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COMPLIANCE AND OUTCOMES OF 5-DAY INTRAMUSCULAR METHOTREXATE FOR LOW RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA AT KIGALI UNIVERSITY TEACHING HOSPITAL, RWANDA

A DISSERTATION TO BE SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNECOLOGY OF THE UNIVERSITY OF RWANDA

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Authors' contributions

This study was carried out in close collaboration between the authors. The author ug wrote the protocol and collected data and initial data analysis. The authors lbm and rs reviewed and rewrite the study design, reviewed the literature and corrected the writing errors and fine touches.

DEDICATION

To the Almighty God who cares about us.

To my wife NYIRANEZA Aurea for your love, care and encouragement.

To our sons, MFURA GANZA Beryl Ercan and IMENA SANGWA Daryl Elvin your hugs and smile gave me strength and focus, my joy is yours

To my Parents, MUKALIMASI Bernadette and Late GASIGWA Anastase I owe my success

To my lovely Sisters and Brothers,

I dedicate this work.

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PRECIS

Five day Intramuscular Methotrexate regimen is feasible and effective in the treatment of low risk Gestational Trophoblastic Neoplasia in a low resource setting.

ABSTRACT

OBJECTIVE: Gestational trophoblastic neoplasia (GTN) complicates approximately 8% of all gestational trophoblastic diseases and its management requires systemic chemotherapy. This study assessed the feasibility and outcomes of low-risk GTN patients treated with intramuscular (IM) 5-day Methotrexate (MTX) at Kigali University Teaching Hospital (CHUK) in Rwanda.

METHODS: A retrospective cross-sectional chart review was conducted at CHUK from September 2015 to September 2017. Inclusion criteria were patients treated for low risk GTN with IM 5-day Methotrexate and for those who experienced remission, a one-year follow up.

RESULTS: Of 44 patients, molar pregnancy preceded GTN in 90.2% of cases and 75.6% were invasive mole by either pathologic report or clinical suspicion of invasion on ultrasound. Factors associated with an increased resistance to treatment included pretreatment β-HCG levels >100,000 mIU/ml (26.7%), tumor size of >3cm (22%) and FIGO/WHO score of 5 or 6 (20% and 33.3%, respectively). Pretreatment hysterectomy was associated with a decreased number of Methotrexate cycles needed for remission and increased response rates. Primary remission on 5-day IM Methotrexate was achieved in 80.49% of patients. Three (6.8%) patients were lost to follow up during the treatment course. Initiation of an outpatient Methotrexate protocol increased adherence. Stomatitis and neutropenia were the most common side effects at 60.9% and 41.5%, respectively, responsible for a mean of 2.3 cycles delayed, but did not impact outcomes.

CONCLUSIONS: Five day IM Methotrexate regimen at CHUK was found to be feasible and effective in the treatment of low risk GTN in a low resource setting. Patients with low risk GTN with factors contributing to a FIGO/WHO score of 5 or 6 have higher rates of resistance to single-agent Methotrexate, requiring alternative chemotherapy regimens.

Key words: Gestational Trophoblastic Neoplasia • Single-agent Chemotherapy • Methotrexate

LIST OF ACRONYMS

GTN: Gestational Trophoblastic Neoplasia

GTD: Gestational Trophoblastic Disease

IM : Intramuscular

MTX: Methotrexate

5D :5-day

CHUK: Kigali University Teaching Hospital

β-HCG: βeta Human Chorionic Gonadotropin

WHO: World Health Organization

FIGO: International Federation of Gynecology and Obstetrics

UK: United Kingdom

USA: United States of America

CMHS: College of Medicine and Health Sciences

IRB: Institutional Review Board

CI: Confidence Interval

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INTRODUCTION

Gestational Trophoblastic disease (GTD) refers to a rare and curable group of tumours that develop from placental tissues. The World Health Organization (WHO) classifies GTD into premalignant conditions including partial hydatidiform mole and complete hydatidiform mole. Malignant GTD, or gestational trophoblastic neoplasia (GTN), includes invasive mole, choriocarcinoma, placental site trophoblastic tumors and epithelioid trophoblastic tumors. When there is persistence of premalignant GTD, mainly evidenced by persistent plateauing or elevation of β-HCG , the condition is then also considered GTN. If not treated, GTN may spread and is eventualy lethal[1].

