

## **A CRITICAL APPRAISAL OF PROPHYLACTIC CHEMOTHERAPY**

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### **15.1 INTRODUCTION**

Molar pregnancies are known to have complications, including theca lutein cysts, preeclampsia, hyperemesis gravidarum, hyperthyroidism, respiratory insufficiency, pulmonary embolism and malignant degeneration or persistent trophoblastic disease (PTD) [1]. The latter is now referred to as post-molar gestational trophoblastic neoplasia (GTN). In the US, it has been reported that around 18% to 29% of molar pregnancies (around 16% to 20% in women with complete hydatidiform mole, and 0.5% to 1% in women with partial hydatidiform mole) develop into GTN [2,3]. In contrast, a study in the Philippines that involved patients at the University of the Philippines-Philippine General Hospital (UP-PGH) showed a 10% incidence of GTN after a complete mole, and 6.2% after a partial mole [1]. Worldwide, the figures for developing GTN following a molar pregnancy are even more variable ranging from 8% to 29%. This variance is likely due to differences in diagnostic criteria used as well as case ascertainment bias across the different countries and case series [4]. Overall, it is estimated that about 50% of women who develop GTN do so after a molar pregnancy [5].

Since the 1970s, scientists have been looking into various means of preventing the development of GTN after molar pregnancy. Surgical prophylaxis through hysterectomy has been performed by some centers, but the disadvantages outweigh the advantages of this method. A number of studies on methotrexate and actinomycin D as chemoprophylactic agents have been performed, but the use of chemoprophylaxis remains controversial.

### **15.2 GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)**

The risk factors for GTN include high-risk complete moles (40% to 57%), advanced age (33% to 37% among >40 years, 56% among >50 years), and multiple molar pregnancies [2, 4]. Table 15.1 shows how complete molar pregnancies can be categorized into low and high risk for subsequent development of GTN depending on various factors including the extent of proliferation of trophoblastic tissue at time of evacuation, the size of the uterus, the size of theca lutein cyst, and the presence of medical complications (i.e., hyperthyroidism, toxemia, respiratory insufficiency) [3, 4, 6, 7].

Table 15.1. Criteria for High-Risk Molar Pregnancies [1, 8, 9]

<b>Criteria</b>	<b>High-risk Molar Pregnancy</b>
Age	< 19 years or >40 years
Serum $\beta$ -HCG prior to evacuation	>100,000 mUI/mL
Gravidity	$\geq 4$
Size of uterus	Larger than expected for gestational age (>4-6 weeks, size >6 cm)
Theca lutein ovarian cysts	Bilateral, $\geq 6$ cm in size
Others	Medical complications (i.e., hyperthyroidism, hyperemesis, preeclampsia, pulmonary insufficiency, disseminated intravascular coagulation) Recurrent molar pregnancies Distant or challenging geographical location Poor compliance to follow-up

GTN may present as invasive non-metastatic disease, metastatic disease or placental site trophoblastic tumors (PSTT) / epithelioid trophoblastic tumors (ETT). The latter are the least common types and have the tendency to remain within the uterus, metastasize at a later stage, and produce low serum  $\beta$ -human chorionic gonadotrophin (hCG) levels [2]. Invasive non-metastatic disease usually presents with the same symptoms as molar pregnancies: irregular vaginal bleeding, theca lutein ovarian cysts, uterine subinvolution or asymmetric uterine enlargement, and persistently elevated serum  $\beta$ -hCG levels. Tumor invasion may bring about complications such as intraperitoneal bleeding from perforation of the myometrium, vaginal hemorrhage from rupture of uterine blood vessels, or abdominal pain and sepsis from infection of the tumor [2, 5, 10]. Metastatic disease occurs in around 4% of post-evacuation complete mole cases, commonly as choriocarcinoma. These tumors are highly vascular which tend to metastasize early. Common sites of metastasis include: lungs (80%), vagina (30%), pelvis (20%), brain (10%), and liver (10%). Complications may be due to hemorrhage at metastatic sites [2, 5]. Histologically, post molar GTN may present as a hydatidiform mole which may be invasive, a choriocarcinoma or rarely as a PSTT/ETT [2].

