National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gestational Trophoblastic Neoplasia

Version 2.2019 — May 6, 2019

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Gestational Trophoblastic Neoplasia

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2019
Gestational Trophoblastic Neoplasia

Updates in Version 2.2019 of the NCCN Guidelines for Gestational Trophoblastic Neoplasia from Version 1.2019 include:
- **The Discussion has been added to correspond with the algorithm (MS-1)**

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NCCN Guidelines Version 2.2019
Hydatidiform Mole (Noninvasive)

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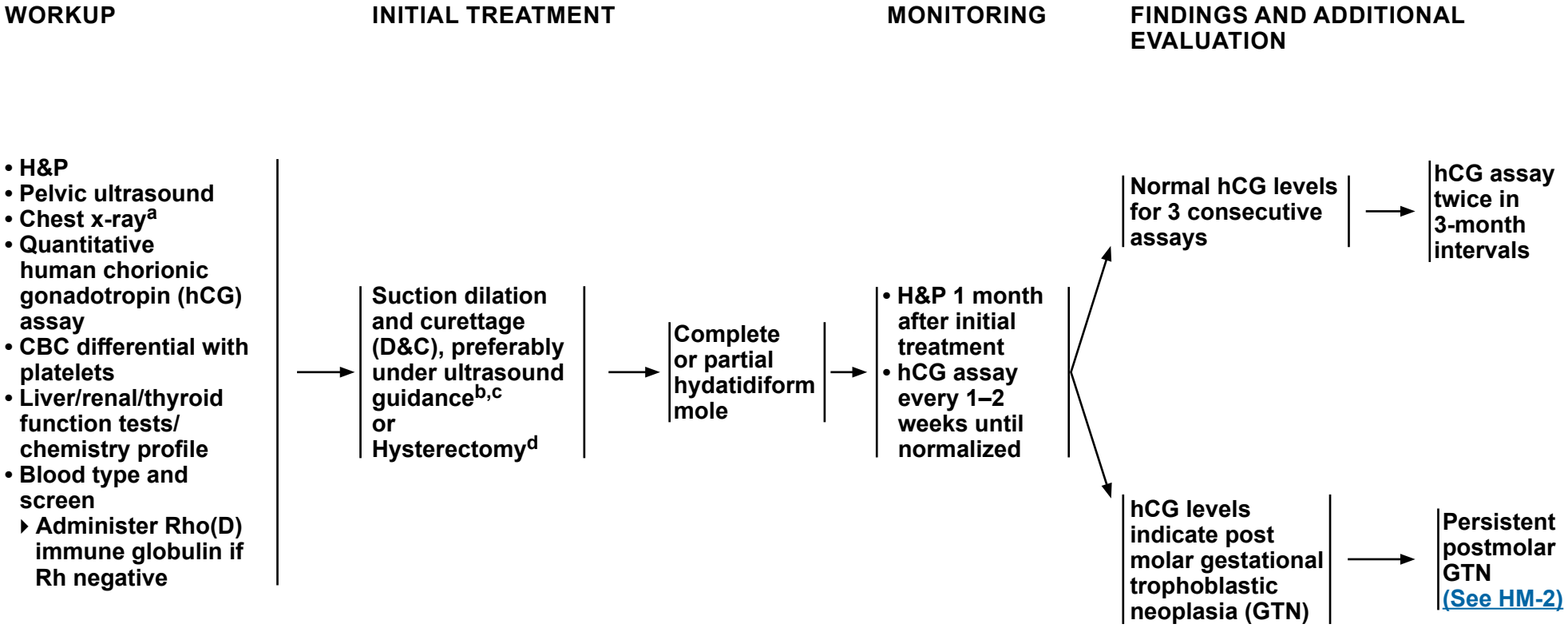

[a]If chest x-ray positive for metastases, manage as GTN after initial uterine evacuation.
[b]Use largest curette feasible. Sharp curettage after suction. Use uterotonic drugs after initiating evacuation of uterus. Oxytocin receptors may be absent.
[c]Prophylactic chemotherapy with methotrexate or dactinomycin may be considered at the time of evacuation of a hydatidiform mole in patients at high risk for postmolar gestational trophoblastic neoplasia (age >40 years, hCG >100,000 mIU/mL, excessive uterine enlargement, and theca lutein cysts >6 cm) when hCG follow-up is unavailable or unreliable (Wang Q, Fu J, Hu L, et al. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. Cochrane Database Sust Rev 2017 Sep 11;9:CD007289).
[d]Hysterectomy may be considered as initial treatment for hydatidiform mole in patients who are older or do not wish to preserve fertility.

Note: All recommendations are category 2A unless otherwise indicated.
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Hydatidiform Mole (Noninvasive)

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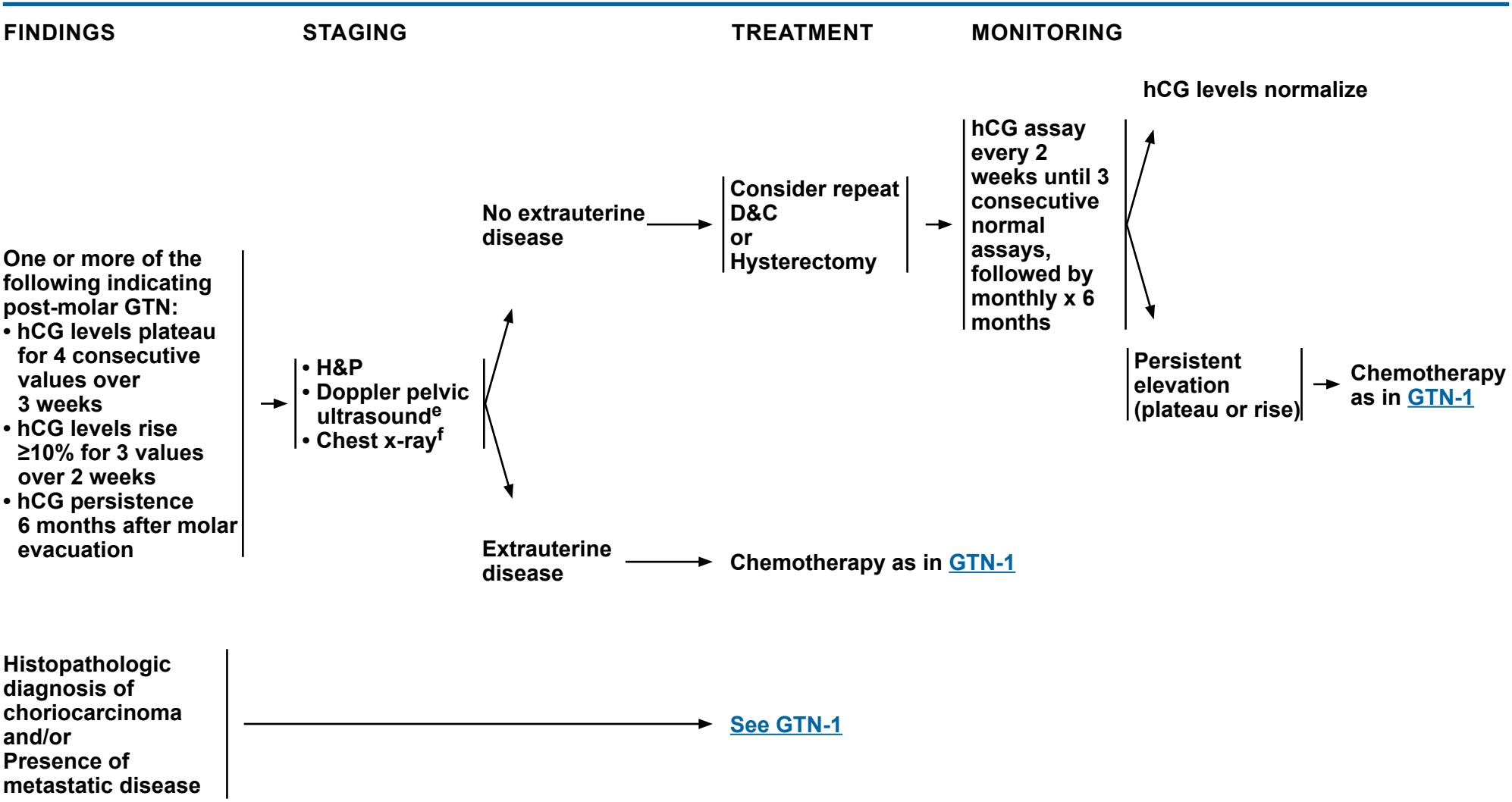

[e]Doppler pelvic ultrasound to confirm absence of pregnancy, measure uterine size, and determine volume and vasculature of tumor within the uterus.
[f]If the chest x-ray is normal, no further imaging is indicated before commencing treatment. If the chest x-ray shows metastases, CT scan of the abdomen/pelvis and MRI of the brain are indicated.

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WORKUP[a]
(unless previously done)

- H&P
- Repeat CBC differential with platelets
- Repeat liver/renal/thyroid function tests/chemistry profile
- Imaging
  - Chest/abdominal/pelvic CT scan with contrast[b]
    - ◊ Brain MRI (preferred) or CT with contrast if pulmonary metastasis
  - Pelvic ultrasound or MRI
- hCG assay[c,d]
- Determine FIGO stage and prognostic score[e]

FINDINGS[f]

Low-risk GTN
(<7 prognostic score)[e] → **(See GTN-2)**

High-risk GTN:
FIGO stages II-III
and ≥7 prognostic score[e]
or
Stage IV → **(See GTN-4)**

Intermediate trophoblastic tumor[g]
- **Placental site trophoblastic tumor (PSTT)**
- **Epithelioid trophoblastic tumor (ETT)**

→ **(See GTN-5)**

[a]If visible lesions are seen in lower genital tract, do NOT biopsy due to risk of hemorrhage.
[b]If contrast is contraindicated, other imaging techniques such as MRI may be considered.
[c]If hCG is elevated with no evidence of disease on imaging, consider possibility of phantom hCG. Consult with laboratory medicine/pathology to test for phantom hCG with serial dilution study or comparison of serum to urine hCG.
[d]If hCG is elevated, but hyperglycosylated hCG is normal, quiescent GTN may be diagnosed and not treated.
[e]See FIGO Staging (ST-1) and Prognostic Scoring Index for GTN (ST-2).
[f]Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.
[g]Prognostic scoring is not valid for intermediate tumors.

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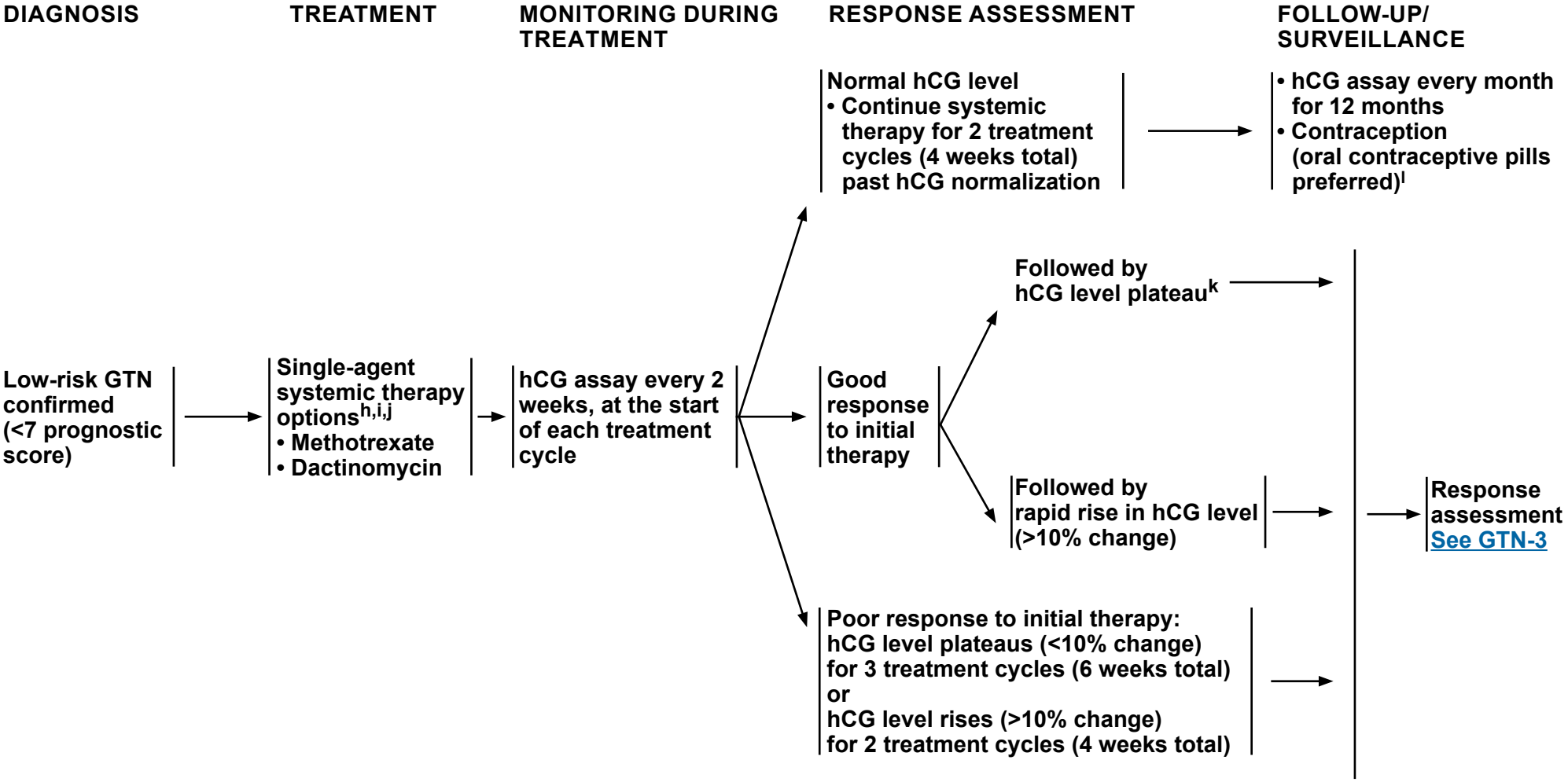

[h]Regimens are continued until 2 full cycle(s) past normalization of the hCG.
[i]Hysterectomy and salpingectomy may be considered if there is localized disease in the uterus and where fertility preservation is not desired. Leave ovaries in situ, even in presence of theca lutein cysts.
[j]See Principles of Systemic Therapy (GTN-A) for specific recommendations.
[k]hCG plateau during treatment can be defined as a <10% decrease in hCG over 2 treatment cycles (4 weeks total).
[l]Oral contraceptive pills are preferred because they suppress endogenous luteinizing hormone (LH)/follicle-stimulating hormone (FSH), which may interfere with hCG measurement at low levels.

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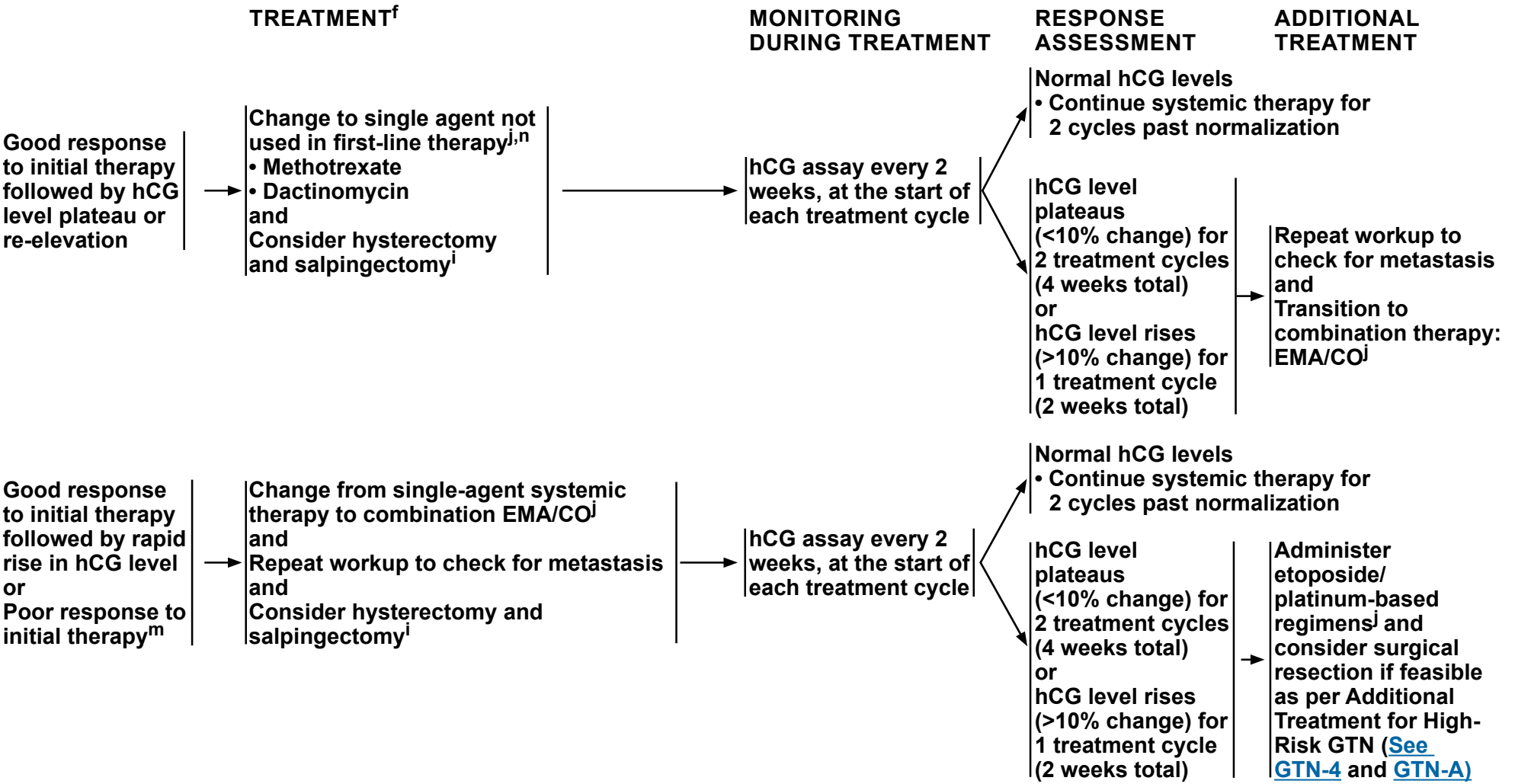

[f]Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.

[i]Hysterectomy and salpingectomy may be considered if there is localized disease in the uterus and where fertility preservation is not desired. Leave ovaries in situ, even in presence of theca lutein cysts.

[j]See Principles of Systemic Therapy (GTN-A) for specific recommendations.

[m]hCG level plateaus (<10% change) for 2 treatment cycles (4 weeks total) or hCG level rises (>10% change) for 1 treatment cycle (2 weeks total).

[n]Do not start a cycle of methotrexate or dactinomycin if the WBC was <3.0 or the ANC was <1.5 or if there was persistent mucositis >grade 1. CBC and chemistries should not be checked during a chemotherapy cycle; they should only be checked at the start of each cycle.

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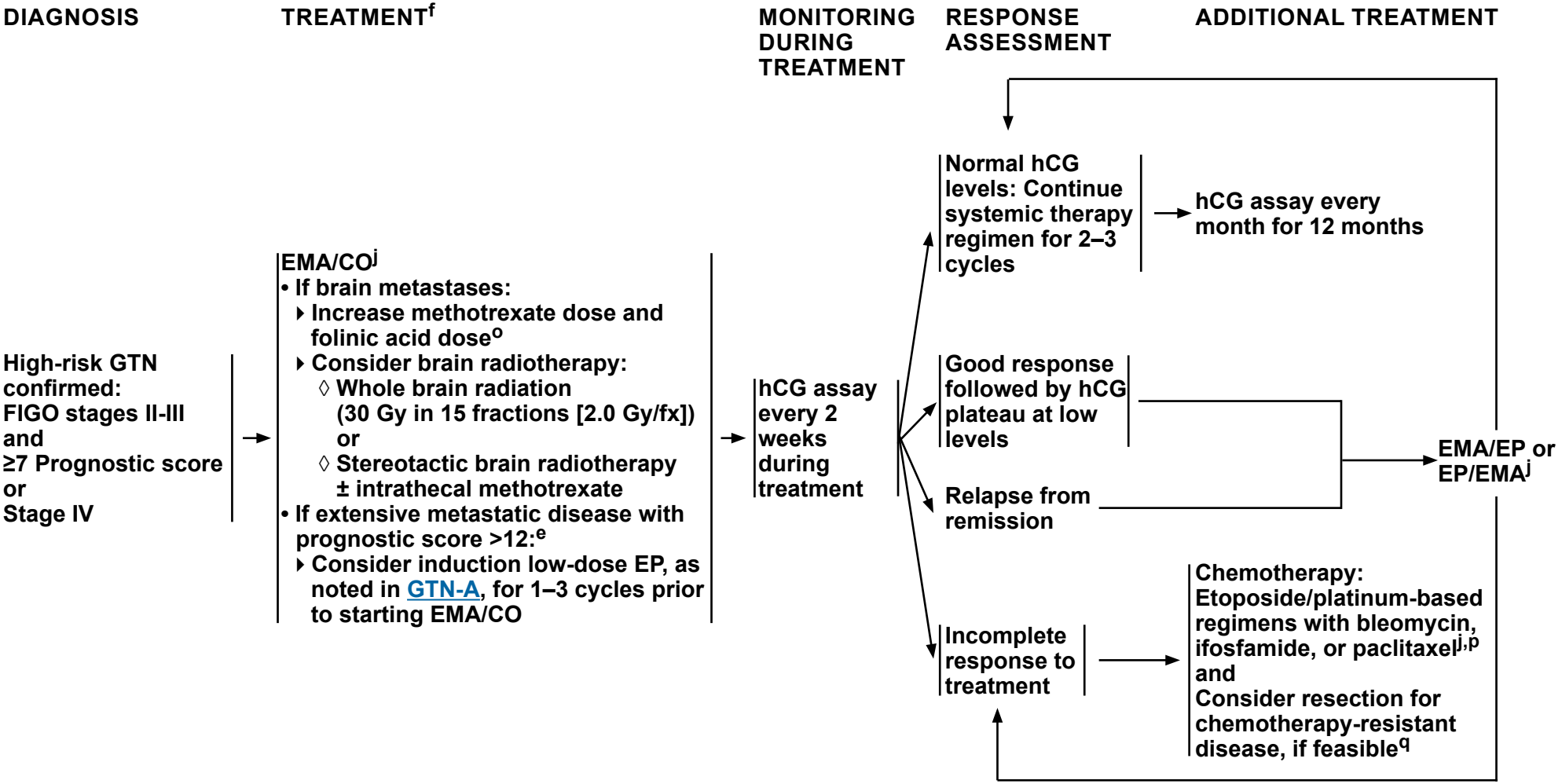

[e]See FIGO Staging (ST-1) and Prognostic Scoring Index for GTN (ST-2).
[f]Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.
[j]See Principles of Systemic Therapy (GTN-A) for specific recommendations.
[o]Increase the methotrexate infusion dose in the EMA/CO protocol to 1000 mg/m^2 and give folinic acid 30 mg every 12 hours for 3 days starting 32 hours after the infusion begins.
[p]Also see Additional Agents Shown to Have Some Activity In Treating Resistant High-Risk GTN (GTN-A).
[q]Consider surgery, especially hysterectomy and pulmonary resection, for chemotherapy-resistant disease.

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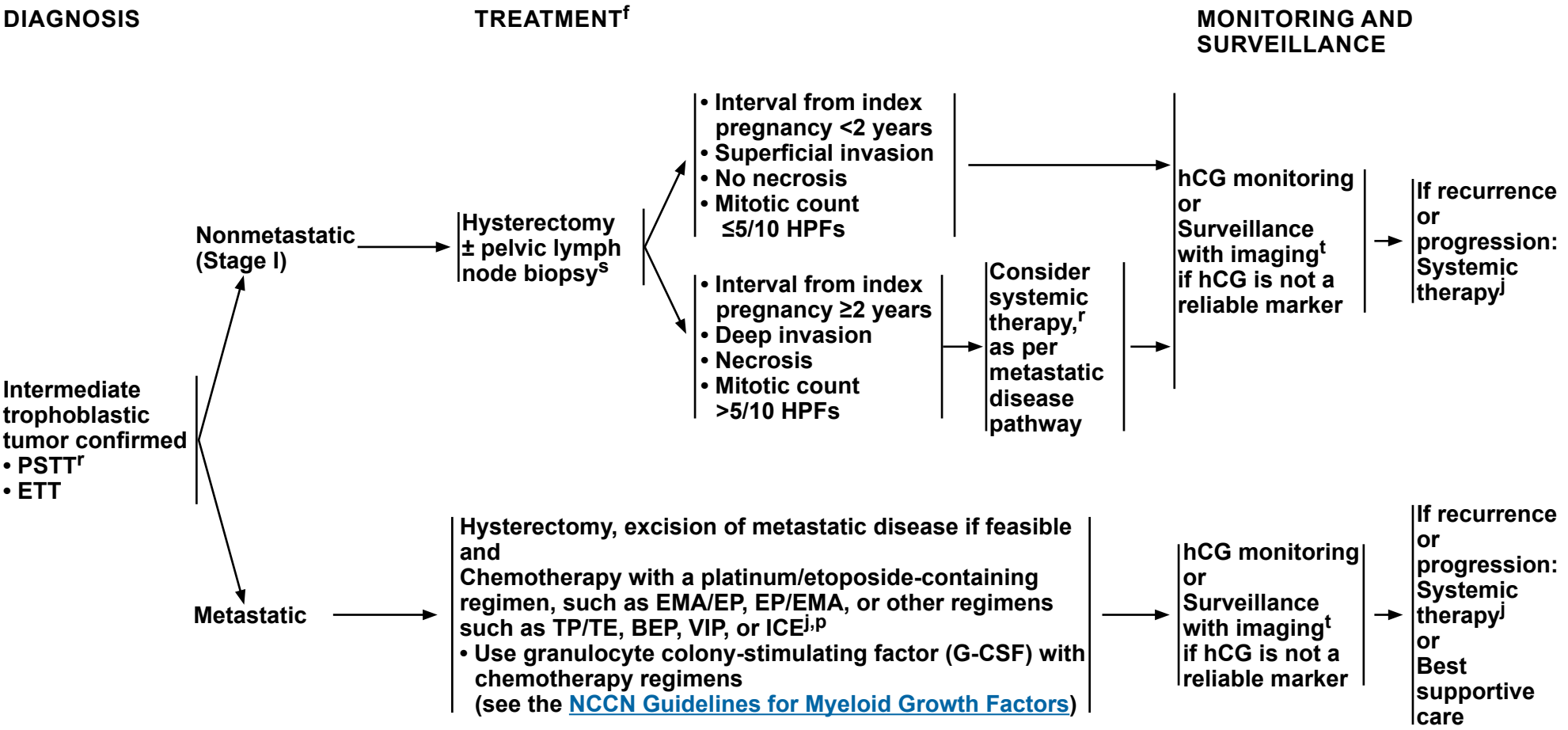

[f]Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.
[j]See Principles of Systemic Therapy (GTN-A) for specific recommendations.
[p]Also see Additional Agents Shown to Have Some Activity In Treating Resistant High-Risk GTN (See GTN-A).
[r]Reported poor prognostic factors in PSTT are high miotic rates (>5/10 HPFs), deep myometrial invasion, extensive coagulative necrosis, lymphovascular space invasion (LVSI), and interval since last pregnancy >2 years. (Baergen RN, Rutgers JL, Young RH, et al. Placental site trophoblastic tumors: a study of 55 cases and review of the literature emphasizing factors of prognostic significance. Gynecol Oncol 2006;100:511-520).
[s]The incidence of pelvic lymph node metastasis in PSTT/ETT is estimated to be between 5% and 15% in clinical stage I tumors. Therefore, pelvic lymph node biopsy should be considered at the time of hysterectomy, especially with large, deeply invasive tumors.
[t]Consider PET/CT for follow-up at the completion of chemotherapy and then every 6–12 months for 2–3 years.

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PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Low-Risk GTN

Regimens	Comments/Considerations
Methotrexate 0.4 mg/kg/day IV or IM (max 25 mg/day) daily x 5 days; Repeat every 14 days (category 1) OR 1 mg/kg IM every other day x 4 days (days 1, 3, 5, and 7) Alternating every other day with leucovorin 15 mg PO, 30 hours after each methotrexate dose on days 2, 4, 6, and 8; Repeat every 14 days (category 1)	• A multiday methotrexate regimen is typically used as first-line therapy for low-risk GTN. Due to its toxicity profile, dactinomycin has most often been used as secondary therapy for patients with methotrexate toxicity or effusions contradicting the use of methotrexate. **NOT RECOMMENDED** • Methotrexate 30–50 mg/m^2 IM weekly OR Methotrexate infusion (eg, 300 mg/m^2 over 12 hours/leucovorin) due to lesser efficacy.
Dactinomycin 10–12 mcg/kg (or 0.5 mg flat dose) IV daily x 5 days; Repeat every 14 days (category 1) OR 1.25 mg/m^2 (max 2 mg) IV pulse; Repeat every 14 days (category 1)	• Dactinomycin pulse regimen should not be used as secondary therapy for methotrexate-resistant disease nor as primary therapy in patients with choriocarcinoma.

Continued

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PRINCIPLES OF SYSTEMIC THERAPY

High-Risk GTN: Primary Therapy Options[a]

Regimens	Comments/Considerations
EMA/CO: Etoposide, Methotrexate, Dactinomycin/Cyclophosphamide, Vincristine **(Repeat every 2 weeks until hCG normalizes, then continue for an additional 6–8 weeks)** • **Etoposide 100 mg/m^2/day IV on days 1 and 2** • **Dactinomycin 0.5 mg IV push on days 1 and 2** • **Methotrexate 300 mg/m^2 IV infusion over 12 hours on day 1; may be given as 100 mg/m^2 IV push immediately followed by 200 mg/m^2 IV infusion over 12 hours** • **Leucovorin 15 mg PO or IM every 12 hours for 4 doses starting 24 hours after start of methotrexate** • **Cyclophosphamide 600 mg/m^2 IV on day 8** • **Vincristine 1 mg/m^2 (maximum of 2 mg) IV over 5–10 minutes on day 8**	• **Consider low-dose induction chemotherapy with etoposide 100 mg/m^2 IV and cisplatin 20 mg/m^2 IV on days 1 and 2 every 7 days for 1–3 courses prior to starting EMA/CO in patients with widely metastatic disease (prognostic score >12) who are at significant risk for pulmonary, intraperitoneal, or intracranial hemorrhage.** • **For secondary prophylaxis of neutropenic fever, or for treatment delay: Filgrastim, 300 mcg SC on days 9–14 of each EMA/CO cycle.** • **For patients with brain metastases, increase the methotrexate infusion dose in the EMA/CO protocol to 1000 mg/m^2 and give leucovorin 30 mg every 12 hours for 3 days starting 32 hours after the infusion begins.**

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Myeloid Growth Factors.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC THERAPY

High-Risk GTN: Primary Therapy Options[a] – Continued

For highest-risk patients, consider: EMA/EP or EP/EMA • EMA/EP (or EP/EMA) regimen is considered the most appropriate therapy for patients who have responded to EMA/CO but have plateauing low hCG levels or have developed re-elevation of hCG levels after a complete response to EMA/CO.	
Regimens	**Comments/Considerations**
EMA/EP: Etoposide, Methotrexate, Dactinomycin/Etoposide, Cisplatin (Repeat every 2 weeks) • Etoposide 100 mg/m^2/day IV on days 1 and 2 • Methotrexate 100 mg/m^2 IV push followed by 200 mg/m^2 IV infusion over 12 hours on day 1 ▸ Leucovorin 15 mg PO or IM every 12 hours for 4 doses starting 24 hours after start of methotrexate • Dactinomycin 0.5 mg IV push on days 1 and 2 • Etoposide 100 mg/m^2 IV on day 8 • Cisplatin 75 mg/m^2 IV on day 8 • Filgrastim 300 mcg SC on days 9–14 of each treatment cycle	On rare occasions, reduction of the EMA by omission of day 2 etoposide and dactinomycin doses may be needed to avoid extended intervals between courses caused by myelosuppression, which is usually overcome by the primary use of filgrastim.
EP/EMA: Etoposide, Cisplatin/Etoposide, Methotrexate, Dactinomycin (Repeat every 2 weeks) • Etoposide 150 mg/m^2 on day 1 • Cisplatin 75 mg/m^2 IV on day 1 • Etoposide 100 mg/m^2 IV on day 8 • Methotrexate 300 mg/m^2 IV infusion over 12 hours on day 8 ▸ Leucovorin 15 mg PO or IM every 12 hours for 4 doses starting 24 hours after start of methotrexate infusion • Dactinomycin 0.5 mg IV on day 8 • Filgrastim 300 mcg SC on days 3–6 and 10–13 of each treatment cycle	For patients with brain metastases, increase the methotrexate infusion dose in the EP/EMA protocol to 1000 mg/m^2 IV infusion over 24 hours and give leucovorin 15 mg every 6 hours for 12 doses starting 32 hours after the start of the methotrexate infusion.

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Myeloid Growth Factors.

Continued

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PRINCIPLES OF SYSTEMIC THERAPY

High-Risk GTN: Therapy for Methotrexate-Resistant GTN[a]

TP/TE: Paclitaxel, Cisplatin / Paclitaxel, Etoposide (Repeat every 2 weeks) • Paclitaxel 135 mg/m^2 IV infusion on day 1 • Cisplatin 75 mg/m^2 IV on day 1 **Alternating every 2 weeks with:** • Paclitaxel 135 mg/m^2 IV infusion on day 15 • Etoposide 150 mg/m^2 IV on day 15 • Administer pegfilgrastim, 6 mg SC on days 2 and 16	**TIP: Paclitaxel, Ifosfamide, Cisplatin (Repeat every 3 weeks)** • Paclitaxel 250 mg/m^2 IV on day 1 • Ifosfamide 1500 mg/m^2 IV on days 2–5 • Mesna 300 mg/m^2 IV before ifosfamide, then at 4 hours and 8 hours from the start of each ifosfamide dose on days 2–5 • Cisplatin 25 mg/m^2/day IV on days 2–5
BEP: Bleomycin, Etoposide, Cisplatin (Repeat every 3 weeks) • Bleomycin 30 units IV on days 1, 8, and 15 • Etoposide 100 mg/m^2/day IV on days 1–4 • Cisplatin 20 mg/m^2/day IV on days 1–4 • Pegfilgrastim 6 mg SC on day 8; OR Filgrastim 300 mcg SC on days 6–14 **Comments/Considerations** • Lifetime dose of bleomycin should not exceed 270 units. • Pulmonary function testing should be performed prior to initiation of therapy and every fourth dose thereafter.	**ICE: Ifosfamide, Carboplatin, Etoposide (Repeat every 3 weeks)** • Ifosfamide 1.2 grams/m^2/day IV on days 1–3 • Mesna 120 mg/m^2/day IV bolus prior to ifosfamide, then 1.2 grams/m^2/day IV infusion over 12 hours after ifosfamide dose on days 1–3 • Carboplatin AUC 4 IV on day 1 • Etoposide 75 mg/m^2/day IV on days 1–3 • Pegfilgrastim 6 mg SC on day 4; OR Filgrastim 300 mcg SC on days 6–14
VIP: Etoposide, Ifosfamide, Cisplatin (Repeat every 3 weeks) • Etoposide 75 mg/m^2/day IV on days 1–4 • Ifosfamide 1.2 grams/m^2/day IV on days 1–4 • Mesna 120 mg/m^2/day IV bolus just prior to ifosfamide, then 1.2 grams/m^2/day IV infusion over 12 hours after ifosfamide dose on days 1–4 • Cisplatin 20 mg/m^2/day IV on days 1–4 • Pegfilgrastim 6 mg SC on day 5; OR Filgrastim 300 mcg SC on days 6–14	**Additional agents/regimens shown to have some activity in treating resistant GTN:** • PD-1/PD-L1 inhibitors (eg, pembrolizumab, nivolumab) • 5-fluorouracil/capecitabine • Gemcitabine ± carboplatin • High-dose chemotherapy with peripheral stem cell transplant

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Myeloid Growth Factors.

Continued

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PRINCIPLES OF SYSTEMIC THERAPY

Intermediate Trophoblastic Tumor (PSTT and ETT)[a]

Regimens	Comments/Considerations
See HIGH-RISK GTN sections for dosage • EMA/EP: Etoposide, methotrexate, dactinomycin/etoposide, cisplatin • EP/EMA: Etoposide, cisplatin/etoposide, methotrexate, dactinomycin • TP/TE: Paclitaxel, cisplatin/paclitaxel, etoposide • BEP: Bleomycin, etoposide, cisplatin • VIP: Etoposide, ifosfamide, cisplatin • ICE: Ifosfamide, carboplatin, etoposide	**Additional agents/regimens shown to have some activity in treating resistant GTN:** • PD-1/PD-L1 inhibitors (eg, pembrolizumab, nivolumab) • 5-fluorouracil/capecitabine • Gemcitabine ± carboplatin • High-dose chemotherapy with peripheral stem cell transplant

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Myeloid Growth Factors.

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FIGO STAGING SYSTEM FOR GTN[a]

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	Lung metastasis
IV	All other distant metastases

Continued

[a]Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

PROGNOSTIC SCORING INDEX FOR GTN[a]

Prognostic factor	Risk score			
	0	1	2	4
Age (years)	<40	≥40	--	--
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	--
Interval from index pregnancy (months)	<4	4-6	7-12	>12
Pretreatment hCG (IU/mL)	$<10^3$	10^3 to $<10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size, including uterus (cm)	<3	3-5	>5	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1-4	5-8	>8
Previous failed chemotherapy	--	--	Single drug	Two or more drugs
Total score	--	--	--	--

- The total score for a patient is obtained by adding the individual scores for each prognostic factor.
- FIGO Prognostic Score
  - Low risk: <7
  - High risk: ≥7

[a]Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Overview

Gestational trophoblastic disease (GTD) refers to a group of benign and malignant tumors that develop in the uterus from placental tissue. Pathogenesis of GTD is unique in that maternal tumors arise from gestational tissue that can have locally invasive or metastatic potential. Historical data on incidence of GTD varies widely by region, with higher incidence reported in Asia compared with Europe and North America. These differences are thought to be due at least in part to varying diagnostic criteria, reporting practices, quality of epidemiologic data, and diet and nutrition. In the United States, the reported incidence of GTD is approximately one out of every 1000 pregnancies.[1-3]

The most common form of GTD is hydatidiform mole (HM), also known as molar pregnancy. HMs are considered a benign, premalignant disease. Malignant forms of GTD are collectively referred to as gestational trophoblastic neoplasia (GTN), and include invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). HM encompasses about 80% of all GTD, invasive moles account for 15%, and choriocarcinoma and other rarer types of GTN comprise the remaining 5%.[4] Cure rates are approaching 100%, and treatment typically allows for fertility preservation.[4,5]

Types of Gestational Trophoblastic Disease

HM occurs as a result of abnormal fertilization and is characterized as complete or partial based on differences in morphology, karyotype, and malignant potential. The majority of complete moles (80%) occur as a result of abnormal fertilization of an ovum lacking nuclear DNA, and have two identical paternal chromosome complements derived from duplication of the haploid genome of a single sperm. The remaining 20% occur as a result of dispermy (fertilization by two sperm). Partial moles occur when an ovum retains its nucleus and abnormal fertilization occurs in one of two ways: 1) fertilization by a single sperm with subsequent paternal chromosome duplication; or 2) via dispermy. Partial HMs can contain fetal tissue, but complete moles do not.

Post-molar GTN, which includes invasive mole and choriocarcinoma, develops in about 15% to 20% of complete moles, but in only 1% to 5% of partial moles.[2,3,6,7] The reported incidence of GTN after molar pregnancy is 18% to 29%.[2,3,8,9] This rate appears to be stable despite the progressively earlier diagnosis of complete HM.[9] Invasive moles arise from extension of HM into the myometrium via tissue or venous channels. Approximately 15% of invasive moles metastasize to the lung or vagina. Persistent elevated human chorionic gonadotropin (hCG) after evacuation of a molar pregnancy most often leads to the diagnosis of invasive mole.[2] Choriocarcinoma develops from villous trophoblast. Features of these malignant epithelial tumors include abnormal trophoblastic hyperplasia and anaplasia, hCG production, absence of chorionic villi, hemorrhage, and necrosis.[2,3] Choriocarcinoma has been reported to occur with different types of pregnancy events, including HM (50%), term or preterm gestation (25%), and tubal pregnancy or abortion (25%). Approximately 2% to 3% of HMs progress to choriocarcinoma.

The intermediate trophoblastic tumors (ITT), including PSTT and ETT, are rare subtypes of GTN with an incidence of about 1 in 100,000 pregnancies, representing approximately 1% of all GTN cases.[10] Most PSTTs follow nonmolar gestations and present months to years after the antecedent pregnancy. Less often, PSTT develops after evacuation of HM.[4] PSTT arises from interstitial trophoblast at the placental implantation site and consists predominately of mononuclear intermediate trophoblast without chorionic villi, infiltrating in sheets or cords between myometrial fibers. It is associated with less vascular invasion, necrosis, and hemorrhage than choriocarcinoma.

ETT is a rare variant of PSTT that simulates carcinoma. Based on morphologic and histochemical features, it appears to develop from

neoplastic transformation of chorionic-type intermediate trophoblast. ETT typically presents years after term delivery.

Hydatidiform Mole

Presentation and Workup

Patients with HM commonly present with vaginal bleeding, typically around 6 to 16 weeks of gestation. Due to widespread ultrasound screening during early pregnancy and accurate hCG testing, most cases of HM are detected prior to the onset of additional signs such as uterine enlargement beyond that expected for gestation date, pre-eclampsia, hyperemesis, anemia, and theca lutein ovarian cysts.[2-4] Partial HMs tend to grow more slowly and may present later in the first or early second trimester, often with symptoms of incomplete or missed abortion and diagnosis made upon histologic examination of the curettage specimen.[2,3]

Initial determination of suspected HM is often made based on ultrasound findings in combination with clinical symptoms and hCG levels. Due to hyperplastic trophoblastic cells in complete HM, many patients will have marked elevations in hCG, at times greater than 100,000 IU/L. However, such elevations in hCG are observed in less than 10% of patients with partial HM. Characteristic ultrasound findings of complete HM include enlarged uterus with a heterogenous mass (ie, snowstorm appearance). Hydropic/swollen chorionic villi lead to the appearance of small cystic spaces, creating a vesicular pattern. However, these characteristics may not be readily observed with the diagnosis of HM early in the first trimester. As molar pregnancy advances, these cystic spaces become larger and more numerous. Features that may be noted on ultrasound imaging of partial HM include focal cystic spaces within the placenta, gestational sac that is empty or elongated along the transverse axis, and/or fetal anomalies or fetal demise.[2-4,8,11]

The NCCN Panel recommends workup of patients with HM to include history and physical; pelvic ultrasound; quantitative hCG assay; complete blood count (CBC) with platelets; liver, renal, and thyroid function tests; as well as blood type and screen. Recommended imaging also includes chest x-ray.

Treatment

Initial treatment of HM in women who wish to preserve fertility is suction dilation and curettage (D&C), preferably performed under ultrasound guidance to reduce the risk of uterine perforation.[8,12] Rho(D) immunoglobulin should be administered at the time of evacuation to patients with Rh-negative blood types.[8] To reduce the risk of heavy bleeding, uterotonic agents (eg, methylergonovine and/or prostaglandins) should be administered during the procedure and continued for several hours postoperatively.[2,13] For women who are older or do not wish to preserve fertility, hysterectomy can be considered as an alternative.[14] Histopathologic review and possible genetic testing confirm the diagnosis.

Prophylactic chemotherapy at the time of uterine evacuation is controversial and may reduce the incidence of post-molar GTN by 3% to 8%. A Cochrane database review (3 randomized controlled trials [RCTs], n = 613) did not conclude sufficient evidence for standard administration of prophylactic chemotherapy to prevent post-molar GTN; however, evidence was suggestive that prophylactic chemotherapy may reduce the risk of progression to GTN among women with complete HM at high risk for malignant transformation.[15] The NCCN Guidelines state that prophylactic methotrexate or dactinomycin can be considered for patients deemed at high risk for post-molar GTN. Risk factors for post-molar GTN include age >40 years, hCG levels in excess of 100,000 mIU/mL, excessive uterine enlargement, and/or theca lutein cysts larger than 6 cm.[2,8,15,16]

Follow-up

Follow-up with hCG monitoring is essential following initial treatment of HM to ensure that hCG levels return to normal. The hCG molecules associated with GTD are more heterogenous and degraded than those associated with normal pregnancy.[2,17] Therefore, monitoring should be performed with a quantitative assay capable of detecting all forms of hCG, including beta-hCG, core hCG, nicked-free beta, beta core, and hypoglycosylated forms.[4,18,19] Post-molar GTN develops in about 15% to 20% of complete moles, but in only 0.1% to 5% of partial moles. Therefore, careful monitoring can facilitate early detection of persistent GTN. Risk of recurrence is low (<2%) following a single molar pregnancy, but increases significantly for women who experience one or more recurrences.[2,3,6,12,13,20]

Once normalized, recurrent elevation of hCG has been reported in less than 1% of patients.[20,21] The occurrence of GTN following hCG normalization is rare after the recommended 6 months of post-normalization hCG monitoring.[22] A recent study showed that patients with complete HM who normalized beyond 56 days post uterine evacuation had a 3.8-fold higher risk of developing post-molar GTN.[20]

The NCCN Panel recommends hCG assay monitoring every one to two weeks until levels have normalized, defined in the guidelines as 3 consecutive normal assays. Following initial normalization, hCG should be measured twice in 3-month intervals to ensure levels remain normal. If hCG levels remain elevated, treat per the post-molar GTN algorithm.

Post-Molar GTN

Post-molar GTN is typically diagnosed by hCG surveillance. The NCCN Guidelines use the FIGO staging criteria for post-molar GTN as meeting one of more of the following criteria after treatment for HM, as indicated by hCG monitoring:[23]

- hCG levels plateau for 4 consecutive values over ≥3 weeks
- hCG levels rise ≥10% for 3 values over ≥2 weeks
- hCG persistence 6 months or more after molar evacuation

Assessment and staging of the post-molar GTN should include history and physical examination, Doppler pelvic ultrasound, and chest x-ray to assess for metastatic disease. Doppler pelvic ultrasound is used to confirm the absence of pregnancy, measure uterine size, and to delineate the volume and vasculature of the tumor. If chest x-ray reveals no evidence of metastatic disease, no further imaging is recommended prior to treatment.

Repeat D&C or hysterectomy can be considered for persistent post-molar GTN.[24-26] An observational study conducted over a period of 10 years examined 544 women who underwent second uterine evacuation for persistent GTD.[26] Following repeat curettage, 68% had no further evidence of disease or chemotherapy requirements. However, chemotherapy requirement was more likely for patients with a histologic confirmation of persistent trophoblastic disease and for urinary hCG levels in excess of 1500 IU/L at time of second evacuation.[26] Several groups have discussed the optimal characteristics of candidates for repeat uterine evacuation.[26-30]

Repeat surgical treatment should be followed by hCG monitoring every 2 weeks until the patient has 3 consecutive normal assays, with monthly hCG monitoring for an additional 6 months. For evidence of metastatic disease, histopathologic diagnosis of choriocarcinoma, or persistent hCG elevation (ie, plateau or rise), follow recommendations for staging and treatment in the algorithms for GTN.

Gestational Trophoblastic Neoplasia

Presentation and Workup

The presentation of GTN can vary depending upon the antecedent pregnancy event and disease type and extent. Post-molar GTN, including

invasive mole or choriocarcinoma, can be associated with irregular bleeding after initial treatment for molar pregnancy, an enlarged and irregular uterus, and bilateral ovarian enlargement. However, these signs may be absent in patients with choriocarcinoma associated with normal, non-molar pregnancies. Trophoblastic tumors have fragile vessels and as a result, metastatic lesions are often hemorrhagic. In addition to bleeding, metastatic lesions may be associated with neurologic or pulmonary symptoms. ETT and PSTT typically present with irregular uterine bleeding arising after some time has passed from a previous pregnancy.[2,3,31]

Workup for GTN includes history and physical examination and metastatic imaging workup, to include chest/abdominal/pelvic CT scan with contrast (or MRI if contrast is contraindicated) as well as brain MRI (preferred) or brain CT if pulmonary metastasis. Visible lesions in the lower genital tract should not be biopsied due to hemorrhage risk. Additionally, the NCCN Panel recommends repeat CBC differential with platelets; liver, renal, and thyroid function testing; and hCG assay. If hCG is elevated with no evidence of disease on imaging, consider the possibility of phantom hCG.[32] Elevated hCG with normal hypoglycosylated hCG may indicate quiescent GTN not requiring immediate/further treatment.[33]

Based on these findings, the GTN should be staged and scored according to the current FIGO staging and prognostic scoring system.[23,34] GTN staging is based on tumor location and extent: stage I disease is uterine-confined, stage II involves direct extension or metastasis to other genital structures, stage III disease is determined by lung metastasis, and stage IV disease includes non-pulmonary distant metastasis. The current FIGO prognostic scoring system was adapted from the WHO classification, which incorporated prognostic factors from Bagshawe's scoring system.[35,36] FIGO prognostic scoring is based on individual risk factors that have been shown to be predictive of GTN that is resistant to single-agent chemotherapy, such as age, antecedent pregnancy, interval from index pregnancy, pretreatment hCG, largest tumor size (including the uterus), site and number of metastases, and previous chemotherapy regimens that were unsuccessful. The sum of individual scores denotes the FIGO prognostic score of low-risk GTN (<7) or high-risk GTN (≥7).[23,34,37] This prognostic scoring system is not valid for the ITTs ETT and PSTT.[10]

