



# Management of resistant or recurrent Gestational trophoblastic neoplasia

M.R SAGHAFI.MD

RADIATION ONCOLOGIST

# DEFINITION:

Patients whose hCG level re-elevates after becoming undetectable are considered to have **recurrent disease**.

In contrast, patients whose hCG level remains elevated despite treatment are considered to have **resistant disease**.

# ESTIMATING THE RISK OF RESISTANT OR RECURRENT DISEASE

Women treated for GTN are at varying risks of developing either resistant or recurrent disease. In one study, the reported **recurrence rates** according to International Federation of Gynecology and Obstetrics (FIGO) staging were as follows :

- Stage I (non-metastatic) – 2 percent
- Stages II and III; **low-risk** GTN – 4 percent
- Stage II to IV; **high-risk** – 13 percent

# PRETREATMENT EVALUATION

All patients who develop chemoresistant or recurrent disease require re-staging. In addition, this evaluation should be repeated each time a new course of treatment is indicated.


Patients who recur or develop resistance often have multiorgan involvement, particularly if they were previously treated for high-risk GTN.

Therefore, re-imaging with chest, abdominal, and pelvic computed tomography (CT) scans and brain magnetic resonance imaging (MRI) should be performed to help guide treatment options. For patients in whom the diagnosis is questionable, positron emission tomography (PET) scanning may aid in the differential characterization of active disease (which should be PET-positive) from fibrotic tumor nodules.

# LOW-RISK GTN


In general, **primary resistance** after single-agent chemotherapy occurs in **10 to 30 percent of patients with low-risk** GTN. However, this figure rises to between **30 and 50** percent of patients with **low-risk GTN in the presence of metastases**.

Patients who develop resistance to the initial single agent usually will respond to an alternative single agent, and only 5 to 10 percent will require multiagent therapy.




There have been no randomized trials comparing single-agent with multiagent chemotherapy for patients with low-risk GTN who experience primary resistance to single-agent chemotherapy.

However, our clinical experience indicates that a second-line single-agent therapy is effective and induces remission in the vast majority of patients. As such, this is our preferred approach



Other institutions, however, use human chorionic gonadotropin (hCG) level at the time of introduction of second-line treatment to determine whether single- or multiagent chemotherapy should be initiated.

For patients with an **hCG level under 300 international units/L**, single-agent actinomycin D (ActD) is their standard choice, while for women with an hCG **>300 international** units/L at the time of treatment, etoposide, methotrexate (MTX), ActD, cyclophosphamide, and vincristine (EMA-CO) is chosen.



Using this cutoff, approximately 95 percent of patients treated with single-agent ActD successfully completed treatment without requiring additional therapy [14]. Of note, some data suggest that patients with higher risk scores (ie, 5 to 6) are at a greater risk of resistant disease compared with those with lower prognostic scores.

This was shown in one single-institution study in which **only 30** percent of these patients went into a sustained remission with second-line monotherapy. These patients characteristically present with a **pretreatment hCG level >100,000 milli-international** units/mL and Doppler ultrasound evidence of **a large tumor burden in their uterus**. For such patients, **multiagent chemotherapy is a reasonable option.**

# Second-line single-agent chemotherapy

For patients treated with MTX, with or without folinic acid (FA), who develop resistant or recurrent disease, we then administer biweekly bolus ActD. In our experience, more than **70 percent** of these patients will achieve sustained remission with second-line ActD and avoid multiagent chemotherapy.

If the initial treatment was ActD, we proceed with treatment using MTX-FA.

In patients with MTX resistance, **single-agent carboplatin** has been utilized with **mixed results** in two studies .

So When available, ActD should be the preferred second-line agent in patients with MTX-resistant, low-risk GTN.

# Progression after second-line single-agent therapy

Patients who have resistant or recurrent disease despite second-line single-agent chemotherapy should be treated with combination chemotherapy. As in patients with high-risk GTN, our regimen of choice is EMA-CO.

