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Original Research

Analysis of the Efficacy of 5-Fluorouracil in the Treatment of Invasive Moles

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Abstract

Background: To evaluate the chemotherapy toxicity of 5-fluorouracil (5-FU) in the treatment of invasive moles. **Methods**: We conducted a retrospective study of therapeutic satisfaction, recurrence, and toxicity in 17 patients treated with 5-FU in the Zhuzhou Central Hospital, from 2015 to 2020. **Results**: After a single-agent 5-FU treatment a complete remission of low-risk invasive moles was observed, and remission of high-risk invasive moles reached rates of 76.5%. After 4–5 chemotherapy cycles, 5-FU reduced serum human chorionic gonadotropin (hCG) to normal levels in invasive moles. Furthermore, a toxicity assessment revealed that 5-FU chemotherapy has low toxicity and is generally acceptable for patients. **Conclusions**: 5-FU offers high efficacy in both low-risk and high-risk invasive moles, with low chemotherapy toxicity.

Keywords: 5-fluorouracil; invasive mole; recurrence; toxicity

1. Introduction

Invasive mole is one subtype of gestational trophoblastic neoplasia (GTN), characterized by the malignant transformation of embryonic trophoblast cells [1,2]. Advances in medical diagnostic and therapeutic technologies have significantly increased the curability of GTN, particularly through application of effective chemotherapy. The 2000 International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO) divides GTN into risk categories through a scoring system, with a score <7 signifying low-risk and ≥ 7 signifying high-risk GTN. Different chemotherapy regimens are recommended according to the risk stratification. Typically, methotrexate (MTX) or actinomycin-D (Act-D) are recommended as single-agent chemotherapy treatment for low-risk GTN, while an etoposide, MTX, Act-D, cyclophosphamide, oncovin (EMA/CO) regimen is recommended as multiagent chemotherapy for high-risk disease [1–3]. Invasive moles are often diagnosed clinically based on persistent human chorionic gonadotropin (hCG) increase after molar removal. Approximately 15% of these cases will metastasize to the lungs or the vagina. Chemotherapy is the predominant treatment for invasive moles, with a cure rate of nearly 100% in low-risk cases and 90% in high-risk instances [3]. However, severe chemotherapy toxicity associated with multidrug chemotherapy frequently prompts the discontinuation of treatment [4].

Floxuridine, Act-D, etoposide, and vincristine (FAEV) constitutes the first-line treatment for both high-risk GTN, as well as low-risk disease (FIGO scores, 5–6) [5,6]. Recently, use of the antineoplastic drug 5-fluorouracil (5-FU) for the treatment of low-risk invasive moles has achieved satisfactory results in China. Furthermore, the toxicity of this regimen appears to be fully tolerated by patients [6,7]. Building upon this basis, a 5-FU-based combined chemotherapy has been developed. In GTN treatments, including invasive moles, 5-FU is used either as a single agent or in combination with other chemotherapeutic agents. Therefore, we conducted a retrospective analysis to determine the therapeutic efficacy and chemotherapy toxicity of 5-FU in both low-risk and high-risk invasive moles.

2. Materials and Methods

2.1 Patients

This was a single-center retrospective study, involving 17 cases of invasive mole treated with 5-FU in the Zhuzhou Central Hospital, from 2015 to 2020. All patients were confirmed as having an invasive mole by pathological diagnosis. Patients were assessed according to the WHO scoring system [8], where a score <7 indicated low-risk, while a score ≥ 7 indicated high-risk case. Blood cell counts (MC80, Mindray Biomedical Electronics Co., Ltd, Shenzhen, Guangdong, China), and liver and renal functions (BS2800, Mindray Biomedical Electronics Co., Ltd, Shenzhen, Guangdong, China) were tested before each course of chemotherapy. Ultrasound (DC-80, Mindray Biomedical Electronics Co., Ltd, Shenzhen, Guangdong, China) was employed to measure the largest tumor size, complemented by chest X-ray (DR-F, 158346HL7, Beijing Gen-

eral Electric Hualun Medical Equipment Co., Ltd, Beijing, China). A computed tomography (CT) (ACCESS CT, 304069, Koninklijke Philips NV, Shanghai, China) scan of the lungs and magnetic resonance imaging (MRI) (Ingenia 3.0T, MR7700, Koninklijke Philips NV, Shanghai, China) of the brain were performed if the X-ray revealed lung metastases. hCG levels (CL8000, Mindray Biomedical Electronics Co., Ltd, Shenzhen, Guangdong, China) were recorded before and after each treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [9]. This study was supported by the Ethics Committee of Zhuzhou Central Hospital (Number: ZZCHEC2021124-01). Informed consent was obtained from all patients.

