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Study of Low-Risk GTN Patients Resistant to First-Line Chemotherapy with MTX in a Tertiary Hospital Center

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ABSTRACT

Background & Objective: This study aimed to determine the response rate and related factors for resistance to single-agent chemotherapy in low-risk GTN patients.

Materials & Methods: In a single-center retrospective descriptive study, all patients diagnosed with low-risk gestational trophoblastic neoplasia, referring to a tertiary hospital center in Mashhad, Iran, between 2013 and 2023, were included. Clinical data were extracted from the hospital registry system. Resistance to first-line single-agent chemotherapy was considered the primary result.

Results: Out of 1015 cases of GTD, 135 cases of gestational trophoblastic neoplasia (13.3%) were recognized. 124(91.8%) patients were diagnosed with low-risk GTN. From low-risk GTN, 37(29.8%) patients received single-agent weekly methotrexate (50 mg/m^2 IM), while 87(70.16%) patients received 8 days of MTX-folinic acid as first-line treatment. 48.6% (N=18/37) did not respond to weekly MTX, and 18.4) patients did not respond to eight days of MTX-folinic acid. All these patients receive second-line chemotherapy. 72.6% (n = 90/124) achieved a complete response on first-line chemotherapy, and 34(27.4%) patients received actinomycin-D in the second line. The mean B-HCG titer before administration of actinomycin-D for 73.5% (n=25/34) patients was 294.4 IU/ml. In the second line, a complete response was achieved in 76.47% (n=26) while 23.53% (n=8) of patients got 3rd-line chemotherapy. The complete response rate for all low-risk GTNs was 100%.

Conclusion: Higher pretreatment serum hCG level, stage II-III, FIGO score 5-6, pathology Choriocarcinoma, and previous-term pregnancy were the risk factors of resistance to first-line chemotherapy with Methotrexate, highlighting the need for precise follow-up of patients with these criteria during the first line on single-agent chemotherapy.

Keywords: Gestational trophoblastic neoplasia, Resistance chemotherapy, Methotrexate, Actinomycin, Molar pregnancy

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1. Introduction

Gestational Trophoblastic Neoplasia (GTN) encompasses the malignant forms of Gestational Trophoblastic Disease (GTD), namely choriocarcinoma, invasive mole, epithelioid trophoblastic tumor, and placental site trophoblastic tumor. If left untreated, these tumors can spread to other parts of the body and become life-threatening due to their metastatic features **(1)**. While GTN most commonly arises from hydatidiform mole, it can also develop following abortion, ectopic pregnancy, or preterm or term gestation **(2)**.

The exact prevalence of Gestational Trophoblastic Neoplasia (GTN) is challenging to determine due to the variability in data regarding the total number of pregnancies and trophoblastic diseases. The remaining 25% can arise after preterm or term gestation **(3)**. GTN that emerges after a molar pregnancy is predominantly invasive mole or choriocarcinoma, with rare

occurrences of Placental-Site Trophoblastic Tumor (PSTT) or Epithelioid Trophoblastic Tumor (ETT). Around 15% of patients with complete molar pregnancy exhibit local invasion, and 5% develop metastatic disease **(4,5)**.

Prompt diagnosis of Gestational Trophoblastic Neoplasia (GTN) is crucial for successful treatment. Delays in diagnosis can lead to metastatic disease, necessitating more intensive and potentially harmful therapies and a poorer prognosis **(6,7)**. The excessive production of beta-human chorionic gonadotropin (β-hCG) by GTN cells enables serum β-hCG levels to diagnose, monitor treatment progress, and evaluate treatment outcomes **(8)**. While Gestational Trophoblastic Neoplasia (GTN) is highly responsive to chemotherapy, it's crucial to distinguish between patients who respond to single-agent therapy and those who require more aggressive multi-agent regimens for remission **(9,10)**. To address this need, the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) developed a combined anatomical staging and clinical prognostic risk scoring system that identifies patients with a higher risk of resistance to single-agent chemotherapy. Patients with a WHO/FIGO risk score of ≤ 6 or stage 1 are categorized as low-risk GTN and treated with single-agent chemotherapy. In contrast, those with a score > 7 or stage 4 are classified as high-risk GTN and receive multi-agent chemotherapy **(11)**.

