

## 11

# PRESENTATION AND MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA IN THE USA

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Gestational trophoblastic neoplasms (GTN) comprise a group of interrelated conditions that have the potential for local invasion and dissemination. They are one of the rare human malignancies that are highly curable even with widespread metastases [1-2]. GTN most commonly occurs after molar gestation, but it may develop after any type of pregnancy. This chapter will review the presentation and management of GTN based primarily upon our experience at the New England Trophoblastic Disease Center (NETDC).

### 11.1 HISTOLOGY OF GTN

Invasive mole (IM) is characterized by the presence of edematous chorionic villi with trophoblastic proliferation that invade directly into the myometrium. Most invasive moles remain localized to the uterus, but require treatment with chemotherapy or surgery to prevent morbidity and mortality caused by uterine perforation, hemorrhage or infection. Metastases to distant sites, particularly the lungs and vagina, do occur and may be in the form of metastatic mole or choriocarcinoma [1,2].

Choriocarcinoma is a pure epithelial malignancy comprising both neoplastic cytotrophoblast and syncytiotrophoblast elements without chorionic villi. Choriocarcinoma is a highly vascular tumor that invades blood vessels and spreads hematogenously and early resulting in potentially life-threatening metastases requiring chemotherapy when diagnosed. [3].

Placental site trophoblastic tumor (PSTT) is a relatively slow-growing variant of choriocarcinoma characterized by absence of villi with proliferation of extravillous intermediate trophoblast cells. They can arise from any antecedent pregnancy and are usually diploid and monomorphic. These rare tumors remain localized to the uterus for long periods, often several months or even years, before metastasizing to regional lymph nodes or other metastatic sites. In contrast to choriocarcinoma, these tumors infiltrate the myometrium and spread via lymphatics in addition to hematogenously [3-6]. The syncytiotrophoblast cells which produce hCG are usually lacking in PSTT resulting in relatively lower levels of hCG secreted by these tumors [5]. Immunohistochemical staining reveals diffuse presence of

cytokeratin, inhibin *a*, and human placental lactogen (hPL), whereas hCG is only present focally [5]. Therefore a large tumor burden may be present before the disease is diagnosed by serum hCG elevation. The Ki-67 labeling index is also usually elevated >10 percent. Cole et al. [7] have shown that PSTT is associated with a higher percentage of free beta-hCG which can help in diagnosis. In general, PSTT are not as sensitive to chemotherapy as other forms of GTN. Surgery, therefore, assumes a larger role in their management+.

Epithelioid trophoblastic tumor (ETT) is another rare form of GTN that develops from neoplastic transformation of chorionic-type extravillous trophoblast [8,9]. Similar to PSTT this tumor can develop from any antecedent pregnancy and can lie dormant in the uterus for months or years before metastasizing. ETT typically presents as a discrete, hemorrhagic, solid and cystic lesion in the uterine wall. Microscopically the tumor is composed of a relatively uniform population of mononucleate intermediate trophoblastic cells that form nests and solid masses. The cells resemble the trophoblastic cells in the chorion laeve and are therefore are designated as 'chorionic-type intermediate trophoblast'. Typically, islands of trophoblastic cells are surrounded by extensive necrosis and associated with a hyaline-like matrix creating a "geographic" pattern that is quite characteristic. Intratumor necrosis and hemorrhage is rarely seen. Its clinical behaviour is similar to PSTT in that it is characterized by slow growth, paucity of symptoms, and low hCG production that makes early detection the exception rather than the rule [8,9]. ETT cells show diffuse expression of immunohistochemical markers including cytokeratin and inhibin *a*. Cyclin E staining is higher in ETT than placental site nodules which can be used to differentiate between the two [10-12].

## **11.2 PRESENTATION OF NON-METASTATIC GTN**

Locally IM occurs in about 15-20 percent of patients after evacuation of complete hydatidiform mole (CHM) and in 1-5 percent of patients following partial hydatidiform mole (PHM) [13,14]. Post-molar GTN occurs more commonly(40-50%) following evacuation of a "high-risk" CHM characterized by pre-evacuation uterine size larger than dates, hCG levels >100,000 IU/l, and bilateral theca lutein cysts of the ovaries caused by high levels of hCG [14]. Most commonly, the diagnosis of post-molar GTN is made when the hCG level rises or plateaus after molar evacuation. The International Federation of Gynecology and Obstetrics (FIGO) standardized the hCG criteria used for the diagnosis of post-molar GTN to include: (1) an hCG level plateau, plus or minus 10 % of baseline recorded over a 3-week duration (days 1,7,14,21); (2) an hCG level rise greater than 10% above baseline recorded over a 2-week duration (days 1,7,14); and (3)

persistence of hCG for more than 6 months after molar evacuation [15,16]. These patients usually present with one or more of the following symptoms: irregular vaginal bleeding, uterine subinvolution or asymmetric enlargement, and theca lutein cysts. Bulky necrotic tumors may be a focus for uterine infection and cause a purulent discharge and pelvic pain. Invasive moles may perforate through the myometrium producing intra-abdominal bleeding, or erode into uterine vessels causing vaginal hemorrhage.

### **11.3 PRESENTATION OF METASTATIC GTN**

Metastases develop in about five percent of patients after CHM and infrequently after PHM, miscarriages and term pregnancies [17]. Metastatic disease is usually characterized by choriocarcinoma which can develop in virtually every body site and often produces symptoms due to abnormal bleeding from that site such as hemoptysis, vaginal bleeding, hepatic rupture, or stroke. The metastases in patients with post-molar GTN frequently consist of embolized invasive molar tissue which produce signs and symptoms similar to metastases from choriocarcinoma [17]. The diagnosis of choriocarcinoma should be considered in any premenopausal woman presenting with metastatic disease from an unknown primary site. A serum hCG determination and exclusion of normal pregnancy are all that is required to diagnose GTN.

#### **11.3.1 PULMONARY METASTASES**

The lungs are the most common site of metastasis. Eighty percent of our patients with metastatic GTN have pulmonary involvement on chest radiographs or computerized tomography (CT) [13]. Patients with pulmonary metastases may have cough, chest pain, hemoptysis, dyspnea or an asymptomatic lesion on imaging. Pulmonary hypertension and right heart strain may develop due to pulmonary artery occlusion by trophoblastic emboli [18]. Because respiratory symptoms may be dramatic and striking, the patient may be thought to have primary pulmonary disease. Importantly, gynecologic symptoms may be minimal or absent. Regrettably, the diagnosis of GTN may only be considered after the patient has undergone thoracotomy.

Four principal pulmonary radiographic patterns are seen in patients with GTN: (1) discrete rounded densities; (2) an alveolar or snowstorm pattern; (3) pleural effusion; or (4) embolic pattern caused by pulmonary arterial occlusion [19-22]. Patients may have pulmonary hypertension in the absence of substantial parenchymal disease. Risk factors for developing early respiratory failure include cyanosis, pulmonary hypertension, anemia, dyspnea and > 50 percent pulmonary opacification [23,24]. Bakri et al. [23] described 75 patients

from Saudi Arabia with pulmonary metastases and observed pleural effusion and >50 percent opacification of the lungs in 48 percent and 33 percent respectively. The extent of pulmonary involvement can vary greatly amongst centers due to the differences in the frequency of early diagnosis. At our center, patients with pulmonary metastases rarely present with respiratory symptoms and have comparatively small nodules on chest radiographs or CT scans. In contrast, patients with extensive pulmonary involvement may develop early respiratory failure requiring mechanical ventilation within one month of presentation. Bakri et al. [23] and Kelly et al. [24] reported a 100 percent mortality in eight and 11 patients, respectively, with early respiratory failure.