2.2 Treatment Methods and Evaluation of Therapeutic Effects

All patients were treated with 5-FU (0.25 g/tube, Shanghai Xudong Haipu Pharmaceutical Co., Ltd, Shanghai, China) (daily dose of 26–27 mg/kg in 500 mL of 5% glucose (500 mL/bottle, Hunan Kelun Pharmaceutical Co., Ltd, Changsha, Hunan, China), administered within 6–8 hours), for 5 consecutive days. The chemotherapy cycle was repeated every 21 days. Serum hCG was measured after each course of chemotherapy, until levels returned to normal. Following the FIGO guidelines recommendation, a minimum of two courses of consolidation chemotherapy were administered following the first negative hCG level. Remission was defined as a normal hCG level for three consecutive weeks (hCG: 0~5 IU/L). Treatment was considered effective if the serum hCG decreased by one logarithm within at least 18 days after the end of each course of chemotherapy. Definition of resistance to monotherapy chemotherapy [10]: primary resistance refers to the appearance of monotherapy therapy in the first two courses of treatment β- hCG elevation or plateau (decrease $<$10%); secondary drug resistance refers to the effectiveness at the beginning of chemotherapy, followed by β- hCG showed plateau or elevation in two courses of treatment. Relapse criteria [10]: after 3 months of complete remission, hCG may increase again (excluding pregnancy) or new lesions may be detected through imaging (ultrasound, X-ray, CT). Alanine aminotransferase/aspartate aminotransferase (ALT/AST) were evaluation indicators. Before chemotherapy, 2 mL of blood was tested on an empty stomach, and it is tested every 7 days.

2.3 Follow-up Criteria after Treatment

Close follow-up was carried out after treatment, at 3 months, 6 months, 1 year, and 2 years after treatment. In general, pregnancy can be achieved after $\geq$12 months after chemotherapy.

2.4 Data Collection

Data collection following first-line treatment included disease stage, WHO prognostic risk factors and score, chemotherapy regimen, number of chemotherapy cycles, treatment response, relapse, and time to first relapse.

Table 1. Clinical characteristics of the 17 patients.

Features	N (%)
Age (years)	
$<$40	14 (82.35)
$\geq$40	3 (17.65)
Antecedent pregnancy	
Hydatidiform mole	1 (5.88)
Abortion	7 (41.18)
Term	9 (52.94)
Largest tumors size	
$<$3 cm	7 (41.18)
3–5 cm	3 (17.65)
$\geq$5 cm	7 (41.18)
FIGO stage	
I	6 (35.29)
II	3 (17.65)
III	8 (47.06)
IV	0
FIGO scores	
$<$7	6 (35.29)
$\geq$7	11 (64.71)
Pretreatment hCG (IU/L)	
$<10^3$	5 (29.41)
10^3–10^4	3 (17.65)
10^4–10^5	9 (52.94)
$>10^5$	0
Sites of metastases	
Lung	5 (29.41)
Vagina	2 (11.76)
Number of metastases	
0	10 (58.82)
1–4	7 (41.18)
5–8	0
$>$8	0
Chemotherapy effect	
Remission	13 (76.47)
Resistance	2 (11.76)
Relapse	2 (11.76)
Toxicity	
Grade 2	4 (23.52)
Grade 3	2 (11.76)
Grade 4	1 (5.88)

N, number; FIGO, International Federation of Gynecology and Obstetrics; hCG, human chorionic gonadotropin.

Table 2. Patient details, hCG levels, and FIGO scores in response to chemotherapy treatment.

Patients	FIGO scores	hCG levels (IU/L)											Chemotherapy toxicity	Sites of metastases
		Chemotherapy cycles												
		1	2	3	4	5	6	7	8	9	10	11		
2	<7	85,672	2056	242.8	65.8	normal	normal							
3	<7	250,000	84,550	8422	502	normal	normal							
10	<7	1160	normal	normal										
11	<7	66,673	842	normal	normal									
12	<7	5347	normal	normal										
13	<7	545,344.9	82,553	15,890	1480	85	normal	normal					Grade 2	
1	≥7	913.3	normal*	normal										
4	≥7	100,000	5230	882	normal	normal							Grade 2	Lung
5	≥7	1949	normal	normal										Lung and vagina
6[#]	≥7	789,783	66,620	10,800	3440 (Act-D)	127	normal	normal					Grade 4	Lung
7	≥7	8369.6	1892	566	144	normal	normal						Grade 3	
8[#]	≥7	125,665	6411	1550	normal	normal								
9	≥7	119,730.5	2891	825	normal	normal								Lung
14[#]	≥7	>200,000	6445	2832	580	166	normal	normal					Grade 2	Vagina
15	≥7	19,862	453	normal	normal									Lung
16[#]	≥7	112,618	6423	3411	1560	566	408	625	2245 (EMA/CO)	142	normal	normal	Grade 3	Vagina
17	≥7	100,000	3286.8	1200	165.4	normal	normal						Grade 2	