Approximately 95% of patients with a Hydatidiform Mole (HM) who develop neoplasia have a low risk of persistent tumor growth. While low-risk GTN is generally considered curable, reported primary remission rates of 49 to 93% highlight the treatment challenges and the various factors influencing its effectiveness **(12)**. For most patients, single-agent chemotherapy with methotrexate or actinomycin is the preferred treatment approach. If the first-line therapy fails, typically due to resistance, it can be readily followed by second-line or, occasionally, third-line chemotherapy, leading to an almost 100% overall survival rate **(3)**. There are few epidemiological studies illustrating the characteristics of patients in different populations. This study aimed to determine the response rates and related factors of single-agent chemotherapy resistance in low-risk GTN patients.

2. Materials and Methods

Study population and procedure

In a single-center retrospective descriptive study, all patients diagnosed with gestational trophoblastic neoplasia based on clinical and histological data, referring to Ghaem Hospital in Mashhad, Iran, between 2013 and 2023, with a registry system, were included in the project. Using the International Federation of Gynecology and Obstetrics (FIGO) cancer committee scoring and staging system, the participants were classified as low risk and high-risk. In this study, a score of 0 to 6 was considered low-risk, indicating a favorable prognosis and the potential for effective treatment with single-agent chemotherapy using Methotrexate (MTX).

Data were extracted and recorded based on a pre-designed checklist using patient files and the HIS system, which includes demographic information, age, parity, BMI, primary tumor pathology, FIGO score, stage, type of treatment, type of surgery, type of Chemotherapy, and the mean number of chemotherapy courses, number of consolidation courses and history of last pregnancy.

The primary result was the cure rate with MTX as first-line single-agent chemotherapy. Primary Resistance to single-agent chemotherapy was defined as either a similar β-HCG level (within 10% variation) for 3 treatment cycles or if β-HCG level rises (>10%) for 2 treatment cycles. Patients were followed up with monthly β-HCG tests for a year after 3 consecutive normal assays to monitor for recurrence of disease. The stage was performed based on clinical, imaging, and laboratory data, including physical examination, serum β-hCG level, complete blood count, liver and kidney function tests, chest X-ray, pelvic Doppler ultrasound, and sometimes CT scan of the chest or abdominal-pelvic.

Patients with resistance to first-line single-agent MTX chemotherapy (34 cases) were compared with patients who responded to initial single-agent MTX chemotherapy (90 controls).

Statistical Analysis

The data was analyzed using SPSS software. A t-test or Mann-Whitney test was used to compare means, and chi-square was used to check frequencies. A significant level of less than 0.05 was considered.

3. Results

From 1015 cases of GTD, 135 patients were diagnosed with GTN in Ghaem Hospital in 10 years. Of 135 GTN cases, 11 were high-risk patients, and 124 were diagnosed with low-risk GTN. Table 1 reports the characteristics of the study population. 58.8% of low-risk GTN patients were under 40, and 41.12% were over 40. In terms of body mass index, 70.9% were in the normal range **(18-24)**, 20.1% were overweight **(24-29)**, and 8% were obese (above 30). 73.3% of patients had a FIGO score of 4 or less, and 26.6% were 5 and 6 (Table 1). 91.9% of patients were in stage I, 2.3% were in stage II, and 4.8% were in stage III. Pathological diagnosis indicated 43.4% of the patients had complete mole, 37.5% partial mole, 4.4% invasive mole, and 5.9% choriocarcinoma. Also, 10.4% had an initial β-hCG titer less than 1000 UI/ml, 20.9% ranged from 1000 to 10,000 UI/ml, 16.9% ranged from 10,000 to 100,000 UI/ml, and 51.6% were higher than 100,000 UI/ml. The type of surgery was curettage suction in 95.16% and primary hysterectomy in 4.8%. The type

of last pregnancy was the term in 7.2%, EP in 2.4%, abortion in 2.4%, and mole in 87.9%.

All patients received first-line MTX chemotherapy (8-day MTX-folinic acid or weekly 50mg/m² IM regimen) with an average of 5.08±1.04 courses for the chemo-resistance group and 5.83±1.02 for the chemo-sensitive group (P=0.0004). In the first-line chemo-resistance group, 52.9% of the patients had received a weekly MTX regimen, and 47% received the 8-day regimen. Of all patients that received weekly MTX as the first line, 48.6% (N=18/37) did not respond, while 18.4% (18.4% (N=16/87) patients did not respond to eight days MTX-Folinic acid (P<0.05). The second line of chemotherapy with actinomycin was performed in the first-line chemotherapy-resistant group. In the first-line resistant group, the average number of courses of actinomycin until undetectable B-HCG was 6.8±1.4 (Table 2).

