | | | | |
| 51 | IV;18 | High risk | Hysterectomy<br>MTX<br>EMA<br>PI, WBRT<br>PT, VAC<br>EMACO | 2 |
| Outcome: Declined further chemotherapy after treated with FA x 1; died of progression of disease at 12 months | | | | |
| Type of GTN: *Choriocarcinoma* | | | | |
| 36 | III;17 | High risk | EMA<br>PI<br>Hysterectomy<br>PI, VAC<br>Single Taxol<br>ICE | 1 |
| Outcome: Refractory after treated with FA x 1; treated with single paclitaxel x 2; lobectomy performed for unsatisfactory response and treated with chest radiotherapy, died of progression of disease at 4 months | | | | |
| Type of GTN: *Postmolar GTN* | | | | |
| 34 | III;10 | High risk | MTX<br>EMA<br>PI | 3 |
| Outcome: Complete remission after FA x 3 cycles, DFS on 24 months | | | | |
| Type of GTN: *Epithelioid trophoblastic tumor* | | | | |
| 35 | I;9 | High risk | MTX<br>Act D<br>EMA<br>EMACO<br>PI | 4 |
| Outcome: Hysterectomy for resistant disease despite FA x 4; complete remission post PT x 3; second relapse received VAC x 3, then TP/TE x 2 cycles and remained on treatment | | | | |
| Type of GTN: *Unknown (No pathological data)* | | | | |
| 27 | III;17 | High risk | EMA<br>EMACO<br>EMAEP<br>PI<br>Taxol | 2 |
| Outcome: Refractory after treated with FA x 2; treated with VAC x 3; lost to follow up after resistant to VAC regimen | | | | |

*GTN=gestational trophoblastic neoplasia, MTX = methotreaxate; EMA = etopside, methotrexate, actinomycin D; PT = carboplatin, placlitaxel; PI = cisplatin, ifosfamide; VAC = vincristine, actinomycin D, cyclophosphamide; WBRT = whole brain radiation; EMACO = etopside, methotrexate, actinomycin D, cyclophosphamide, vincristin; ICE = ifosfamide, cisplatin, etoposide ; TP/TE = paclitaxel, cisplatin, etoposide; EMAEP = etopside, methotrexate, actinomycin D, cisplatin, etoposide

**Table 2. The toxicity profile of patients treated with 5 FU plus Act D regimens (total cycle = 12)**

| No patient | Cycle | Intervention | Toxicity |
|---|---|---|---|
| 1 | 1 | - | Grade 4 neutropenia (febrile neutropenia)<br>Grade 3 diarrhea (day 9-11)<br>Grade 2 mucositis |
| 2 | 1 | GCSF prophylaxis x 5 days | Grade 4 neutropenia<br>Grade 3 mucositis |
| 3 | 1 | - | Grade 4 febrile neutropenia<br>Grade 3 mucositis |
| | 2 | 20% decrease dose of 5FU | Grade 1 anemia (nadir day 21)<br>Grade 3 mucositis day 13 |
| | 3 | GCSF prophylaxis x 5 days | None |
| 4 | 1 | Fixed dose of 5FU 1000 mg/day | Grade 2 anemia<br>Grade 3 mucositis |
| | 2 | - | Grade 1 anemia<br>Grade 2 mucositis |
| | 3 | - | Grade 1 anemia<br>Grade 3 mucositis |
| | 4 | - | Grade 3 mucositis |
| 5 | 1 | - | Grade 3 mucositis |
| | 2 | - | Grade 3 mucositis |

*5FU = 5 fluorouracil, GCSF=granulocyte colony stimulating factor

## Results

There were five patients who received 5 FU plus Act D in the study period. The details of each patient were noted in Table 1. The median age of the patients was 35 years old with a range of 27-51 years. Four patients were in the Federation of Gynecological and Obstetrics (FIGO) stage III to IV with a WHO score between 8 and 18 while the rest were in FIGO stage I with a WHO score equaling 9.

All studied patients were previously heavily treated with at least three regimens of various chemotherapy protocols as shown in Table 1. Two patients underwent a simple hysterectomy before being treated with 5 FU plus Act D. The pathology of the uterus showed molar pregnancy and choriocarcinoma in each case. One patient underwent a hysterectomy after resistance to 5 FU plus Act D and the final pathology revealed an epithelioid trophoblastic tumor.

Regarding the response of the 5 FU plus Act D regimen, two patients showed good response to this regimen with one of them achieving complete remission while the other refused further treatment with this regimen after receiving two cycles because she could not tolerate the serious diarrhea and she died of the disease three months later. The patient who achieved complete remission was 34 years old and was diagnosed as GTN stage III with WHO score of eight. She initially received three regimens of chemotherapy. The sequence of these regimens consisted of one cycle of single methotrexate followed by two cycles

of EMA (etoposide plus methotrexate and actinomycin D). She developed drug hypersensitivity with etoposide and the chemotherapy was changed to a cisplatin plus ifosfamide regimen. She demonstrated remission after receiving six cycles of cisplatin plus ifosfamide but after one month of the last cycle, her serum B-hCG was rising and she was then given 5 FU plus Act D regimen. Surprisingly after only one cycle of 5 FU plus Act D regimen, her serum B-hCG declined to a normal level and she was given two more cycles of 5 FU plus Act D regimen afterward for the maintenance dose. The patient is still in remission up to the present time after three years.

