RESEARCH ARTICLE

Treatment of Extremely High Risk and Resistant Gestational Trophoblastic Neoplasia Patients in King Chulalongkorn Memorial Hospital

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Abstract

Background: Gestational trophoblastic neoplasia (GTN) is a spectrum of disease with abnormal trophoblastic proliferation. Treatment is based on FIGO stage and WHO risk factor scores. Patients whose score is 12 or more are considered as at extremely high risk with a high likelihood of resistance to first line treatment. Optimal therapy is therefore controversial. Objective: This study was conducted in order to summarize the regimen used for extremely high risk or resistant GTN patients in our institution the in past 10 years. Materials and Methods: All the charts of GTN patients classified as extremely high risk, recurrent or resistant during 1 January 2002 to 31 December 2011 were reviewed. Criteria for diagnosis of GTN were also assessed to confirm the diagnosis. FIGO stage and WHO risk prognostic score were also re-calculated to ensure the accuracy of the information. Patient characteristics were reviewed in the aspects of age, weight, height, BMI, presenting symptoms, metastatic area, lesions, FIGO stage, WHO risk factor score, serum hCG level, treatment regimen, adjuvant treatments, side effects and response to treatment, including disease free survival. Results: Eight patients meeting the criteria of extremely high risk or resistant GTN were included in this review. Mean age was 33.6 years (SD= 13.5, range 17-53). Of the total, 3 were stage III (37.5%) and 5 were stage IV (62.5%). Mean duration from previous pregnancies to GTN was 17.6 months (SD 9.9). Mean serum hCG level was 864,589 mIU/ml (SD 98,151). Presenting symptoms of the patients were various such as hemoptysis, abdominal pain, headache, heavy vaginal bleeding and stroke. The most commonly used first line chemotherapeutic regimen in our institution was the VAC regimen which was given to 4 of 8 patients in this study. The most common second line chemotherapy was EMACO. Adjuvant radiation was given to most of the patients who had brain metastasis. Most of the patients have to delay chemotherapy for 1-2 weeks due to grade 2-3 leukopenia and require G-CSF to rescue from neutropenia. Five form 8 patients were still survived. Mean of disease free survival was 20.4 months. Two patients died of the disease, while another one patient died from sepsis of pressure sore wound. None of surviving patients developed recurrence of disease after complete treatment. Conclusions: In extremely high risk GTN patients, main treatment is multi-agent chemotherapy. In our institution, we usually use VAC as a first line treatment of high risk GTN, but since resistance is quite common, this may not suitable for extremely high risk GTN patients. The most commonly used second line multi-agent chemotherapy in our institution is EMA-CO. Adjuvant brain radiation was administered to most of the patients with brain metastasis in our institution. The survival rate is comparable to previous reviews. Our treatment demonstrated differences from other institutions but the survival is comparable. The limitation of this review is the number of cases is small due to rarity of the disease. Further trials or multicenter analyses may be considered.

Keywords: Gestational trophoblastic neoplasia - high risk cases - salvage treatment - recurrence

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Introduction

Gestational trophoblastic neoplasia (GTN) is a spectrum of diseases with abnormal trophoblastic proliferation. GTN includes invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) (Lurain, 2011). GTN is diagnosed clinically and classified by FIGO anatomical staging and WHO risk factor scoring system (Hertz et al., 1956; Lurain et al., 1995; Osborne et al., 2012). Criteria for diagnosis of postmolar GTN include at least 1 of the followings (Osborne et al., 2012). *i*) Plateau of hCG level for 4 consecutive values over 3 weeks; *ii*) Rising of hCG >10% for 3 values over 2 weeks; *iii*) Persistence of hCG more than 6 months after molar evacuation; *iv*) Histopathologic diagnosis of Choriocarcinoma; *v*) Presence of metastatic

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disease

Previously, GTN was a high mortality disease. Thanks to the improvement of the efficacy of chemotherapeutic agents, nowadays GTN is considered as a curable disease. Treatment of GTN is based on FIGO stage and WHO risk factors score (Roberts et al., 1996). Patients whose score are less than 7 are classified as low risk patients. Single agent chemotherapy is considered as the first line treatment for low risk patients. Two most commonly used single agent chemotherapies are Methotrexate and Actinomycin D. On the other hand, patients whose score are 7 or more are classified as high risk GTN and multi-agent chemotherapy should be administered as first line treatment for these patients (Lurain, 2011).