The incidence of GTD varies between different areas of the world, with higher rates found in Indonesia (around 10/1000 pregnancies), Mexico (4.6/1000) and Japan (2/1000), and lower rates in North America and Europe (<1/1000).Prevalences differ according to whether studies are population based or hospital based and may differ between regions within the same country. The etiology of GTD is not fully understood. Nevertheless, a previous molar pregnancy and advanced or very young maternal age are associated with an increased risk of GTD. Other factors such as ethnicity, poor nutrition, viral infections and environmental factors may also contribute[2]

Generally, molar pregnancies subside spontaneously after uterine evacuation without need for chemotherapy. However, approximately 16% of complete moles and 0.5% of partial moles persist and chemotherapy is needed. Molar progression to GTN results in an enlarging uterine mass that may invade locally or metastasize to other sites (vagina, lung, liver or brain), and lead to death if not treated. The most common clinical manifestations of post-molar GTN are vaginal bleeding, uterine and ovarian enlargement, and raised β-HCG levels[2] When treating GTN, physicians select the most appropriate chemotherapy regimen by utilizing the FIGO/WHO scoring system . A score of 0–6 is considered to have a low risk of resistance to single agent chemotherapy, while a score of 7 or more predicts a high risk of resistance and leads to a recommendation for multiagent chemotherapy.

After serum β-HCG levels normalize, additional courses of consolidation chemotherapy are recommended to avoid relapse. The likelihood of having disease relapse in low risk GTN patients is estimated at 2% in non-metastatic GTN and 4% in metastatic GTN[3]. Different regimens of MTX are available for the treatment of low risk GTN[4]. one treatment option is Methotrexate 0.4mg/kg/day administered intramuscularly for 5 days and repeated every 14 days. The primary failure rate for this regimen is 11%–15% for nonmetastatic disease and 27%–33% for metastatic disease. A alternative regimen, MTX 50mg IM or 1mg/kg every other day for 4 doses with leucovorin 15mg or 0.1mg/kg 24–30 hours after each dose of MTX, this regimen is largely used in the UK and the USA, but has a 20%–25% primary failure rate. Weekly Methotrexate 50mg/m^2 IM has became a popular outpatient regimen in some countries due to its convenience, however it is associated with a 30% primary failure rate. If failure happens with primary therapy, without progression of disease, patients may be switched to an extended MTX regimen or to actinomycin D, depending on their original regimen[4] Resistance with or relapse after single agent therapy requires treatment with multi-agent chemotherapy, which is associated with increased morbitiy, risk of secondary malignancies and early menopause[5]

The true prevalence of GTN throughout Rwanda is unknown. The prevalence of GTD in a single study at CHUK in 2014 was found to be 1.5/1000[6] As this was prevalence from a single site, these numbers may underrepresent the true prevalence for the country. Gestational trophobalstic neoplasia rates in Rwanda are suspected to be much higher than those in the US and Europe, as cases present routinely to the district hospitals and referral centers throughout the country. A multidisciplinary approach to management of GTN in low resource settings can be challenging. Therefore, the present study was conducted to assess the feasibility and outcomes of patients diagnosed with low-risk GTN and treated with a 5D IM Methotrexate regimen at CHUK.

MATERIALS AND METHODS

This study was a retrospective cross-sectional chart review, conducted at CHUK, over a 2-year period from 1st September 2015 to 1st September 2017. The study cohort included all women diagnosed with low risk GTN and treated with 5D IM MTX (0.4mg/kg/day, maximum dose 25mg/day). A one year follow up was required for those experiencing complete remission. Chart review was performed from the archive, and data were collected through a questionnaire. The information recorded included; maternal age, number of pregnancies, gestational event leading to GTN, greatest tumor size, size ,location and number of metastasis, pathologic diagnosis if available, pre-treatment β-HCG, FIGO/WHO score, side effects and outcome on 5D IM MTX. Demographic data as well as events of the hospital course were recorded.