Women who have had a molar pregnancy evacuated are closely monitored and followed to detect malignant transformation at its early stages. As with the diagnosis of molar pregnancies,  $\beta$ -hCG is also used as a marker of disease progression or recurrence. Sensitive bioassays for the measurement of  $\beta$ -hCG levels, which are more accurate than pregnancy kits that measure  $\beta$ -hCG in urine, are already available worldwide. Weekly determination of serum  $\beta$ -hCG is recommended for women who underwent evacuation of molar pregnancy, until three successive weeks of normal levels is achieved, after which monthly determination is performed for 6 to 12 months, then every 4 months for the following year, and then annually [5, 6]. Though not practiced everywhere, some centers still measure the ratio of serum  $\beta$ -hCG to CSF  $\beta$ -hCG for the detection of occult brain metastasis (ratio of <60% in brain metastases) in patients with confirmed lung metastases [2, 5]. Some healthcare professionals make use of CA-125 as a marker of GTN. However, there is no clear evidence that this is beneficial in the management of these patients. Imaging modalities such as x-rays, CT scans or MRIs have been used to detect metastasis [5].

### **15.3 BASIS FOR CHEMOPROPHYLAXIS**

After the evacuation of a molar pregnancy, around 20% of patients experience local uterine invasion, while around 4% have metastases [2]. Attempts to lessen the incidence of GTN in

molar pregnancies have led to prophylactic hysterectomy and prophylactic chemotherapy. However, the former is not applicable to all affected patients since it causes loss of reproductive capability of the individual and because metastasis to other sites is not eliminated [7, 11, 12]. It was in 1966 when Lewis and colleagues first described the use of prophylactic chemotherapy in the management of post molar GTN. Since trophoblastic cells, including that of GTN, are highly sensitive to chemotherapy, many practitioners believe that administration of the same agents that are known to eliminate trophoblast tumor cells may prevent the progression of molar disease to malignancy. Additionally, the malignant transformation after molar pregnancy is likely to be biologically predetermined and potentially malignant trophoblastic cells metastasize through the bloodstream during evacuation of molar pregnancy. Therefore, the presence of high levels of cytotoxic agents in the blood during this time may lessen the occurrence of metastasis and invasion of these cells, and hasten the regression of trophoblastic tissue in large-volume cases [3, 8, 11, 13].

Despite these seemingly sound foundations for prophylactic chemotherapy, it is still an unpopular option among specialists due to the fact that it still is not able to completely prevent the occurrence of post-molar GTN. As mentioned, only a small proportion of patients with molar pregnancies will develop GTN, and all of these patients will basically be cured because treatment is available and effective. Also, agents used for chemoprophylaxis may cause serious adverse effects, with some anecdotal reports of death [11, 12]. Finally, prophylactic chemotherapy may promote poor compliance with follow-up among patients since it offers a false sense of security [14].

The idea of using methotrexate in trophoblastic disease was first introduced in 1948, when Hertz demonstrated that fetal tissues needed high levels of folic acid to develop, and that the growth of trophoblastic tissue in the genital tracts of experimental animals can be inhibited by methotrexate, an anti-folic agent. After this, several studies were performed, including one where methotrexate was shown to lower the levels of hCG in blood, and another which reported that this agent can cause fetal death [15]. Methotrexate and actinomycin D have been mainstays in the primary chemotherapy of GTN for years. These two agents are also used in various studies for chemoprophylaxis against GTN [10, 15].

## **15.4 CHEMOPROPHYLAXIS REGIMENS STUDIED**

### **15.4.1 Methotrexate**

A folic acid analog, methotrexate, inhibits tetrahydrofolate synthesis by binding the catalytic site of dihydrofolate reductase. This causes a block in various processes that ultimately impede the formation of DNA, RNA and proteins, making methotrexate an effective cytotoxic agent for the treatment of various cancers, including colorectal, anal, breast, gastroesophageal, head and neck, hepatocellular, and gynecologic cancers. This drug may be administered through various routes including oral, intramuscular (IM), intravenous (IV) or intrathecal and is eliminated mainly through the kidneys. The toxic effects of methotrexate—the most common of which are nausea, mucositis, diarrhea, myelotoxicity, neurotoxicity, pneumonitis and nephrotoxicity—can be minimized by co-administration of the reduced folate, leucovorin (folinic acid). Leucovorin rescue is usually given when high doses of methotrexate are needed. Resistance to this drug can develop due to various mechanisms [16].