### 11.3.2 VAGINAL METASTASES

Vaginal metastases occur in 30 percent of our patients with metastatic GTN and may consist of either IM or choriocarcinoma spread hematogenously [17]. Vaginal lesions are most commonly located suburethrally or in the fornices, and present with a purulent discharge or irregular bleeding. Biopsy should be avoided because of their extreme vascularity and tendency to hemorrhage [13]. In general vaginal metastases respond well to treatment. When vaginal hemorrhage occurs embolization of the feeder vessel can be used to control blood loss [25].

### 11.3.3 CEREBRAL AND HEPATIC METASTASES

Cerebral and hepatic metastases occur in about 10 percent of our patients with metastatic GTN [1]. Cerebral and hepatic involvement are most commonly seen in patients with a non-molar antecedent pregnancy with protracted delays in diagnosis greater than 4 months and high hCG levels. Among 39 patients with brain metastases from GTN, Newlands et al. [26] noted that the antecedent pregnancy was a term pregnancy, abortion, or stillborn in 23 (59%), 10 (26%), and one (3%) patient, respectively (88% non-molar). Virtually all patients with cerebral and hepatic lesions have concurrent pulmonary and/or vaginal involvement.

Cerebral metastases are usually asymptomatic when lesions are small, but as the disease progresses patients develop the classic neurologic signs including headache, vomiting, seizures, visual disturbances and/or slurred speech before experiencing a major bleed that causes hemiparesis or coma [27,28]. Neurological symptoms were present in all 34 patients reported by Liu et al. [29] and in 66 (96%) of 69 patients and in 20 (87%) of 23 patients described by Athanassiou et al. [30] and Bakri et al. [31], respectively.

Patients with hepatic metastases less frequently present with symptoms that are attributable to hepatic involvement. Bakri et al. [32] reported that only five (26%) of 19 patients with liver

involvement presented with epigastric pain, jaundice and /or intraperitoneal bleeding. Most of these patients presented with symptoms related to other metastatic sites.

Metastases to other organs such as the kidneys, spleen and gastrointestinal tract occurs in <5 percent of patients with metastatic GTN[13].

#### 11.3.4 HYPERTHYROIDISM

Patients with high hCG levels(>100,000 IU/l) may develop biochemical evidence of hyperthyroidism with elevation of the serum free thyroxine. Clinical evidence of thyrotoxicity is generally not seen, however, until the hCG level is > 300,000 IU/l [33,34]. Although the identity of the thyrotropic factor in GTN is controversial, some investigators have reported that highly purified hCG appears to have intrinsic thyroid-stimulating activity [35].

Patients with untreated or poorly controlled hyperthyroidism may develop thyroid storm at the time of surgery [34,36]. Thyroid storm is characterized by hyperthermia, delirium, coma, atrial fibrillation, and acute pulmonary edema associated with cardiac failure. While blood samples should be drawn for laboratory confirmation, the diagnosis of thyroid storm must be made clinically so that treatment can be promptly instituted. The administration of  $\beta$ -adrenergic blocking agents prevents or rapidly reverses many of the cardiovascular and metabolic complications of thyroid storm. A pulmonary artery catheter may also be helpful to monitor cardiovascular status and guide fluid replacement [37].

### 11.4 DIAGNOSIS AND PRETHERAPY EVALUATION OF GTN

Post-molar GTN is diagnosed on the basis of hCG values as discussed above. Women with GTN after non-molar pregnancies may present with or without gynecological and/or systemic symptoms making the diagnosis difficult [36]. Abnormal bleeding after any pregnancy should be evaluated with hCG testing to exclude the diagnosis of GTN [38]. Biopsy of metastases to make a diagnosis should, in most instances, be avoided because of the risk of hemorrhage. The differential diagnosis of an elevated hCG test in the absence of a normal or ectopic pregnancy includes: (1) an hCG-producing germ cell tumor of the ovary, (2) non-gestational choriocarcinoma, or (3) ectopically produced hCG from a non-trophoblastic tumor, and (4) false positive hCG tests.

#### 11.4.1 FALSE POSITIVE HCG TESTS

It is also important to be aware that false positive serum hCG measurements (so-called phantom hCG) occur from interference in the hCG immunometric assays, most often because of the presence of non-specific heterophilic antibodies in patient's serum [38-40]. Phantom hCG results, even above 700 IU/l, have been reported with a wide variety of monoclonal immunometric assays. Phantom hCG should be suspected if hCG values plateau at relatively low levels and do not respond to therapeutic maneuvers such as methotrexate (MTX) given for presumed ectopic pregnancy. Work-up should include evaluation of serum hCG using a variety of assay techniques at different dilutions of the patient's serum combined with a urinary hCG test (if the serum level is above threshold for the urinary assay), since these molecules are too large to traverse the kidney tubules. Characteristically, false-positive hCG assays usually will not be affected by serial dilution of patient sera, will have marked variability using different assay techniques, and will not be detectable in urinary assays. Perimenopausal women may also present with persistent low hCG levels of pituitary origin which can be suppressed by the administration of oral contraceptive agents [41]. If there is any doubt about the diagnosis of GTN it is important to exclude the possibility of phantom hCG before subjecting patients with low persistent levels of hCG to hysterectomy or chemotherapy [42].

#### 11.4.2 INITIAL EVALUATION

The optimal management of GTN requires a thorough assessment of the extent of disease and risk factors prior to the initiation of treatment. All patients should undergo a careful evaluation including a complete history and physical examination, blood work including measurement of hCG, hepatic, renal, and thyroid function tests, and determination of the complete blood count. Clotting function studies and blood type and screen are sometimes indicated. A careful pelvic examination to identify vaginal and pelvic metastases should be performed. Disseminated metastases usually are only seen if pulmonary and/or vaginal lesions are noted [43]. The metastatic work-up should include a chest x-ray, brain magnetic resonance imaging (MRI) or CT scan, and abdominopelvic CT or MRI scans. At the NETDC we frequently combine CT scanning of the chest, abdomen and pelvis, but only perform brain imaging if the chest x-ray or CT scan is positive, since metastases at high-risk sites rarely occur without pulmonary and/or vaginal involvement [44]. Up to 40% of patients treated for post-molar GTN with negative chest x-rays have pulmonary lesions on chest CT scans [45,46]. A pelvic ultrasonogram is scheduled in addition to the routine pelvic CT scan if the patient presents with vaginal bleeding. MRI or CT scans of the liver will document most metastases in patients with abnormal liver function tests. Head MRI or CT scanning has successfully facilitated the early

diagnosis of asymptomatic cerebral lesions [30].

Measuring the cerebrospinal fluid (CSF) hCG level to exclude cerebral involvement had also been found to be useful in patients with normal brain imaging. The plasma/ CSF hCG ratio tends to be <60 in the presence of cerebral metastases [47]. However, rapid changes in plasma hCG levels may not be promptly reflected in the CSF such that a single plasma/CSF hCG ratio may be misleading [48]. Bakri et al. [49] reported that the serum/CSF hCG ratio was >60 in five of ten patients with cerebral metastases. Improved brain imaging including the use of positron emission tomography (PET) has facilitated the early diagnosis of brain metastases without the need for spinal taps [50].

Pelvic ultrasonography is useful in detecting extensive uterine involvement and in identifying sites of resistant uterine tumor [51,52]. The sensitivity of pelvic ultrasound in detecting uterine disease is improved by the use of transvaginal ultrasonography (TVUS) as well as colour flow Doppler [53-55]. TVUS is useful in selecting patients who would benefit from hysterectomy because it can accurately and non-invasively detect extensive uterine wall involvement.