Note: *, normal indicates hCG <5 IU/L. [#], 1. Patient 6, severe chemotherapy toxicity, changed to Act-D in cycle 4; 2. Patients 8 and 14, relapse after six months of follow-up. The patient 8 underwent hysterectomy and by 3 cycles of EMA/CO courses chemotherapy. The patient 14 underwent 4 cycles of EMA/CO chemotherapy after relapse. Patient 16 developed drug resistance after the seventh chemotherapy, and the eighth chemotherapy was changed to EMA/CO regimen, and remission was achieved after 3 courses of chemotherapy. Act-D, actinomycin-D; EMA/CO, etoposide, MTX (methotrexate), Act-D, cyclophosphamide, oncovin; hCG, human chorionic gonadotropin.

Table 3. Toxicity of 5-FU regimen.

Variable	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening or disabling AE)
Hemoglobin	1	0	0
Leukocytes	3	1	0
Platelets	1	1	0
Creatinine	0	0	0
ALT/AST	2	1	0
Mucosa	1	0	0
Vomit	4	2	1
No. of patients	4	2	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AE, adverse event; 5-FU, 5-fluorouracil.

3. Results

3.1 Patient Characteristics

The medical records of 17 patients revealed a diagnosis of invasive mole, of which 6 were low-risk and 11 were high-risk. 14 (82.35%) patients were aged $<$40 years and 3 (17.65%) were aged $\geq$40 years. The size of the largest tumor was $<$3 cm, 3–5 cm, and $>$5 cm, observed in 7 (41.18%), 3 (17.65%), and 7 (41.18%) patients, respectively. 6 patients (35.29%) were classified as FIGO stage I, 3 (17.65%) as stage II, and 8 (47.06%) as FIGO stage III, and no patient fell into the stage IV classification. 7 patients had metastases, including 5 with lung metastases and 2 with vaginal metastases. 1 patient had metastases in both the lung and in the vagina (Table 1).

3.2 5-FU is Effective in Both Low- and High-Risk Invasive Moles

After treatment with single-agent 5-FU, 13 (76.5%) patients achieved remission, 1 (5.9%) was resistant to treatment, 2 (11.8%) relapsed, and only 1 (5.9%) patient was switched to Act-D treatment due to severe chemotherapy toxicity. All drug-resistant and relapsed patients achieved recovery after completing three courses of EMA/CO treatment.

We next analyzed remission rates in both low-risk and high-risk invasive moles. 6 (100%) low-risk patients had complete remission. Among 11 high-risk patients, 7 (63.6%) had complete remission, 1 (9.1%) was resistant to treatment, 2 (18.2%) had a relapse, and 1 (9.1%) experienced severe chemotherapy toxicity requiring a drug change (Table 2).

3.3 5-FU Reduces the Level of Serum hCG to Normal in Invasive Moles

Next, we evaluated the serum hCG levels of all patients, both in the pretreatment and after each treatment. Out of 5 patients with hCG $<10^3$ IU/L, 4 achieved complete remission after 3 cycles of chemotherapy, while 1 was switched to Act-D due to grade 4 toxicity, and achieved remission after 2 cycles of 5-FU chemotherapy. 3 out of 3 (100%) patients with serum hCG levels between 10^3 and 10^4 IU/L achieved remission after 5–6 cycles of 5-FU chemotherapy. Among 9 patients with hCG levels between 10^4 and 10^5 IU/L, 3 achieved remission after 8 cycles of 5-FU chemotherapy, while 5 patients had remission after 5–7 cycles of 5-FU chemotherapy. 1 patient was dissatisfied with the decrease in hCG and switched to EMA/CO in the 8th course of 5-FU treatment (Tables 2,3).