For patients who do not respond to initial combination chemotherapy, alternative regimens can be offered. However, other modalities, including surgery, may be reasonably pursued.



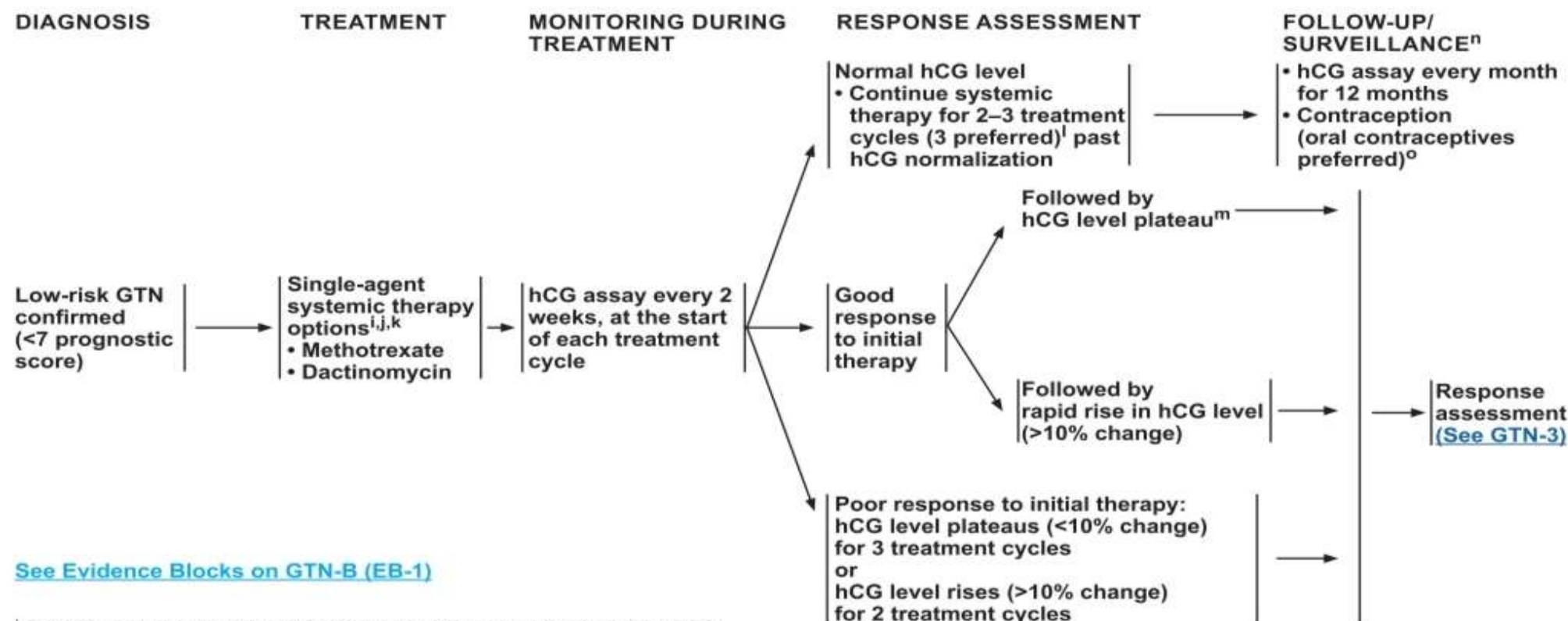
# NCCN Guidelines Version 1.2022

## Gestational Trophoblastic Neoplasia

### NCCN Evidence Blocks™

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

#### PRIMARY TREATMENT FOR LOW-RISK GTN



[See Evidence Blocks on GTN-B \(EB-1\)](#)

<sup>i</sup> Regimens are continued until 2–3 full cycles past normalization of the hCG.

<sup>j</sup> Hysterectomy with salpingectomy or repeat endometrial curettage may be considered if there is localized disease in the uterus. Hysterectomy is preferred and where fertility preservation is not desired. Leave ovaries in situ, even in presence of theca lutein cysts.