Although histologic confirmation is not required for treatment of GTN, it may be useful in determining antecedent pregnancy and selection of chemotherapy. Biopsy of metastatic lesions to obtain a pathologic diagnosis is generally not recommended because of the risk of hemorrhage. However, if the diagnosis of GTN is in question, a biopsy may be needed.

## **11.5 STAGING**

The International Federation of Gynecology and Obstetrics (FIGO) adopted an anatomical staging system for GTN (Table 11.1) [38,56,57]. Stage I includes all patients with persistently elevated hCG levels whose tumor is confined to the uterine corpus. Stage II comprises all patients with tumor outside of the uterus, but localized to the pelvis and/or vagina. Stage III disease includes all patients with pulmonary metastases on chest x-ray with or without uterine, pelvic or vaginal involvement. Stage IV patients have extensive tumor burdens with involvement of the brain, liver, kidney, spleen and /or gastrointestinal tract, as well as other distant sites. Stage IV disease usually follows a non-molar antecedent pregnancy and generally has the histological pattern of choriocarcinoma. Patients with stage IV disease are at highest risk of developing resistance to chemotherapy and dying of their disease.

Table 11.1 FIGO anatomic staging for gestational trophoblastic neoplasia

Stage I Disease confined to the uterus.

Stage II Disease extends outside the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)

Stage III Disease extends to the lungs, with or without known genital tract involvement.

Stage IV All other metastatic sites.

### 11.5.1 PROGNOSTIC SCORE

It is also helpful to use prognostic variables to predict the likelihood that a patient will develop drug resistance which, in turn, assists the clinician in selecting the most appropriate chemotherapy regimen. The World Health Organization (WHO) published a prognostic scoring system which reliably predicts the potential for chemotherapy resistance (Table 11.2) [56,57]. Most of the prognostic factors relate to sites of metastases, tumor burden (hCG level, number and size of metastases), duration of disease, and extent of prior chemotherapy exposure and resistance. When the prognostic score is 7 or greater, the patient is considered high-risk and requires intensive multi-agent chemotherapy to achieve an optimal outcome. In general, patients with stage I GTN have a low-risk score and patients with stage IV have a high-risk score. The distinction between low- and high- risk, therefore, primarily applies mainly to stages II and III disease.

**Table 11.2** Scoring system based on prognostic factors

Prognostic factors	Score <sup>b</sup>			
	0	1	2	4
Age (years)	<40	>39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval from index pregnancy (months) <sup>a</sup>	<4	4-7	7-12	>12
Pre-treatment serum hCG (mIU/ml)	<10 <sup>3</sup>	<10 <sup>3</sup> -10 <sup>4</sup>	10 <sup>4</sup> -10 <sup>5</sup>	10 <sup>5</sup>
Largest tumor size , including uterine tumor		3-5cm	>5cm	
Site of metastases	Lung	Spleen Kidney	GI tract Liver	Brain
No. of metastases identified		1-4	4-8	>8
Prior chemotherapy			Single drug	2 or more drugs

<sup>a</sup>Interval time (months) between end of antecedent pregnancy and start of chemotherapy.

<sup>b</sup>The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score <7=low risk; 7 or >7 = high risk.

The use of a prognostic scoring system is more predictive of clinical outcome than the use of individual high-risk factors. Dubeshter et al. [58] reported complete remission in all 21 patients with traditional high-risk factors whose WHO Prognostic Score was 7 or less; interestingly, 14 (67%) of these patients attained complete remission with single agent therapy. Similarly other investigators have reported that the WHO scoring system, which integrates several prognostic variables, is more predictive of outcome than reliance upon individual high-risk factors [59-62]. The FIGO stage is designated by a Roman numeral and is followed by the modified WHO Prognostic Score designated by an Arabic number separated by a colon(e.g., II:6) [57].

Although most low-risk patients will be cured with single-agents, approximately 70 percent of patients with WHO Prognostic Scores of 5 and 6 will ultimately require the use of combination chemotherapy to achieve remission [63,64]. In general, the less toxic single-agent therapy should be used initially in this subgroup and multiagent regimens reserved for those patients whose response to monotherapy is suboptimal. Studies are ongoing to better define which “low-risk” patients may benefit from primary treatment with combination chemotherapy.

#### 11.5.2 MANAGEMENT OF STAGE I GTN

Primary remission rates of patients treated for low-risk non-metastatic and low-risk metastatic GTN are similar using a variety of chemotherapy agents [65-67]. Essentially, all patients with this condition can be cured, usually without the need for hysterectomy. The NETDC protocol for the management of stage I GTN and the results of treatment are summarized in Tables 11.3 and 11.4. The selection of therapy is based primarily upon the patient’s desire to retain fertility.

Table 11.3 Treatment Protocol, Stage I GTN, NETDC

*INITIAL*

Sequential single agent chemotherapy (MTX/ACTD)  
Hysterectomy with adjunctive MTX

*RESISTANT*

Combination chemotherapy (EMACO)  
Hysterectomy with adjunctive actinomycinD or  
Local resection with adjunctive actinomycinD

Table 11.4 Remission therapy, Stage I, NETDC, July 1965 to December 2013

<i>Remission therapy</i>	<i>No. of patients</i>	<i>No. of remissions (%)</i>
<i>Initial Therapy</i>	624	520 (83.3)
Sequential MTX/ACTD		478 (91.9)
Hysterectomy*		35 (6.7)
Combination chemotherapy(MAC, EMA)		7 (1.4)
<i>Resistant</i>	104	104 (16.7)
Combination Chemotherapy(MAC,EMA, EMACO)		78 (75)
Surgery(Hysterectomy, Local resection)*		19 (18.3)
Other		7 (6.7)
<i>Total</i>	624 (100)	624 (100)

MTX= methotrexate; ACTD= actinomycin D; MAC= methotrexate, actinomycin D, cyclophosphamide;  
 EMA= etoposide, methotrexate, actinomycin D;  
 EMACO=etoposide, methotrexate, actinomycin D, cyclophosphamide, oncovin.

\*with adjunctive chemotherapy

### 11.5.3 ROLE OF HYSTERECTOMY

If the patient no longer wishes to preserve fertility, hysterectomy with adjunctive single-agent chemotherapy is recommended as primary treatment for Stage I non-metastatic GTN at the NETDC.

Adjunctive chemotherapy is utilized because occult pulmonary metastases have been reported in 40 percent of patients with presumed non-metastatic disease[45,46,68]. The rationale for the use of adjunctive chemotherapy is twofold: (1) to provide cytotoxic levels of chemotherapeutic agents in tissue and the blood stream in case viable tumor cells are disseminated at surgery, and (2) to treat occult metastases that may already be present. Chemotherapy can be safely administered at the time of surgery without increasing operative morbidity. All patients should be counselled that chemotherapy may still be required if follow-up hCG levels indicate the presence of occult metastases. At the NETDC primary hysterectomy and adjuvant chemotherapy was performed in 35 patients and all attained complete remission with no further therapy[69]. None of the patients experienced post-operative bleeding, infection, or wound complications.

