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Low-risk gestational trophoblastic neoplastic outcome after primary treatment with low-dose methotrexate from 2005 to 2017

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Summary

Purpose: To retrospectively assess the efficacy and toxicity of single-agent methotrexate (MTX) regimen applied to patients treated in Anhui provincial hospital with low-risk gestational trophoblastic neoplasia (LR-GTN). *Materials and Methods:* Between 2005 and 2017, on the basis of International Federation of Gynecology and Obstetrics (FIGO 2000) criteria for staging and scoring system, 66 patients with LR-GTN were treated with single-agent MTX. The authors describe their clinical characteristics, resistance/remission/recurrence rates, and treatment toxicity. *Results:* All patients achieved remission and maintained disease-free status until the moment of analysis. The five-day MTX protocol can achieve a 63.6% remission rate. Resistance to this regimen was obviously related with age and higher pre-treatment hCG. Severe blood toxicity (grade 3 or 4) was shown in four (6.1%) of 66 cases, of which one (1.5%) case was grade 4. *Conclusions:* For patients diagnosed with LR-GTN, a five-day MTX regimen is an appropriate treatment associating a low rate of toxicity to a high rate of remission.

Key words: 2000 International Federation of Gynecology and Obstetrics scoring; Low-risk gestational trophoblastic neoplasia; Methotrexate; Efficacy; Toxicity.

Introduction

Gestational trophoblastic neoplasia (GTN) is an infrequent disease, the cure rates of which can reach about 100% in low-risk GTN (LR-GTN) patients and 94% in high-risk GTN (HR-GTN) patients [except for placental site trophoblastic tumor/epithelioid trophoblastic tumor (PSTT/ETT)] because of the hypersensitivity of GTN to chemotherapy [1-4]. In Asians, this disease is more common than in other developed countries, such as Europe, due to poverty and genetic influences [5]. Patients with GTN are divided into two groups: LR-GTN or HR-GTN on the basis of the International Federation of Gynecology and Obstetrics (FIGO) criteria for scoring and staging system. It is known that the cure rate for LR-GTN is high [6]; therefore, how to reduce both long- and short-term toxicities with less chemotherapy cycles, while not affecting the outcome, is the most important factors the clinical researchers have confronted. In the present center, the authors have the dilemma of no support of Act-D in the market at one time, thus low-dose methotrexate (MTX) is the most common selection. Herein, they have collected 66 cases of LR-GTN cured by single-agent MTX to evaluate the complete remission rate, development of resistance, relapse, survival, and side effects in the present center.

Materials and Methods

From January 2005 to December 2017, LR-GTN (scores ≤ 6), 66 Stage I~III GTNs were registered primarily treated with single-agent MTX chemotherapy protocol in Anhui Provincial Hospital. All the 66 patients were in accordance with the following essential conditions: scored ≤ 6 and Stage I~III GTN, received at least one cycle of single-agent MTX chemotherapy as primary treatment, never received chemotherapy before, and without ETT or PSTT. This study was approved by the Institutional Review Board of Anhui Provincial Hospital and all the 66 patients were selected based on the institutional databases review.

The initial diagnosis of LR-GTN (scores ≤ 6), 66 Stage I~III GTN was made according to FIGO 2000 staging prognostic scoring system. The authors evaluated the following factors associated with this disease: age, clinical presentation, a complete medical history, gynecological examinations, imaging examinations such as CT and vaginal ultrasonography, a blood sample to measure the levels of β-hCG before treatment, blood count, and liver and renal function assessments. According to the FIGO 2000 scoring system, patients were staged and scored.

