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## Original Article

## Low-risk gestational trophoblastic neoplasia outcome after treatment with VMP regimen from 2005 to 2017

Chen-Chen Zhu<sup>1</sup>, Han-Yuan Liu<sup>1</sup>, Ying Wei, Zhen Shen, Li-Li Qian, Wei-Guo Song, Juan Wang, Da-Bao Wu, Xue-Fen Zhang, Ying Zhou\*

Department of Obstetrics and Gynecology, Anhui Provincial Hospital, Anhui Medical University, Hefei, Anhui 230001, PR China

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## ABSTRACT

**Objective:** To evaluate the efficacy and toxicity of VMP regimen applied to the patients with low-risk gestational trophoblastic neoplasia (LR-GTN) treated in Anhui provincial hospital.**Materials and methods:** Between 2005 and 2017, 87 patients with low-risk gestational trophoblastic neoplasia received VMP regimen, consisted of vincristine (VCR), methotrexate (MTX) and platinum (cisplatin, carboplatin or nedaplatin), 68 of whom received VMP as their first-line chemotherapy, and 19 methotrexate-failed patients received VMP regimen as their second-line chemotherapy. The staging and scoring system was based on International Federation of Gynecology and Obstetrics (FIGO 2000) criteria. We describe and analyze their baseline characteristics, remission/resistance/recurrence rates, adverse reactions and prognosis.**Results:** The first-line VMP protocol can achieve an 83.8% remission rate and it tended to develop resistance when the pretreatment  $\beta$ -hCG reaches 7503.5 IU/L, and can achieve complete remission with FAV and EMA-CO as the salvage regimen. Among the 19 methotrexate-failed patients, 2 of whom were yet resistant to VMP regimen, followed by several courses of salvage chemotherapy such as FAV and EMP, and achieved 89.5% remission rate in second-line VMP group. Resistance to this regimen was obviously related with higher pre-treatment HCG whether used as primary or salvage treatment. Severe myelosuppression (grade 3 or 4) was shown in 4 (5.9%) of 68 cases, of which none was grade 4.**Conclusion:** For patients diagnosed with LR-GTN VMP regimen was a safe and effective treatment with a high rate of remission.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Gestational trophoblastic neoplasia (GTN) is a group of gynecological malignant tumors with a high cure rate close to 90% [1]. Based on the International Federation of Gynecology and Obstetrics (FIGO) criteria for scoring and staging system, Gestational trophoblastic neoplasia is divided into two parts: high-risk GTN and low-risk GTN. At present, it has been reported that over 90% [2], 93% [3] about 100% low-risk GTN patients and 86–94% high-risk GTN patients can achieve complete remission [4–6] due to the high sensitivity of GTN to chemotherapy. Asian LR-GTN patients usually have more aggressive progression of disease, possibly caused by biological variations and irregular chemotherapy, which leads to higher risk requiring a second line regimen to achieve remission [7]. Now that most of the gestational trophoblastic tumor patients

are young women, there is a pressing need to select an appropriate treatment in order to maintain the reproductive function of the patients as much as possible, and reduce the occurrence of side effect as well as reduce the drug resistance and recurrence rate of low-risk GTN.

In our center, methotrexate has been widely used; we also applied VMP (consisting of vincristine (VCR), methotrexate (MTX) and platinum (cisplatin, carboplatin or nedaplatin)) as a treatment regimen. This study retrospective analyzed the clinical characteristics and treatment of the 87 patients with LR-GTN received VMP regimen treated in Anhui Provincial Hospital between 2005 and 2017, to evaluate the efficacy and toxicity of the VMP regimen.

## Materials and methods

## Patients and methods

Between January 2005 and December 2017, 86 low-risk GTN patients (FIGO Stage I–III, scores  $\leq 6$ ), were treated in Anhui

\* Corresponding author. Fax: +86 551 62283292.