According to high risk group, they are sub-classified into high risk and extremely high risk subtype. The patients whose score are 12 or more are considered as extremely high risk which has higher chance of resistance to first line treatment (Osborne et al., 2012). Some literatures claimed that EMA-CO regimen has lower response rate than EMA-EP when it was administered as first line treatment (Osborne et al., 2012). Moreover, mortality rate of extremely high risk GTN is significantly more than high risk GTN whose scores are less than 12. In extremely high risk patients who have brain and liver metastasis, survival rate is as low as 10% (Lurain, 2011). Cure rate of extremely high risk patients is 82% which is much poor than high risk GTN whose scores are less than 12 (Lurain, 2011). However, the treatment of extremely high risk group is still controversy. Cochrane database review shows that there is no randomized controlled trial comparing the regimen of treatment in high risk and recurrent GTN (Alazzam et al., 2012; Deng et al., 2013). Moreover, there is no consensus about the gold standard of treatment in the extremely high risk GTN. Nowadays, treatment of extremely high risk GTN patients is varies. Moreover, treatment regimens especially in second or third line chemotherapy in extremely high risk are different in each institution. While several regimen of multi-agent chemotherapy are used, the prognosis is still poor. This study was conducted in order to summarize the regimen used in extremely high risk or resistance GTN patients in our institution in past 10 year's duration.

Materials and Methods

After approval from ethical committee was received, this retrospective study was conducted. All GTN charts were reviewed in order to select extremely high risk, recurrent or resistant cases. All the extremely high risk and resistant GTN patients during 1 January 2002 and 31 December 2011were review.

Extremely high risk GTN is defined as patients whose score are 12 or more. Recurrent or resistant GTN is defined as high risk GTN patients who resisted first line multi-agent chemotherapy. After of all GTN patients' charts were reviewed, we can identified 8 cases of extremely high risk and resistant GTN patients. Criteria for diagnosis of GTN were reviewed to confirm the diagnosis for those patients. FIGO stage and WHO risk prognostic score were also re-calculated to ensure the accuracy of the information. Patient characteristics were reviewed in the aspect of age, weight, height, and BMI. Other date such as presenting symptoms, metastatic area, number of lesions, FIGO stage, WHO risk factors score, serum hCG level, treatment regimen, adjuvant treatments, side effects and response of treatment including disease free survival are also collected.After all data were collected, statistic process was performed by SPSS version 17. All the data were calculated with mean, mode, median, percentage and SD.

Results

Retrospective chart review was conducted. All charts of GTN patients whom attended in King Chulalongkorn Memorial Hospital during January 2002 and 31 December 2011 were reviewed. Data were collected. Eight patients whom met the criteria of extremely high risk or resistant GTN were included in this reviewed. Mean age of the patients was 33.6 years (SD=13.5, range 17-53). From total 8 patients, 3 of them were stage III (37.5%) and 5 of them were stage IV (62.5%). According to previous pregnancy history, 5 form 8 patients (62.5%) had previous abortion, 2 of them had previous term pregnancy (25%) and the other one patient had history to molar pregnancy (12.5%). Details of previous pregnancy of each patient are presents in table 1. Duration form previous pregnancy ranged from 7-36 months. Mean duration between previous pregnancies to GTN is 17.6 month (SD 9.9). Mean BMI was 20.7 kg/m^2 (SD 3.55, range 15.6-25). Pretreatment serum hCG level ranged from 200,000 to 3,109,700 mIU/ml. Mean serum hCG level was 864,589.63 mIU/ml (SD 98,151). Presenting symptoms of the patients were varies such as hemoptysis, abdominal pain, headache, heavy vaginal bleeding and stroke. However, the most common presenting symptoms in the patients with brain metastasis were headache. Sixty percent of them (3 from