Methotrexate is effective in the treatment of post molar GTN: as a single agent, it can cure roughly two thirds of low-risk GTNs but when used in combination with other cytotoxic drugs the cure rate is about 100% in low and around 90% in high risk GTN [4]. In chemoprophylaxis

following molar evacuation before development of overt GTN, cure rates for low risk moles are around 100% and for high risk moles vary from 80-90% [3]. At the UP-PGH methotrexate is routinely administered as a single course of 0.3-0.4 mg/kg/day IM for 5 days after evacuation on an out-patient basis [9, 17, 18]. Among studies that made use of methotrexate as chemoprophylaxis to prevent GTN after a molar pregnancy, there have been reports of adverse events that include stomatitis, myelotoxicity, stomatitis, alopecia, and gastrointestinal toxicity [3]. Folinic acid can be co-administered with methotrexate in order to minimize toxicity, and is added to the regimen of patients in the Philippines who exhibit hypersensitivity or adverse effects [9, 17, 18]. As a primary chemotherapeutic agent, the effectiveness of this combination is high; however, resistance is also high occurring in around 20% of cases [10]. The Philippine Society for the study of Trophoblastic Diseases recommends that chemoprophylaxis be contraindicated for patients with hemoglobin <100 mg/dL or hematocrit of <0.3, WBC count of <3, ANC of  $\leq 1.5$ , platelet count of <100, active infection, and/or liver or renal dysfunction [9].

#### **15.4.2 Actinomycin D**

Actinomycin D is a cytotoxic antibiotic that exerts its cell-killing effects directly on DNA. This drug inserts itself in the minor groove of the DNA and hinders the movement of polymerase, subsequently preventing transcription. It is administered as Actinomycin D 10  $\mu\text{g}/\text{kg}$  IV for 5 days within 1 week after evacuation. Known adverse effects of actinomycin D include nausea, vomiting and myelosuppression [19].

Actinomycin D is not commonly used in the Philippines due to the need for hospital admission and overall treatment cost. It is used as a chemoprophylactic agent in patients who develop hypersensitivity or adverse reactions to methotrexate [18]. Reported side effects of actinomycin D as a chemoprophylactic agent for PTD include nausea, vomiting, mucositis, skin rash, alopecia, and hepatotoxicity [8, 10].

#### **15.4.3 Studies on Methotrexate and Actinomycin D as Chemoprophylactic Agents**

There have been a number of regimens and studies looking at this issue summarised in Table 15.2. In a Cochrane review, Fu and his team compared prophylactic methotrexate and actinomycin D based on three studies:

In 1986, Kashimura and colleagues performed a random selection of 420 patients with complete molar pregnancies (low- or high-risk) to study the efficacy of prophylactic methotrexate in the prevention of PTD compared to no prophylaxis. The treatment group received a single course of methotrexate 10 mg daily for 7 days within 3 weeks after molar evacuation; the control group did not receive any treatment. Kashimura reported a decrease in the incidence of subsequent GTN: from 19.1% in the control group to 7.5% in the treatment group. He added that adverse events were reported in 27.3% of the patients who received treatment, but none were serious [3, 20].

Also in 1986, Kim and colleagues enrolled 133 patients with complete molar pregnancies (low- or high-risk) in a prospective randomized study with similar goals as Kashimura. The treatment group received a single course of methotrexate 1 mg/kg/day IM on days 1, 3, 5 and 7 with folinic acid rescue 0.1 mg/kg/day IM on days 2, 4, 6 and 8; the control group did not receive any treatment. Evacuation was performed on days 3 or 4. Their study revealed a reduction in the incidence of GTN from 47% to 14%, but patients from

the treatment group who developed GTN needed more chemotherapy courses [3, 21, 22].

Limpongsanurak and his colleagues involved 60 patients with molar pregnancies (high-risk only) in a randomized study to determine the efficacy of actinomycin D in the prevention of GTN compared to no prophylaxis. The treatment group received 10 µg/kg IV daily for 5 days, initiated within a week after molar evacuation; the control group did not receive any treatment. He reported a significant reduction in the incidence of GTN from 50% in the control group to 13.8% in the treatment group. This equates to a 72.4% decrease in the occurrence of malignant transformation of molar pregnancy into GTN [3, 22, 23].

Results of the three studies revealed that the reduction in the incidence of GTN in the treatment groups (no difference in either methotrexate or actinomycin D) was significant compared to the control group. Moreover, when only patients with high-risk molar pregnancies were included in the analysis, there was still a significant drop in the incidence of GTN compared to the control group. Another important finding pointed out by Fu was that the treatment groups in two of the studies reviewed demonstrated a longer time to GTN diagnosis compared to the control groups. Though not extensively reported, adverse effects mentioned in the three studies included myelosuppression, hepatotoxicity, and alopecia. One important issue looked into by Fu was the development of drug resistance since methotrexate and actinomycin D are both used as first-line chemotherapeutic agents for the management of trophoblastic malignancies. The study by Kim showed that patients from the treatment group who developed GTN needed more chemotherapy courses when compared to those from the control group. This data suggests that a different chemotherapeutic agent may be considered in the treatment of GTN in women who received chemoprophylaxis [3].