3.4 The Toxicity of 5-FU Chemotherapy is Very Low

Finally, we assessed the toxicity of 5-FU chemotherapy. 4 patients experienced grade 2 toxicity, 2 experienced grade 3, and 1 patient experienced grade 4 toxicity. The major chemotherapy toxicities of 5-FU experienced by the patients are gastrointestinal reactions (vomiting), low leukocyte and low hemoglobin levels, thrombocytopenia, abnormal liver function, and oral mucosal reactions. In the present study, all 4 patients with grade 2 abnormalities experienced vomiting, 1 in 4 patients experienced myelosuppression (granulocyte, hemoglobin, thrombocytopenia), 1 patient had oral mucosal ulcers, 2 patients had alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and 2 patients had neutropenia. Vomiting in 2 patients was classified as chemotherapy toxicity grade 3; 1 patient had granulocytopenia and thrombocytopenia, and the other had abnormal liver function. Vomiting was observed in the patient classified as toxicity grade 4 (Tables 2,3)

4. Discussion

At present, the cure rate for GTN through chemotherapy is close to 100%. Low-risk GTN is usually treated with a single agent (MTX, Act-D), while EMA/CO is recommended for high-risk GTN [11]. However, research into 5-FU for the treatment of GTN has mainly been conducted in China. Since the 1960s, 5-FU monotherapy has been employed for the treatment of low-risk GTN, demonstrating effective outcomes and minimal chemotherapy toxicity [12].

In the current study, we retrospectively studied 5-FU monotherapy for the treatment of high-risk and low-risk invasive moles in order to observe its therapeutic effect and chemotherapy toxicity. We found a remission rate of 76.5% (13/17) for the use of 5-FU in the treatment of inva-

sive moles, including 100% (6/6) and 72.7% (8/11) remission rates for low-risk and high-risk invasive moles, respectively. In comparison with previous studies, the remission rates of MTX or Act-D monotherapy for the treatment of low-risk GTN are reported to be 77–94% [13]. While our remission rate for low-risk invasive moles surpasses that of MTX or Act-D monotherapy, it is important to note that our sample size is too small to fully assess the response rate of 5-FU monotherapy. However, this study still demonstrates the advantage of 5-FU in the treatment of low-risk invasive moles. Our data also demonstrate that the use of 5-FU to treat low-risk invasive moles did not lead to severe chemotherapy toxicity, with only 1 case of grade 2 toxicity reported.

For high-risk invasive moles, the remission rate here observed was 76.5%. Previous studies using a combination of EMA/CO for the treatment of high-risk invasive moles have reported remission rates of 75% [11,14], which is consistent with our study. However, in our study, 5-FU exhibited acceptable chemotherapy toxicity for high-risk invasive moles. Only 2 out of the 11 patients experienced grade 3 and 4 toxicity, with gastrointestinal symptoms (vomiting), being the predominant chemotherapy-related toxicity event. Regarding the hematologic toxicity of EMA/CO, the incidence rates of grade 3–4 neutropenia, thrombocytopenia, and anemia were 6.9–19.5%, 4.6%, and 2.3%, respectively [15]. Some studies have reported that the probability of single-agent chemotherapy resistance is significantly greater for a FIGO 2000 score of 5–6 compared to those with scores 1–4 [16,17]. This is considered indicative of high-risk GTN chemotherapy. Additionally, for high-risk GTN, regimens such as FAEV, or combination of 5-FU plus Act-D can also be used [18].

In our study, 1 patient, aged 42 years, with no fertility requirements, underwent a hysterectomy after recurrence and remission following 4 courses of an EMA/CO regimen. Surgery is recommended for adjuvant chemotherapy, mainly to control significant bleeding, remove drug-resistant lesions, reduce tumor burden, and shorten the course of chemotherapy 2 [19]. Hysterectomy is an alternative surgical regimen for patients at a high-risk of postmolar GTN, when fertility is not a concern. However, systemic chemotherapy, as opposed to surgery, is typically the first-choice strategy for treating lung metastases [20,21].

5. Conclusions

In our study clearly reveals the satisfactory efficacy and low chemotherapeutic toxicity of low-dose 5-FU in the treatment of GTN. This provides an alternative reference regimen for the treatment of GTN in both low-risk and high-risk cases. In future studies, we plan to analyze a larger sample size to explore this further, especially in the context of treating high-risk GTN.

Availability of Data and Materials

Availability of Data and Materials obtained through the corresponding author's email.

Author Contributions

CL and PO were responsible for analyzing the data, and composing the manuscript. MX and YT were devoted to acquiring and analyzing of the data. YT and MX were contributed to reviewing the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript, and confirmed the authenticity of all the raw data.

Ethics Approval and Consent to Participate

In this study, informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Zhuzhou Central Hospital (approval number: ZZCHEC2021124-01).

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Conflict of Interest

The authors declare no conflict of interest.

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