Outcomes of Prophylactic Chemotherapy in Patients with High-Risk Hydatidiform Mole at Tu Du Hospital in Vietnam

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Abstract

Objective: To compare the incidence rate of gestational trophoblastic neoplasia in patients with high-risk hydatidiform mole between patients that receive prophylactic chemotherapy compared to patients that do not receive the treatment. Patients were evaluated and followed for duration of six months at Tu Du hospital.

Methods: A prospective cohort study that recruited all patients with high-risk hydatidiform mole admitted to Tu Du hospital between August 2012 through November 2013 and 56 patients underwent prophylactic chemotherapy with MTX-FA, while the other 112 patients did not. After six months, the results were evaluated by comparing the rate of gestational trophoblastic neoplasia among two groups.

Results: The incidence rate of gestational trophoblastic neoplasia between the group with prophylactic chemotherapy to the control group were 25% versus 14.3%. However, statistical significance was not found (p > 0.05; CI 95%: 0.67 – 3.45). There was steady regression of serum βhCG levels in chemoprophylaxis group with a mean time of 8.5 weeks (± 2.3 weeks) compared to the 9.5 weeks (± 2.1 weeks) in group without chemoprophylaxis (P = 0.01). There were some side effects in the MTX-FA as noted such as nausea (39.3%), anorexia (37.5%), and dry mouth (37.5%).

Conclusions: Applying prophylactic chemotherapy routinely would not help reduce the rate of gestational trophoblastic neoplasia in patients with high-risk hydatidiform mole.

Keywords: High-risk hydatidiform mole; Gestational trophoblastic neoplasia

Introduction

Hydatidiform mole (HM) is a kind of gestational trophoblastic disease. The incidence of HM vary in different regions of the world (0.6 – 2.0 per 1000 pregnancies) [1]. After molar evacuation, about 20% of complete hydatidiform moles (CHM) develop into gestational trophoblastic neoplasia including invasive mole and choriocarcinoma. Its morbidity and mortality rates are much worse. Prophylactic chemotherapy is used to prevent gestational trophoblastic neoplasia (GTN) post HM. However, the use of prophylactic chemotherapy in patients with HM will increase the cost, time, and side effects. This remains a controversial problem since the risk of developing GTN is 20%.

According to Kim DS, et al. [2], among high-risk patients, the incidence of GTN was 14.3% in the chemoprophylactic group with Methotrexate versus 47.4% in the control group. Similarly, Uberti, et al. [3], showed the incidence of GTN was 18.4% in patients that used Actinomycin D versus 34.3% in the control group.

However, according to Ayhan A et al. [4], the incidence of postmolar GTN did not decrease in patients with high-risk hydatidiform mole when prophylactic chemotherapy was used (25.0% vs 26.2%). Moreover, in Kashimura, et al. [5] study, he concluded that the prophylactic chemotherapy did not eliminate the occurrence of choriocarcinoma but consequently patients experienced more side effects from the treatment.

In 2011, 959 molar pregnancy patients were admitted at Tu Du hospital, which included 754 patients with high-risk hydatidiform moles. Although we manage about 1000 HM patients every year, there is no evidence based medicine published that showed the use of prophylactic chemotherapy being effective. We conducted this study to determine whether the use prophylactic chemotherapy among the high-risk hydatidiform mole patients would prove beneficial. The participants were observed up to six months at Tu Du hospital.

Study Objectives

1. To compare the incidence rate of gestational trophoblastic neoplasia among patients with high-risk hydatidiform mole between groups using prophylactic chemotherapy with those groups that did not have the treatment.
2. To compare the time needed to achieve the regression of serum βhCG levels to an undetectable level between the two groups.
3. Report the side effects of the prophylactic chemotherapy study group.

Methods

Study Design

Prospective cohort study

Research Population

Patients with high-risk hydatidiform mole were categorized by Goldstein’s criterion and admitted to Tu Du hospital.

Sampling Population

Patients with high-risk hydatidiform mole admitted to Tu Du hospital from August, 2012 to November, 2013.

Inclusion Criteria

All patients with high-risk hydatidiform mole during study time were divided into two groups: Chemoprophylactic group called “exposed” and control group called "unexposed".

Exclusion Criteria

- Failed to obtain the study’s consent form
- Patients were D&C from the other hospitals
- Patients diagnosed GTN
• Patients with mental disorders
• Abnormal renal or hepatic functions
• Contraindications with MTX

Sample size

\[ n = \frac{\left(\frac{z^2 \cdot p(1-p) + p^2(1-p^2) + \sqrt{2 \cdot p^2(1-p^2)}}{p^2(1-p^2)}\right)^2}{(p^2)} \]

P1: (12.5%); The incidence of GTN in the high-risk HM patients that were treated with Methotrexate-Folinic Acid at Tu Du hospital (2011 Tudu’s data).

P2: The incidence of GTN in high-risk HM patients without chemoprophylactic, according Kim’s study, p2 = 3.3 p1 [2].

Sample power is 90% and alpha is 95%.

With an expectation of 10% lost in follow ups, a sample size of 56 was calculated for each arm.

Definition of main factors

High-risk hydatidiform mole: Patient with hydatidiform mole with at least one of these risk factors [6]:
• Maternal age ≥ 40 years
• Serum \( \beta \)hCG levels ≥ 100,000 mUI/ml
• Large for dates uterus
• Theca – lutein cyst ≥ 6 cm in diameter
• Antecedent gestational trophoblastic disease
• Associated preeclampsia, hyperthyroidism, and trophoblastic embolisation.

GTN: Gestational Trophoblastic Neoplasia is diagnosed with at least one of these [7]:
• The plateau of \( \beta \)hCG levels lasting for a period of 3 weeks or longer on days 1, 7, 14, 21 or
• There is a rise in \( \beta \)hCG levels for three consecutive weekly measurements, over a period of two weeks or longer, days 1, 7, 14 or
• There is histological diagnosis of choriocarcinoma or
• The \( \beta \)hCG level remains elevated for 6 months or more.

Complete remission: The serum \( \beta \)hCG level become negative on three consecutive measurements.

• \( \beta \)hCG measured by immunofluorescence assays technique with minimum level of being detected is 5 IU/ml.
• Time taken for regression of serum \( \beta \)hCG (week): From the time of molar evacuation to the first time negative serum \( \beta \)hCG is measured.

Study Procedures

Step 1 – Screening

At Tu Du hospital, patients with hydatidiform mole are admitted to the oncology department and are examined carefully. \( \beta \)hCG levels, ultrasound, complete blood count, renal function, hepatic function, and urine samples will be completed. After identifying the diagnosis and classifying the risk category, molar evacuation will be carried out in the operation room. Low risk hydatidiform mole patients will be monitored in outpatient.

Step 2 – Grouping

After evacuation, high risk hydatidiform mole will be divided into two groups with two different treatment regimens by senior doctors in the oncology department. One group will be treated with prophylactic chemotherapy using MTX-FA for 8 days at the hospital. After treatment, the patient will be followed and observed in outpatient. The other group will serve as the control group without any interventions, but will continued to be observed for the reminding 6 months for the study. Chemoprophylactic regimen includes Methotrexate and Folinic Acid for 8 days: intramuscular MTX (1mg/kg/day) on days 1, 3, 5, 7 and Folinic Acid (0.1mg/kg/day) on days 2, 4, 6, and 8.

Step 3 – Enrolling

This is a prospective observation cohort study. Participants voluntarily enrolled in the study and treatment methods are randomized. We will recorded observations, collected data, and followed up with patients during the 6 month study. We invited patients to join our study after they were diagnosed and divided into two treatment groups by senior doctors in oncology department. We also explained the method and the purpose of the study to patients. Patients who accepted to enroll would sign their consent form and there was no discrimination towards patient who did not want to commit to the study.

Step 4 - Data Collecting

Data was collected from clinical examinations and laboratory test results were recorded during admittance and during the study. Each patient was assigned a number to manage the results more conveniently.

Step 5 - Manage post molar pregnancy

The management of post molar pregnancy was similar between chemoprophylactic group and control group during the 6 months. Patients were followed up with every other week. However, they were asked to come to hospital immediately if they had abnormal symptoms such as vaginal bleeding, headache, or abdominal pain. For each routine exam, patients were evaluated on clinical presentation, serum \( \beta \)hCG level, and ultrasound results. Patients were readmitted as soon as they were diagnosed gestational trophoblastic neoplasia. The management of post molar pregnancy would end when complete remission was confirmed.

Results and Discussion

From August 2012 to November 2013, 215 patients with hydatidiform moles were admitted at Tu Du hospital. Of those, 170 patients were high-risk HM and 45 patients were low-risk HM. None of the patients with high-risk HM refused to join the study, however 2 patients prematurely stopped treatment. Thus, 168 high-risk HM were followed and observed over the 6 month study. There were 56 patients who received chemoprophylactic treatment, while the other 112 patients served as the control group who did not receive any interventions.

Outcomes of Chemoprophylactic Group

The mean time taken to reach negative serum \( \beta \)hCG after molar evacuation was 8.5 ± 2.3 weeks in chemophrophylactic group versus 9.5 ± 2.1 weeks in the control group. There was significant difference in the duration until negative serum \( \beta \)hCG was reached between the two groups with \( P \) value < 0.05. This is statistically significance; however this did not prove to be clinically significant.

In addition, Renu Sharma’s study (2011) demonstrated similar results (7.3 weeks in chemoprophylactic group vs. 9.7 weeks in
made up the control group. Among these, 56 patients were randomly selected to receive MTX-FA as prophylactic chemotherapy compared to the 112 patients that underwent prophylactic chemotherapy. We noted some minor side effects of chemoprophylactic include nausea (39.3%), anorexia (37.5%), and dry mouth (37.5%). Our study suggests that prophylactic chemotherapy should not be used routinely among high-risk HM patients who under chemoprophylactic and 25% among high-risk HM patients who served as our control group. However, there was no significant difference found (P value > 0.05). This conclusion is similar with Ayhan A’s study (25% vs. 26.2%) but differ from the study of Kim DS and Uberti. Due to the limitation of time, we followed up on patients for only 6 months. Our study design was not RCT. These could have attributed to the different results from other previous studies.

Conclusion

From August 2012 to November 2013, 168 high-risk hydatidiform moles patients were admitted to Tu Du hospital. Of those, 56 patients were randomly selected to receive MTX-FA as prophylactic chemotherapy compared to the 112 patients that made up the control group [8]. Furthermore, Geng’s et al. study [9] concluded that the mean time it took to reach negative serum βhCG levels in chemoprophylactic group was 10.1 weeks. This difference could be due to the positive cut offs for serum βhCG levels (5mUI/ml in our study vs. 2 mUI/ml in Geng’s study).

Side Effects

There were no serious side effects amongst patients that underwent prophylactic chemotherapy. We noted some minor side effects such as nausea (39.3%), anorexia (37.5%), and dry mouth (37.5%).

Table 1: Patients’ characteristics at based line. (*): Chi – squared test

Comment: The above table described all socio-demographic characteristics, risk factors of patients with high-risk hydatidiform mole at base line. There were no major differences in all characteristics between the two groups.

counsel group) [8]. Furthermore, Geng’s et al. study [9] concluded that the mean time it took to reach negative serum βhCG levels in chemoprophylactic group was 10.1 weeks. This difference could be due to the positive cut offs for serum βhCG levels (5mUI/ml in our study vs. 2 mUI/ml in Geng’s study).

Table 2: Incidence of GTN after 6 months follow – up. (*) Multivariate Poisson

Comment: We searched for the correlation between chemoprophylactic and GTN. In order to control for confounder factors, we used the multivariate Poisson model including 4 other independent variables. After the 6 months followed up, the rate of GTN was 14.3% among the high-risk HM patients who under chemoprophylactic and 25% among high-risk HM patients who served as our control group. However, there was no significant difference found (P value > 0.05). This conclusion is similar with Ayhan A’s study (25% vs. 26.2%) but differ from the study of Kim DS and Uberti. Due to the limitation of time, we followed up on patients for only 6 months. Our study design was not RCT. These could have attributed to the different results from other previous studies.

Table 3: Time needed to achieve negative serum βhCG, (*) T-Test.

diagnosed 14.3% amongst the chemoprophylactic group compared to our control group which was 25%. Data showed that prophylactic chemotherapy did not reduce the occurrence of postmolar GTN significantly in high-risk HM (p > 0.05).

However, the mean time taken to reach negative serum βhCG levels after molar evacuation in chemoprophylactic groups were shorter by one week compared to the control group (p < 0.05). The minor side effects of chemoprophylactic include nausea (39.3%), anorexia (37.5%), and dry mouth (37.5%). Our study suggests that prophylactic chemotherapy should not be used routinely among high-risk HM patients. Instead, we recommend that serum βhCG levels and clinical signs and symptoms be carefully observed every other week after evacuation until complete remission can be confirmed. These procedures will help reduce hospital cost and avoid unnecessary side effects of chemotherapy. Ultimately, it ensures the safety and efficacy of treatment for high-risk HM patients.

Reference


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