<sup>k</sup> See [Systemic Therapy for GTN \(GTN-B\)](#) for specific recommendations.

<sup>l</sup> Lybol C, et al. Gynecol Oncol 2012;125:576-579.

<sup>m</sup> hCG plateau during treatment can be defined as a <10% decrease in hCG over 3 treatment cycles.

<sup>n</sup> See [Principles of Gynecologic Surveillance \(GTN-C\)](#)



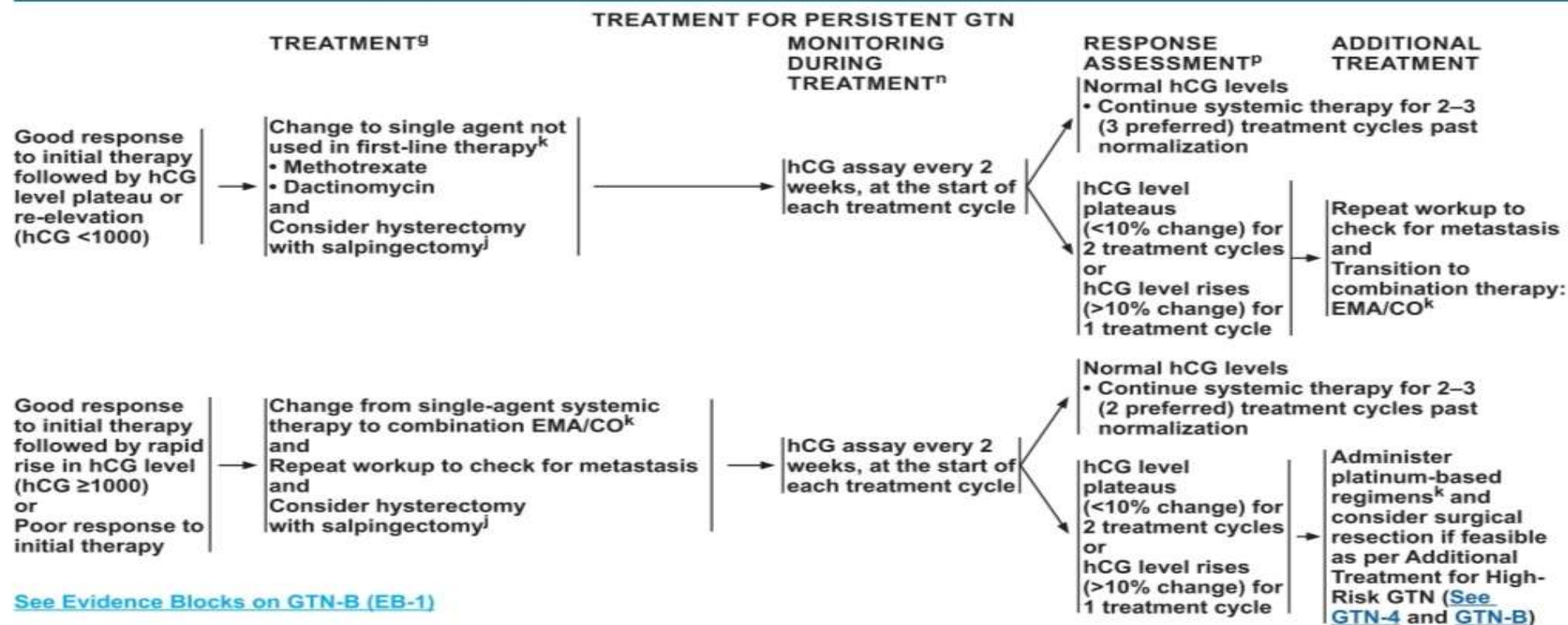
National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 1.2022

## Gestational Trophoblastic Neoplasia

### NCCN Evidence Blocks™

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)



[See Evidence Blocks on GTN-B \(EB-1\)](#)

<sup>g</sup> Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.

<sup>j</sup> Hysterectomy with salpingectomy or repeat endometrial curettage may be considered if there is localized disease in the uterus. Hysterectomy is preferred where fertility preservation is not desired. Leave ovaries in situ, even in presence of theca lutein cysts.

<sup>k</sup> See [Systemic Therapy for GTN \(GTN-B\)](#) for specific recommendations.

<sup>n</sup> See [Principles of Gynecologic Survivorship \(GTN-C\)](#).

<sup>p</sup> Post-treatment imaging is not recommended for follow-up after hCG normalization in patients with post-molar GTN or choriocarcinoma, where hCG is a reliable tumor marker.

# HIGH-RISK GTN


Despite the success of primary therapy with etoposide, methotrexate (MTX), and actinomycin D (ActD) alternating with cyclophosphamide plus vincristine (EMA-CO), roughly 30 to 40 percent of women with high-risk metastatic GTN will have an incomplete response to first-line therapy or will relapse from remission and will need additional multiagent chemotherapy with or without other treatment modalities.

Risk factors for resistant or recurrent disease include the presence of multiple metastases to sites other than the lung and vagina, and inadequate first-line chemotherapy.

# Second-line combination therapy

Although there are no universally accepted evidence-based guidelines for second-line treatment for patients who develop resistant or recurrent disease on first-line multiagent chemotherapy, our approach is as follows:

For patients previously treated with EMA-CO, we administer the multiagent chemotherapy combination consisting of EMA followed by etoposide plus cisplatin (EMA-EP).



Neutropenia may become an issue for patients receiving EMA-CO followed by EMA-EP, and in our clinical experience, prolonged neutropenia develops by the second or third cycle. Therefore, growth factor support (ie, filgrastim) is usually required .

In addition to chemotherapy, these patients may benefit from surgical excision of localized, persistent tumor .

Patients who were not treated with EMA-CO in the first-line setting should undergo treatment with this combination in the second-line setting.

# LATER-LINE THERAPY

For patients with resistant or recurrent disease despite two prior combination regimens, a number of alternative regimens can be administered. However, none of these regimens have been used in a sufficient number of patients to identify one as being the optimal choice.

It is important to re-stage patients prior to the initiation of a new regimen so that the extent of disease may be appropriately characterized and to evaluate for a potential role for surgical treatment. Case reports of patients treated with these later-line regimens do not indicate that one is preferred over another.

# Multiagent therapy

## TE-TP

— Paclitaxel and etoposide alternating weekly with paclitaxel and cisplatin (TE-TP) has had encouraging results in heavily pretreated patients. It appears to be well tolerated as well, though the experience remains quite limited.

## PC

The combination of paclitaxel and carboplatin (PC) was shown in one prospective study of 65 patients to produce remissions in approximately 60 percent of patients at a median follow-up of 30 months and may be an appropriate option for those wishing to avoid the possible increased risk for secondary tumors associated with etoposide-containing regimens



## **BEP**

The combination of bleomycin, etoposide, and cisplatin (BEP) is an available regimen, widely used to treat germ cell tumors of the ovary and testicle. In one report of 16 patients with EMA-CO-resistant disease, 11 patients (69 percent) had a complete response, and nine (56 percent) Survived.

## **ICE**

— The combination of ifosfamide, etoposide, and cisplatin (ICE) is often administered to men with recurrent or chemorefractory testicular cancer. Its use in women with recurrent or resistant GTN is limited. In one experience that included six patients, four had a complete remission, and three ultimately survived



## **PVB**

— Cisplatin, vinblastine, and bleomycin (PVB) has only been reported in small case series of patients with high-risk, drug-resistant GTN. The complete remission rates range from 18 to 62 percent.

## **FU plus ActD**

— High-dose fluorouracil (FU) in conjunction with actinomycin D (ActD) is commonly used in Asia, though the experience with this regimen is limited. For example, one series of 11 patients reported a complete remission rate of 82 percent .