### 11.5.4 THE MANAGEMENT OF PLACENTAL SITE AND EPITHELIOID TROPHOBLASTIC TUMORS

Patients with PSTT and ETT require special consideration because of the unique nature of their disease. We believe the primary therapy of all patients with non-metastatic PSTT and ETT should be hysterectomy because this variant of choriocarcinoma is relatively

resistant to chemotherapy[4,70-74]. If deep myometrial involvement is present it is our policy to also perform a pelvic lymphadenectomy. Unlike choriocarcinoma, these tumors tend to remain localized in the uterus for long periods of time before metastasizing to regional lymph nodes or other metastatic sites[5,6]. Once metastases occur both PSTT and ETT have a high mortality rate. Kingdon et al. [75]in their review of deaths from GTN found that 30 percent of those dying from GTN had PSTT histology. In the absence of demonstrable metastases, no further treatment is required. Despite the tumor's relative resistance to chemotherapy, some patients with metastatic PSTT have achieved remission with intensive multiagent regimens [4,76-79]. The interval between antecedent pregnancy and diagnosis appears to be the most important risk factor in identifying those patients at risk of dying. Papadopoulos et al. [70], in reviewing the clinical experience with 34 patients at Charing Cross Hospital, found that a long interval from the antecedent pregnancy to clinical presentation was the most important prognostic factor. Whereas all 27 patients survived when the interval was less than four years, all 7 patients died when the interval exceeded 4 years. Similarly, Lathrop et al. [74] in a review of 43 patients reported that all 10 fatal cases of PSTT had more than a 2-year interval from antecedent pregnancy to diagnosis. Lathrop also observed that the mitotic rate of the tumor was another prognostic factor, but Papadopoulos was unable to confirm this finding. In a recent review from Memorial Sloan Kettering Cancer Center 17 of 171 (10%) of patients with GTN had PSTT [76]. Eight of these women (50%) presented with localized disease and 6 (35%) presented with extra-pulmonary metastases. All eight women with localized disease underwent hysterectomy and 7 of the 8 received chemotherapy. All but one woman with early stage disease are alive and disease-free. The one patient in this group who died was diagnosed 5 years after a miscarriage and developed chemoresistant cerebral metastases. Of the 6 patients who presented with extra-pulmonary metastases, 5 ultimately died from their disease despite multiagent chemotherapy.

Although universally accepted guidelines on how to manage PSTT and ETT are not available because of their rarity, given their aggressive clinical behavior the use of multimodal therapy with surgery, radiation and chemotherapy has improved survival. The use of multiagent protocols with either EMACO or EMAEP have been shown to be curative in patients with lymphatic spread and extrauterine disease [77-80]. Although not applicable to the majority of patients, fertility-sparing surgery has also been employed successfully [81,82].

#### 11.5.5 ROLE OF CHEMOTHERAPY

Single agent chemotherapy is generally accepted to be the preferred

treatment in patients with stage I disease who desire to preserve fertility [13,65]. There is no consensus regarding what should be the favored primary single agent regimen for low-risk GTN. Nonetheless it is generally felt that 5-day MTX, 5-day ACTD, MTX-FA and bolus ACTD seem to be more effective than either weekly intramuscular MTX or MTX infusion. At the NETDC we initially use MTX-FA for primary treatment in low-risk patients. If a patient develops resistance to MTX-FA we then administer bolus ACTD. If the patient is resistant to both MTX and ACTD we then treat with combination therapy. At the NETDC primary single agent chemotherapy induced complete remission in 478 (82.1%) of 582 patients who did not undergo primary combination chemotherapy or hysterectomy. The remaining 104 patients who were resistant to single agent chemotherapy achieved remission with combination chemotherapy and/or surgical intervention. Local uterine resection with adjunctive chemotherapy should be considered in patients who desire to retain fertility with chemotherapy resistant intramyometrial disease when the tumor is well circumscribed as determined by TVUS or MRI. Seven patients with stage I disease were treated with primary combination chemotherapy because of a high prognostic score.

#### 11.5.6 ROLE OF REPEAT CURETTAGE

The role of repeat curettage in lieu of initiating cytotoxic therapy in the setting of an hCG rise or plateau is controversial. Some investigators have reported that repeat curettage induces remission or influences treatment in less than 20 percent of patients with uterine perforation occurring in 4.8-8 percent [83,84]. In contrast, Pezeshki and associates [85] reported that 368 (68%) of 544 patients entered spontaneous remission after repeat evacuation, with no patients requiring hysterectomy for perforation. Patients with persistent histologic evidence of GTN and those with hCG levels above 1500 mIU/ml were significantly less likely to respond to the second curettage. Because we believe that the vast majority of patients with post-molar GTN have locally invasive disease, it is our practice at the NETDC to perform a repeat curettage only if a patient has persistent uterine bleeding with TVUS evidence of residual molar tissue [86].

### 11.6 MANAGEMENT OF STAGES II AND III GTN

Tables 11.5 – 11.7 summarize the current NETDC protocols for the management of stages II and III disease and the results of therapy we have achieved. In general, we treat patients with low-risk WHO scores (<7) with primary single-agent chemotherapy with excellent results, and patients with high-risk scores with primary combination therapy to achieve an optimal outcome. Recent data from Charing Cross Hospital indicate that only 30 percent of low-risk patients with a

WHO Prognostic Score of 5-6 can be cured with monotherapy which suggests that a multidrug regimen should be administered initially. These patients characteristically present with pre-treatment hCG levels >100,000 IU/l and Doppler ultrasound evidence of a large tumor burden [87].

Table 11.5 Treatment Protocol, Stages II and III GTN, NETDC

<i>Low-risk<sup>a</sup></i>	
Initial:	Single-agent chemotherapy(Sequential MTX/ACTD)
Resistant:	Combination chemotherapy(EMACO)
<i>High risk<sup>a</sup></i>	
Initial:	Combination chemotherapy(EMACO)
Resistant:	Second-line combination chemotherapy(EMAEP*, TP/TE**, BEP***) Surgical resection of localized metastases

\*EMAEP=Etoposide, methotrexate, actinomycinD, etoposide, carboplatin

\*\*TP/TE=Taxol,carboplatin, etoposide

\*\*BEP= bleomycin, etoposide, carboplatin

Table 11.6 Remission therapy, Stage II, NETDC, July 1965 to December 2013

<i>Remission therapy</i>	<i>No. of patients</i>	<i>No. of remissions (%)</i>
<i>Low risk</i>	21(56.8%)	21(100)
Initial:		17(81)
	Sequential MTX/ACTD	16(76.2)
	Combination Chemotherapy*	1(4.8)
Resistant:		4(19)
	Combination chemotherapy**	3
	Salvage therapy	1
<i>High risk</i>	16(43.2%)	16(100)
Initial:		11(68.8)
	Sequential Mtx/ActD	7
	Combination Chemotherapy**	4
Resistant:		5(31.2)
	Combination Chemotherapy**	5

<i>Total</i>	37(100%)	37(100)
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MTX=methotrexate; ACTD=actinomycin D;  
 \*MAC=methotrexate, actinomycin D, cyclophosphamide;  
 \*\*EMACO=etoposide, methotrexate, actinomycin D, cyclophosphamide, oncovin.  
 EMAEP=etoposide, methotrexate, actinomycin D, carboplatin

Table 11.7 Remission therapy, Stage III, NETDC, July 1965 to December 2013

<i>Remission therapy</i>	<i>No. of patients</i>	<i>No. of remissions (%)</i>
<i>Low risk</i>	154 (67.5%)	154 (100)
Initial:		120 (77.9%)
Sequential MTX/ACTD		113
Combination chemotherapy (MAC, EMA, EMACO)		7
Resistant:	34	34 (22.1)
Sequential MTX/ACTD		1
Combination chemotherapy (MAC,EMA, EMACO, EMAEP)		33
<i>High risk</i>	74 (32.5%)	71 (95.9)*
Initial:	59	59 (79.7)
Sequential MTX/ACTD		14
Combination chemotherapy (MAC,EMA, EMACO, EMAEP)		45
Resistant:	15	12 (16.3)*
Combination chemotherapy (MAC, EMA,EMACO)		11
Salvage chemotherapy (EMAEP, BVP, TE/TP)		1
<i>Total</i>	228 (100%)	225 (98.7)*

MTX=methotrexate; ACTD=actinomycin D; MAC=methotrexate, actinomycin D, cyclophosphamide; EMA=etoposide, methotrexate, actinomycin D; BVP=vinblastine, cisplatin, bleomycin, EMACO=etoposide, methotrexate, actinomycin D, cyclophosphamide, oncovin; EMAEP=etoposide, methotrexate, actinomycin D, carboplatin;TE/TP=taxol, etoposide, platinum

\*1 Death, 2 Alive with disease

All thirty-seven patients with stage II GTN treated at the NETDC attained complete remission. Single agent chemotherapy induced complete remission in 16 (76.2%) of 21 low-risk patients, but only 7 (43.8%) of 16 high-risk patients.