Raw data were exported to SPSS 16.0 version 16.0 then cleaned and analysed. Descriptive statistics were calculated for all variables. In bi-variate analysis, crude odds ratio and confidence interval were determined to select candidate variables for multivariate analysis at the level significance ($p<0.05$). Binary and multivariate logistic regressions were used to determine the adjusted odds ratio and corresponding 95% confidence interval. A maximum likelihood estimate of the independent effect of the predictor variables was used to see the level of significance. The strength of association was interpreted using the adjusted odds ratio and 95% CI. Ethical approval was obtained from the Institutional Review Board (IRB) of the College of Medicine and Health Sciences at the University of Rwanda (IRB #2018, CMHS #012)

RESULTS

Over a 2-year period, 44 patients were diagnosed with low risk GTN by FIGO/WHO risk score (Table 1) and treated with 5D IM MTX (0.4mg/kg/day, maximum dose 25mg/day). Patient demographics are presented in Table 2. The majority of our population was between 20-35 years of age (56.1%), with a mean age 36 years. The majority was from Kigali city (28.3%) and were farmers (68.3%), regarded as low social economic status in Rwanda.

Molar pregnancy was the antecedent pregnancy event to GTN in 90.2% of cases, and term deliveries in 2.4%. Most cases of GTN were found to be invasive mole (75.6%), by clinical or pathologic diagnosis, and 24.4% had pathologic confirmation of choriocarcinoma.More than half of our population (61%) had a pretreatment β-HCG between 10,000 -100,000 mIU/ml, and 22% had levels >100,000 mIU/ml. The prognostic FIGO/WHO score was 6 in 36.6% of our patients. Only 4 low risk patients were found to have metastases (1 lung, 3 vaginal) (Table 3).

Complete remission was achieved in 80.49% of patients and 19.51% experienced resistance to MTX requiring multiple-agent chemotherapy, as single agent actinomycin D is not administered in Rwanda. We observed no case of disease relapse after complete remission. Three patients (6.8%) were lost to follow up along the treatment course. Of the patients who underwent pre-treatment hysterectomy, 82.4% had a complete remission compared to 79.2% that had complete remission after evacuation or no pretreatment procedure. Patients requiring ≥10cycles of MTX cycles, 28.6% showed resistance, similar to those requiring 6-9 cycles of MTX at 26.3%. Only one of the 15 patients that received ≤5 cycles of MTX developed resistance. Of patients who had pretreatment hysterectomy, 71.4% required ≤5 cycles of MTX to achieve remission, whereas only 21.1% of those

without pretreatment hysterectomy had complete remission with ≤5 cycles of MTX (p =0.013) (Table 4).

Eighty percent of patients with choriocarcinoma and 80.6% with an invasive mole experienced complete remission on 5D IM MTX. A pre-treatment β-HCG ≥100,000 mIU/ml was associated with a rate of MTX resistance of 33.3%.A FIGO/WHO score of 6 was associated with a resistance rate of 33.3% and patients with metastatic disease had a resistance rate of 25% versus 18.9% in those with non-metastatic disease(Table 5). Patients resistant to MTX had a mean of 8.4±2.4 cycles (range 5-13) vs. 6.6±2.4 cycles (range 4-12) for those with complete remission (OR 1.7 CI-0.2-3.6, P=0.080). The total time to complete remission was ≤3 months in 33.3% of patients (n=11), 4 to 6 months in 42.4% (n=14), 7 to 12 months in 21.2% (n=7) and 13 months in 3.0% (n=1). Sides effects were experienced by 26 patients (63.4%) among the study cohort, stomatitis was the most frequent (60.9%) side effect of 5D IM MTX. Neutropenia and nausea were the next most common at 41.5% and 12.2%, respectively. Dose reductions were necessary in 34.1% of patients and thirteen (31.7) patients experienced treatment delays due to side effects. Most (75%) had a delay of ≤ 2 cycles. Only 3 (25%) patients were delayed for 3 or 4 cycles.There was no association found between treatment delays and disease resistance (p=0.709)

DISCUSSION

Malignant conditions are often challenging to address in low-resource settings due to their need for multidisciplinary management and high cost of care, However, GTN is very responsive to chemotherapy and low-risk disease is treated with single-agent therapy[7] This study revealed that excellent outcomes can be achieved despite limited resources. At CHUK, the major referral center for the country of Rwanda, we recorded a primary remission rate for low risk GTN of 80.49% on a 5D IM MTX regimen. When making our choice of available MTX protocols for low risk GTN, we had many variables to consider in our setting. While in many high resource countries, weekly IM