The results of comparing chemo-resistant and chemo-sensitive patients are summarized in Table 3. Chemo-resistant patients had a significantly higher initial β-hCG level than chemo-sensitive patients (P<0.05). Also, these patients were in higher stages and had higher FIGO scores (scores 5-6) (P<0.05). The mean B-HCG titer before administration of Actinomycin-D for 73.5% (n=25/34) of patients was 294.4 IU/ml, and for 20.5% (n=7/34) of patients, it was 3834 IU/ml. 5 patients (20%) with B-HCG titer <1000 (mean: 294.4 IU/ml) and 3 patients (42.8%) with B-HCG titer 1000-10000 IU/ml) (P=0.02) have resistance to actinomycin-D. The mean number of second-line actinomycin chemotherapy cycles was 6.8±1.4. The mean number of consolidations actinomycin chemotherapy cycles after normalized B-HCG titer wasssss 1.02. The rate of choriocarcinoma diagnosis in chemo-resistant patients was significantly higher than that of chemo-sensitive patients (P<0.05). Other factors, body mass index, age, parity, and types of molar pregnancy, did not show any significant difference between groups (P>0.05).

Out of 34 cases resistant to the first line of chemotherapy with MTX, eight patients (23.5%) were also resistant to the second line of chemotherapy with actinomycin. A combination chemotherapy regime with EMA-CO was prescribed for them, and all eight patients finally achieved a negative B-HCG titer. In the first year of follow-up, one of the 124 patients with low-risk GTN had a recurrence, which was subjected to salvage therapy and partial lobectomy of the right lung. Finally, the beta titer was negative, and the patient had no recurrence for 12 months. The complete response rate for all low-risk GTN was 100%.

Table 1. Study population characteristics (low-risk GTN)

Variable		Number of patients (n=124)	Percentage (%)
Age	<40	73	%58.8
	≥40	51	%41.12
Pathology	Complete Molar	59	%43.4
	Partial Molar	51	%37.5
	Mole invasive	6	%4.4
	Choriocarcinoma	8	%5.9
BMI	Normal (18-24)	88	%70.9
	Overweight (25-29)	25	%20.1
	Obese (≥30)	11	%8
serum hCG level (UI/ml)	<1000	13	%10.4
	1000-10,000	26	%20.9
	10,000-100,000	21	%16.9
	≥100,000	64	%51.6
FIGO anatomical staging	I	114	%91.9
	II	4	%3.2
	III	6	%4.8
FIGO scores	≤4	91	%73.3
	5-6	33	%26.6
Surgery	Curettage	115	%84.6
	Hysterectomy	6	%4.8
Type of last pregnancy	Term	9	7.2%
	Ep	3	2.4%
	Abortion	3	2.4%
	Mole	109	87.9%

Table 2. Treatment procedure of the study population

2-A:

Chemotherapy	Weekly MTX	8 days MTX-Folinic acid
First-line chemoresistance (N=34)	18(%52.9)	16(%47.0)
First-line chemo-sensitive (N=90)	19(%21.1)	71(%78.9)

2-B:

	Chemo-resistance	Chemo-sensitive
Number of first-line chemotherapy cycles (mean±SD)	5.08±1.04	5.83±1.02

2-C:

Number of second-line actinomycin chemotherapy cycles (mean±SD)	6.8±1.4
Number of consolidations actinomycin chemotherapy cycles (mean±SD)	2±1.02

Table 3. Comparing characteristics of the study population between chemo-resistant and chemo-sensitive patients

