Response to Initial Treatment of Low and Intermediate Risk Gestational Trophoblastic Disease with Methotrexate and Folinic Acid

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Objectives: *To evaluate the response and toxicity of methotrexate and folinic acid given as primary treatment of low and intermediate risk gestational trophoblastic disease (GTD).*
Material and Method: *Medical records review was performed in patients who received methotrexate and folinic acid as a primary treatment of low and intermediate risk persistent GTD between January 1992 and December 2001. Response was defined as decline of beta human chorionic gonadotropin (hCG) to ≤ 5 mIU/ml (remission) after methotrexate and folinic acid treatment. Response rate was estimated and factors associated with response were evaluated.*
Results: *Ninety four eligible patients were treated with intramuscular methotrexate and folinic acid. Complete remission was achieved in 64 cases (68%, 95%CI 58-78%). Mucositis (6.4%) and hepatotoxicity (6.4%) were the most common toxicity of methotrexate in the present study and none of these toxic effects was life threatening. Factors associated with response were initial serum hCG ≤ 10,000 mIU/ml and stage I disease.*
Conclusion: *Methotrexate with folinic acid is effective treatment for low and intermediate risk GTD with minimal severe toxicity.*

Keywords: *Gestational trophoblastic disease, Methotrexate with folinic acid, Response, Toxicity*

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Gestational trophoblastic disease (GTD) is among the rare human tumors that can be cured even in the presence of widespread dissemination[1,2]. Its classification includes a spectrum of interrelated tumors, including complete and partial hydatidiform mole, placental-site trophoblastic tumor, invasive mole, and choriocarcinoma. All have the potential to persist and to metastasis to local or distant structures[3].

The worldwide incidence of trophoblastic disease ranges between 0.5-8.3 per 1000 live births[4]. In Siriraj Hospital, the incidence of molar pregnancy in 2002 is 4 in 1000 deliveries. Most of the worldwide GTD patients have no further problems following evacuation of the mole, but about 5-20% require chemotherapy for persistent disease[2,3,5].

There have been several suggested modifications or staging protocols for patient classification, such as FIGO staging and WHO scoring system. In Siriraj Hospital, persistent GTD patients were scored by modified WHO scoring system. If the score was in the low risk (score ≤ 4) or intermediate risk (score 5-7) group, the patients would be treated with low dose methotrexate and folinic acid. Cure rate of GTD is high, therefore single agent treatment is the priority without compromising outcome.

The aim of this study was to evaluate the response and toxicity of low dose methotrexate with folinic acid treatment in patients with non-high risk persistent GTD (score ≤ 7).

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Material and Method

Over a 10-year period from January 1992 to December 2001, the authors reviewed the medical records of all patients who were diagnosed with non-high risk persistent GTD (score ≤ 7) and treated with methotrexate and folinic acid as primary therapy at the Gynecologic Oncology division, Siriraj Hospital, Mahidol University. Patients were scored according to the modified WHO scoring system (Table 1).

Data collection included age, gravidity, parity, antecedent pregnancy, duration of disease, initial hCG level, histological diagnosis (if available),staging (FIGO staging[6]), number of courses of chemotherapy, time required to achieve remission, surgical procedure (hysterectomy), response to treatment, drug toxicities, and length of follow up. Modified WHO prognostic scores were also calculated and were retrospectively assigned when all necessary information was available in patients treated before widespread use of the scores.

The diagnosis of persistent GTD was based on clinical, tumor marker, histopathologic and radiographic findings after a molar pregnancy or other antecedent gestation[7]. The patients should have a persistent plateau (the change of hCG less than 10% for at least 3 consecutive weeks) or rising 10% or more of the pre-treatment hCG values for at least 2 weeks.