MTX is used due to convenience, time to remission can take longer, and remission rates are found to be inferior to multidose single agent regimens with more patients requiring alternate single agent chemotherapy with actinomycin D[7].In our setting chemotherapy is currently only available to patients with public insurance at 2 hospitals in the country, CHUK and Butaro District Hospital in the northern Rwanda. However, gynecologists are not currently on staff at Butaro. Also, despite CHUK being the country's main referral hospital, the only chemotherapy currently administered at CHUK is IM MTX. Butaro Hospital, the only hospital in the country that administers intravenous chemotherapy to patients with public or no insurance, does not offer actinomycin D as an alternative when patients fail single agent MTX.Methotrexate failures are treated with multi-agent chemotherapy. We also had to consider the number of visits it would require to obtain laboratory follow up and treatment, as well as which regimen would give the most rapid rate of response. Although the majority of our patients do hold some form of public insurance to pay for laboratory tests and medications, travel from remote areas of the country to CHUK can limit their ability to obtain, or continue with treatment that often lasts for many months.The mean number of cycles required to achieve complete response was 6.6. These results are similar to those found by Gueye at the University of Dakar who also evaluated treatment of GTN in a low resource country, and found the mean number of 5D IM MTX cycles until complete remission was 6.9[8] Our loss to follow up rate was 6.8%. This was mainly attributed to inpatient only management during protocol initiation, but with the introduction of an outpatient treatment option, no new cases of loss to follow up were recorded. The majority of patients that come from remote areas for treatment were grateful for inpatient treatment, however those living in Kigali city were often discouraged by the requirement of a 5 day inpatient admission for a daily IM injection, taking them away from family and work.

Encouragingly, our remission rate of 80.49% was similar to the 81% primary remission rate on single agent 5D IV MTX 0.4mg/kg daily for 5 days every 14 days for low risk GTN observed at the Brewer Trophoblastic Disease Center of Northwestern University.[9] Yarandi et al. performed a randomized

clinical trial between 2010-2013 of low risk GTN on 5D IV MTX 0.4mg/kg daily for 5 days every 14 days which revealed a complete remission rate of 78.1%, Lurain et al.also found a 89.3% primary remission rate using the same regimen[10] . However, Kizaki et al, at Chiba University in Japan (1980–2009) and Tokyo Women's University (2010–2014) found a lower primary remission rate of 64.7% on 5D IM MTX 0.4mg/kg[11].The author associates this higher resistance with the median pre-treatment β-HCG levels and frequency of pre-treatment hCG levels of ≥50,000 mIU/mL, which were significantly higher in the drug resistant group. Our results revealed that molar pregnancy was the preceding pregnancy event prior to low risk GTN in 90.2% of cases, consistent with reports in the literature as the most common preceding event[12]. Our study was limited by the insufficient information we received on the gestational events that preceeded GTN among many of our patients that were referred from district hospitals. They often arrived with limited information about previous evacuations, and rarely ever had pathology performed on intrauterine contents when evacuated. Therefore, we made our best judgement concerning the preceeding event based on the patient's history. This could potentially lead to underscoring in the FIGO/WHO system.

Studies have shown that low risk GTN patients with a FIGO score of 6 and/or a high baselineβ-HCG level (>100,000 mIU/ml) are more likely to develop resistance to single agent chemotherapy and will require multi-agent chemotherapy.[3] The results from the present study were consistent with these findings, as patients with a FIGO/WHO risk score of 6 or hCG level of >100,000 mIU/ml had higher rates of resistance to 5D IM methotrexate, with only 66.7% of these patients achieving a complete remission. At Sheffield Centre for Trophoblastic Disease, Weston Park Hospital, UK, patients with low risk GTN were treated with IM Methotrexate 50mg every other day (1,3,5,7) alternating with 15mg of folinic acid. Resistance rates were 81% among patients with FIGO/WHO score of 6 and 84% among patients with β-HCG ≥100,000 mIU/ml,and 33 of the 36 patients who scored FIGO/WHO 6 also had a FIGO/WHO score of 4 for hCG level[13].The increased resistance in patients with β-HCG ≥100,000mIU/ml was not statisitically significant in our study. This may be explained by the limited number of patients in our study population. Another challenge we face with

