Chemoprophylaxis in the prevention of postmolar gestational trophoblastic neoplasia: A 5-year review*

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ABSTRACT

Background: Administration of chemotherapy to prevent postmolar gestational trophoblastic neoplasia was first implemented in the 1960's. However, its use has remained controversial.

Objectives: This study aimed to describe the effect of chemoprophylaxis in preventing progression of hydatidiform mole to gestational trophoblastic neoplasia among patients managed in a tertiary hospital in Davao City from 2011 to 2015.

Materials & Method: This retrospective cross-sectional study evaluated 123 cases of hydatidiform mole who were managed at a tertiary hospital in Davao City from the years 2011 to 2015. The patients' charts were retrieved to get the clinico-demographic profile, progression to gestational trophoblastic neoplasia, and occurrence of adverse effects secondary to chemoprophylaxis. Patients with rising or plateauing beta human chorionic gonadotropin titer were identified within the 3-year period from molar evacuation. Collected data were analyzed using frequency and percentage distribution.

Results: The mean age of the patients was 30.5 years, 24% of whom were noted in women more than 40 years of age. The average age of gestation on admission was 14.89 weeks. All patients had a histopathologic diagnosis of complete mole and at least one risk factor for developing postmolar gestational trophoblastic neoplasia. Patients did not experience any significant side effect to chemoprophylaxis. None of the patients developed gestational trophoblastic neoplasia within the 3-year period of monitoring.

Conclusion: The administration of chemoprophylaxis to patients diagnosed with hydatidiform mole may be effective against the development of postmolar gestational trophoblastic neoplasia.

Keywords: chemoprophylaxis, gestational trophoblastic neoplasia, hydatidiform mole, postmolar gestational trophoblastic disease

INTRODUCTION

Gestational trophoblastic disease (GTD) describes a heterogeneous spectrum of diseases of abnormal trophoblastic proliferation ranging from benign to malignant forms.[1] Hydatidiform mole (HM) is an abnormal conception with excessive trophoblastic proliferation, with little or no fetal development.[2] It is characterized by an overgrowth of fetal chorionic tissue within the uterus and is classified under the benign trophoblastic lesions.

The worldwide incidence of hydatidiform mole only accounts for 1-2 in 100 pregnancies. In Southeast Asia, its incidence remains to be 7 to 10 times higher than in Europe and in North America wherein Indonesia has one of the highest reported incidence rates of 1 in 77 pregancies.[2] In the Philippines, the reported national prevalence rate of hydatidiform mole in the years 2002 to 2008 is 2.4 per 1000 pregnancies.[3] Based on the admissions record of a tertiary hospital in Davao City, trophoblastic disease admissions increased from 15 to 40% in the years 2013 to 2015.

Molar pregnancies are classified as complete (CHM) or partial hydatidiform mole (PHM) depending on their gross and microscopic appearance as well as chromosomal pattern.[4] Partial hydatidiform moles usually have a triploid karyotype, derived from maternal and paternal origins, whereas CHMs are diploid and have paternal origin only. Patients with HM are managed by evacuation of the molar products. In a proportion of these women, gestational trophoblastic neoplasia (GTN), the malignant form of GTDs, develop. As such, close post-evacuation monitoring through regular serum beta human chorionic gonadotropin (BhCG) measurements is recommended for the early detection of GTN.

The potential for malignant transformation differs between complete and partial hydatidiform mole.

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Approximately 8-29% of CHM and 2-4% of PHM progress to become persistent gestational trophoblastic disease. Studies have shown that the risk of developing the malignant sequelae of a benign disease is higher with a large-for-date uterus, serum BhCG >100,000 mIU/ml, theca lutein cysts >6cm in diameter, uterine size >16 weeks, maternal age >40 years, severe trophoblastic proliferation, a history of molar pregnancy and presence of medical complications associated with molar gestation.[2,4]

Identification of high-risk molar pregnancies is relevant to institute measures to prevent development of post molar gestational trophoblastic disease (PMGTD). Administration of chemoprophylaxis is currently being used in order to prevent progression to GTN. This strategy was first conceived and implemented in 1966 based on these premises: the trophoblastic tumor cells are highly sensitive to certain chemotherapeutic agents particularly methotrexate and actinomycin-D, the development of GTN after evacuation of CHM is biologically determined, the mechanism for the development of GTN is hematogenous spread, and that high levels of cytotoxic agents at the time of molar evacuation could reduce the incidence of both locally invasive and metastatic GTN.[5,6] However, some authorities do not recommend the use of chemoprophylaxis because of its toxicity. Additionally, the long-term prognosis for women with hydatidiform mole is not improved.[7] The practice of giving chemoprophylaxis remains to be controversial although the clinical practice guidelines of the Philippine Society for the Study of Trophoblastic Diseases recommends chemoprophylaxis in situations where patients are at risk for PMGTD and when post-evacuation surveillance is doubtful.[2]

As such, this study was conducted to further investigate the utility of chemoprophylaxis as a measure to prevent postmolar malignant degeneration.