E-mail address: [caddie1234@gmail.com](mailto:caddie1234@gmail.com) (Y. Zhou).<sup>1</sup> These authors contributed equally to the present study.

provincial hospital with VMP regimen, VMP regimen contains vincristine (VCR): 2.0 mg, Day 1, MTX: 0.4 mg/kg/d, Day 1–5 and platinum (cisplatin 75mg/m<sup>2</sup> or nedaplatin 80mg/m<sup>2</sup> or carboplatin AUC = 5); repeated every 3 weeks. All of the patients have stayed in the hospital for 5 days. Of these, 68 patients received VMP regimen as the primary treatment, 19 patients received VMP regimen as their salvage treatment who were failed with methotrexate. All selected 86 cases meet the following requirements: diagnosed as low-risk gestational trophoblastic neoplasia on the basis of FIGO/WHO (2000) scoring system with stage I–III and scored  $\leq 6$ ; received at least one cycle of VMP regimen as their first-line or second-line chemotherapy; never received any treatment in other hospitals after diagnosed as GTN; without PSTT or ETT. Anhui provincial hospital institutional review committee approvals for this study, all the 87 patients were selected on the basis of the institutional database.

#### Pretreatment evaluation

The LR-GTN diagnosis was made based on FIGO/WHO 2000 scoring system. 87 Selected cases were evaluated clinically in the following ways: age, medical history, clinical presentation, gynecological examinations, imaging examinations including chest X-ray and pelvic or vaginal Doppler ultrasound scan etc,  $\beta$ -human serum chorionic gonadotropin ( $\beta$ -hCG) pretreatment, and hematopoietic/liver/renal function assessments.

#### Chemotherapy regimen

VMP regimen: Vincristine (VCR) 2.0 mg i.v. day 1, MTX 0.4 mg/kg·d, i.m. day 1–5, and cisplatin (DDP) 75 mg/m<sup>2</sup>, 3 days of intravenous drop, repeated every 3 weeks.

MTX single agent: MTX 0.4 mg/kg·d, i.m. day 1–5, repeated every 2 weeks.

#### Evaluation after treatment

$\beta$ -human serum chorionic gonadotropin ( $\beta$ -hCG) was monitored every week during treatment, which was one of the most important indicator of efficacy. Hematologic, liver and renal functions were regularly examined as well. Imaging examination was also performed [5].

It was defined as complete remission (CR) that maintained a normal  $\beta$ -hCG (<3 IU/L) (according to the hospital laboratory kit instruction) level for at least three consecutive weeks, and then they would receive 1–3 consolidation chemotherapy [8]. After CR, monthly monitoring of  $\beta$ -hCG was still required for one year after CR. There are several different definitions of resistance, in American Rosenfeld Cancer Center, treatment failure was defined as hCG decreasing less than 10% for 4 times or during more than 2 weeks measured hCG increasing more than 20% for 3 times [9]. In Sheffield Centre for Trophoblastic Disease, the resistance was defined as a consecutive rise in at least twice measured hCG over 4 weeks or at least 3 consecutive hCG levels failed to adequately decrease (<25%) over the same time period [10]. In our hospital, resistance was defined that After 2 courses of treatment, blood HCG have not decreased by 1 logarithms or imaging examination showed that tumor lesions increased, and even new metastasis appeared to be drug-resistant [11]. In our study, we assessed toxicity on the basis of the National Cancer Institute (NCI) Common Toxicity criteria version 2.0 [12].

#### Statistical analysis

In this study, the data was statistical analyzed with Graph Pad Prism and SPSS Data Editor 16.0. The clinical data of selected cases

were analyzed qualitatively and quantitatively in order to find the risk factors associated with VMP resistance. It was considered statistically significant if  $P < 0.05$ .