Variables		Chemo-resistance (N=34)	Chemo-sensitive (N=90)	P-value
Age (years) *		37.52±13.23	34.35±11.73	0. 20
Pre-treatment serum hCG level (UI/ml) *		32941±1059	30968±1070	<0.001
BMI *		23.5±3.4	22.9±3.6	0.73
Parity *		3.2±2.6	2.37±1.4	0.30
History of molar pregnancy	Yes	3(8.8%)	19(21.1%)	0.11
	No	31(91.1%)	71(78.8%)	
Stage	I	24(%70.5)	90(%100)	
	II-III	10(%29.4)	0(0)	<0.001
FIGO score	≤4	18(52.9%)	56(62.2 %)	
	5-6	16(47.0%)	34(37.7%)	<0.001
Surgery	Suction & Curettage	31(91.17%)	87(96.6%)	
	Primary Hysterectomy	3(8.82%)	3(3.3%)	0.31
Pathology	Complete Mole	14(41.1%)	45(50%)	
	Partial Mole	13 (38.2%)	38(42.2%)	
	Invasive Mole	2 (5.8%)	4(4.4%)	
	Choriocarcinoma	5(14.7%)	3(3.3%)	<0.001
Type of last pregnancy	Term Ep Abortion GTD	5(14.7%) 2(5.88%) 1(2.94%) 26(76.47%)	4(4.4%) 1(1.1%) 2(2.2%) 83(92.2%)	<0.001
Mean B-HCG titer before actinomycin-D	<1000(mean:294.4 IU/ml) 1000-10000(mean:3834 IU/ml) >10000(mean:38665 IU/ml/)	25(73.5%) 7(20.5%) 2(5.8%)		

* Mean±SD

4. Discussion

Gestational Trophoblastic Neoplasia (GTN) classified as low risk under the FIGO/WHO scoring system (0-6) has an exceptional cure rate, with an overall survival rate approaching 100%. For most low-risk GTN patients, first-line single-agent chemotherapy

with either methotrexate or actinomycin-D is the recommended treatment, demonstrating overall complete Human Chorionic Gonadotropin (hCG) response rates ranging from 60% to 90% in predominantly retrospective, non-randomized studies. However, approximately 25% to 30% of low-risk GTN patients may develop resistance to initial single-agent chemotherapy, with elevated FIGO scores, choriocarcinoma diagnosis, higher pretreatment hCG levels, and the presence of metastatic disease being associated with increased resistance **(13)**. However, there are few epidemiological studies illustrating the characteristics of the patients in different populations.

Summary of Main Results

This study aimed to determine the complete response rate and related factors of single-agent chemotherapy resistance with MTX in a group of low-risk GTN patients in Northeast Iran in the tertiary hospital center for the first time. Our findings indicated a complete response of 72.6% in the first line of therapy with methotrexate and 76.5% in the second line following ACT-D consumption, while 6.4% of all low-risk GTN patients (23.5% first-line chemo-resistance with MTX) went on to get 3rd-line chemotherapy. One patient had recurrence during follow-up. A 53-year-old woman with vaginal bleeding and a serum B-HCG titer 1500 IU/ml, a 3 cm cystic mass in the uterine cavity on the ultrasound, and a normal chest x-ray underwent suction and curettage. The pathology report was for the complete mole. At the serial weekly follow-up, serum B-HCG increased in the third week, and a total hysterectomy was done. The pathology report was atrophic endometrium. In the follow-up serum, the B-HCG titer was negative for three consecutive weeks, and B-HCG was checked monthly. In the ninth month, B-HCG had risen (219 IU/ml), and metastasis workup was negative. MTX (50 mg/m2 IM, weekly) was prescribed. After 4 courses, B-HCG was raised, and the agent was changed to actinomycin (1.25 mg/m² every 2 weeks). She received actinomycin for 4 cycles with 2 consolidation courses. After 4 months of follow-up, the serum B-HCG titer had risen (614 IU/ml). Metastasis workup was done. Hypermetabolic metastasis in the anterior segment of the lower lobe of the right lung was detected. Combined chemotherapy with EMA-CO was prescribed for 4 cycles with 5 consolidation courses. After 3 months' follow-up, serum B-HCG again had risen (256 IU/ml), and EMA-EP chemotherapy was prescribed for 3 cycles with 5 consolidation courses. Serum B-HCG titer was raised after 3 months, and right lung partial lobectomy with TP-TE chemotherapy was done for 3 cycles and 4 consolidation courses. B-HCG has been negatived for 12 months.

Higher pretreatment serum β-hCG level, stage II-III, FIGO score 5-6, previous term pregnancy, and Choriocarcinoma were the risk factors of resistance to first-line therapy by methotrexate.