Table 1. Details of Disease and Treatment in Each Patient

#Case	Age	Stage	Score	Previous	Presenting symptoms	hCG (mIU/ml)	1st line× cycle	Adjuvant treatment	2nd line× cycle	3rd line× cycle	result pregnancy	DFI (months)
1	47	III	16	Abortion	hemoptysis	1,125,000	VAC×7	No	No	No	NED	55
2	20	IV	17	Abortion	Headache	692,771	VAC×8	Brain RT	EMACO×5	No	NED	61
3	17	IV	17	Abortion	Abdominal pain	3,109,700	EP×2	Brain RT	EMACO×15	No	NED	19
4	33	III	11	Term	Vaginal bleeding	200,000	VAC×3	TAH	EP×6 and Brain RT	No	Dead	7
5	35	IV	18	Molar	headache	1,000,000	EMACO×13	Brain RT	No	No	NED	60
6	21	IV	15	Abortion	headache	404,755	VAC×3	No	EMACO×5 and TAH splenectomy	ICE×1, TP/TE×2, Carbo/Gem×2	Dead	0
7	53	IV	18	Abortion	Hemiparesis	315054	EP×1	Brain RT	EMACO×8	No	Dead/(Sepsis)	6
8	43	III	12	Term	Massive vaginal bleeding	69437	Cis-5FU	Pelvic RT	EMACO×7	No	NED	10

5 patients) presented with headache. Another one brain metastasis patient presented with sudden hemiparesis and required emergency craniotomy. While the patients who did not have brain metastasis presented with hemoptysis, vaginal bleeding and abdominal pain. Mean of largest tumor diameter was 4.75 cm (SD 0.71, range 3-5 cm). Mean number of metastasis was 6.25 (SD 2.66, range 1-8 lesions).

According to the physical status of the patients before treatment, their ECOG score were varied. Most of their ECOG scores were 1-2 (62.5%) while, 37.5% were ECOG score 3. Half of the patients had anemia before starting chemotherapy. Chest film abnormalities were identified in 50% of the patients. Most of the patients presenting with hemoptysis had abnormal chest film. According to brain metastasis, three patients underwent craniotomy before administered chemotherapy due to increase intracranial pressure form intracranial hemorrhage. In the aspect of bleeding complication, one patient had to undergo uterine arteries embolization before starting chemotherapy because of massive vaginal bleeding form vaginal metastasis. Focusing on metastatic sites, fifty percent of the patients have lung metastatic lesions in chest film. Vaginal metastasis was identified in 2 patients and uterine lesions were also identified in 3 patients. Brain metastasis was found in 5 from 8 patients and only 1 of them died (20%). Liver metastasis was also found in 2 from 8 patients and 1 on them died (50%).

On the aspect of the treatment, the most commonly used first line chemotherapeutic regimen in our institution is VAC regimen which was given to 4 form 8 patients in this study. EP regimen was given to 2 patients and the rest of the patients received EMACO and Cisplatin-5FU regimens. Most of the patients who resisted VAC received EMACO regimen as a second line chemotherapy. From this reason, the most common second line chemotherapy in our institution was EMACO. The other regimens used as second line and third lines were EMA-EP, ICE, TP/TE and Cisplatin- Gemcitabine. However, response rate of those regimens were not impressive. Adjuvant radiation was given to most of the patient who had brain metastasis. Surgical intervention was used for many reasons in some patients such as in order to get rid of resistant foci in patient number 6 and for control bleeding in the patient number 4. Details of each patient were demonstrated in Table 1. According to the side effects of chemotherapy, the most common side effect was bone marrow suppression. Most of the patients had to delay chemotherapy for 1-2 weeks due to grade 2-3 leukopenia and required G-CSF to rescue them from neutropenia.