## Results

#### Patients' characteristics

Between 2005 and 2017, 87 low-risk gestational trophoblastic neoplasia patients received VMP regimen and salvage chemotherapy were cured ultimately and no recurrence was found during follow-up in Anhui Provincial Hospital. The salvage chemotherapy included FAV (FUDR + dactinomycin + vincristine), EMA-CO (etoposide + dactinomycin + methotrexate + cyclophosphamide + vincristine) and EMP (etoposide + methotrexate + platinum) protocol. We studied these 2 groups of patients who received VMP regimen as first-line or second-line chemotherapy.

The clinical characteristics of the 68 cases treated with VMP protocol as primary chemotherapy were displayed in Table 1, of which mean age diagnosis was 28.5 years old, range 19–54. 73.5% of the cases had hydatidiform mole before diagnosed as GTN; 82.4% of the last pregnancies happened within four months; the number of invasive mole was almost four times as large as that of choriocarcinoma; the hCG value was no more than 100,000 IU/L in 94.1% of patients; 64.7% of the patients had pulmonary metastases.

The overall primary complete remission rate was 63.6% (42/66) after receiving single agent MTX protocol in our center [11], whereas 24 patients (36.4%) developed resistance during the treatment process. 19 cases of MTX-failed GTN were treated with VMP salvage multiple-agent chemotherapy, the characteristics of these 19 cases were displayed in Table 2. Before diagnosed as GTN 89.5% of the patients had hydatidiform mole; 94.7% of the patients had postmolar GTN; 10.5% of the patients had an hCG over 10,000 mIU/mL at the start of using VMP.

#### Response to chemotherapy

For the group of patients applying VMP regimen as primary treatment, the mean number of VMP courses required to achieve complete remission was 3.54 (range, 1–6). In all, 67 (83.8%) patients had complete remission but 11 patients (16.2%) turned to second-line chemotherapy, FAV and EMA-CO. We compared the characteristics of the patients who successfully responded to VMP with those of the VMP-failed group. The differences were summarized in Table 3. There was no statistical difference in the antecedent pregnancy, pathologic type, interval from index pregnancy between these two groups. The difference in pretreatment hCG level was statistically significant between two groups ( $P < 0.05$ ). It tended to occur resistance when the pretreatment hCG reaches 7503.5 IU/L according to the cutoff value.

19 cases of MTX-failed GTN who treated with VMP multiple-agent as salvage chemotherapy, 89.5% (17/19) of whom achieved a complete remission and no recurrence. 2 patients were resistant to VMP; one patient (FIGO stage III, score 1) received 4 cycle of FAV (FUDR + dactinomycin + vincristine) as her third-line chemotherapy including 2 cycle of consolidation chemotherapy. The other patient (FIGO stage III, score 6) achieved complete remission after receiving 2 cycles of FAV (second-line chemotherapy) and 4 cycle of EMP (etoposide + methotrexate + platinum) (third-line chemotherapy) including 2 cycle of consolidation chemotherapy. Both of these patients had not recurred during following-up.

For all 87 patients who used VMP as their first-line and second-line chemotherapy, the overall complete remission rate of this protocol reached 85.1% (74/87). We compared the characteristics of all these patients who had successful responses to VMP regimen

**Table 1**

Baseline characteristics of patients with low-risk GTD treated with VMP regimen as first-line chemotherapy (n = 68, media age = 28.5, range 19–54).

Characteristic	No.	%
Age (y)		
<40	58	85.3
≥40	10	14.7
Antecedent pregnancy (AP)		
Hydatidiform mole	50	73.5
Spontaneous abortion	13	19.1
Term pregnancy	5	7.4
Pretreatment hCG (IU/L)		
<1000	30	44.1
1000–10000	19	27.9
10,000–100,000	15	22.1
>100,000	4	5.9
Clinicopathologic type		
Postmolar GTN/Invasive mole	54	79.4
Choriocarcinoma	14	20.6
Interval from index pregnancy (month)		
<4	56	82.4
4–6	8	11.8
7–12	2	2.9
>12	2	2.9
FIGO stage		
I	11	16.2
II	5	7.4
III	52	76.5
FIGO score		
≤2	32	47.1
3–4	23	33.8
5–6	13	19.1
largest tumor size, including uterus (cm)		
–	29	42.6
3–5 cm	14	20.6
≥5 cm	25	36.8
Pulmonary metastasis	44	64.7
Vagina metastasis	0	0
Other metastasis	1	1.5

with those of the VMP-failed group, and found that resistance to VMP regimen was evidently related with higher hCG before using VMP chemotherapy (P value = 0.005).