## FUDR

— In one series, floxuridine (FUDR) in combination with ActD, etoposide, and vindesine was reported to induce remission in all 21 patients, all of whom had evidence of chemotherapy-resistant disease .Floxuridine-based regimens have also been reported to be highly elective in placental site trophoblastic tumor (PSTT), which is relatively resistant to chemotherapy .

# Single-agent therapy

Very limited data suggest that single-agent treatment may provide benefit in patients with previously treated recurrent, advanced, or metastatic GTN. These include:

**Paclitaxel** – Case reports indicate that paclitaxel may be an active agent following prior treatment. However, the experience with singleagent paclitaxel therapy remains quite limited .

**Capecitabine** – A case report indicates that capecitabine may also be active in the management of relapsed high-risk GTN .

**Pegylated liposomal doxorubicin** – Pegylated liposomal doxorubicin was reported to induce complete remission in two patients with chemotherapy-resistant high-risk GTN with brain metastases and having received multiple prior lines of chemotherapy

# Investigational therapies

New investigational therapies for GTN include immune checkpoint inhibitors and molecularly targeted agents. The rationale for immunotherapy in this disease is histologic evidence that GTNs strongly express programmed cell death ligand 1 (PD-L1).

Avelumab

Pembrolizumab

bevacizumab



National  
Comprehensive  
Cancer  
Network®

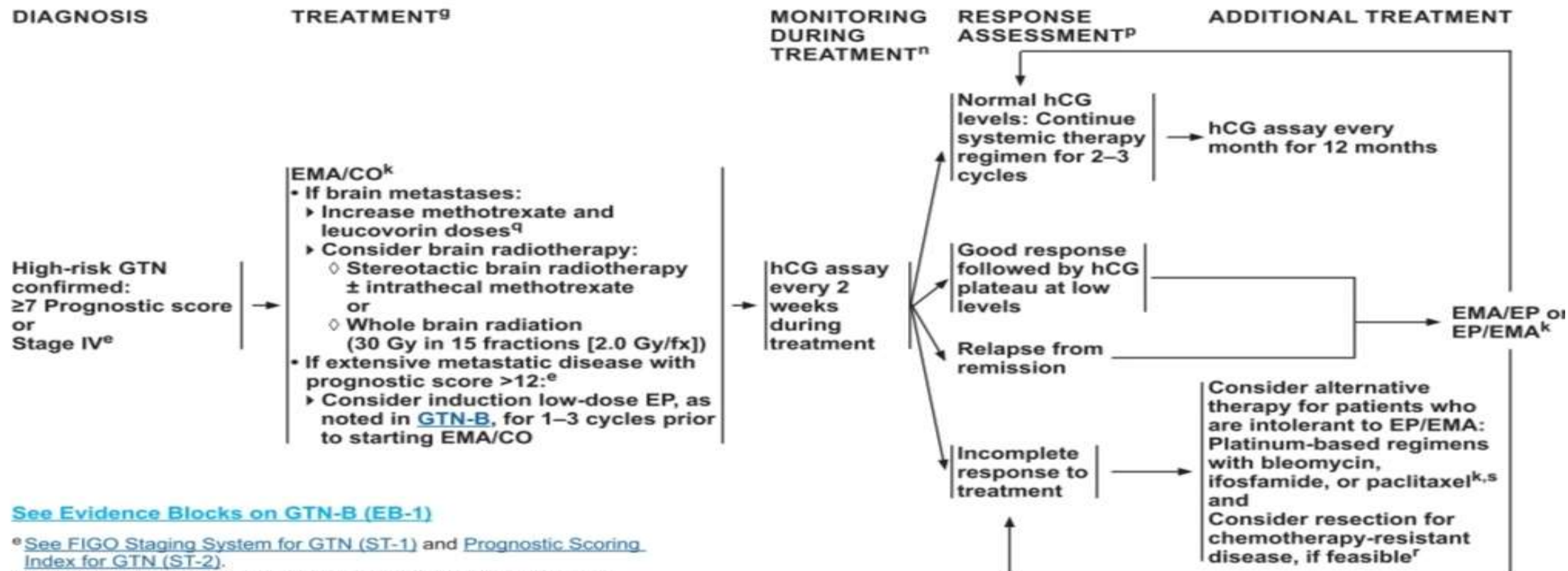
# NCCN Guidelines Version 1.2022

## Gestational Trophoblastic Neoplasia

### NCCN Evidence Blocks™

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

#### PRIMARY TREATMENT FOR HIGH-RISK GTN



[See Evidence Blocks on GTN-B \(EB-1\)](#)

<sup>e</sup> See [FIGO Staging System for GTN \(ST-1\)](#) and [Prognostic Scoring Index for GTN \(ST-2\)](#).

<sup>g</sup> Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.

<sup>k</sup> See [Systemic Therapy for GTN \(GTN-B\)](#) for specific recommendations.

<sup>n</sup> See [Principles of Gynecologic Survivorship \(GTN-C\)](#).

<sup>p</sup> Post-treatment imaging is not recommended for follow-up after hCG normalization in patients with post-molar GTN or choriocarcinoma, where hCG is a reliable tumor marker.

<sup>q</sup> For dosing modifications for brain metastases, [See Systemic Therapy for GTN \(GTN-B 2 of 6\)](#).

<sup>r</sup> Also see [Additional Agents Shown to Have Some Activity in Treating Multiagent Chemotherapy-Resistant GTN \(GTN-B 5 of 6\)](#).

<sup>s</sup> Consider surgery, especially hysterectomy with salpingectomy and pulmonary resection, for chemotherapy-resistant disease.

# Role of Surgery

— For patients with recurrent or resistant GTN, a surgical approach may be curative. However, decisions regarding surgery must be individualized based upon the clinical scenario. The efficacy, feasibility, and type of surgery vary depending upon the site and extent of metastases

# Uterine disease


— Hysterectomy should be avoided if possible, especially for women who desire future childbearing. However, it may be indicated after chemotherapy, especially for heavy bleeding, large bulky intrauterine disease, or in the presence of sepsis .

Hysterectomy may also be performed to manage chemotherapy resistance to reduce tumor burden.

# Pulmonary metastases

Although pulmonary disease is usually chemosensitive, resection of chemoresistant lung nodules can be curative and should be considered when the metastasis is solitary and limited to one lung and the  $\beta$ -hCG is  $<1,000$  mIU/mL.

Normalization of  $\beta$ -hCG within 1 to 2 weeks after resection of a pulmonary lesion is a good indication of a favorable outcome.



When evaluating patients for thoracotomy, it is important to remember that lung nodules can persist for several months or years after completion of chemotherapy and normalization of  $\beta$ -hCG. These nodules may represent areas of scar tissue or nonviable tumor, which the use of PET or PET/CT may help to determine.

# Brain metastases

Surgery can also play a role in the management of cerebral metastases. Multimodality therapy including chemotherapy with surgical resection and irradiation (whole-brain and/or stereotactic radiation) has improved overall survival from 46% to 64% in the past 14 years, even when metastases developed during chemotherapy.

Craniotomy is indicated for the resection of peripheral, solitary, drug-resistant lesions and can be life saving in the management of intracranial hemorrhage or increased intracranial pressure.

# Hepatic metastases

— Management of persistent liver metastases can be a particularly difficult and challenging problem. Hepatic resection or selective embolization may be used in select cases to control bleeding or excise resistant tumor . Because of their hypervascular nature, biopsy should not be performed because of the potential for life-threatening hemorrhage.

# IS THERE A ROLE FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT?

The use of high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HDSCT) is not clear, and the experience with this is mainly limited to case reports.

However, the use of autologous hematopoietic stem cell transplant, which is associated with profound immunosuppression, should be avoided during the COVID-19 pandemic