In 1996, Park, Kim and Lee evaluated the risk factors for GTN and the role of chemoprophylaxis in its management. Patients with molar pregnancies were ranked based on their risk profiles ( $\beta$ -HCG level, patient age, gestational age, size of uterus, theca lutein ovarian cysts, histologic grade of molar tissue, medical complications, history of molar pregnancy/ies, ABO blood type) into low-, medium- and high-risk groups. Each risk group were then divided into control groups which did not receive any treatment, and treatment groups which received either methotrexate and folinic acid or actinomycin D. Study results revealed a significantly lower incidence of GTN among those who received chemoprophylaxis (vs. those who did not) in the high risk group, whereas there was no difference between those who received chemoprophylaxis and those who did not in the medium- and low-risk groups. Metastatic disease also occurred less and time to remission was significantly shorter among those who received treatment. The researchers concluded that chemoprophylaxis may benefit patients who fulfill the high-risk criteria used in their study [24].

Ayhan and colleagues investigated the efficacy of methotrexate in preventing the malignant transformation of molar pregnancies in low- and high-risk subjects. Their results revealed that the administration of methotrexate as prophylactic chemotherapy did not change the incidence of postmolar trophoblastic disease in both low- and high-risk groups. Additionally, the high drug toxicity and mortality rates among subjects in the treatment group showed that prophylactic chemotherapy with methotrexate for post-molar pregnancies was not effective and was not recommended [25].

A paper by Kaye investigated the complications that are associated with oral methotrexate chemoprophylaxis for GTN in Mulago Hospital in Kampala, Uganda in a prospective study. The

adverse effects experienced by patients, usually during or after the third course, included mucositis (pharyngitis, stomatitis, esophagitis, conjunctivitis, colitis, diarrhea), hematological toxicity (anemia, thrombocytopenia and leukopenia), and hepatotoxicity. The author concluded that the use of methotrexate for chemoprophylaxis is safe and well-tolerated in the first two courses of therapy. However, as the duration of treatment increases, the toxic effects and complications also increase. Chemoprophylaxis also did not afford protection from metastatic disease [26].

Sivanesaratnam mentioned in his paper that their center at the University of Malaya in Kuala Lumpur, Malaysia used to administer methotrexate as chemoprophylaxis for GTN during the management of molar pregnancies, either through evacuation or hysterectomy, in the early 1970s. All of the 41 patients who received treatment did not develop GTN at 3 years, but two had presented with metastatic disease after 6 and 7 years. This practice was, however, discontinued; instead, the center made use of “selective preventive chemotherapy” wherein only patients who fulfilled specific criteria (i.e., rate of  $\beta$ -HCG level decline and trend of  $\beta$ -HCG level) received chemoprophylaxis [12].

Uberti et al looked at the efficacy of actinomycin D in reducing the occurrence of GTN in adolescents with high-risk molar pregnancies. Their study showed that the number of patients who developed GTN was significantly decreased in the treatment group compared to the control group. They added that there was no difference in the time from evacuation to diagnosis of the malignancy between the two groups, and there was no difference in the number of courses needed for successful treatment as well. Lastly, there were only a few adverse events reported, which included minor hepatotoxicity and alopecia. The researchers concluded that single dose actinomycin D may have a role in the chemoprophylaxis of GTN and may bring down the cost of medical care and morbidity without affecting patient compliance to monitoring and follow-up [8].

In 2009, Uberti and colleagues performed a retrospective analysis to determine the efficacy of actinomycin D as a chemoprophylactic agent for GTNs in patients with high-risk moles. Their paper reported that there was a reduction in the incidence of GTN among treated patients as well as cost of treatment and emotional complications. There was no effect on compliance to follow-up and morbidity. In another paper that made use of the same approach in the same population, Uberti and colleagues mentioned that the reproductive outcomes of women who received chemoprophylaxis were not affected by the treatment [27, 28].

A study performed by Sharma and Gupta also showed that GTN occurred less in the group of high-risk patients treated with prophylactic methotrexate compared to the control group, associated with a faster decline in the serum  $\beta$ -HCG level of treated patients. Toxicity was reported to occur in 33% of patients who received methotrexate, though all were not life-threatening [11].