#### Assessment of toxicity

We collect the blood test, liver and renal functions results of all patients during their treatment, the criteria for renal, hepatic and hematologic toxicity we used were those of CTCAE of the NCI [13].

**Table 2**

VMP for Methotrexate-Failed Low-Risk GTN Patient Characteristics (n = 19, media age = 32.3, range 18–55).

Characteristic	No.	%
Age		
<40	14	73.7
≥40	5	26.3
Antecedent pregnancy		
Hydatidiform mole	17	89.5
Abortion	1	5.3
Term	1	5.3
Clinicopathology		
Postmolar GTN	18	94.7
Choriocarcinoma	1	5.3
FIGO Stage		
I	7	36.8
III	12	63.2
FIGO Score		
<3	14	73.7
≥3	5	26.3
hCG at start of VMP		
<1000 mIU/mL	11	57.9
1000–10,000 mIU/mL	6	31.6
≥10,000 mIU/mL	2	10.5
largest tumor size, including uterus (cm)		
–	15	78.9
3–5 cm	3	15.8
≥5 cm	1	5.3

The hematologic/liver/renal toxicity were noted in Table 4. There were no patients died from toxicity, and serious adverse reactions (grade 3 or 4) were mainly myelosuppression happened to 4 patients (14.8%), of which none was grade 4. We observed 3 cases of minimally abnormal LFTs. Most patients have mild or no side effects, nausea, vomiting, constipation and alopecia happened occasionally.

#### Role of surgical intervention

5/87 (5.75%) patients underwent surgery as part of treatment in our study, among whom 1 underwent pulmonary resection, 1 underwent hysterectomy, 1 underwent uterine lesions wedge resection, 1 underwent total hysterectomy + left salpingo-oophorectomy, 1 underwent left salpingo-oophorectomy + tubal ligation who were diagnosed as ovarian choriocarcinoma. For the 5 patient undergoing surgery, 3/5 (60%) received chemotherapy before and after surgery because of resistance, and 2 of them (40%) received surgery as initial treatment with adjuvant chemotherapy. There were no differences in the complete remission rate between patients that underwent surgery and those who did not (p = 1).

#### Follow-ups

There were nine patients who tried to conceive after chemotherapy and eight (88.9%) patients became pregnant. A total of 12 conceptions occurred, resulting in three abortions and 7 term pregnancies without any molar pregnancies. There were not congenital abnormalities, and all seven babies showed normal development and growth. It was worthwhile that the woman who achieved a CR after undergoing a uterine lesions resection and 7 cycle of chemotherapy delivered a baby 1.5 years later. After treatment, the pre-menopausal patient resumed menstruation within  $2 \pm 1.27$  months, except for women undergoing hysterectomy.