OBJECTIVES

General Objective:

This study aimed to describe the effect of chemoprophylaxis in preventing progression to GTN among HM patients managed in a tertiary hospital in Davao City from 2011 to 2015.

Specific Objectives:

1. To describe the clinico-demographic profile of patients diagnosed with hydatidiform mole in a tertiary hospital in Davao City in terms of age, parity, antecedent pregnancy prior to hydatidiform mole, age of gestation (AOG) on admission, baseline BhCG level, and histopathologic result;
2. To determine the percentage of patients who progressed to GTN based on plateauing or rising BhCG titers among HM patients who were given Methotrexate as chemoprophylaxis;
3. To determine the time interval from molar evacuation to development of GTN
4. To determine the safety of chemoprophylaxis administration.

MATERIALS & METHODS

Study Design

This was a retrospective cross-sectional study approved by the hospital ethics board.

Study Population

The subjects included in this study were patients who were diagnosed with hydatidiform mole and managed at a tertiary hospital in Davao City from 2011 to 2015. Patients who were considered to be at high-risk of developing GTN based on the criteria set by the Philippine Society for the Study of Trophoblastic Diseases were given chemoprophylaxis in the form of methotrexate after molar evacuation. Post evacuation BhCG surveillance was done at the out-patient department trophoblastic clinic. Patients who were not given chemoprophylaxis were excluded from the study. Additionally, those who failed to follow up or had incomplete follow up after molar evacuation as well as patients without post-evacuation BhCG surveillance were not included in the study.

Sampling Procedure

Total enumeration was used for this study. Ideal sample size for this study was computed using Epi Info version 7.1.4.0 with the following assumptions: (1) the total population size of patients with hydatidiform mole seen in SPMC was 320; (2) the outcome, occurrence of PMGTD, occurs in up to 15.4% of patients;[6] (3) the desired precision was 5%. In a computation for the rate of having progression of PMGTD among patients who had HM carried out at <5% level of significance, a sample size of 123 patients was needed.

Data Collection and Instrumentation

This study used the secondary or archival data from the hospital records and trophoblastic registry of the Department of Obstetrics and Gynecology of a tertiary hospital in Davao City. The hospital records were utilized for the identification of patients who were admitted between the years 2011 to 2015 with the diagnosis of hydatidiform mole and received chemoprophylaxis after molar evacuation. A patient received chemoprophylaxis if she had at least one of the following risk factors for the development of GTN, based on the recommendations listed

in the Clinical Practice Guidelines of the Philippine Society for the Study of Trophoblastic Diseases: advanced maternal age ≥40 years; uterine size larger than gestation by ≥6 weeks; serum BhCG titer ≥ 100,000 mIU/ml; theca lutein cyst (s) ≥ 6cm; presence of any medical complication associated with increased trophoblastic proliferation, recurrent hydatidiform mole and a documented hydatidiform mole with a live normal twin.[2] Chemoprophylaxis was given in the form of daily Methotrexate intramuscular injection at a dose of 0.4 mg/kg for five days.

The patient registry of the Section of Trophoblastic Diseases of the department of Obstetrics and Gynecology was reviewed to retrieve the following data: age, parity, antecedent pregnancy prior to hydatidiform mole, age of gestation (AOG) on admission, baseline BhCG level, histopathologic result, indication for chemoprophylaxis, outpatient BhCG monitoring, progression to GTN, and adverse effects of Methotrexate.

Patients' serum BhCG titers were monitored according to standard protocol: BhCG titer was determined one week after molar evacuation and then every two weeks until the titers became normal (<5 mIU/l) for two consecutive determinations, after which BhCG monitoring was done monthly to complete 6 months. Patients were advised to avoid pregnancy during the monitoring period.[2]

Progression to GTN or development of PMGTD was diagnosed when any of the following conditions was detected: Plateauing BhCG levels for four consecutive weekly measurements over a period of at least 3 weeks (days 0, 7, 14, 21); rising BhCG levels for three weekly consecutive measurements, over at least a period of 2 weeks (days 0, 7, 14) and histologic diagnosis of choriocarcinoma.[2,3]

Data Analysis

The demographic and clinical profile of patients were analyzed descriptively using mean and standard deviation for continuous data and frequency and percentage for categorical data. The incidence and risk factors were expressed as frequency and percentage.

RESULTS

Clinico-Demographic Profile of the Patients

Table 1 presents the clinico-demographic profile of the 123 patients included in the study. Results showed that the average age of the patients was 30.5, with the age group between 18-34 as the predominant group. There were 85, out of 123 patients (69%) who had a normal pregnancy as the antecedent pregnancy. The mean age of gestation at the time of admission was 14.89 weeks, with more than 95% of the patients having a gestational age of more than 8 weeks. Around 86% (106/123) of the patients had a BhCG more than 100,000 mIU/ml, with an average level of 300,568.38 mIU/ml. All of the patients had a histopathologic finding of complete hydatidiform mole.

Prevalence of Progression to Gestational Trophoblastic Neoplasia

None of the 123 patients who were included in this study had progression to GTN in the 3-year period of monitoring.

Risk Factors for PMGTD

Table 2 is a tabulation of the identifiable risk factors present in the patients included in the study for which chemoprophylaxis was given. The results showed that 84% of the cases (106/123) had serum BhCG levels of more than 100,000 mIU/ml, 34% (43/123) had uterine size 6 weeks larger than the gestational age, 24% (30/123) had advanced maternal age of more than 40 years and only 1% of the cases (1/123) had theca lutein cyst of more than 6 cm. Of the 123 cases included in the study, 38% (46/123) had medical conditions associated with trophoblastic proliferation. Thirty-two percent of the cases (39/123) with medical complications had thyrotoxicosis while 5% of the cases (6/123) had preeclampsia/eclampsia. Only 1% of the cases (1/123) had recurrent hydatidiform mole.

Safety of Chemoprophylaxis Administration

Table 3 shows the occurrence of the common side effects of methotrexate as an agent for chemoprophylaxis. Among the 123 cases documented with hydatidiform mole patients who received chemoprophylaxis, only 1, or 1% of the cases experienced vomiting.

DISCUSSION

The mean age of the patients included in this study was 30.5 years, which confirms the fact that most cases still occur in the peak of a woman's reproductive age.[1] This study, also showed that 24% of the cases (30/123) were in women who conceived after 40 years of age, supporting the results of other studies that the incidence of hydatidiform mole increases up to 5 to 10-fold in women with an advanced age.[1,8]

History of a prior hydatidiform mole is a known risk factor in having recurrent mole in future pregnancies. A patient with a hydatidiform mole has a 1% risk of another molar pregnancy. The risk increases to 25 % following 2 or more molar pregnancies.[1] In the study, only 1% of the cases (1/123) had a previous molar pregnancy. Majority of the patients had a normal pregnancy prior

Table 1. Likelihood Estimates of Unmet Need for Family Planning Among Postpartum Women Admitted in a Tertiary Hospital (Logistic regression analysis) n= 197

Characteristics	Values
Mean Age ± SD, years	30.5+10.06
Age Classification, frequency %	
<18	13 (11%)
18-34	68 (55%)
35-40	17 (14%)
>40	25 (20%)
TOTAL	123 (100%)
Mean Parity ± SD	2.45+2.69
Parity Classification	
0	32 (26%)
1-4	70 (57%)
>5	21 (17%)
TOTAL	123 (100%)
Antecedent pregnancy, frequency %	
Normal	85 (69%)
H-mole	1 (1%)
Abortion	7 (6%)
Not Applicable	30 (24%)
TOTAL	123 (100%)
Mean age of gestation ± SD, weeks	14.89+4.62
Age of gestation classification	
<4 weeks	10 (8%)
4-8 weeks	7 (6%)
>8 weeks	106 (86%)
TOTAL	123 (100%)
Mean baseline BhCG level± SD, mIU/mL	300568.38+332211.46
Baseline BhCG level classification	
<50,000	10 (8%)
50,000-100,000	7 (6%)
>100,000	106 (86%)
TOTAL	123 (100%)
Histopathologic result, frequency %	
Complete Mole	123 (100%)
Partial Mole	0 (0%)
GTN	0 (0%)
TOTAL	123 (100%)

to developing HM. This result may further explain that extremes of maternal age and history of previous molar pregnancy are not the only risk factors that may lead to the development of hydatidiform moles. Other factors that have been implicated in the development of HM include decreased animal fat and beta-carotene intake or genetic predisposition.[1]