Regarding the three unresponsive patients, the first one revealed progression after she received only one cycle of 5 FU plus Act D and still no remission even after receiving many treatment modalities that consisted of changing chemotherapy to paclitaxel followed by a lobectomy for pulmonary lesion and then chest-radiotherapy after that. Finally, she died of disease four months after she received 5FU plus Act D. The second patient was administered four cycles of 5 FU plus Act D with the decrease of serum beta-hCG during three first cycles of this regimen. However, after the fourth cycle, the serum beta-hCG was rising again. She underwent a hysterectomy later with the final pathology revealing an epithelioid trophoblastic tumor as mention above. She was further treated with various chemotherapy regimens and continues on treatment until now. The last patient was refractory after received two cycles of 5FU plus Act D and she was further treated with three cycles of the VAC (vincristine , actinomycin D, cyclophosphamide) regimen. Unfortunately, she did not achieve any response with the VAC regimen and was lost to follow up afterward.

Regarding the toxicity profile of 5 FU plus Act D regimen given in the present study, the severe toxicity was grade three diarrhea that occurred in the first cycle. Furthermore, the most common toxicity was WHO grade two to three mucositis that occurred in 11 from 12 cycles (91.7%) as showed in Table 2. About the hematologic toxicity, grade four neutropenia was observed in three cycles while grade one to two anemia occurred in four cycles. The intervention to decrease the toxicity in the next cycles consisted of the decrease in the 5 FU dosage to prevent severe mucositis and granulocyte stimulating factor (GCSF) was given to avoid severe neutropenia.

## Discussion

EMA/CO is an effective and well-tolerated regimen for patients with high-risk GTN. Previous publications revealed that EMA/CO induced complete remission in 76-86% for patients with metastases with a high-risk WHO score (Bolis et al., 1988; Bower et al., 1997). However, salvage treatment with alternative agents is needed after failure with the initial chemotherapy or recurrence after the first remission. Various regimens have been reported in the literature such as EMA/EP, ICE (ifosfamide, carboplatin, etoposide), BEP (bleomycin, etoposide, cisplatin), combinations of 5-FU, MTX and etoposide with the response rate ranging from 30% to 93% (Lurain et al., 2006; Wang et al., 2006; Zhao et al., 2009).

The chemotherapeutic regimen of 5-FU combined with Act D was one of the most significant regimens. Only two publications mentioned this regimen (Matsui et al., 2002; Zhao et al.,2009.). The first one was published by the Japanese authors who reported the response of 5 FU plus Act D in ten resistant GTN patients. Of those patients, seven patients developed drug resistance while receiving the etoposide plus methotrexate plus actinomycin D (EMA) regimen, one patient revealed recurrent disease after receiving EMA regimen and the remaining two patients showed recurrence of disease after receiving the EMA/CO regimen. The dosage of 5FU plus Act D regimen in this article was 1,500 mg of 5FU and 0.5 mg of Act D given intravenously on day one through five every two to three weeks. The overall remission rate was 80%. For the toxicity, with a total of 78 cycles of 5FU plus Act D, the authors reported grade three and four leukopenia as 19.2% and thrombocytopenia as 14.1%,. In addition, they reported a grade three hepatotoxicity in only 8.9%. Other common adverse reactions were grade one or two nausea and emesis. The other report was from Chinese authors which was recently published presenting the outcome of the combination of 5 FU and Act D as the primary treatment in 220 patients with GTN (Zhao et al. 2009). The dosage of this regimen consisted of 26-28 mg/kg of 5 FU with 6 $\mu$g/kg of Act D administered intravenous daily for eight days. The response rate from this report was as high as 94%. The most common toxicity of this regimen was vomiting that was observed in 22.5% of the patients followed by diarrhea (16.7%), oral mucositis (14.4%), leukopenia (18.9%), thrombocytopenia (12.6%) and elevated liver enzymes (9%). All of the adverse effects were mild and resolved before the next cycle.

The present study showed that salvage chemotherapy with 5FU plus Act D is successful in one of five patients (20%). Our study revealed a very low response rate when compared to the previous studies. This might be from the different patients studied. Matsui et al and Zhao et al administered this regimen as second and first line, respectively while the present study used this regimen as at least the fourth line. Thus, the results of our study were lower than those reports. However, this regimen revealed a good outcome when administered as not more than the third line drug. Regarding toxicity, the present study showed the main adverse effect was mucositis and myelosuppression. Leukopenia occurred in most cycles, and febrile neutropenia developed in two cycles of this regimen. However, these toxicities were manageable except one patient who developed serious diarrhea.

In conclusion, the combination chemotherapy with 5 FU plus Act D revealed modest activity for refractory GTN patients who previously received an extensive chemotherapy regimen. The toxicity is predictable and manageable.

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