#### Discussion

FIGO prognostic scoring system has been used for nearly 20 years since 2000 [14]. Due to the high sensitivity of LR-GTN to chemotherapy, the cure rate of low-risk GTN was over 90% [2,6], but there was still not an international standard about the most appropriate treatment of low-risk GTN. Patients with low-risk GTN should be treated individualized on the basis of guidelines and clinical experience. The first line and single drug can choose methotrexate, actinomycin or 5-FU, and methotrexate was the most common clinical first-line chemotherapy regimen [15], while 5-FU was preferred in Peking Union Medical College Hospital Based on current evidence at present, and other commonly used chemotherapy regimens were etoposide, and various kinds of combined chemotherapy regimens. Because of the certain damage to the skin and other tissues, which was easy to cause local tissue damage, plus treatment was expensive [16], Act-D was not the most appropriate first-line treatment option, even complete remission rate can reach over 90% [17] In Sheffield Centre for Trophoblastic Disease, patients with LR-GTN of whom FIGO score was 6 or FIGO stage was III should receive selective therapy between MTX/FA and combination chemotherapy [18]. In Peking Union Medical College Hospital, for patients with pre-treatment hCG>10,000 IU/L or clinic pathologic diagnosis of choriocarcinoma or a FIGO score greater than 4, it was more appropriate to use combination chemotherapy directly. Abuse of combined therapy without individualized treatment can lead to overtreatment. There were evidences of an increased risk of leukemia after EMA-CO, and combined treatment may result in the premature ovarian failure (POF) increasing the risk of earlier

**Table 3**

Factors associated with resistance to first-line chemotherapy with VMP for low-risk GTN.

Characteristic		Complete remission	Resistance	P-value
Number of patients	68	57	11	/
Mean age (range)	30.47 (19–54)	30.86	30.92	/
Age	<36	43	10	0.462
	≥36	14	1	
Antecedent pregnancy (AP)	Hydatidiform mole	41	9	0.800
	Spontaneous abortion	12	1	
	Term pregnancy	4	1	
Pretreatment hCG (IU/L)	<7500	43	4	0.027
	≥7500	14	7	
Clinicopathologic type	Postmolar GTN/Invasive mole	44	10	0.533
	Choriocarcinoma	13	1	
Interval from index pregnancy (month)	<4	46	10	0.491
	4–6	7	1	
	7–12	2	0	
	>12	2	0	
FIGO stage	I	9	2	1
	II	5	0	
	III	43	9	
FIGO score	≤2	27	5	0.261
	3–4	21	2	
	5–6	9	4	
largest tumor size, including uterus (cm)	–	25	4	0.587
	3–5 cm	12	2	
	≥5 cm	20	5	
Pulmonary metastasis		36	8	1
Vagina metastasis		0	0	
Other metastasis		1	0	

menopause, compared the menopausal age of cases receiving combined or single agent chemotherapy (13% before 40 years old and 36% before 45 years old vs. 1% before 40 years old and 7% before 45 years old.) [19]. MTX single agent and the VMP combined regimen were commonly used for the patients with low-risk GTN in our center. MTX, acting on S phase of cell cycle, was the first-line treatment for GTN, to which the epithelial cells and mucosal cells with fast metabolism were more sensitive and in a dose-dependent manner [20]. VCR, acting mainly in M phase of cell cycle, inhibited the aggregation of tubulin and the formation of spindles, as well as synchronized the proliferation of cells. It was often used on the first day of chemotherapy 3 h in advance to increasing the efficacy of other chemotherapy drugs. DDP, a cell cycle nonspecific agent, inhibited the DNA replication process in cancer cells which was effective to patients failed with first-line chemotherapy. The combination of the above three drugs met the requirements of drug selection for combined chemotherapy and the compatibility was reasonable. The purpose of using combined chemotherapy was to play the synergistic role of drugs, especially for patients with high risk of developing drug resistance, in order to maximize the drugs' efficacy and delay the occurrence of drug resistance. The VMP regimen used in this study was less used at home and abroad, but in the more than ten years treatment between 2005 and 2017, the

response of patients to the VMP protocol was gratifying and the effect was sensational.