According to the FIGO 2000 guidelines [7], all patients received MTX 0.4 mg/kg intramuscular q.d.×5 d every 14 days as first-line treatment for low-risk GTN. Serum β-hCG levels every week were used to evaluate the curative effect. The concentrations of β-hCG were tested in serum by an in-house competitive radioimmunoassay, which uses a polyclonal rabbit anti-serum. A total blood cell count, and liver and renal function was also investigated. Imaging was tested every two to three cycles of chemotherapy. Surgical treatment was carefully chosen in patients

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Table 1. — *Baseline characteristics of patients with LR-GTD (n=66).*

Characteristic		No.	%
Age (years)	<40	53	80.3
	≥40	13	19.7
Antecedent pregnancy (AP)	Hydatidiform mole	58	87.88
	Spontaneous abortion	7	10.61
	Term pregnancy	1	1.52
Pretreatment hCG (IU/L)	< 1,000	25	37.88
	1,000-10,000	25	37.88
	10,000-100,000	15	22.73
	> 100,000	1	1.52
Clinicopathologic type	Postmolar GTN/invasive mole	62	93.94
	Choriocarcinoma	4	6.06
Interval from index pregnancy (months)	< 4	60	90.91
	4-6	4 6.	06
	7-12	2	3.03
FIGO Stage	I	28	42.42
	II	0	0
	III	38	57.58
FIGO score	≤2	54	81.82
	3-4	8	12.12
	5-6	4	6.06
Pulmonary metastasis		38	57.58
Vagina metastasis		0	0
Other metastasis		0	0
Hysterectomy		3	4.55

with a life-threatening bleeding caused by GTN or drug-resistant patients.

Complete remission (CR) was given definition as a normal β-hCG level for three continuous weeks. β-hCG was monitored monthly for a year after CR. Treatment was continued in all cases until the β-hCG values was normal (<3 IU /L) for six weeks. Resistance was defined as a reduction less than 10% in β-hCG level over three continuous weeks, or an increase greater than 20% maintained over two continuous weeks, or the signs of new metastasis [8]. Relapse was defined as an enhancement of β-hCG three months after CR if in the absence of a confirmed pregnancy. Toxicity was assessed according to the National Cancer Institute (NCI) Common Toxicity criteria version 2.0 [9]. All side-effects were documented.

SPSS Data Editor 16.0 and Graph Pad Prism were used in this study. The clinical information of these patients underwent univariate analysis to detect the resistant to MTX interrelated hazard factors. The univariate analysis was achieved by qualitative and quantitative parameters. $P < 0.05$ was considered to have statistical significance.

Results

Between 2005 and 2017, 66 patients were diagnosed with LR non-metastatic (Stage I) and metastatic (Stages II–III, score < 7) GTN defined by FIGO received primary single-agent MTX chemotherapy at Anhui Provincial Hospital. Patient and clinical characteristics are presented in Table 1. The age range of these patients was 18-55 (mean age: 31.9 ± 9.0) years; 87.88% of the patients had an original diagnosis of hydatidiform mole, 90.91% of the patients had a disease duration of less than four months, and 98.48% of the patients had a pre-treatment hCG value of less than 100,000 mIU/mL. The common initial clinical presentation of the patients was vaginal bleeding (27/66 patients). Lung metastatic disease was found in 38 patients (57.58%) and no other metastasis was found.

Three patients (4.55%) underwent adjuvant hysterectomy procedures. One patient underwent hysterectomy before the initiation of chemotherapy, then was treated with single agent MTX for four cycles. Two patients underwent hysterectomy after chemotherapy due to a stabilization in hCG level, one underwent MTX protocol, and the other was changed to the VMP (bortezomib, melphalan, prednisolone) regimen.

The mean duration of therapy was 5.48 ± 2.82 (range 2–12) weeks. The entire primary CR ratio was 63.6% of the original single agent MTX chemotherapy (42/66). The average chemotherapy cycle number was 2.74 ± 1.41 (range 1-6) cycles. Resistance to single-agent MTX chemotherapy was obviously related with age ($p = 0.028$) and higher pretreatment hCG ($p = 0.016$) (Table 2). Other factors, such as antecedent pregnancy, clinicopathologic type, duration of disease, FIGO stage, FIGO score, adjuvant hysterectomy, and metastasis had no statistically effect on resistance to original MTX chemotherapy. According to ROC curve (Figure 1), resistance was likely to occur when the pretreatment hCG reached 2,820.5 IU/L by calculating the cut-off value. The ROC curve of pretreatment hCG with AUC=0.718, 95% IC=0.509-0.847.