managing GTN patients is the inconsistency in β-HCG results among different labs within the country and even within our own laboratory. More often when results are suspected as erroneous, they are falsely low. Therefore, this could also contribute to our lack of statistical significance in our resistant patients with β-HCG >100,000 mIU/ml, and could also contribute to inaccurate FIGO/WHO risk scoring. The factor we did find to significantly decrease the rate of resistance to our 5D IM methotrexate regimen was pre-treatment hysterectomy (P=0.013).This was also reported by Eysbouts et al during their assessment of the added value of hysterectomy in the management of GTN in the the Netherlands[14].

Gastrointestinal disorders have been reported as the most common side effects of MTX, affecting up to 73% of patients[15]. The most common gastrointestinal adverse event observed in our study was oral mucositis at 60.9%. Kizaki et al, at Tokyo Women's Medical University,observed that mucositis complicated 30.7% of patients treated with a similar 5D IM MTX regimen. Maesto et al., at The New England Trophoblastic Disease Center, found mucositis in 40% of patients on 8-Day MTX/Folic acid regimen. Mucositis gradually subsides, leaving no scars, over a period of 2–3 weeks after drug administration[16]. Oral salt water rinse is currently advised daily in all of our patients at the initiaiton of MTX to try to decrease mucositis rates[17].

Overall, the outcome of women diagnosed and treated for low-risk GTN at CHUK is favorable. Five-day IM Methotrexate appeared to be feasible and safe with tolerable side effects. However, pre-treatment HCG levels of ≥100,000 mIU/mL and a FIGO/WHO risk score of 6 influenced the development of MTX resistance. Our study was limited by the relatively small number of patients diagnosed with low risk GTN during our study period compared with that of larger Gestational Trophoblastic Diseases Centers. However, we believe this data is important in defining a feasible treatment regimen in a low resource setting, taking into consideration multiple treatment barriers.

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Table 1 FIGO/WHO Scoring system for gestational trophoblastic neoplasia[7]

Table 1
FIGO/WHO scoring system for gestational trophoblastic neoplasia.

International Federation of Gynaecology and Obstetrics (FIGO)/World Health Organisation (WHO) score	0	1	2	4
Age (years)	<40	⩾40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4–6	7–13	>13
Pre-treatment HCG (iu/l)	<1000	1000–10,000	10,000–100,000	>100,000
Largest tumour mass (cm)	<3	3–5	>5	–
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Monotherapy	Combined therapy

hCG is human chorionic gonadotrophin.
Score is calculated by the addition of each variable score to gain a total score.
Total scores are classified as low risk of resistance if 0–6 and high risk if more than 7.

Table 2 Socio-demographic characteristics of participants

Socio-demographics	Frequency (N=41)	%
Age		
20-35 years	23	56.1
>35 years	18	43.9
Marital status		
Married	36	87.8
Single	2	4.9
Divorced	2	4.9
Cohabiting	1	2.4
Province		
Kigali	12	29.3
North	8	19.5
South	10	24.4
East	8	19.5
West	3	7.3
Occupation		
Farmer	28	68.3
Government employee	1	2.4
Business/self employed	9	22.0
Unemployed	3	7.3

Table 3 Characteristics of GTN

Variables	Frequency	%
Gestational event leading to GTN		
Molar pregnancy	37	90.2
Abortion	3	7.3
SVD	1	2.4
Greatest tumor size		
<3 cm	5	12.2
3-4 cm	32	78.0
>= 5cm	4	9.8
Pathological characteristics		
Choriocarcinoma	10	24.4
Invasive mole	31	75.6
Baseline B-HCG (mIU/ml)		
<1,000	1	2.4
1,000-10,000	6	14.6
10,000-100,000	25	61.0
>100,000	9	22.0
FIGO prognostic score		
3&4	11	26.8
5	15	36.6
6	15	36.6
Metastasis (Lung n=1, vagina n=3)		
Yes	4	9.8
No	37	90.2

Table 4 Methotrexate cycles required for complete remission according to pre-treatment intervention