Methotrexate was currently the main first-line chemotherapy widely used. In our study the patients received VMP protocol could achieved 83.5% and 89.5% complete remission rate as the first or second line chemotherapy, and the overall complete remission rate reached 85.1% (74/87). The complete remission rate obtained in our study was higher than that of 77.5% achieved by Gihad's series research which applied MTX 1 mg/kg on days 1, 3, 5, and 7, plus folinic acid per os at a dose of 10 mg on days 2, 4, 6, and 8 to low-risk GTNs [21]. As for weekly intramuscular methotrexate agent, the first-line chemotherapy complete remission rate was only 74.3% and 79.6% [22,23]. The 5-day methotrexate regimen attained the complete remission rate of 81%, and that of the Act-D regimen as the second-line chemotherapy was 75% [24]. The mean number of courses patients required to achieve complete remission was 3.54 (range, 1–6), with VMP regimen as primary chemotherapy, shorter than that of weekly/5 days/8 days MTX [25–27]. Compared with methotrexate single agent, the VMP regimen does have a higher therapeutic effect.

In our center, most patients have mild or no side effects, and serious adverse reactions were mainly myelosuppression happened to 14.8% patients. Nausea, vomiting, constipation and alopecia occasionally happened but they didn't affect the continuation of the treatment. As for patients received methotrexate single agent in other center, severe hematopoietic/liver/renal toxicity was noted in 4.2% of cases and significant toxicity encountered was stomatitis in 26% patients [28]. Severe adverse reactions were often an important cause of interruption in chemotherapy, so we chose MTX and platinum as low-dose multi-day therapy in order to reduce the side effects of combined chemotherapy. Our results showed that the toxicity of the VMP protocol above the II degree was lower than that of other protocol reported in the literature [29–31]. As the EMA-CO and FAV regimen had an acute attack of hepatitis, VMP can be preferred as salvage treatment for patients with hepatitis and liver damage during chemotherapy.

**Table 4**

Toxicity of VMP regimen.

Variable	Grade 1	Grade 2	Grade 3	Grade 4	Total
hemoglobin	12	4	4	0	20
leukocytes	8	3	0	0	11
platelets	2	0	0	0	2
creatinine	0	0	0	0	
AST	0	1	0	0	1
ALT	1	1	0	0	2
No. of patients	17	6	4	0	27

AE, adverse event.

ALT, alanine aminotransferase.

AST, aspartate aminotransferase.



The drug resistance of tumor cells was one of the main reasons for the failure of chemotherapy, and the replacement of more effective chemotherapy regimen, usually combined chemotherapy, has a possibility of increasing the toxicity. Therefore, it was the key to solve the problem by evaluating the risk of drug resistance and taking appropriate measures to reduce the incidence of drug resistance. In our study, whether as a first-line or second-line regimen, the incidence of drug resistance in patients receiving VMP was significantly related to pre-treatment  $\beta$ -hCG values. When VMP was administered as a primary treatment, it tended to develop resistance when the pretreatment  $\beta$ -hCG reaches 7503.5 IU/L according to the cut-off value. And when MTX was administered as a primary treatment in our center, it tended to develop resistance when the pretreatment  $\beta$ -hCG > 2800 IU/L in our previous research [11]. Meanwhile, since the sample size as a second-line chemotherapy regimen was too small, we only analyzed the correlation between overall drug resistance of VMP regimen and pre-treatment  $\beta$ -hCG in order to avoid excessive bias. The results showed that there was a significant correlation between overall drug resistance in VMP regimen and  $\beta$ -hCG value before use. The  $\beta$ -hCG value was an important indication to judge the curative effect of chemotherapy regimen, and it was also of great reference value to guide the change of chemotherapy regimen in the event of drug resistance. In Sheffield Centre for Trophoblastic Disease, patients with LR-GTN received MTX/FA as their primary treatment, once drug resistance occurred with an hCG level of <150 IU/L (300 IU/L since July 2010), single agent dactinomycin (ActD) was administered. If  $\beta$ -hCG levels were above 150 IU/L (300 IU/L since July 2010), combination chemotherapy etoposide and dactinomycin (EA) or single agent carboplatin was given. 75% patients treated have been successfully salvaged with this regimen [32]. Similarly, in Charing Cross Hospital, the threshold value was 300 IU/L and achieved a 99% remission rate, compared to this value of 100 IU/L with a 87% remission rate, greatly improved the remission rate of second-line chemotherapy [33]. For low-risk GTNs, other related risk factors for drug resistance were FIGO scoring, staging and antecedent pregnancy ( $P < 0.05$ ) etc. [22].