Two hundred twenty-eight patients with stage III GTN were treated at the NETDC and all but one achieved remission. Single agent chemotherapy induced complete remission in 113(73.4%) of 154 low-risk patients, but only 14(18.9%) of 74 patients with high-risk scores. All patients who were resistant to single agent therapy subsequently achieved remission with multi-agent regimens. There was one death in the high-risk group.

Several investigators have confirmed that single agent chemotherapy can achieve high remission rates in patients with metastatic GTN with low-risk scores. Table 11.8 outlines the experience from four centers which shows that 128 (87.1%) of 147 patients with low risk metastatic disease achieved remission with single agent chemotherapy [58,61,88,89]. All patients resistant to single agent chemotherapy subsequently achieved remission with combination therapy, except two patients reported by Ayhan et al. [88].

Table 11.8 Results of single-agent chemotherapy in low-risk metastatic GTN

Author	Remission with single-agent chemotherapy	Eventual remission rate (%)
DuBeshter <i>et al.</i> [58]	48/55 (87.3%)	55/55 (100)
Dubuc-Lissoir <i>et al.</i> [61]	21/25 (84%)	25/25 (100)
Ayhan <i>et al.</i> [88]	9/15 (60%)	13/15 (87)
Soper <i>et al.</i> [89]	50/52 (96.1%)	52/52 (100)
<i>Total</i>	128/147 (87.1%)	145/145 (98.6)

#### 11.6.1 MANAGEMENT OF VAGINAL METASTASES

The management of vaginal metastases may be problematic in these patients since profuse bleeding can occur because the implants are highly friable and vascular. Once chemotherapy is started and the lesions begin to regress, however, bleeding is less likely to occur. If bleeding is a problem, it usually can be controlled by packing the vagina or by angiographic embolization of the hypogastric arteries. Yingna et al [90] reported that 18 (35.3%) of 51 patients with vaginal metastases presented with vaginal hemorrhage. Bleeding was controlled by vaginal packing in 16 patients and angiographic embolization in two. Tse et al.[91] in a 20-year retrospective study confirmed that angiographic embolization appeared to be an attractive and promising alternative to hysterectomy and arterial ligation.

#### 11.6.2 ROLE OF THORACOTOMY

Thoracotomy has a definite but limited role in the treatment of stage III disease. Lung resection is indicated if the diagnosis of GTN is seriously in doubt, since there are primary lung tumors and metastases from non-trophoblastic tumors that produce hCG ectopically. A viable metastatic trophoblastic implant that persists despite intensive multi-agent chemotherapy can be successfully resected [92-94]. Surgery should not be undertaken, however, until the presence of other metastatic sites are ruled out by imaging with either radioisotope-labelled hCG antibody [95] or PET scans [50]. Tomada et

al [96] reviewed their experience with pulmonary resection in 19 patients with chemotherapy-resistant GTN. They proposed the following guidelines for successful resection: (a) good surgical candidate, (b) primary malignancy is controlled, (c) no evidence of other metastatic sites, (d) pulmonary metastasis is limited to one lung, and (e) hCG level is <1000 mIU/ml. Complete remission was achieved in 14 out of 15 patients who met all five criteria, but in only one of the four patients who had one or more unfavorable clinical features. Similarly, Jones et al. [97] reported that six (66.6%) of nine carefully selected patients with drug-resistant pulmonary GTN attained complete remission following lung resection. Several investigators have reported that undetectable hCG levels within one to two weeks of resection of a solitary nodule is highly predictive of a favorable outcome [92,98-102]. Alifrangis et al.[103] confirmed the criteria for thoracotomy but also reported that multiple resections over time or resection of more than one lesion can result in salvage after failure of standard or high-dose chemotherapy. It is important to emphasize that fibrotic nodules may persist indefinitely on chest radiographs after complete gonadotropin remission is achieved. As long as the hCG level is undetectable, these lesions should not be treated surgically.

### 11.6.3 ROLE OF HYSTERECTOMY

Hysterectomy may be required in patients with metastatic disease because of infection or bleeding [69,92,104-106]. Hysterectomy is also beneficial in patients with bulky uterine disease because it reduces tumor burden and limits the exposure to cytotoxic drugs. This may be particularly helpful during periods of significant marrow toxicity when the use of cytotoxic agents that induce marrow suppression is limited. However, in patients with metastatic GTN hysterectomy should not be used in lieu of chemotherapy. Cagayan et al. [106] reported that of 134 women with GTN, 13(9%) underwent hysterectomy for profuse bleeding and 31(24%) underwent hysterectomy for uterine rupture. Removal of the ovaries is usually not indicated, even in the presence of theca lutein cysts, since metastatic disease rarely involves the ovaries. Theca lutein cysts usually regress spontaneously or can be aspirated to reduce the risk of torsion. It has been amply documented that hysterectomy can be carried out safely during a cycle of chemotherapy without increasing morbidity[69,104].

### 11.7 MANAGEMENT OF STAGE IV GTN

Patients with stage IV GTN are at the greatest risk for developing rapidly progressive tumor and dying despite intensive therapy . All patients with stage IV disease should be treated initially with intensive

multi-agent chemotherapy and the selective use of radiation therapy and surgery. Survival reported by various trophoblastic disease centers ranges up to 86 percent [107]. In contrast to patients with low-risk disease, early hysterectomy does not appear to improve their outcome [92].

The NETDC protocol for the management of stage IV GTN and the results of our treatment are summarized in Table 11.9 and 11.10. Before 1975, only six (30%) of 20 patients with stage IV tumors achieved complete remission. After 1975, 25 (75.5%) of 33 patients were cured of their disease. This dramatic improvement in survival resulted from the introduction of intensive multi-modal therapy as primary treatment in all high-risk patients.

Table 11.9 Treatment Protocol, Stage IV GTN, NETDC

<i>Initial</i>	
Combination chemotherapy (EMACO)	
Brain:	Whole head radiation (3000 cGY) or localized radiation Craniotomy to manage complications Resection of peripheral metastases
Liver:	Local resection to manage complications Embolization
<i>Resistant</i>	
Second-line combination chemotherapy (EMAEP, TP/TE, BVP, ICE)	
EMACO=etoposide, methotrexate, actinomycin D, cyclophosphamide, oncovin; EMAEP=etoposide, methotrexate, actinomycin D, carboplatin; TP/TE=Taxol, etoposide, carboplatin BVP=bleomycin, velban, carboplatin; ICE=ifosfamide, carboplatin, etoposide	

Table 11.10 Remission therapy, Stage IV, NETDC, July 1965 to June 2006

<i>Remission therapy<sup>a</sup></i>	<i>No. of remissions (%)</i>
<1975	
Initial: Sequential MTX/ACTD	5
Resistant: MAC	1
	6/20 (30%)
>1975	
Initial: Sequential MTX/ACTD	2
Combination chemotherapy (MAC, EMACO, EMAEP)	10
Resistant: Combination chemotherapy (EMA,EMACO, EMAEP)	4
Salvage chemotherapy (CHAMOCA, BEP, TP/TE,ICE)	9
	25/33(75.5%)

<sup>a</sup>Radiotherapy and surgery utilized when indicated. HD, high dose; MTX, methotrexate; ACTD, actinomycin D; MAC, methotrexate, actinomycin D, cyclophosphamide; CHAMOCA, Bagshawe multi-agent regimen; BEP, etoposide, cisplatin, bleomycin; EMA, etoposide, methotrexate, actinomycin D; TP/TE, taxol, carboplatin, etoposide.