Focusing on the survival, 5 form 8 patients were still survived. Mean of disease free survival was 20.37 months. Disease free interval ranged from 0-61 months. Three patients died (the cases number 4, 6 and 7). Both of the patients who died of the disease (case number 4 and 6) resisted second line and third line chemotherapy and then progressed during chemotherapy administration. The case number 4 presented with heavy vaginal bleeding from vaginal metastasis. She received VAC regimen as a first line chemotherapy. During her first cycle of VAC, she developed heavy vaginal bleeding and hysterectomy was performed in order to stop bleeding. After the operation, VAC regimen was continued. Unfortunately, her hCG level rose after 5th cycle of VAC regimen. Metastatic work up was performed and new lesions of brain metastasis were identified. Therefore, the regimen was changed into EP regimen for 5 cycles and brain RT was administered. Complete remission was achieved. However, the patient lost to follow up and came to hospital again 7 months later with hemiparesis from recurrent brain metastasis and finally death before re-induction of chemotherapy was started. Another case that died of disease is case number 6. She presented with headache from intracranial hemorrhage. She was referred from other hospital to neurosurgeon and craniotomy was donefor stop bleeding. The pathological report was choriocarcinoma. After that, gynecologic oncologist was consult. She received brain RT and VAC regimen for 3 cycles then her hCG elevated again. EMACO regimen was administered and TAH with splenectomy was performed to remove the resistant foci. However, her hCG was continue rising. ICE, TP/TE and Carboplatin-Gemcitabine regimens were given but the disease still progressed. The patient died 9 months after start treatment. Another one patient who died from other causes is the case number 7; she died of sepsis from pressure sore wound infection in 6 months after complete remission was achieved. None of survival patients developed recurrence of the disease after complete treatment.

Discussion

GTN is a rare trophoblastic disease. Spectrum of the disease is varies from non-metastatic to systematic metastatic diseases.Treatment of GTN is depended on FIGO stage and WHO risk factors scores. In extremely high risk GTN patients, main treatment is multi-agent chemotherapy (Osborne R et al., 2012). Some literatures suggest that EMA-EP should be used as the first line chemotherapy instead of EMA-CO because response rate of EMA-EP is better than EMA-CO (Cyriac S et al., 2011. However, some still insist to use EMA- CO as the first line treatment (Lurain et al., 2010; Alazzam et al., 2012; Deng et al., 2013). In our institution, we usually use VAC as a first line treatment of high risk GTN. There is a retrospective review about metastatic GTN in our institution during January 1984 to December 1995 (Limpongsanurak et al., 1999) .From that review, low risk GTN patients were received Actinomycin D and their complete remission rate was 94.7%. In high risk GTN patients who received VAC regimen (Vincristine 1 mg on day 1, Actinomycin D 10 microgram/kg/d on day 1-5 and Cyclophosphamide 200mg/d on day 1-5 for every 14-21 days) as a first line treatment, their complete remission rate was 86.7% (Limpongsanurak et al., 1999). Response rate of VAC regimen in high risk GTN is very good. However, response rate of VAC regimen in extremely high risk patients was inconclusive from that review. From this study, VAC regimen resistance is commonly found in extremely high risk GTN patients in our institution. For this reason, VAC regimen may not be suitable for extremely high risk GTN patients.

Second line treatment of extremely high risk GTN is more controversy. Some literatures claimed that 20-30% of high risk GTN failed first line treatment and had to receive second line chemotherapy. In patients who resisted second line chemotherapy, third line chemotherapy may be considered. Several regimens were proposed as third line treatment such as TP/TE, BEP, ICE, Carboplatin/Gemcitabine (Bianconi et al., 2007; Wong et al., 2008; Patel et al., 2010; Feng et al., 2011; Alazzam et al., 2012; Lurain et al., 2012). The efficacy of those regimens was acceptable (Bianconi et al., 2007; Feng et al., 2011; Lurain et al., 2012). Owing to the rarity of the cases, there are no randomized controlled trials compare the efficacy of those regimens. Nowadays, there are only case series and small trials to demonstrate the efficacy of each regimen. The most commonly used second line multi-agent chemotherapy in our institution is EMA-CO which is different from other studies that use EMA-CO as first line treatment. Adjuvant brain radiation was administered to most of the patients with brain metastasis in our institution to prevent intracranial hemorrhage. According to surgical intervention in GTN, the aims for surgery were to remove of resistant foci and treat the complications such as bleeding or infection (Lurain, 2011; Osborne et al., 2012). In our institution, some surgical interventions are used to control complications such as hysterectomy for bleeding complication and some surgical interventions are used to remove the resistant foci. The reason for surgical intervention in this study is correlated to previous reviews (Lurain et al., 1995; Patel et al., 2010; Rodriguez et al., 2010). Multimodality treatment can improve overall survival of resistant GTN patients (Lurain, 2011; Osborne et al., 2012).

Our extremely high risk GTN patients survived 5 from 8 patients which was 62.5%. The survival rate was comparable to previous reviews that survival of brain metastasis patients was approximate 60-70% (Lurain, 2011). However, survival rate was rapidly decreased when the patients have liver metastasis and worst in lever and brain metastases. From our series, 4 from 5 brain metastatic patients survived. Survival rate from this review was 80% in brain metastatic patients. However, survival rate is only 50% in liver metastatic cases.

This review is a single institution review cases of extremely high risk and resistant GTN. Our treatment has some differences from other institutions but the survival is comparable. The limitation of this review is the number of cases is small due to rarity of the disease. Further trial or multicenter analysis may be considered.

References

Alazzam M, Tidy J, Osborne R, et al (2012). Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. Cochrane *Database Syst Rev*, **12**, 8891.

Bianconi M, Jankilevich G, Otero S, Nassif J, Storino C (2007). Successful salvage of a relapsed high risk gestational trophoblastic neoplasia patient using capecitabine. *Gynecol Oncol*, **106**, 268-71.

Cyriac S, Rajendranath R, Sridevi V, Sagar TG (2011). Etoposide, cisplatin-etoposide, methotrexate, actinomycin-D as primary treatment for management of very-high-risk gestational trophoblastic neoplasia. *Int J Gynaecol Obstet*, **115**, 37-9.

Deng L, Zhang J, Wu T, Lawrie TA (2013). Combination chemotherapy for primary treatment of high-risk gestational trophoblastic tumour. *Cochrane Database Syst Rev*, **1**, 5196.

Feng F, Xiang Y, Wan X, Geng S, Wang T (2011). Salvage combination chemotherapy with floxuridine, dactinomycin, etoposide, and vincristine (FAEV) for patients with relapsed/chemoresistant gestational trophoblastic neoplasia. *Ann Oncol*, **22**, 1588-94.

Hertz R, Li Mc, Spencer Db (1956). Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. *Proc Soc Exp Biol Med*, **93**, 361-6.

Limpongsanurak S, Sitthisomwong T (1999). Metastatic Gestational Trophoblastic Neoplasia at King Chulalongkorn Memorial Hospital. *Trophoblast Res*, **13**, 205-11.

Lurain JR, Elfstrand EP (1995). Single-agent methotrexate chemotherapy for the treatment of nonmetastatic gestational trophoblastic tumors. *Am J Obstet Gynecol*, **172**, 574-9.

Lurain JR, Singh DK, Schink JC (2010). Management of metastatic high-risk gestational trophoblastic neoplasia: FIGO stages II-IV: risk factor score ≥ 7. *J Reprod Med*, **55**, 199-207.

Lurain JR (2011). Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. *Am J Obstet Gynecol*, **204**, 11-8.

Lurain JR, Schink JC (2012). Importance of salvage therapy in the management of high-risk gestational trophoblastic neoplasia. *J Reprod Med*, **57**, 219-24.

Osborne R, Dodge J (2012). Gestational trophoblastic neoplasia. *Obstet Gynecol Clin North Am*, **39**, 195-212.

Patel SM, Desai A (2010). Management of drug resistant gestational trophoblastic neoplasia. *J Reprod Med*, **55**, 296-300.

Roberts JP, Lurain JR (1996). Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy. *Am J Obstet Gynecol*, **174**, 1917-23

Rodriguez N, Goldstein DP, Berkowitz RS (2010). Treating gestational trophoblastic disease. *Expert Opin Pharmacother*, **11**, 3027-39.

Wang J, Short D, Sebire NJ, et al (2008). Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol*, **19**, 1578-83.