Table 2. Risk Factors of Post-Molar GTD

Risk Factors	Values
Advanced maternal age >40 years	30 (24%)
Uterine size larger than gestation by > 6 weeks	43 (34%)
Serum BhCG titer > 100,000 mIU/ml	104 (84%)
Theca lutein cyst (s) > 6cm	1 (1%)
Presence of any medical complication associated with increased trophoblastic proliferation such as:	**Values**
Preeclampsia	6 (5%)
Thyrotoxicosis	39 (32%)
Pulmonary insufficiency	0 (0%)
Disseminated intravascular coagulopathy	0 (0%)
Recurrent hydatidiform mole	1 (1%)
Documented hydatidiform mole with a coexisting normal twin	0 (0%)

Table 2. Safety of Chemoprophylaxis Administration

Side Effects	0 (0%)
Nausea	0 (0%)
Vomiting	1(1%)
Stomatitis	0 (0%)
Rashes	0 (0%)

Results of this study showed that the average gestation at the time of diagnosis was 14.89 weeks, which was relatively lower than the average gestational age of 17 weeks reported in the 1960s.[1] This implies that hydatidiform mole is now diagnosed earlier, which may be due to earlier consultation by patients and the widespread use of ultrasonography.

All patients included in this study had a histopathologic diagnosis of complete hydatidiform mole, which is in consonance with the reports that CHM is the most common type of HM.[1] Majority of the patients had a BhCG level of more than 100,000 mIU/ml on diagnosis. Such a finding is consistent with the presentation of complete molar pregnancies, especially if diagnosed during the late first trimester or early second trimester.[4]

Due to the risk of developing the malignant sequelae of HM, administration of prophylactic chemotherapy has been recommended by the Philippine Society for the Study of Trophoblastic Diseases for high-risk molar pregnancies.[2] In the guidelines drafted by the society, occurrence of one of the following risk factors necessitates administration of chemoprophylaxis: patients with advanced maternal age ≥40 years, uterine size larger than gestation by ≥ 6 weeks, serum BhCG titer

≥ 100,000 mIU/ml, theca lutein cyst ≥6cm, presence of any medical complication associated with increased trophoblastic proliferation such as preeclampsia, thyrotoxicosis; pulmonary insufficiency and disseminated intravascular coagulopathy, recurrent hydatidiform mole and documented hydatidiform mole with a coexisting normal twin.[2] All patients included in the current study had at least one risk factor for the development of GTN. These patients were given chemoprophylaxis using methotrexate at 0.4mg/kg given intramuscular for 5 days and were noted to have no occurrence of post-molar gestational trophoblastic diseases within a 3-year period of monitoring.

Currently, the practice of giving chemoprophylaxis has remained to be a controversial issue among trophoblastic disease specialists. In the study of Kim et al, chemoprophylaxis reduced the incidence of persistent trophoblastic disease in patients with high-risk HM. However, among patients who developed PMGTD, chemoprophylaxis increased the incidence of tumor resistance and morbidity.[5] The authors concluded that, although prophylactic chemotherapy with methotrexate and citrovorum factor rescue may be helpful for high-risk patients who cannot be followed up or whose compliance is in question, careful follow-up remains the most important way to identify patients who should eventually receive chemotherapy.[5] The study of Park and associates, on the other hand, strongly supported the use of prophylactic chemotherapy for patients at high-risk of developing PMGTD. Prophylactic chemotherapy not only helped to reduce the risk of developing PMGTD, it also shortened the time required to achieve normal BhCG titers.[9]

A randomized controlled trial on the efficacy of methotrexate in preventing PMGTD among patients with high-risk complete hydatidiform mole, was conducted at the Philippine General Hospital from 2007-2013. Results showed that the incidence of PMGTD was 16.67 % for the treatment group, and 38.71% for the control group. The computed risk ratio was 0.43 (95% CI, 0.17-1.047, p value = 0.07). Based on this study, Methotrexate may be useful in preventing PMGTD, particularly in high-risk patients and to patients with high probability of failure to follow up.[6]

A recent Cochrane systematic review concluded that, while chemoprophylaxis may reduce the risk of progression to GTN in women with CMs who are at a high risk of malignant transformation, it may also increase drug resistance, delay treatment of GTN and expose women to toxic side effects. As such, the authors did not recommend the practice of giving chemoprophylaxis.

In the current study, none of the patients developed GTN during the study period. Only 1% of the cases (1/123) experienced vomiting during and after administration of chemoprophylaxis. However, no strong conclusions can be drawn from these results due to the limited number of patients included in the study.

CONCLUSION

Based on the results of this study, it would seem that the administration of chemoprophylaxis in the form of Methotrexate to patients diagnosed with high-risk hydatidiform mole was effective against development of PMGTD in a 3-year period of monitoring. Additionally, no adverse side effect was noted with the administration of Methotrexate. However, no strong conclusions can be drawn from these results due to the limited number of patients included in the study. ■

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