Treatment Protocol

The patients received intramuscular methotrexate 50 mg on alternative days (day 1, 3, 5, 7) with folinic acid 15 mg at alternative days (day 2, 4, 6, 8) every two weeks as primary treatment. Serial quantitative beta human chorionic gonadotropin (hCG) levels were determined before each treatment course. Complete remission was diagnosed after three consecutive weekly hCG levels were within normal range (< 5 mIU/ml). After remission, hCG levels were determined monthly for 12 months,every other month for 6 months, every 3 months for the next 12 months, and every 6 months thereafter[8].

Chemotherapeutic agents were changed when resistance or severe toxic reaction to drug occurred. Resistance was diagnosed by two static (the change of hCG less than 10% for 3 consecutive courses) or an increase (20% or more rising) in hCG level. Toxic reaction was diagnosed by history, physical examination, hematologic studies and blood chemistry. If the toxic reaction was considered minor, the same therapy was usually continued with a 20% dose reduction[8].

Toxicity

Complete blood counts with platelet counts and serum glutamic-oxaloacetic transaminase (SGOT) levels were measured prior to chemotherapy and during the follow-up period. The criteria for hematologic and hepatic toxicity were as follows: granulocyte count < 1,500/ml was defined as neutropenia, platelet count < 100,000/ml as thrombocytopenia and SGOT > 50 units as hepatic toxicity[7]. Patients were routinely asked about the development of stomatitis, conjunctivitis, rash, alo-pecia, marked nausea and vomiting, and pleurisy, and their response was noted in their records.

Statistical analysis

The association between response to treatment and following factors; age, stage, score and initial serum hCG were determined with Chi-Square as appropriate. Statistical significance was indicated when p value <0.05.

Table 1. Modified WHO scoring system that is used in Siriraj Hospital

Prognostic factors	SCORE			
	0	1	2	4
Age (years)	≤39	>39	-	-
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	-
Months from last pregnancy	<4	4-6	7-12	>12
Pretreatment hCG (mIU/ml)	$<10^3$	10^3-10^4	$>1^4$-10^5	$>10^5$
Largest tumor size (cm)	-	3-4 cm	≥5 cm	-
Site of metastasis	-	Spleen, kidney	Gastrointestinal tract, liver	Brain
Number of metastasis	-	1-4	5-8	>8
Prior chemotherapy	-	-	Single drug	Two or more drugs

≤ 4 low risk; 5-7 intermediate risk; ≥ 8 high risk

Results

Between January 1992 and December 2001, a total of 94 patients with non-high risk GTD were treated with methotrexate and folinic acid as first line chemotherapy. The demographic characteristics are presented in Table 2.

The average age of the patients was 29 years. Among the 94 patients, 67 (71.3%) had FIGO stage I disease, 6 (6.4%) had stage II disease, 19 (20.2%) had stage III disease, and 2 (2.1%) had stage IV disease. Median score was 2 (range, 0-7). Mean serum β-hCG before start treatment was 27,275 mIU/ml. Median course of methotrexate was 6 (range, 2-14). Median time of follow-up was 29 months (range, 1-110).

Complete remission from first-line treatment with methotrexate was achieved in 64 patients (68%, 95%CI 58-78%). Remission rate of low and intermediate risk patient was 72.5% and 42.9% respectively. Thirty patients (31.9%) received second-line salvage chemotherapy. Eighteen of them (60%) were treated with Actinomycin D, 6 (20%) were treated with MAC (Methotrexate, Actinomycin D, Chlorambucil), 4 patients received EMACO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine). One patient received etoposide and one patient received MAE (Methotrexate, Actinomycin D and Etoposide). In those who had first and second-line treatment, complete remission was attained in 91 patients (96.8%). The reasons for second line chemotherapy were resistance to methotrexate in 30 cases and rising SGOT in 1 case. Three patients needed third-line chemotherapy (1- MAC, 1- etoposide, 1- EMA-CO). Overall response rate was 100% after third-line chemotherapy.

Table 3 shows response to methotrexate ac-cording to the patients characteristics. Patients with initial hCG > 10,000 were more likely to responsed compared with hCG > 10,000 (80% and 55% respectively, p = 0.014).

With regard to FIGO staging, a significant higher response was observed among patients with stage I compared to stage II–IV (p = 0.004). Age < 40 years and score ≤ 4 also showed a higher response but did not achieve statistical significance.

Table 2. Characteristics of 94 patients

	Median (range)
Age (Mean ± SD, years)	29 ± 9
No. of courses of methotrexate	6 (2-14)
Follow up time (months)	29 (1-110)
Time to remission (weeks)	10 (6-26)
	N (%)
Stage	
I	67 (71.3%)
II	6 (6.4%)
III	19 (20.2%)
IV	2 (2.1%)
Score	
≤4	80 (85.1%)
5-7	14 (14.9%)
Initial serum -hCG (mIU/ml)	
≤10,000	47 (50.0%)
> 10,000	47 (50.0%)

Table 3. Response to methotrexate according to patients' characteristics

		Response N (%)	No response N (%)	p value
Age (years)	<40	57 (71.3%)	23 (28.7%)	0.585
	≥40	7 (50.0%)	7 (50.0%)	
Initial serum	≤10,000	38 (80.9%)	9 (19.1%)	0.014
hCG (mIU/ml)	>10,000	26 (55.3%)	21 (44.7%)	
FIGO Stage	I	53 (79.1%)	14 (20.9%)	0.004*
	II	2 (33.3%)	4 (66.7%)	
	III	8 (42.1%)	11 (57.9%)	
	IV	1 (50.0%)	1 (50.0%)	
Score	≤4	58 (72.5%)	22 (27.5%)	0.058
	>4	6 (42.9%)	8 (57.1%)	
Total		64 (68.0%)	30 (32.0%)	

*compare stage I to stage II-IV

Table 4. Side effects of treatment (n = 94)

	N (%)
Nausea/vomiting	1 (1.1%)
Mucositis	6 (6.4%)
Hepatotoxicity	6 (6.4%)
Thrombocytopenia	1 (1.1%)
Neutropenia	3 (3.2%)
Hyperpigmentation	1 (1.1%)
No side effect	76 (80.9%)

Methotrexate toxicity occurred in 18 patients (19.2%), none of the toxic effect was life threatening. Mucositis and hepatotoxicity were the most common toxicity. Three patients had neutropenia and one patient had thrombocytopenia.

Discussion

Gestational trophoblastic disease is extremely responsive to chemotherapy[9]. Therefore, in addition to achieving long-term cure, minimizing both long and short-term toxicity must be an important factor in evaluating the treatment. It is difficult to compare treatment results for persistent GTD across the world because of the heterogeneity of patient groups selected for single or multiagent chemotherapy, and because of the wide varieties in chemotherapy regimen used.

Since the initial experience of using methotrexate in the treatment of trophoblastic disease in the 1950s, it has proved to be an active agent with minimal severe toxicity in the treatment of low risk patients.

For many years,UK centers have used the low dose intramuscular methotrexate regimen. Initial report on 487 patients from Charing Cross[10] and 115 from Sheffield[11] confirmed its efficacy, although it was noted that up to 30% of patients needed second line treatment due to resistance or less frequently toxicity.

In the present study, the overall response rate of low and intermediate risk were 68% (95%CI, 58-78%). The response rate was equal to previous studies by Khan[3], Roberts[8] and Berkowitz[12] who reported an overall response rate of low and intermediate risk GTD patients whose initial treatment with methotrexate and folinic acid was 72%, 65.6% and 68.2%,respectively.

When the response rate of low and intermediate risk GTD patients were considered separately, the response rate of low and intermediate risk was 72.5%, and 42.9% respectively. Compared to a previous study, Goldstein[6] reported that single agent chemotherapy produced remission in 55 out of 66 (87%) and 13 out of 17 (76%) of low and intermediate risk patients respectively. Other authors have also reported remission rates of over 80% for this group of patients[13-15].Exposure to combined chemotherapy, but not methotrexate and folinic acid was reported to, increase the risk of developing second tumors[9].Intermediate risk patients could be treated with both single or multiple-agents. In the present study, intermediate risk patients (score 5-7) are treated in the same way as those who were low risk.

The statistically significant factors in the present study that associated with response to methotrexate and folinic acid in low and intermediate risk GTD patients are initial serum hCG level and staging. Compared to Roberts' study[8], patients in whom initial therapy failed tended to be older, had higher pretreatment hCG levels and higher WHO scores than those successfully treated, but the only statistically significant finding was staging.

Most patients had minimal side effects. These side effects were mucositis (6.4%), hepatotoxicity (6.4%), neutropenia (3.2%), and thrombocytopenia (1.1%). Compared a to previous study, Berkowitz[12] reported in 1986 that methotrexate when administered with folinic acid was associated with granulocytopenia, thrombocytopenia, and hepatotoxicity in 5.9%, 1.6%, and 14.1% of patients, respectively.

Conclusion

Patients with a score ≤ 7 according to modified WHO scoring can be successfully treated with methotrexate and folinic acid as first line chemotherapy. A high cure rate can be achieved without greater morbidity. Methotrexate remains the treatment of choice for pa-tients with low risk GTD. With close monitoring of hCG levels and with the institution of sequential single agent chemotherapy or combination chemotherapy as soon as drug resistance is diagnosed, the cure rate for this disease should approach 100%.

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การตอบสนองต่อการเริ่มรักษา gestational trophoblastic disease ในกลุ่มความเสี่ยงต่ำและปานกลาง ด้วย methotrexate ร่วมกับ folinic acid

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วัตถุประสงค์: เพื่อประเมินการตอบสนอง และผลข้างเคียงของการใช้ methotrexate ร่วมกับ folinic acid ในการเริ่มรักษา gestational trophoblastic disease (GTD) ที่เป็นกลุ่มความเสี่ยงต่ำและปานกลาง

วัสดุและวิธีการ: ทำการทบทวนข้อมูลจากประวัติการรักษาของผู้ป่วยGTD ที่เป็นกลุ่มความเสี่ยงต่ำ และปานกลาง ที่ได้รับการรักษาด้วย methotrexate และ folinic acid ระหว่างเดือน มกราคม พ.ศ. 2535 ถึง ธันวาคม พ.ศ. 2544 โดยการตอบสนองต่อการรักษาหมายถึงระดับ beta human chorionic gonadotropin (hCG) ลดลงจนกระทั่งมีค่าไม่เกิน 5 mIU/ml หลังจากได้รับการรักษาด้วย methotrexate ร่วมกับ folinic acid แล้วประเมินอัตราการตอบสนองต่อการรักษาและปัจจัยที่มีความสัมพันธ์กัน

ผลการศึกษา: มีผู้ป่วย 94 คนได้รับการรักษาโดยการฉีด methotrexate ร่วมกับ folinic acid เข้ากล้าม พบว่าผู้ป่วย 64 คน (ร้อยละ 68, 95%CI 58-78%) ตอบสนองต่อการรักษา ผลข้างเคียงที่พบมากที่สุด คือ mucositis (ร้อยละ 6.4) และ hepatotoxicity (ร้อยละ6.4) และไม่พบผลข้างเคียงที่เป็นอันตรายถึงชีวิต ปัจจัยที่สัมพันธ์กับการตอบสนองต่อการรักษาในการวิจัยนี้คือ ระดับ hCG ที่มีค่าไม่เกิน 10,000 mIU/ml และการที่โรคอยู่ใน stage I

สรุป: Methotrexate ร่วมกับ folinic acid ใช้รักษา GTD ในกลุ่มความเสี่ยงต่ำและปานกลางได้ผลดี มีผลข้างเคียงเกิดขึ้นน้อยและไม่รุนแรง