Toxicity was assessed in 66 patients, no deaths occurred

Table 2. — *Factors associated with resistance to first-line methotrexate chemotherapy for low-risk.*

Characteristic		Complete remission	Resistance	*p*-value
Number of patients		42 (63.6%)	24 (36.4%)	
Age (years)	< 3. 0	17	17	0.028
	30-40	16	3	
	40-50	8	2	
	≥ 5 0	1	2	
Antecedent pregnancy (AP)	Hydatidiform mole	37	21	0.624
	Spontaneous abortion	5	2	
	Term pregnancy	0	1	
Pretreatment hCG (IU/L)	< 1,000	21	4	0.016
	1,000-10,000	14	11	
	10,000-100,000	6	9	
	> 100,000	1	0	
Clinicopathologic type	Postmolar GTN/invasive mole	40	22	0.618
	Choriocarcinoma	2	2	
Interval from index pregnancy (month)	< 4	38	22	0.515
	4-6	2	2	
	7-12	2	0	
FIGO stage	I	18	10	0.925
	III	24	14	
FIGO score	≤ 2	36	18	0.261
	3-4	5	3	
	5-6	1	3	
Pulmonary metastasis		24	14	
Hysterectomy		2	1	

Table 3. — *Toxicity of low-dose methotrexate regimen.*

variable	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening or disabling AE)
Hemoglobin	8	2	1
Leukocytes	11	0	0
Platelets	0	0	0
Creatinine	2	0	0
AST	1	0	0
ALT	1	1	0
Total number of patients	21	3	1

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

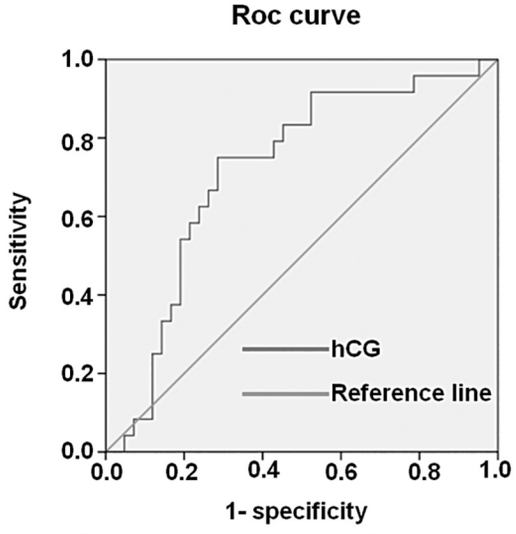

Figure 1. — Description of pretreatment hCG to assess whether patients treated with MTX had drug resistance.

related to toxicity. Liver, renal function, and blood toxicity are shown in Table 3. Myelosuppression was the main significant side effect; severe (grade 3 or 4) laboratory test results related to toxicity occurred in four (6.1%) cases, of which one (1.5%) was grade 4.Nausea was an unusual side effect and there was no alopecia associated with MTX. No patient was sent to hospital to receive treatment due to toxicity (Table 3).

Discussion

International use of 2000 FIGO scoring system advocated by Kohorn *et al.* and Ngan *et al.* [7, 10, 11], was a landmark decision for the homogeneous allocation of therapy for GTN which has the most significant CR among solid tumors. Although the patients with LR-GTN can almost acquire 100% cure rate [6, 12-14], the regimen of first-line selection is not in line with centers around the world. Actinomycin D or single-agent MTX or other com-

bined chemotherapy were all in use for treatment. Since MTX protocols were considered as first-line treatment for LR-GTN by many centers, there is no consensus on MTX regimen depending on physician experience. Thus, the effect and toxicity of single-agent MTX still need to be investigated, as well as its usage methods.