Results in the Context of Published Literature

Like the previous investigations reporting rates of complete response to methotrexate as a first-line treatment of about 70% to 79% **(4,14)**, the present study found a complete response rate of 72.6% following methotrexate consumption. However, this range is wide, as in another study remission after the first line of monotherapy using Methotrexate/folinic acid was 95.1% **(15)**. Although several studies used actinomycin in some patients as the first line of the treatment program, in the studied population, due to the higher toxicity profile of Actinomycin-D we chose MTX for first-line single-agent chemotherapy in low-risk GTN patients and all subjects were under Methotrexate regimens. According to the study findings, the rate of transitioning to second-line monotherapy due to resistance to first-line treatment was 27%, which aligns with the rates reported for the use of methotrexate **(16,17)**. Moreover, the remission rate after second-line actinomycin was 76.5%, a little lower than the previous investigation. A study on patients failing Methotrexate therapy reported that the response rate for Act-D was 82.02% **(18)**.

Numerous investigations have examined factors that predict resistance to methotrexate or actinomycin monotherapy. The present study identified high serum hCG level, stage 2,3, FIGO score 5-6, previous term pregnancy, and Choriocarcinoma as risk factors of Methotrexate resistance. While the FIGO score is a widely used multi-marker factor to assess the risk of treatment failure with single-agent chemotherapy, our findings indicate that individual markers also play a significant role in predicting resistance. A previous study found a strong association between primary tumor size, presence of metastases, and pre-treatment beta-human chorionic gonadotropin (β-hCG) levels with resistance to treatment **(16)**. Moreover, pretreatment hCG, uterine artery pulsatility index, and presence of lung metastases were introduced as predictive of resistance to first-line therapy in women with low-risk GTN **(19-21)**. As many studies were conducted on low samples, with different demographics and clinicopathological information, and various treatment regimens, these findings are controversial and need to be confirmed using large cohort studies, applying multivariable analysis, or systematic meta-analyses.

The present study indicated that 32% (16/50) of patients with FIGO score 5-6 were resistant to monotherapy by Methotrexate, almost like other investigations, with a resistance rate of 25% to 40% for these patients **(22,23)**, whereas some studies have reported higher resistance rate ranging between 60% to 80% of patients with a score of 5-6 **(24-26)**. However, consistently, all patients who experienced treatment failure with first-line single-agent chemotherapy were cured with sequential single-agent chemotherapy or multiagent chemotherapy with or without the use of salvage surgery **(23)**.

Strengths and Weaknesses

This study, which was conducted at a single institution and utilized retrospective data obtained from electronic medical records, was a non-randomized retrospective investigation with a small sample size. In this study, we did not compare high-risk cases directly treated by EMACO to those subsequently treated by Act-D and EMA-CO after first-line MTX failure.

We determined the complete response rate and related factors of single-agent chemotherapy resistance with MTX in full detail in a group of low-risk GTN patients in Northeast Iran in the tertiary hospital center for the first time.

Implications for Practice and Future Research

It must emphasize the need for further prospective study with precise study design to validate our findings through high-quality, large-scale, multi-center randomized controlled trials.

5. Conclusion

The incidence rate of low-risk GTN was 91.85% in the considered population of gestational trophoblastic neoplasia, with a response rate of 72.6% after monotherapy using Methotrexate chemotherapy and 76.47% after second-line actinomycin chemotherapy. Due to the higher toxicity profile of Actinomycin-D, we chose MTX for first-line single-agent chemotherapy in low-risk GTN patients. The complete response rate for Actinomycin-D as the secondary line for chemoresistance to MTX was 76.5%, so second-line actinomycin chemotherapy is recommended. Higher pretreatment serum hCG level, stage II-III, FIGO score 5-6, pathology Choriocarcinoma, and previous-term pregnancy were the risk factors of resistance to first-line chemotherapy with Methotrexate, highlighting the need for precise follow-up of patients with these criteria during the first line on single-agent chemotherapy.

6. Declarations

Acknowledgments

None.

Ethical Considerations

Considering Iran's national committee for ethics in biomedical research lows. It’s not necessary to get an Ethical Approval code for narrative review

Authors' Contributions

E.S. was involved in the interpretation and collection of data. E.S. M.F. B.H. M.H.M. F.H.S. B.D. and Z.Y. were involved in writing and editing the manuscript. All the authors reviewed the paper and approved the final version of the manuscript.

Conflict of Interest

There are no conflicts of interest for authors in this study

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