In the Philippines, a double blind randomized controlled trial by Estrella and Billod determined the efficacy of methotrexate as a chemoprophylactic agent in patients with high-risk molar pregnancies. Their results revealed a lower incidence of GTN among patients in the treatment group as compared to the control (16.67% of those in the treatment group and 38.71% of those in the control group). This demonstrates that methotrexate may protect an individual from the development of GTN. Poor compliance with regard to follow-up and  $\beta$ -HCG monitoring was noted. Only 8.2% of patients who received treatment reported adverse effects [29].

Table 15.2. Summary of regimen used in various studies [3, 11, 21, 23, 24, 25]

<b>Drug</b>	<b>Regimen/Dosage</b>	<b>Study</b>
Methotrexate	Methotrexate 1 mg/kg/day IM on days 1, 3, 5 and 7 and citrovorum factor rescue 0.1 mg/kg/day IM on days 2, 4, 6 and 8, then evacuation on days 3 or 4	Kim 1986
	Methotrexate 1 mg/kg on days 1, 3, 5 and 7 and citrovorum factor (0.1 mg/kg on days 2, 4, 6 and 8 started at the time of evacuation	Park 1996
	Methotrexate 10 mg daily (IM or PO) for 7 days within 3 weeks after evacuation	Kashimura 1986, Koga 1968
	Methotrexate 0.4 mg/kg/day PO, not exceeding 25 mg/day in 3 divided doses for 5 days after suction and evacuation; 2 <sup>nd</sup> course after 2 weeks if required based on serum $\beta$ -HCG levels	Sharma & Gupta 2010
	Methotrexate 0.4 mg/kg/day IM for 5 days, starting at the time of evacuation (suction curettage, sharp curettage, hysterectomy, or salpingectomy)	Ayhan 1990
	Methotrexate 0.4 mg/kg/day IM for 5 days, within 14 days from evacuation	Estrella & Billod, 2011
	Methotrexate 0.4 mg/kg/day PO (25 mg/day) in 3 divided doses (10 mg, 5 mg, 10 mg) for 9-16 days (1-8 courses)	Kaye 2002
	Methotrexate 0.3 mg/kg/day for 5 days, evacuation on day 3	Goldstein 1971
	Methotrexate 10 mg/day PO for 5 days every 3 weeks for 3 cycles	Fasoli 1982
	Methotrexate 50 mg in 500 mL dextrose infusion during evacuation or hysterectomy until 3-4 hours after	Sivanesaratnam 2003
Actinomycin D	Actinomycin D 10 $\mu$ g/kg IV for 5 days within 1 week after evacuation	Limpongsanurak 2001
	Actinomycin D 9-12 $\mu$ g/kg/day for 5 days, evacuation on day 3	Goldstein 1971
	Actinomycin D 12 $\mu$ g/kg/day IV for 5 days, evacuation on day 3	Goldstein 1974, Goldstein 1981
	Actinomycin D 12 $\mu$ g/kg/day IV for 5 days started at the time of evacuation	Park 1996
	Actinomycin D 1.25 mg/m <sup>2</sup> IV given 1 hour before evacuation (single dose)	Uberti 2006, Uberti 2009

#### **15.4.4 Other Agents Studied as Chemoprophylactic Agents for GTN**

A study by Andrijono and Muhalil tested the efficacy of vitamin A (retinoic acid) in the prevention of malignant transformation of molar pregnancies. This study was based on the premise of previous reports that intracellular retinol would be metabolized into retinoic acid which inhibits cellular proliferation, and promotes cell differentiation and apoptosis. Furthermore, previous epidemiological studies have been shown that the levels of vitamin A were lower in women who had molar pregnancies when compared to those who had normal pregnancies. The group reported that treatment with vitamin A resulted in a lower rate of malignant transformation of molar pregnancies with 28.6% of the control group developing

GTN compared to 6.3% of the treatment group. Also, the dose of vitamin A given to the treatment group did not bring about adverse effects (i.e., elevated SGOT and SGPT) [29].

## 15.5 CONCLUSION

The use of prophylactic chemotherapy for GTN is controversial and is not recommended in most countries. However, as in the Philippines, it can be considered an option for high-risk patients who may have compliance issues, and those in settings where tests for serum  $\beta$ -hCG level determination is not available [1, 7, 8, 14, 22]. Where prophylactic chemotherapy is to be performed, it may be beneficial to make use of a cytotoxic agent other than that used for routine chemotherapy to avoid drug resistance which may be the cause for treatment failure or a prolonged chemotherapy course [13]. If methotrexate is used as a chemoprophylactic agent, co-administration of folinic acid may be beneficial in reducing the toxic effects of the drug. Finally, it is important to note that close follow-up and monitoring is still important despite the administration of chemoprophylaxis [9].

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