For patients with LR-GTN who don't require preserve fertility function, hysterectomy can significantly reduce the risk of recurrence and drug resistance. For young women with requirement of fertility function, fertility-sparing uterine lesion resection also can have a good prognosis, with a pregnancy rate reaching more than 80%. 94% of patients returned to normal menstruation, within 1 year after obtaining CR [34]. There have been many cases of healthy childbirths after the cure of gestational trophoblastic neoplasia at home and abroad, and shown no difference between these babies and normal newborns in the growth and development. In our study, nine patients tried to conceive after chemotherapy and eight (88.9%) patients became pregnant, resulting in three abortions and seven term pregnancies with normal development and growth. The pre-menopausal patient resumed menstruation within an average of  $2 \pm 1.27$  months, except for women undergoing hysterectomy.

In a recently published European Society for Medical Oncology guideline which gives a clear general overview of GTD [5], all patients will need a chest X-ray, but as possible pulmonary micro-metastases do not influence the outcome, computed tomography (CT) of the chest is not needed if the chest X-ray is normal. However, if pulmonary lesions are seen, complete staging with body CT and magnetic resonance imaging (MRI) of the brain is indicated to exclude more widespread disease. In our center, 94.4% (51/54) of FIGO III patients receive chest CT scan. In order to avoid insufficient treatment, we judged the scores using CT results which led to an increase in the proportion of FIGO III patients in our study. Meanwhile, Anhui province is still a poor province with some of GTN patients in China. Some of LR-GTN without lung metastasis were

treated in the municipal or district hospitals. Thus, our LR-GTN patients were mostly in stage III in our center (as a provincial hospital). This unusual case distribution of stage I ~ III might be owing to the special Chinese situations such as large population and different levels of hospital with different kinds of patients. Because of the difference of  $\beta$ -hCG measurement methods, the threshold value of  $\beta$ -hCG in foreign research centers was not the same as the standard of our center, but our common goals was to decide the next treatment plan according to the high risk factors of drug resistance. Due to the increase of dose and variety of chemotherapy drugs and the less use in other center, the toxicity of VMP on low risk gestational trophoblastic tumor has not been compared with other single agent chemotherapy systematically. In addition, this study was not randomized, we tended to choose patients with low-risk GTN in 4–6 scores to administrate VMP regimen to get quick complete remission, possibly resulted in bias.

In summary, Although GTN has become the first malignant solid tumor to be cured by chemotherapy, the best initial treatment for gestational trophoblastic neoplasia has yet to be identified at home and abroad [35]. At present, because of the feasibility of using MTX, it was suggested to use it as the first-line treatment of LR-GTN, and the 8-day regimen was recommended on the basis of its high efficacy and low cost [31,36]. Owing to the special Chinese situations such as large population of patients, far away from the hospital and no adequate hospital beds, both the doctors and the patients need to achieve complete remission with fewer cycles and longer hospital interval. MTX 5-day protocol is recommended to 2 week for one cycle; once the patient delayed in hospital, he will come across chemo-resistant. In our study, the efficacy of VMP regimen was higher than that of MTX or Act-D single agent chemotherapy. [21–24], and when the VMP regimen was used as the initial chemotherapy regimen, if the pre-treatment  $\beta$ -hCG value was higher than 7500 IU/L, the patient has a tendency to develop drug resistance. Resistance to VMP regimen was obviously related with higher pre-treatment HCG whether used as primary or salvage treatment. Most of our patients have no or mild side effects and would not affect the continuation of the treatment. As VMP was indeed a more aggressive protocol, for patients diagnosed with LR-GTN had high risk factors of developing drug-resistance, we recommend that the VMP regimen was a safe and effective treatment to get quick complete remission.

## Conflicts of interest statement and funding/support statement

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