The original regimen applied to treat GTN in NIH patients was intramuscular injection MTX 0.4mg/kg/day for five days, with cycles repeated every 14 days; in this center, 58 patients with non-metastatic GTN were treated with this protocol; only 7% patients showed no response and 3/4 were changed to single-agent actinomycin D [15]. In the Lurain *et al.* study, 185/337 (54.90%) cases with non-metastatic GTN were cured with this protocol from the Brewer trophoblastic disease center [16]. Other patients using five-day IM methotrexate regimen had similar results. However, it is noted that MTX, metabolized in the liver, should not be used if the patients show compromised liver function or other liver diseases [17, 18].

Five-day MTX regimen was also evaluated by other groups with different usage methods. Lurain *et al.* showed that the CR rate was 82% with primary MTX 0.4 mg/kg IV push q.d.(max 25 mg)×5 days every 14 days chemotherapy every other week in 368 cases with LR-GTN [19]. Another report showed that 253 non-metastatic GTN patients achieved an initial 89% remission rate [20]. Chapman-Davis *et al.* reported that the CR rate to primary IV five-day MTX chemotherapy was 81% (290/358) [21].

Eight-day MTX-folinic acid was another common protocol selected by other centers. McNeish *et al.* showed a 67% CR with eight-day MTX-folinic acid at Charing Cross Hospital (London, UK) [22]. You *et al.* reported a 53.3% sensitivity with eight-day MTX-folinic acid regimen [23]. EI-Helw *et al.* showed a 77% CR with eighty-day MTX-folinic acid before 2000, and 61.6% from 2000 to 2006 in their center [24]. Chalouhi *et al.* reported an overall remission rate after single-agent eight-day MTX protocol of 77.5% [25]. McGrath *et al.* reported that 11/37 (29.7%) patients with a pre-treatment hCG >100,000 IU/L and LR-GTN were treated successfully with eight-day MTX treatment [26]. Taylor *et al.* assessed for treatment response in 289 LR-GTN cases, and the CR of eight-day MTX/FA was 19%, with a score of 6, compared with 66% in patients with a score of 0–5 ($p < 0.0001$)[27]. Sita-Lumsden *et al.* reported 57% CR in 579 cases with LR-GTN using eight-day MTX/FA as first-line therapy [28]. Therefore, CR can reach about 50%-77% with MTX eight-day regimen. However, to acquire remission, the eight–day MTX-folinic acid regimen was often related to a more frequent requirement for salvage multi-agent chemotherapy, which was inconvenient, and more expensive [20–30].

Previous reports have not shown high remission rates by MTX weekly usage. Gilani *et al,* reported 46.7% successful response using MTX (30 mg/m^2/weekly/IM) [29]. Osborne *et al.* reported a 53% CR with MTX (30 mg/m^2/weekly/IM)[30]. Yarandi *et al.* reported that 48.14% of patients achieved CR with MTX (30 mg/m^2/weekly/IM) group [8].

In summary, the five-day MTX protocol used as primary therapy of LR-GTN is more favorable than the similar MTX regimen used in reports [17–19]. MTX used in IM doses has the benefit of reduced cost, convenience, and less toxicity such as hematologic suppression and mucositis, but it is an inappropriate therapy in patients with GTN with high scores and hCG levels. When the patients with LR-GTN failed with MTX treatment due to chemoresistance and toxicity, single agent actinomycin D, combination chemotherapy, as well as surgery, might be the subsequent cure regimens. Nevertheless, actinomycin D will produce local tissues injury if IV extravasation occurs and has a more toxic side-effect profile than MTX; combination chemotherapy probably gives rise to early menopause and is also related with an incidence of second tumors, especially colon cancer, myeloid leukemia, and breast cancer [31]. It is urgent to evaluate a proper single agent MTX regimen for the LR-GTN patients, especially in young patients that require fertility-sparing and are not willing to accept hysterectomy; the mortality and morbidity are nine-fold higher when an inexperienced doctor treats this kind of patients [25, 32]. In this study, resistance to single-agent MTX chemotherapy was obviously related to age and higher pre-treatment hCG. Most of the patients with a 4-6 score with LR-GTN were selected with primary combined chemotherapy using less cycles to achieve a quicker CR for later pregnancy in thus center, which might affect the results of the relation of the scores and the resistance to single-agent MTX chemotherapy.

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