### 11.7.1 MANAGEMENT OF LIVER METASTASES

The management of liver metastases is particularly challenging because of the risk of severe hemorrhage. Biopsy is rarely indicated and should not be performed because of the possibility of severe hemorrhage. Hepatic metastases are associated with a poor prognosis even with intensive chemotherapy. However, most patients with liver involvement can be successfully treated with chemotherapy alone. Wong et al. [108] noted that nine out of 10 patients with hepatic involvement achieved complete remission with primary intensive combination chemotherapy without hepatic irradiation. Bakri and associates [32] also reported that five (62.5%) of eight patients with liver metastases treated with combination chemotherapy alone responded completely. In the most recent series from Charing Cross Hospital, after excluding early deaths, the cause-specific survival was 68 percent in patients with liver metastases [109]. Over the past few years a number of additional therapeutic modalities have been described for patients with chemotherapy-resistant hepatic tumors. Grumbine et al. [110] reported the use of selective occlusion of the hepatic arteries and concurrent combination chemotherapy in a patient with bleeding liver metastases who ultimately attained remission. Hepatic resection is occasionally required to control bleeding, and can also be used to excise a peripheral resistant lesion [99].

#### 11.7.2 MANAGEMENT OF CEREBRAL METASTASES

The management of cerebral metastases remains controversial [111-117]. Radiation therapy has been used concurrently with chemotherapy in an attempt to limit acute hemorrhagic complications. Brain irradiation combined with systemic therapy results in cure rates up to 75% among patients who initially present with brain metastases [111]. However, a similar primary remission rate has been reported among patients treated with intensive chemotherapy alone in conjunction with neurosurgical intervention when indicated [114].

Radiation therapy is promptly instituted at the NETDC when cerebral metastases are detected. Radiation therapy is both hemostatic and tumoricidal. The presence of multiple lesions requires treatment to the whole head, whilst a solitary tumor can be treated locally. Excellent results have also been achieved in selected cases with local resection, particularly when the tumor is solitary and located peripherally [114]. Brace [115] was the first to report that brain irradiation may contribute to the eradication of trophoblastic cerebral involvement and reduces the risk of spontaneous cerebral hemorrhage when chemotherapy is used concurrently. Yordan et al. [116] reported that deaths due to cerebral involvement occurred in 11 (44%) of 25 patients treated with chemotherapy alone, but in none of 18 patients treated with brain irradiation.

Excellent cure rates have also been reported in patients with cerebral

metastases with intensive chemotherapy alone. Rustin et al [114] have documented excellent remission rates in patients with brain involvement who were treated with chemotherapy alone. Intensive combination chemotherapy including high dose intravenous and intrathecal MTX induced sustained remission in 13 (86%) of 15 patients with cerebral lesions. Newlands et al. [26] updated the Charing Cross experience in treating brain metastases. Excluding four patients who died within 48 hours of admission, 30 (86%) of 35 patients achieved complete remission. The patients with superficial solitary brain metastases underwent craniotomy at the start of therapy.

Craniotomy may also be necessary to provide acute decompression or to control bleeding. Craniotomy should also be performed to manage life-threatening complications thereby providing an opportunity to get the disease under control with chemotherapy. Infrequently cerebral metastases may be resectable when they become resistant to chemotherapy. Evans et al. [113] reported complete remission in three of four patients who underwent craniotomy to relieve intracranial pressure, and in two of three patients undergoing craniotomy for resection of chemotherapy-resistant tumor. Athanassiou and colleagues [30] similarly reported that four of five patients undergoing craniotomy for acute intracranial complications were ultimately cured. Fortunately, most patients with cerebral metastases who achieve remission have no residual neurological deficit unless a bleed has occurred.

However, we have observed rare cases of significant dementia and progressive memory loss in patients who received whole head irradiation. Although the controversy regarding the optimal treatment protocol for cerebral metastases has not been resolved, Soper and colleagues have recently documented the benefits of an individualized multidisciplinary approach to the treatment of these patients [117]. Neubauer et al. [118] have reported that multimodal therapy including chemotherapy, surgical resection and radiation therapy(whole brain or stereotactic) has improved overall survival from 46 to 64 percent in the last 14 years.

## **11.8 CHEMOTHERAPY**

### **11.8.1 SINGLE-AGENT CHEMOTHERAPY**

The sequential use of single-agent chemotherapy with MTX and Actinomycin D (ACTD) has achieved excellent and comparable remission rates in both non-metastatic and low-risk metastatic GTN [119-121]. Several regimens using MTX and ACTD have been effectively used in the treatment of GTN, but there have been no randomized, prospective studies comparing all of these protocols.

However, there is an ongoing Gynecologic Group trial evaluating pulsed ACTD versus 8-day MTX or weekly IM MTX. To date, these studies suggest that 5-day MTX or 5-day ACTD regimens, the 8-day MTX/FA regimen and bolus ACTD are more effective than either the weekly intramuscular (IM) or intermittent intravenous (IV) infusion of MTX. The wide variability in outcomes can be explained by differences in dose, frequency, route of administration and patient selection [122]. An optimal regimen would maximize response rate while minimizing morbidity and cost. Single-agent chemotherapy should be administered at a fixed time interval to optimize the effect. ACTD regimens may provide a slightly higher primary remission rate than MTX, but generally are associated with more toxicity [123]. For this reason they are usually used as second-line therapy or for initial therapy in patients who are not appropriate for MTX for reasons like the presence of liver dysfunction.

At the NETDC, MTX with Folinic Acid (FA) rescue has been the preferred single-agent regimen for the primary therapy of low-risk GTN since 1974 [124-127]. ACTD as the primary agent is reserved for patients with pre-existing hepatic abnormalities. Chemotherapy is administered every two weeks, toxicity permitting, until the hCG level becomes undetectable at which point consolidation therapy is recommended. It has recently been reported that three cycles of the last effective agent administered after gonadotropin remission is achieved is associated with a significant reduction in the risk of relapse [128]. Between September 1974 and September 1984, 185 patients were treated with primary MTX/FA at the NETDC [125]. Complete remission was induced in 162 (87.6%) patients. MTX/FA induced remission in 147 (90.2%) of 163 patients with stage I and in 15 (68.2%) of 22 patients with low-risk stages II and III. Among the 23 patients who were resistant to MTX, 14 (61%) achieved remission with ACTD. Remission was accomplished with combination chemotherapy in the remaining nine patients. Complete sustained remission was achieved following one course of MTX-FA in 132 (81.5%) of these patients. After three consecutive weeks of non-detectable hCG values were attained, only two (1.1%) patients with non-metastatic disease developed tumor recurrence. Hammond et al. [104] reported that when single-agent chemotherapy was administered at a fixed time-interval and induced remission in patients with non-metastatic GTN, relapse occurred in 2% of patients. Resistance to MTX/FA was more common in patients with choriocarcinoma, metastases, and pretreatment hCG levels >50,000 IU/L. Following MTX/FA, granulocytopenia (white blood count <1500/mm<sup>3</sup>), thrombocytopenia (platelets <100,000/mm<sup>3</sup>) and hepatotoxicity (serum glutamic oxaloacetic transaminase (SGOT) >50 U/l) developed in three (1.6%), 11 (5.9%) and 26 (14.1%) patients, respectively. No patient developed sepsis or required platelet transfusion due to myelosuppression. MTX not only achieved an excellent remission rate with minimal toxicity, but also effectively

limited chemotherapy exposure. The MTX/FA regimen utilized between 1975 and 1985 consisted of intramuscular injections of MTX 1 mg/kg on days 1,3,5 and 7, and FA 0.1 mg/kg, IM or PO, on days 2,4,6 and 8. The effectiveness of this regimen is thought to be partly attributable to the prolonged exposure to MTX. ACTD is administered intravenously at a dose of 10-12 µg/kg daily for 5 consecutive days. Although highly effective, it is significantly more toxic than MTX, which limits its use as a primary agent. ACTD should be used instead of MTX when there is evidence of significant hepatotoxicity.

The most widely used regimen in the United States has been the weekly intramuscular injection of MTX at a dose of 30-50 mg/m<sup>2</sup> [111]. The main disadvantage of this regimen is the length of time it takes to achieve remission which in some cases has taken up to 15 to 20 weekly treatments. When resistance to weekly MTX develops, bolus ACTD is utilized at a dose of 1.25 mg/m<sup>2</sup> biweekly [129-131]. A few clinicians have used alternating cycles of MTX and ACTD to treat low-risk patients, but the experience is small. Most gynecologic oncologists will use one agent at a time to expose the patient's tumor to the fewest chemotherapeutic agents and to reserve other agents in case resistance develops. Because of concerns for acute and chronic toxicity, agents such as etoposide, 5-fluorouracil, 6-mercaptopurine, and cisplatin are rarely used for treatment of low-risk disease in the United States [111], although they had been used in Asia as primary therapy for low-risk GTN [132].

Recent studies have shed light on some important aspects of monotherapy. Maesta et al. [133] used multivariate analysis to study the prognostic factors that affect time to remission in low-risk GTN patients and concluded that complete molar histology, the presence of metastases, and a higher FIGO score were the main factors associated with longer time to remission. Chapman-Davis et al. [134] stressed the importance of dose-intensive treatment in low-risk GTN patients treated initially with the 5-day MTX regimen. Importantly, Shah et al. [135] performed a cost analysis of single-agent chemotherapy in low-risk GTN patients and concluded that 8-day MTX-FA regimen was consistently less expensive than ACTD. In general, primary treatment failure with single-agent chemotherapy occurs in 10-30 percent of patients with non-metastatic GTN, and in 30-50 percent of low-risk patients with metastatic disease. Patients who develop resistance to the initial single-agent usually respond to the alternative single-agent. Only approximately 15 percent of patients with low-risk GTN will require multiagent therapy to achieve a complete sustained remission.

### 11.8.2 COMBINATION CHEMOTHERAPY

Triple therapy consisting of MTX, ACTD and cyclophosphamide or chlorambucil (MAC) was the preferred combination drug regimen at

the NETDC until approximately 1985 [136]. However, it became apparent that triple therapy induced remission in only about half of patients with high-risk metastatic GTN. Table 11.11 reviews the response rate to primary triple therapy in patients with metastatic GTN and a high risk score from six centers [58, 60-62,88,137]. Collectively, triple therapy induced a complete response in only 47 (51%) of 92 patients.

Etoposide (VP16) was first reported in 1977 to have antitumor activity in patients with GTN who were resistant to other chemotherapeutic agents [138]. When etoposide was administered as primary therapy, it induced complete remission in 56 (93%) of 60 patients with non-metastatic or low-risk metastatic GTN [132]. In 1984, Bagshawe described a new combination regimen that included etoposide, MTX, ACTD, cyclophosphamide and vincristine (EMACO) which achieved an 83% remission rate in patients with high-risk GTN [139].

EMACO has become the preferred primary regimen for patients with high-risk metastatic GTN generally throughout the world [140-145]. Table 11.12 reviews the results of primary EMACO therapy in high-risk metastatic GTN from four centers [138,140,142,143]. Quinn et al. [144] observed that primary EMACO induced complete sustained remission in 61 (94%) of 65 patients with a WHO score  $\geq 5$ . Bolis et al. [140], Lurain et al. [145], and Soper et al [143] have also reported that EMACO induced complete remission in 16 (94%) of 17, 20 (67%) of 30, and 4 (67%) of 6 high-risk GTN patients, respectively. Furthermore, Bower et al. [112] and Kim et al [141] reported that primary EMACO induced remission in 130 (86.1%) of 151 patients and in 87 (90.56%) of 96 high-risk patients, respectively. The EMACO regimen is generally well tolerated and treatment seldom has to be suspended because of toxicity.

If patients become resistant to EMACO, they are then treated with modification of this regimen by substituting cisplatin ( $75 \text{ mg/m}^2$ ) and etoposide ( $150 \text{ mg/m}^2$ ) on day 8 (EMAEP). Bower et al. [112] reported that EMAEP alone or in conjunction with surgery induced remission in 16 (76%) of 21 patients who were resistant to EMACO. Lurain et al [145] also noted the efficacy of using platinum. He observed that eight of 10 patients (80%) resistant to EMACO were remitted with platinum-based chemotherapy. In a more recent update of their experience, Lurain and Schink[146]reported that 23(82%) of 28 patients with resistance to EMACO achieved remission with etoposide/platinum-based regimens. If patients develop resistance to EMACO, surgical intervention may also be necessary to remove sites of resistant disease. For those women with ultra high risk GTN Alifrangis et al. [147] suggests that induction with EP before EMACO eliminates early deaths and improves survival.

In 1996 Rustin et al. [148] reported that the use of etoposide was associated with an increase in the relative risk of later secondary

tumors including myeloid leukemia, melanoma, colon and breast cancer by 16.6, 3.4, 4.6, and 5.8, respectively, in patients who receive more than 2 gms/m<sup>2</sup>. The increased risk for breast cancer did not become apparent until after 25 years. Among all patients who were treated with etoposide, 1.5% subsequently developed leukemia. However, the most recent data from Charing Cross Hospital based on 30,638 years of patient follow-up indicate that there is a low-risk of second tumors (risk-0.9%) [149]. We use etoposide as part of multiagent regimens for patients with low-risk GTN resistant to monotherapy, and for primary treatment of patients with high-risk metastatic disease [150]. Second-line therapy with etoposide in combination with cisplatin, and bleomycin (BEP) or vinblastine in combination with cisplatin and bleomycin [PVB] have also been shown to be effective in patients with resistant GTN. Gordon et al. [151] reported that PVB induced complete sustained remission in two of 11 patients with prior resistance to triple therapy. DuBeshter et al. [152] and Azab et al. [153] also reported complete remission with PVB in four of seven and five of eight patients, respectively, with drug-resistant GTN. Lurain and Nejad [154] reported lasting remissions in 9 of 10 high-risk patients resistant to EMACO treated with either EMAEP or BEP.

The potential role of autologous bone marrow transplantation or stem cell rescue in GTN has yet to be defined. However, individual cases have been reported where ultra high-dose chemotherapy with autologous bone marrow or stem cell support has induced complete remission in patients with refractory disease [155,156].

Despite the efficacy of the well-recognized regimens currently in use, efforts continue to identify new agents that are effective when GTN becomes resistant. Although ifosfamide and paclitaxel (Taxol) are both active in treating GTN, further studies must be carried out to determine their potential role in either primary treatment or second-line therapy [157]. Osborne and associates [158] have reported that a novel three-drug doublet regimen consisting of paclitaxel, etoposide and cisplatin (TE/TP) induced complete remission in two patients with relapsed high-risk GTN. Wan et al. [159] analyzed the efficacy of floxuridine (FUDR)-containing regimens in patients with invasive mole and choriocarcinoma, some of whom had become resistant to other regimens. Twenty-one patients with drug-resistant GTN received FUDR-containing regimens and all patients achieved remission. Matsui et al. [160] found that 5FU in combination with ACTD could also be used as salvage therapy since they observed complete remission in 9 of 11 (82%) patients.

High risk patients or patients with resistant disease who require combination chemotherapy must be treated intensively to achieve remission. We administer combination chemotherapy as frequently as toxicity permits, usually at two week intervals, until the patient attains three consecutive non-detectable hCG values. Three additional courses of chemotherapy are then administered as consolidation

therapy to reduce the risk of relapse.

Table 11.11 Results of primary triple therapy in high-risk metastatic GTN

Author	<i>Complete response with triple therapy</i>	
DuBeshter <i>et al.</i> [58]	5/11	(45%)
Gordon <i>et al.</i> [60]	11/24	(46%)
Dubuc-Lissoir <i>et al.</i> [61]	11/22	(50%)
Mortakis and Braga [62]	12/20	(60%)
Ayhan <i>et al.</i> [88]	3/7	(43%)
Curry <i>et al.</i> [137]	5/8	(63%)
Total	47/92	(51%)

Table 11.12 Results of primary EMA-CO in high-risk metastatic GTN

Author	<i>Complete response with EMA-CO</i>	
Bolis <i>et al.</i> [140]	16/17	(94%)
Newlands <i>et al.</i> [138]	53/76	(70%)
Schink <i>et al.</i> [142]	3/5	(60%)
Soper <i>et al.</i> [143]	4/6	(67%)
Total	76/104	(73%)

## 1.9 FOLLOW-UP

All patients with stages I, II and III GTN are followed with weekly hCG levels until undetectable for three weeks, and then monthly for 12 months. Patients with stage IV disease who enter complete remission are monitored with monthly hCG levels until undetectable for 24 months because they have an increased risk for late relapse. After 12 or 24 months of follow-up, it is advisable to follow patients every six months for five years, although the risk of late relapse in the vast majority of patients after one year is negligible.

Mutch *et al.* [161] reported recurrences after initial remission in 2% of patients with non-metastatic GTN, 4% of patients with good prognosis metastatic GTN (i.e., low risk) and 13% of patients with poor prognosis (i.e., high risk) disease. Recurrences occurred within three and 18 months in 50% and 85% of patients respectively. Similarly, we observed relapse in 2.9% of stage I, 8.3% of stage II, 4.2% of stage III and 9.1% of stage IV patients. The mean time to recurrence from the last non-detectable hCG level was 6 months and did not differ among the four stages [162]. All patients with stages I,

II, and III GTN who developed recurrence were subsequently cured, whereas both stage IV patients who recurred died of their disease.

Some attempt has been made to identify risk factors for recurrence. Ngan et al. [163] reporting the 20-year experience treating GTN in Hong Kong observed that the median interval from remission to relapse was 6.5 months. They concluded that the most important risk factors for recurrence were patients who defaulted treatment or follow-up, and those who presented with massive disease. Yang et al. [164] studied 901 patients receiving treatment in Beijing and found that the mean interval from remission to relapse was 15.3 months. The four recurrence-associated risk factors in this study identified by multivariate analysis were: (1) clinical stage, (2) an interval of >12 months between the antecedent pregnancy and the start of chemotherapy, (3) a negative blood B-hCG titre after seven courses of chemotherapy, and (4) less than two courses of consolidation chemotherapy.

Patients are encouraged to use reliable contraception during gonadotropin follow-up. Oral contraceptives may be of particular benefit for patients who receive intensive or prolonged chemotherapy. Some drugs used may induce ovarian dysfunction and thereby cause elevated serum levels of luteinizing hormone, which could interfere with measurement of low levels of hCG in some less specific assay systems. We do not recommend the insertion of intrauterine devices until the patient is in gonadotropin remission because of the possibility of infection, bleeding and perforation if viable tumor is present in the uterine cavity.

## **11.10 SUBSEQUENT PREGNANCIES**

Patients who have been successfully treated for GTN can generally expect normal reproductive function in the future [165-167]. Table 11.13 summarizes the pregnancy outcomes in 667 subsequent pregnancies in patients treated between July 1965 and December 2013 for all stages of GTN at the NETDC. There does not appear to be any evidence of impaired pregnancy outcome in these patients as compared to the general population. It is particularly reassuring that there is no higher incidence of first trimester miscarriage or congenital abnormalities in light of the fact that chemotherapeutic agents may be teratogenic and mutagenic.

The experience from the NETDC and 10 other centers data have been reported concerning the outcome of 3191 pregnancies [165-175]. These subsequent pregnancies resulted in 2342 (73.4%) live births, 89 (4.7%) premature deliveries, 40 (1.3%) stillbirths, and 457 (14.3%) spontaneous abortions. Although the frequency of stillbirths appears to be somewhat increased, congenital malformations were noted in only 46 (1.6%) infants, which is consistent with the general population. Woolas et al. [173] noted that there was no difference in

either the conception rate or pregnancy outcome between women treated with single-agent MTX and those receiving combination therapy. Furthermore, only 7% of women who wished to become pregnant failed to conceive.

In general, patients who achieve primary remission with various kinds of chemotherapy may anticipate a normal future reproductive career [175]. However, patients occasionally become pregnant before the recommended 12 month follow-up period has lapsed. When a patient's hCG level re-elevates after completing chemotherapy, the use of TVUS enables the clinician to distinguish between a normal intercurrent pregnancy from disease recurrence. Matsui et al [176] have reported that pregnancies which occur within six months after remission are at an increased risk of abnormalities including miscarriage, stillbirths and repeat moles. However, Williams et al. [177] in a cohort of 1204 patients with early pregnancy following chemotherapy for GTN observed no increase in abnormalities.

Table 11.13 Subsequent pregnancies outcomes, all Stages, NETDC, July 1965 to December 2013

<i>Outcome</i>	<i>No Patients (%)</i>	<i>No Deliveries (%)</i>
Term delivery	446	66.8
Stillbirth	10	1.5
Premature delivery	44	6.6
Spontaneous abortion	123	18.4
Ectopic pregnancy	7	1.0
Repeat molar pregnancy	9	1.3
Congenital malformation(all)	12/500	2.4
<b>TOTAL NO. PREGNANCIES</b>	<b>667</b>	

\*January 1979 to December 2013

## 11.11 PSYCHOSOCIAL CONSEQUENCES OF GTN

Women who develop GTN may experience significant mood disturbance, marital and sexual problems, and concerns over future fertility [178-181]. Because GTN is a consequence of pregnancy, patients and their partners must confront the loss of a pregnancy at the same time they face concerns regarding malignancy. Patients may experience clinically significant levels of anxiety, fatigue, anger, confusion, sexual problems, and concern for future pregnancy that may last for protracted periods of time. Patients with active disease are particularly at risk for severe psychological reactions.

Psychosocial assessments and interventions should be provided to patients with GTN and their partners, and should be targeted to patients in the metastatic and active disease groups in particular. The psychological and social stresses related to persistent GTN may last for

many years beyond complete remission. Even five to ten years after attaining complete remission 51% of patients indicate that they would be somewhat likely to participate in a counseling program to discuss psychosocial issues raised by having GTN.

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