Surgical intervention	Outcome after 5D-MTX	5D-Methotrexate cycles			P value
		1-5 cycles	6-9 cycles	10-13 cycles	
Hysterectomy	Complete remission	10 (71.4%)	2 (14.3%)	2 (14.3%)	0.013
	Resistance	0 (0.0%)	3 (100.0%)	0 (0.0%)	
Evacuation or no procedure	Complete remission	4 (21.1%)	12 (63.2%)	3 (15.8%)	0.477
	Resistance	1 (20.0%)	2 (40.0%)	2 (40.0%)	

Table 5 GTN characteristics and outcome

	Outcome		0R (95% CI)	P value
	Complete remission	Resistance		
Gestational event leading to GTN				
Molar pregnancy	29 (78.4%)	8 (21.6%)	0.86 (0.03-23.2)	0.93
Abortion	3 (100.0%	0 (0.0%)	0.42(0.01-33.5)	0.703
SVD	1 (100%)	0 (0.0%)	Ref	
Greatest tumor size				
<3 cm	5 (100%)	0 (0.0%)	Ref	
3-4 cm	25 (78.1%)	7 (21.9%)	3.2 (0.16-65.4)	0.444
>= 5cm	3 (75.0%)	1 (25.0%)	4.7 (0.15-151)	0.381
Pathological characteristics				
Choriocarcinoma	7 (77.8%)	2 (22.2%)	0.91 (0.15-5.60)	0.922
Invasive mole	23 (79.3%)	6 (20.7%)		
Baseline B-hCG (mIU/ml)				
<1,000	1 (100%)	0 (0.0%)	Ref	
1,000-10,000	6 (100%)	0 (0.0%)	0.23 (0.01-17.0)	0.504
10,000-100,000	20 (80.0%)	5 (20.0%)	0.8 (0.02-22.6)	0.898
>100,000	6 (66.7%)	3 (33.3%)	1.6 (0.05-51.1)	0.785
FIGO prognostic score				
3&4	11 (100.0%)	0 (0.0%)	Ref	
5	12 (80.0%)	3 (20.0%)	6.4 (0.2-138.6)	0.234
6	10 (66.7%)	5 (33.3%)	12 (0.5-245.3)	0.105
Metastasis (Lung n=1, vagina n=3)				
Yes	3 (75%)	1 (25%)	1.4 (0.12-15.8)	0.771
No	30 (81.1%)	7 (18.9%)		

CHUK/OBGYN Department

INVESTIGATOR: Dr UWITONZE Gilbert

SUPERVISOR: Dr Lisa Bazzett-MATABELE

RESEARCH QUESTIONNAIRE

Title:

OUTCOMES OF WOMEN WITH LOW-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA TREATED WITH 5-DAY METHOTREXATE REGIMEN AT CHUK

PARTICIPANT IDENTIFICATION

Initials:
File Number:

Patient demographic information

1. Age

2. Province of origin:

3. Occupation:

a)Farming
b) Civil Servant
c) Business
d) Health worker/
e) Others(Specify)

4.Marital Status

a) Single
b) Married
c) Divorced
d) Cohabiting
e) Widow
f)Separated

Gynecology Obstetrical Antecedents

5.Gravidity:

6.parity:

7.Abortions:

8.preterm deliveries:
9.Hydatiform moles:

Clinical data

10.Gestational Age:

11.Gestational event leading to GTN :1.Molar pregnancy
2.Abortion
3.Term Delivery
4.Other :

12. Interval months from end of
Gestational event to diagnosis:

13. Interval time from first evacuation to treatement:

14.Pre-treatment B-HCG:
Baseline bhcg (if different from pretreatment bhcg):

15.Greatest Tumor size :

16.Location of metastases:

17.Number of Metastases:

18:FIGO/WHO Prognostic score:

19. Hysterectomy or
evacuation for treatment:
20. If Hysterectomy, done after treatment initiated : Yes
No
21.Number of cycles of 5D Methotrexate:

22.outcome after 5D Methotrexate therapy: 1.complete remission
2.Resistance requiring change to new agent
3.Relapse
4.death
5.other

23. Duration in months until Complete Remission(if applicable):

24.Pathology result (if available)

25.Side effects of MTX?
1.Neutropenia (ANC<1500)
2.Stomatitis
3. Nausea
4. Alopecia
5. Other

26. Delay in treatment due to side effects ? 1.yes
2. No
27 How many cycles were delayed: