

RESEARCH ARTICLE

Outcomes of Metastatic Gestational Trophoblastic Neoplasia: Fourteen Year Experience from a Northern Thailand Tertiary Care Center

Prapaporn Suprasert*, Sitthicha Siriaree, Manatsawee Manopunya

Abstract

Metastatic gestational trophoblastic neoplasia (GTN) is an uncommon cancer. The principal treatment consists of chemotherapy with or without surgery or radiotherapy. We here retrospectively reviewed the outcomes of metastatic GTN treated at our institute between January, 1999 and December, 2013. Sixty-three patients met the criteria. The median age was 30.0 years and almost 90% were referral cases. Nearly 40% of the studied patients presented with vaginal bleeding while 22.2% were asymptomatic. The most common antecedent pregnancy was hydatidiform mole (57.1%) followed by term pregnancy (20.6%). The median interval time from antecedent pregnancy to the development of GTN was three months and the median pretreatment B-hCG was 58,274 mIU/ml. Stage III (74.6%) was the most common staging followed by stage IV (20.6%) and stage II (4.8%). The most frequent surgery was hysterectomy (31.7%). Thoracotomy and craniotomy were performed in three and two patients, respectively. The most common first line chemotherapy regimen was methotrexate and folinic acid (36.5%) followed by EMA (etoposide, methotrexate, actinomycin D) (34.9%), EMACO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) (17.5%) with the remission rate of 66.7%. Nearly one-third of the patients were given a subsequent chemotherapy regimen after failure with the first line therapy and showed a final response rate of 73.0%. However, in stage IV, the response to first line treatment was only 38.5%. In conclusion, the outcomes of metastatic GTN were poor especially with the higher stages.

Keywords: Metastatic gestational trophoblastic neoplasia - outcomes - treatment - Thailand

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Introduction

Gestational trophoblastic neoplasia (GTN) is the malignant form of gestational trophoblastic disease, an uncommon disease of the placenta consisting of invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (EST). Both PSTT and EST are very rare diseases while invasive mole and choriocarcinoma are frequently found in this type of tumor (Seckl et al., 2013). The incidence of choriocarcinoma varied between two and seven per 100,000 pregnancies (Sharifi et al., 2014). GTN often occurred subsequently from molar pregnancy in 60%, from abortion in 30% and from normal pregnancy or ectopic pregnancy in the remaining patients (Seckl et al., 2013). The characteristics of invasive mole and choriocarcinoma are quite different from PSTT and EST. Both invasive mole and choriocarcinoma present with a high level of human chorionic gonadotropin (hCG) and show high cure rates with chemotherapy. On the contrary, PSTT and EST have low hCG level and were very resistant to chemotherapy (Biscaro et al., 2015).

FIGO suggested that GTN should include only invasive mole and gestational choriocarcinoma due to their similar characteristics (Ngan et al., 2012). GTN often metastasizes via hematologic spreading to the lungs in about 80%, to the vagina in 30% and to the brain or liver in 10% (Biscaro et al., 2015). The FIGO staging system was revised in 2000 with a definition of metastasis to the genital organs as stage II, to the lungs as stage III and other organ metastasis as stage IV. The treatment is dependent on the WHO risk score. The low risk patients included GTN cases with disease confined to the uterus or stages II and III that showed a total risk score less than seven while high risk is defined as the GTN patients with a total risk score of at least seven or stage IV (Ngan et al., 2012; Froeling and Seckl, 2014; Biscaro et al., 2015). To date, the principle management of metastatic GTN is single or a combination of chemotherapy with or without adjuvant surgery and radiotherapy. The most common chemotherapy regimen has been EMACO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) that achieved primary remission varying between 54 and 91% (Biscaro et al., 2015). In Thailand, there is still limited data regarding

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand *For correspondence: psuprase@gmail.com

the outcomes of the treatment of metastatic GTN and we recently reported the experience over twelve years of our center for treatment of non-metastatic GTN with impressive outcomes (Suprasert and Manopunya, 2015). To complete the series of GTN treated at our institute, this retrospective review was conducted to identify the clinical picture and outcomes of treatment in these groups of patients. The results will be beneficial for the improvement of treatment in this rare disease.

Materials and Methods

After the local Ethics Committee approved our protocol, the patients who were diagnosed with metastatic GTN treated at Chiang Mai University Hospital between January, 1999 and December, 2013 were retrospectively reviewed. Neither PSTT nor ETT were included. After being diagnosed as GTN with the standard criteria (Ngan et al., 2012), the patients received a complete physical and pelvic examination and further routine investigation with chest x-ray and/or pelvic ultrasonography. If the CXR revealed metastasis or abnormal neuro signs were presented, the CT- scan of brain were done subsequently.

Table 1. Basic Clinical Data (N= 63)

| | N (%) |
|---|-----------------------|
| Median Age (Range, Year) | 30.0(15-54) |
| Address | |
| Chiang Mai | 21 (33.3) |
| Chiang Rai | 9 (14.3) |
| Mae Hong Son | 5 (7.9) |
| Lamphun | 5 (7.9) |
| Other | 23 (36.5) |
| Referral Cases | 58 (92.1) |
| Symptom | |
| None | 14 (22.2) |
| Vaginal Bleeding | 24 (38.1) |
| Hemoptysis | 7(11.1) |
| Abdominal Pain | 6(9.5) |
| Other | 12 (19.0) |
| Antecedent Pregnancy | |
| Complete Mole | 36 (57.1) |
| Term Pregnancy | 13(20.6) |
| Abortion | 8(12.7) |
| Unknown | 5 (7.9) |
| Median Interval (Range, Months) | 3.0 (1-384) |
| Median Pretreatment B-hCG (range, mIU/ml) | 58,274 (58-4,124,000) |
| Abnormal Chest X-ray | 52(82.5) |
| Number of Pelvic Ultrasonography | 47 |
| Abnormal Pelvic Ultrasonography | 36 (76.6) |
| Number of CT-brain | 52 |
| Abnormal CT-brain | 8(15.4) |

The abdominal CT-scan or MRI was done in some patients whose clinical indicated. The treatment depended on the attending physician.

The basic clinical data, the antecedent pregnancy, the histology, the level of pretreatment B-hCG, the imaging results, the type and cycle of chemotherapy, the surgical intervention and the outcomes of treatment were collected. Descriptive data of all studied patients were presented as median with range and discrete data were recorded as number and percentages. SPSS for Windows program (Version 17.0, Chicago, IL, USA) were used to analyze the statistical data.

Results

Sixty-three patients met the inclusion criteria and were recruited into this study. The basic clinical data was presented in Table 1. The median age was 30.0 years old with a range from 15-54 years old with about one-third living in Chiang Mai. However, over 90% of the participants were referral cases. Of these patients, eight cases were given chemotherapy from their primary hospital for treatment in seven cases and for prophylactic chemotherapy in one case. About 20% of the studied patients were asymptomatic while about one-third presented with abnormal vaginal bleeding. The most frequent antecedent pregnancy was hydatidiform mole followed by term pregnancy and abortion. The median interval time from the latest pregnancy to diagnosis of GTN was three months. The median pretreatment of B-hCG was 58,274 mIU/ml. Fifty-two patients had an abnormal chest x-ray and all of them were further investigated with a brain CT which showed positive results in eight cases. The pelvic ultrasonography was done in 47 cases and the lesion was found in 36 cases. Only eight cases (12.7%) had tissue diagnosis confirmed as choriocarcinoma. The FIGO staging of the studied patients were as follows: stage II in three cases (4.8%), stage III

Table 2. Type of Surgical Intervention

| | N (%) |
|--|---------|
| Vaginal Biopsy | 1(3.6) |
| Arterial Embolization | 1(3.6) |
| TAH | 9(32.1) |
| TAH and BSO | 5(17.8) |
| TAH and Right SO and Wedge Resection at Jejunum | 3(10.7) |
| TAH and Right SO and Repaired Bladder and Ureter | 1(3.6) |
| TAH /Pulmonary Wedge Resection* | 2(7.1) |
| Left SO | 1(3.6) |
| Right SO | 1(3.6) |
| Explore Laparotomy | 1(3.6) |
| Thoracotomy | 1(3.6) |
| Craniotomy | 2(7.1) |
| Total | 28(100) |

TAH= Total abdominal hysterectomy; BSO = Bilateral salpingo-oophorectomy; SO = Salpingo-oophorectomy; *TAH a lung resection later

Outcomes of Metastatic Gestational Trophoblastic Neoplasia: 14 Year Experience from a Northern Thai Tertiary Care Center in 47 cases (74.6%) and stage IV in 13 cases (20.6%). A single metastasis site was found in 45 cases (71.4%) while in the remaining 18 cases (28.6%) were found multiple metastasis sites. However, the most common involvement organ was the lung found in over 90% of the studied patients. Of these patients with lung metastasis, five cases were detected by CT-scan. The details of the metastatic sites were noted in Table 2.

Regarding the treatment, surgical intervention was performed in 28 cases with the details shown in Table 3. The most common procedure was hysterectomy followed by adnexectomy. Moreover, complicated surgery such as craniotomy and thoracotomy including laparoscopic pulmonary wedge resection were done in two and three cases, respectively.

Regarding chemotherapy, all of the studied patients received various regimens as noted in Table 4. For first line treatment, the single methotrexate (MTX) was given in one-third of the patients and the most common combination regimen was etoposide + MTX + actinomycin D (EMA) followed by etoposide + MTX + actinomycin D+ cyclophosphamide and vincristine (EMA-CO) regimen. Unfortunately, 23 cases (36.5%) did not respond to first line chemotherapy and needed to receive a second line treatment and some of them were given further many regimens for salvage chemotherapy. Lastly, two cases received eight regimens of chemotherapy.

Concerning the response rate of treatment by first line chemotherapy, the overall response rate was 66.7% with the best response as 100% was found in stage II while stage III achieved the response rate at 72.3% and the response rate was very poor as 38.5% in stage IV. Finally, with the median follow up time at 35.5 months (1-158 month), 46 patients (73.0%) still in remission while nine cases (14.3%) were still alive with their disease and two cases died whereas six patients were lost to follow up.

Table 5 summarized 13 patients with stage IV. Their outcome was very poor. Brain metastasis was the most frequent metastasis site that was found in nine cases and all received whole brain radiation combined with chemotherapy. Only two cases of brain metastasis

underwent craniotomy. Of these brain metastasis patients, treatment failed occurred in eight cases. However, two cases were in remission. The first one was treated with

Table 3. Organ Site of Metastasis

| | N |
|--------------------|------------|
| Single | 45 (71.4%) |
| Lung | 40 |
| Vagina | 1 |
| Brain | 1 |
| Cervix | 1 |
| Fallopian Tube | 1 |
| Kidney | 1 |
| Combination | 18 (28.6%) |
| Lung/Vagina | 4 |
| Lung/Brain | 5 |
| Lung/Bladder | 2 |
| Lung/Cervix | 1 |
| Lung/Liver | 1 |
| Lung/Vagina/Brain | 2 |
| Lung/Liver/Brain | 1 |
| Lung/Liver/Jejunum | 1 |
| Liver/Spleen | 1 |

Table 4. Chemotherapy

| | N(%) |
|---|----------|
| First Line (N = 63) | |
| MTX+FA | 23(36.5) |
| MTX* | 1(1.6) |
| EMA | 22(34.9) |
| EMP | 6(9.5) |
| EMACO | 11(17.5) |
| Median Number of Cycles (Range) | 6(1-15) |
| Second Line (N = 23) | |
| Actinomycin D | 5(7.8) |
| Weekly MTX | 1(1.6) |
| EMA | 5(7.8) |
| EMACO | 4(6.3) |
| EM-PE | 1(1.6) |
| Cisplatin and Ifosfamide | 3(4.7) |
| Carboplatin and Etoposide | 1(1.6) |
| Cisplatin and Etoposide | 2(3.2) |
| BEP | 1(1.6) |
| Median Number of Cycles (Range) | 4(1-14) |
| Third Line (N = 13) | |
| EMA | 1(1) |
| EMA-CO | 2 |
| EMA-CE | 1 |
| Cisplatin and Fosfamide | 5 |
| ICE | 2 |
| VAC | 1 |
| Etoposide | 1 |
| Paclitaxel | 1 |
| Median Number of Cycles (Range) | 4(2-11) |
| Forth line (N = 9) | |
| EMA-CO | 1(1.6) |
| Cisplatin and Ifosfamide | 2(3.1) |
| Actinomycin D+5 Fluorouracil | 2(3.1) |
| PVB | 1(1.6) |
| Carboplatin and Paclitaxel | 1(1.6) |
| Paclitaxel | 2(3.1) |
| Median Number of Cycles (Range) | 3(1-7) |
| Fifth Line (N = 6) | |
| ICE | 1 (1.6) |
| VAC | 1 (1.6) |
| BEP | 1 (1.6) |
| Cisplatin and Bleomycin and Vincristine | 1 (1.6) |
| Carboplatin and Paclitaxel | 1(1.6) |
| paclitaxel | 2(3.1) |
| Median Number of Cycles (Range) | 1(1-4) |
| Sixth Line (N=4) | |
| Actinomycin D+5 Fluorouracil | 1 (1.6) |
| EMACO | 1(1.6) |
| ICE | 2(3.1) |
| Median Number of Cycles (Range) | 2.5(1-5) |
| Seventh line (N=3) | |
| VAC | 1(1.6) |
| Actinomycin D+5 Fluorouracil | 2(3.1) |
| Median Number of Cycles (Range) | 2(1-2) |
| Eighth line (N = 2) | |
| Paclitaxel | 2(3.1) |
| Median Number of Cycles (Range) | 1(1) |

MTX, M = Methotrexate, FA = Folinic acid, E= etoposide, A = actinomycin D, P=cisplatin, C = cyclophosphamide, O,V = vincristine, B = bleomycin, I = ifosfamide

Table 5. Stage IV Patients (N=13)

| Code | Age | Antecedent pregnancy | Symptom | Site of Metastasis | Treatment | Outcome |
|------|-----|----------------------|-------------------|----------------------------|--|------------------------|
| NP | 55 | Abortion | Vomiting | Lungs and Brain | Craniotomy -> WBRT / EMA x 5 -> EMACO x 3 | AWD ->Lost |
| FK | 60 | Term | Vaginal Bleeding | Lungs and Vagina and brain | TAH&BSO-> WBRT +EMACO x 4 ->PI x 4 -> paclitaxel x 1 | Death |
| PM | 48 | Mole | Vaginal Bleeding | Lungs and Brain | TAH-> MTX&FA x 3->3 years-> lung&brain metastasis -> WBRT+ EMA x 2 -> PI x 3 -> PT x 3 -> VAC x 1-> EMACO x 5 -> Act D& 5 FU x 2 | AWD ->Lost |
| JS | 38 | Mole | GI Hemorrhage | Jejunum and Lung and Liver | Explore laparotomy due to excessive GI bleed -> MTX | Death |
| KP | 16 | Abortion | Unknown | Brain | Craniotomy -> WBRT &EMA x 3 ->BEP x 3 -> remission | Remission Pregnancy |
| AP | 25 | Mole | Abdominal Pain | Kidney | Explore Laparotomy -> EMP x 8 | Remission |
| UP | 33 | Term | Vaginal Bleeding | Lung and Brain | TAH -> EMA x 6 -> PE x 4 -> ICE x 4 -> paclitaxel x 3 -> CBV x 2 | AWD |
| WJ | 27 | Abortion | Vaginal Bleeding | Lung and Vagina and Brain | TAH -> EMACO x 12 | Remission |
| GB | 21 | Mole | Hemoptysis | Lung and Brain | WBRT &EMACO x 3 | AWD -> lost |
| KK | 48 | Mole | Vaginal Bleeding | Lung and Brain | TAB&BSO -> EMACO x 16 -> EMPE x 8 -> PI x 6 | AWD -> lost |
| DR | 17 | Mole | Dyspnea/Hematuria | Lung and Bladder | EMACOx2 ->lost | AWD -> lost |
| KT | 27 | Term | Seizure | Lung and Liver and Brain | WBRT &EMACO x 6 | AWD -> lost |
| SS | 30 | Term | Vaginal Bleeding | Liver and Spleen | EMACO x 15 | Remission |

WBRT = Whole brain radiation, TAH= Total abdominal hysterectomy, BSO = Bilateral salpingo-oophorectomy, GI = gastrointestinal, AWD = Alive with disease; MTX, M = Methotrexate, FA = Folic acid, E= etoposide, A,ACT D = actinomycin D , 5FU = 5 fluorouracil, P =cisplatin, C = cyclophosphamide, O,V = vincristine, B = bleomycin, I = ifosfamide, PT = carboplatin and paclitaxel

craniotomy, whole brain radiation and chemotherapy and became pregnant after complete treatment. She had single site metastasis. However, no other imaging was performed for her before treatment. The second case was treated with whole brain radiation and chemotherapy. She was also found to have lung and vagina metastasis. She underwent a hysterectomy after complete chemotherapy. The most severe case of stage IV patients was a 38-year old that presented with severe lower gastrointestinal hemorrhage. She had emergency surgery performed due to the massive bleeding from her jejunum and liver involvement and nothing could be done. She was given only one dose of MTX and passed away.

Discussion

The present study reviewed the clinical characteristics of metastatic GTN. We found pulmonary metastasis as high as 90% which was slightly more frequent than the previous report at 80%. However, brain metastasis and vaginal metastasis were found about 10% similar

to a former report (Biscaro et al., 2015). About the antecedent pregnancy, term pregnancy was found in 20% especially in stage IV that was found as high as 30% in the present study. This was more frequent than that observed in non-metastasis GTN which we recently reported term antecedent pregnancy at 3.7% (Suprasert and Manopunya,2015). This data supported a previous study that showed antecedent term pregnancy was often found in higher stages and it raised the score in the WHO scoring system (Froeling and Seckl, 2014). High levels of B-hCG were observed in metastatic GTN patients. The pretreatment B-hCG in the present study was about 58,274 mIU/mL that was around ten times higher than non-metastatic GTN patients in our recent study (Suprasert and Manopunya, 2015).

Regarding management modality, chemotherapy is the main treatment. Single drug with MTX or actinomycin D was allowed in patients with metastasis who had FIGO scoring less than seven usually in stage II or III. In the present study, single MTX was given in about 30% as first line drug and 8% in second line drug. For patients with

a score greater than seven, many combination regimens were studied in many publications such as EMACO, EMA, MAC (methotrexate, actinomycin D, chlorambucil), CHAMOCA (cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan and vincristine) (Deng et al., 2013; Even et al., 2014; Fülöp et al., 2014). However, the data from Cochrane Collaboration review suggested that CHAMOCA should not be recommended for GTN due to more toxicity and it was not more effective than the MAC regimen from randomized controlled trials (RCT). Currently, the most widely used as first line combination chemotherapy for high risk GTN is EMACO due to fewer side effects and good efficacy that showed a response rate in a range from 54 to 91%, even though this regimen did not rigorously compare to MAC in RCT (Deng et al., 2013; Fülöp et al., 2014; Biscaro et al., 2015). Concerning EMA regimen, Even et al. recently reported a very impressive complete response rate at 94.7% in 95 high risk GTN patients (Even et al., 2014). In the present study, the response achieved from various first lines of chemotherapy was 66% which was in a range of previous study (Biscaro et al., 2015). To improve the outcome of EMACO regimen, Alifrangis et al. from Charing Cross Gestational Trophoblastic Disease Centre presented a better outcome with induction low dose etoposide and cisplatin (EP) before giving an EMACO regimen in selected high risk patients that were defined as hCG > 100,000 IU/L and a score over 12. The authors compared 33 patients who received induction course of etoposide 100 mg/m² and cisplatin 20 mg/m² for one to two courses before start of EMACO with 107 patients who were given only the EMACO regimen. The results showed a significantly lower early death rate in patients with EP induction (0.7%) when compared to patients without EP induction (7.2%) (Alifrangis et al., 2013).

In the cases of resistance to first line chemotherapy, various regimens were previously reported with modest outcomes such as EMACE (etoposide, methotrexate, actinomycin D, cisplatin, etoposide), TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide), Act-D & 5FU (actinomycin D & 5 fluorouracil), BEP (bleomycin, etoposide, cisplatin), ICE (ifosfamide, cisplatin, etoposide) (Manopunya and Suprasert, 2012; Biscaro et al., 2015). In the present study, 36% of the studied patients were resistant to first line chemotherapy. This resistance rate was similar to the previous report that found 20-30% of high risk patients experienced resistance to first line chemotherapy (Biscaro et al., 2015). Ngan et al. suggested that surgery might play a role in selected cases who presented with lung, liver, brain, or other site involvement that did not regress with chemotherapy regimen (Ngan et al., 2012). In the present study, about 44% underwent surgical intervention with favorable outcomes.

Regarding management in brain metastasis, the treatment consisted of chemotherapy with EMACO or EMACE regimen and whole brain radiation and craniotomy in some cases with a solitary lesion (Biscaro et al., 2015). However, Savage et al. from Charing Cross Gestational Trophoblastic Disease Centre recently reported the alternative treatment with intrathecal methotrexate combined with high dose EMACO regimen.

Their result of treatment achieved a response rate of 85% (Savage et al., 2015) that was higher than the study from Brewer Trophoblastic Disease Center that utilized a combination chemotherapy with brain irradiation and found the response rate about 51% (Neubauer et al., 2012). In the present study, we did not give intrathecal MTX in cases with nine brain metastatic patients and we found only two cases achieved remission while the other cases had very poor outcomes.

The limitation of this study was the inability to identify the FIGO prognostic score due to the missing data of the score in most cases. However, the strength of this report was the study that revealed the outcomes of metastatic GTN with a greater number of these rare disease patients.

In finally, the outcomes of metastatic GTN with the first and second line treatment of chemotherapy was poor especially in higher stage. Other management modalities should continue to be studied to improve the treatment outcomes of this rare disease.

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