

Treatment Results of Methotrexate and Folinic Acid as Primary Chemotherapy for Nonmetastatic Gestational Trophoblastic Neoplasia

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Objective: To evaluate the efficacy and toxicity of methotrexate and folinic acid (MTX-FA) chemotherapy in patients with nonmetastatic gestational trophoblastic neoplasia (NMGTN)

Material and Method: Between 1997 and 2003, a total of 67 patients with NMGTN received treatment at the Chiang Mai University Hospital. Of the 67 patients, 55 were initially treated with methotrexate 1.0 mg/kg intramuscularly (IM) on day 1,3,5, and 7 and folinic acid 0.1 mg/kg IM on day 2,4,6 and 8. Treatment courses were repeated every 14 days. Clinical characteristics and outcomes were analyzed.

Results: All 55 patients with NMGTN were cured. Of the 55 patients initially treated with MTX-FA, 49 (89%) achieved complete remission. Six (11%) patients developed methotrexate resistance, 3 were cured with actinomycin D, 1 were cured with 5-fluorouracil followed by etoposide, 2 required hysterectomy to attain remission. No serious toxicity was noted.

Conclusion: Methotrexate and folinic acid chemotherapy is highly effective and well-tolerated in treating patients with nonmetastatic gestational trophoblastic neoplasia.

Keywords: Gestational trophoblastic neoplasia, Choriocarcinoma, Methotrexate, Chemotherapy

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Gestational trophoblastic neoplasia (GTN) most commonly occurs after hydatidiform mole, but it may follow abortion, ectopic pregnancy, and normal pregnancy. The diagnosis of GTN is usually made on the basis of persistently elevated human chorionic gonadotropin (hCG) titers after surgical evacuation of a hydatidiform mole. The risk of malignant sequelae or GTN after molar gestation requiring further treatment ranged from 20-50%⁽¹⁻⁵⁾ depending on the criteria for diagnosis of persistent trophoblastic disease as evidenced by continued elevation of the hCG level, the severity of molar pregnancy, i.e. low or high risk, and the administration of chemoprophylaxis before termination of molar pregnancy.

The diagnosis of nonmetastatic GTN (NMGTN) after mole evacuation is usually based on a rising or plateauing hCG titer and metastatic workups show no evidence of extrauterine trophoblastic disease. Various chemotherapy regimens, e.g. methotrexate, actinomycin D, and etoposide have been used in the treatment of NMGTN with cure rates approaching 100%⁽⁶⁻¹³⁾.

The present study was a retrospective review of the authors' experience with the use of methotrexate and folinic acid as primary chemotherapy for NMGTN in Chiang Mai University Hospital. The effectiveness of this regimen as well as resistance and toxicity was evaluated, and overall cure rate of NMGTN was also determined.

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Material and Method

The medical records of 103 patients with gestational trophoblastic neoplasia (GTN) who were treated in Chiang Mai University Hospital between January 1997 and December 2003 were reviewed. The patient characteristics including age, antecedent pregnancy, pretreatment hCG level, pathologic diagnosis if known, type and number of course of chemotherapy, toxicity and treatment outcome were analyzed. Grading of toxicity was based on the Gynecologic Oncology Group Common Toxicity Criteria⁽¹⁴⁾.

After a diagnosis of GTN, metastatic investigations were carried out, including physical examination, chest x-ray, pelvic ultrasonography, computed tomography of the pelvis, abdomen, chest and brain when indicated. Complete blood count, serum hCG level, liver function and renal function tests were evaluated. Diagnosis of post molar NMGTN was primarily based on 2 consecutive risings (> 10%) or 3 consecutive plateauings (< 10%) of weekly hCG titers, and no metastasis was detected elsewhere.

Patients with NMGTN were initially treated with methotrexate 1.0 mg per kg intramuscularly every other day for 4 doses and folinic acid 0.1 mg per kg intramuscularly 24 hours after each dose of methotrexate. Treatment courses were repeated every 14 days or 7-day window. Chemotherapy was postponed in cases of grade 3 or 4 toxicity. Patients with abnormal liver function or methotrexate-resistant were treated with actinomycin D 12 ug per kg intravenously daily for 5 days every 2 weeks. Combination chemotherapy of methotrexate, etoposide, and actinomycin D were given to patients after failure of 2 sequential single agents.

Serial serum hCG levels were determined before each course of chemotherapy. Complete remission was diagnosed after 3 consecutive weekly hCG levels were within normal range. Additional 1 course of chemotherapy was given after the first normal hCG level. After remission, hCG levels were evaluated every 2 weeks for 3 months, every month for 3 months every other month for 6 months, and every 6 months thereafter. Temporary contraception, usually with birth-control pills was advised for 1 year after completion of chemotherapy.

Results

During the study period, 67 (65%), 8 (7.8%), and 28 (27.2%) patients were diagnosed as NMGTN, low-risk metastatic GTN, and high-risk metastatic GTN, respectively. The clinical features and treatment

Table 1. Baseline Characteristics (n = 67)

Clinical features	NMGTN
Age (years)	
Mean	29.2
Median	27.0
Range	15-53
Antecedent pregnancy	
Molar	63 (94.0%)
Abortion	2 (3.0%)
Term	2 (3.0%)
Pretreatment hCG (IU/L)	
Mean	86,245
Median	10,580
Range	20-1,031,500
Primary Treatment	
Methotrexate & Folinic acid	59
Actinomycin D	2
Hysterectomy	5
No treatment	1

methods of 67 patients with NMGTN are demonstrated in Table 1. Over 94% of cases followed molar pregnancy.

Of 67 NMGTN patients, 2 were initially treated and cured with actinomycin D for 2 and 4 courses respectively. Five patients underwent hysterectomy prior to initiation of chemotherapy, 3 for severe bleeding, and 2 (aged 46 and 53 years) for persistent elevation of hCG post molar pregnancy. These 5 patients were subsequently treated with 1 to 6 courses of methotrexate and folinic and achieved remission. One patient left the hospital without treatment and could not be contacted. The remaining 59 patients received methotrexate and folinic acid as primary chemotherapy, but 4 were lost to follow-up during treatment. Therefore, 55 patients were eligible for evaluation of treatment outcome.

Of 55 patients treated initially with methotrexate and folinic acid, 49 (89%) attained complete remission. The mean and median numbers of chemotherapy courses were 4.7 and 4 respectively, with a range of 1 to 9 courses. Of the 6 patients with resistance to methotrexate, 3 were cured with actinomycin D given for 3, 4 and 4 courses, respectively, 1 was cured with 4 courses of 5-fluorouracil followed by 3 courses of etoposide. One of the remaining 2 patients were treated with hysterectomy followed by 5 courses of etoposide to attain remission. Etoposide was used in this case because actinomycin D was not available in this

hospital at that time. The other one failed actinomycin D, combination of etoposide and cisplatin, and combination of etoposide, methotrexate and actinomycin D. She was cured with hysterectomy and specimens revealed placental site trophoblastic tumor.

Severe toxicity of chemotherapy requiring hospital admission, a change to another chemotherapeutic agent or dose reduction in subsequent course was not found. Five patients experienced mild stomatitis manageable with mouth care. No patient had abnormal liver function test during methotrexate and folinic acid treatment.

Discussion

Patients with NMGTN usually have a good prognosis, virtually all patients are cured with chemotherapy with or without adjuvant hysterectomy as shown in the present study and in previous reports^(7,12,13,14-17). The 55 patients treated initially with methotrexate and folinic acid in the present study had primary complete remission rate of 89% comparable to that of Berkowitz et al using the same regimen⁽¹⁸⁾. Six patients (10%) developed methotrexate resistance but could be cured later, 3 with single-agent actinomycin D, 1 with sequential 5-FU and etoposide, 1 with hysterectomy followed by etoposide and 1 with hysterectomy alone. Generally, methotrexate-resistant NMGTN are curable by subsequent various chemotherapeutic agents, although hysterectomy is required in some cases. Resistance to methotrexate was more frequently found in patients with pretreatment hCG levels > 50,000 IU/L, nonmolar antecedent pregnancy and clinicopathologic diagnosis of choriocarcinoma^(12,18). Of the 6 patients with methotrexate resistance in the present study, 1 had choriocarcinoma, 1 had placental site trophoblastic tumor and only 1 had hCG > 50,000 IU/L.

Methotrexate and folinic acid (MTX-FA) were selected to treat NMGTN in this hospital because of the reduced toxicity, i.e. hematologic, dermatologic and hepatic toxicities compared with methotrexate alone^(7,18,19). No serious toxicity was noted in the present study. Most of the toxicities were mild and manageable. Although some authors reported a higher incidence of methotrexate resistance in patients receiving MTX-FA (27.5%) compared with methotrexate alone (7.7%)⁽⁷⁾, the advantage of decreased toxicity was the authors' main reason to use MTX-FA for NMGTN patients. All methotrexate-resistant patients achieved complete remission with subsequent treatment in the present study.

Actinomycin D is a highly effective chemotherapeutic agents in the treatment of NMGTN^(10,11). This agent was used both as primary and secondary treatment in the present study. It is also an appropriate regimen for patients with liver or renal disease contraindicating methotrexate use. In the present series, 2 patients treated initially with actinomycin D attained complete remission, and 3 of 6 patients with methotrexate resistance were cured with actinomycin D alone.

In the present series, 3 patients underwent emergency hysterectomy for severe uterine bleeding and then attained remission after 4, 4, and 6 courses of MTX-FA respectively. Although adjuvant hysterectomy in patients with NMGTN has been reported to decrease the amount of chemotherapy courses required to achieve remission^(16,20), surgical intervention is usually restricted to removal of chemotherapy-resistant foci and control of hemorrhage and infection in emergency cases^(16,21). Adjuvant hysterectomy is considered unnecessary in treating NMGTN, since nearly all patients are cured with chemotherapy alone.

In conclusion, methotrexate and folinic acid chemotherapy appeared to be highly effective and well-tolerated in treating NMGTN.

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ผลการรักษามะเร็งเนื้อรกชนิดไม่แพร่กระจายด้วยยาเคมีบำบัด methotrexate และ folinic acid

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วัตถุประสงค์: เพื่อประเมินประสิทธิภาพและพิษของยาเคมีบำบัด methotrexate และ folinic acid ในการรักษาผู้ป่วยมะเร็งเนื้อรกชนิดไม่แพร่กระจาย

วัสดุและวิธีการ: ในช่วงปี พ.ศ. 2540 - พ.ศ. 2546 มีผู้ป่วยมะเร็งเนื้อรกชนิดไม่แพร่กระจายมารับการรักษาที่โรงพยาบาลมหาราชนครเชียงใหม่ ทั้งหมด 67 ราย ในจำนวนนี้มี 55 ราย ที่ได้รับการรักษาด้วยยา methotrexate 1.0 มก./กก. ฉีดเข้ากล้ามเนื้อในวันที่ 1, 3, 5 และ 7 ร่วมกับการให้ยา folinic acid 0.1 มก./กก. ฉีดเข้ากล้ามเนื้อในวันที่ 2, 4, 6 และ 8 โดยให้การรักษาทุก 14 วัน และวิเคราะห์ลักษณะทางคลินิกและผลการรักษา

ผลการศึกษา: ผู้ป่วยมะเร็งเนื้อรกชนิดไม่แพร่กระจายทั้ง 55 ราย หายจากโรค โดยผู้ป่วย 49 ราย (ร้อยละ 89) หายจากโรคด้วยการให้ยา methotrexate และ folinic acid อีก 6 รายที่เหลือ (ร้อยละ 11) ต้องต่อยา methotrexate แต่รักษาหายด้วยการให้ยา actinomycin D 3 ราย รักษาหายด้วยยา 5 - fluorouracil ตามด้วยยา etoposide 1 ราย และรักษาหายด้วยการตัดมดลูกออก 2 ราย ไม่พบว่ามีพิษของยาชนิดรุนแรง

สรุป: ยาเคมีบำบัด methotrexate และ folinic acid มีประสิทธิภาพสูงและมีพิษของยาไม่รุนแรงในการรักษาผู้ป่วยมะเร็งเนื้อรกชนิดไม่แพร่กระจาย