Low-Risk GTN

First-line Therapy

Low-risk GTN encompasses cases with a FIGO prognostic score of six or less. Standard front-line treatment for low-risk GTN is single-agent chemotherapy using methotrexate or dactinomycin. Numerous studies have evaluated these agents, but differences in inclusion criteria and dosage regimens have made it challenging to determine a superior regimen. While some consider methotrexate to have a more favorable adverse effect profile, dactinomycin may achieve similar or better efficacy with a less-frequent infusion schedule.[4,18,37-39] A 2016 Cochrane Database review of RCTs in low-risk GTN showed with moderate-certainty evidence that first-line methotrexate may be more likely to fail than dactinomycin (risk ratio [RR], 3.55; 95% confidence interval [CI], 1.81–6.95; 6 trials, 577 participants; I(2) = 61%).[39] Similarly, the authors concluded that dactinomycin is more likely to lead to a primary cure than methotrexate (RR, 0.65; 95% CI, 0.57–0.75; six trials, 577 participants; I(2) = 26%).[39] However, 55% of the data came from trials of weekly IM methotrexate, which seems to be less effective than the 5- or 8-day methotrexate regimens. A now closed for lack of accrual phase III RCT (NCT01535053) comparing pulse dactinomycin to multiday methotrexate regimens noted primary remission rates of 75% for pulse dactinomycin versus 88.5% for the multiday methotrexate regimens (5-day > 8-day). Overall quality-of-life scores were similar. Alopecia was more common with dactinomycin, mucositis was more common with the methotrexate regimens, and no patient required multiagent chemotherapy or salvage surgery to reach remission.[40]

Currently supported regimens of dactinomycin include a 5-day regimen (10–12 mcg/kg or flat 0.5 mg dose IV, repeated every 2 weeks) or a dactinomycin pulse regimen (1.25 mg/m^2, IV, repeated every 2 weeks).[18] Primary remission rates for initial treatment with 5-day dactinomycin range from 77% to 94%, and for pulse dactinomycin, from 69% to 90%.[37] For methotrexate, currently supported regimens include 5-day methotrexate (0.4 mg/kg IV or IM daily x 5 days, repeated every 2 weeks) or an 8-day regimen of methotrexate alternating with leucovorin rescue (1.0–1.5 mg/kg IM, every other day x 4 days, alternating with leucovorin, 15 mg PO, repeated every 2 weeks).[18] Primary remission rates for multiday methotrexate regimens range from 87% to 93% for the 5-day protocol, and from 74% to 93% for 8-day methotrexate with leucovorin rescue.[37]

Methotrexate regimens that are no longer recommended due to lesser efficacy include weekly IM methotrexate (30–50 mg/m^2) and pulse-dose IV infusion methotrexate.[37,41,42] Although weekly IM methotrexate was successful in 70% of patients with a prognostic score of 0–1, the success rate fell to 40% and 12% with a prognostic score of 2–4 and 5–6, respectively.[4,41] In a large case series (n = 618), 8-day methotrexate was comparatively more successful when analyzed by prognostic score subgrouping.[43]

The guidelines note that a multiday methotrexate regimen is typically used as first-line therapy in low-risk GTN due to its generally favorable toxicity profile. Dactinomycin is often used as a secondary therapy for patients with methotrexate toxicity or effusions contradicting the use of methotrexate. Alternative single-agent options for treatment of low-risk GTN that are primarily used in Asia include etoposide and fluorouracil.[37,44,45]

NCCN Panel consensus recommendations for monitoring of chemotherapy response is hCG assay at least every one to two weeks.[38] Upon hCG normalization, continuation of therapy is recommended for 2 to 3 additional treatment cycles past normalization to minimize the risk of recurrence.[3,5,18] Surveillance should include monthly hCG for 1 year, along with contraception (oral contraception preferred). Chemotherapy resistance is indicated by a plateau in hCG over 3 consecutive cycles or a rise in hCG over 2 consecutive cycles.[4,38] Second-line chemotherapy is then indicated.

Second-line Therapy

Currently, there are no RCT data on second-line therapy for low-risk GTN, but general evidence and consensus supports a change to the alternative single-agent chemotherapy for patients who have had a good initial response to chemotherapy but experience hCG plateau, or for patients who experience toxicity that limits the dose or frequency of treatment.[4,18,46] Adjuvant hysterectomy and salpingectomy can be considered for patients with localized disease in the uterus for whom fertility preservation is not desired. The ovaries are left in situ, even in the presence of theca lutein cysts.

Second-line dactinomycin is considered to have an acceptable response rate in patients with low levels of hCG, but multiagent chemotherapy may be favored in the second-line setting for patients whose hCG exceeds a given threshold.[43,47,48] The hCG threshold for considering dactinomycin versus multiagent regimens has been debated and revised over time.[3,18,43,48,49]

Dactinomycin has been associated with complete response rate of approximately 75% in large case series of patients with methotrexate-resistant GTN.[50,51] A retrospective review of 358 patients with low-risk GTN identified 68 patients who were determined to have resistant disease after a 5-day methotrexate regimen (n = 68). The complete response rate to secondary dactinomycin was 75%, and all patients who required third-line multiagent chemotherapy with or without surgery achieved permanent remission. Clinicopathologic diagnosis of choriocarcinoma (vs. post-molar

GTN) was significantly associated with resistance to secondary dactinomycin.[50] In a recent retrospective review of 877 patients with GTN initially treated with 8-day methotrexate, 103 patients required second-line therapy and were placed on a 5-day dactinomycin protocol.[51] Complete response to second-line dactinomycin was observed among 75.7% (n = 78). Among the 25 patients who required third-line treatment for resistant disease or relapse, overall survival was 100%.[51]

Multiagent Therapy

For disease that is resistant to single-agent chemotherapy, repeat disease workup for metastasis and transition to combination chemotherapy. The following criteria warrant a switch to a multiagent regimen: poor response to initial therapy, significant elevation in hCG level, development of metastasis, or resistance to sequential single-agent chemotherapy regimens.[3,5] The most commonly used regimen in this setting is EMA/CO (etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine).[43,46,52] The use of EMA/CO in this setting is based upon its efficacy in managing high-risk GTN.[53] Cure rates with EMA/CO approach 100% even in the presence of relapsed/resistant low-risk GTN.[3,5,52] For persistent or recurrent disease after EMA/CO combination therapy, treat per the high-risk GTN algorithm with etoposide/platinum-based regimens and surgical resection as feasible.

High-Risk GTN

High-risk GTN is defined as FIGO stages II-III disease with a prognostic score ≥7, or FIGO stage IV disease.[23,34] High-risk disease is relatively rare among patients with post-molar GTN, estimated at only 6% (39/618) in a large case series.[43] High-risk GTN should be treated with multiagent chemotherapy. Adjuvant surgery or radiation therapy may be included. With a multimodal approach, cure rates have reached approximately 90%, including almost all patients with only lung/vaginal metastases and 70% for patients with stage IV disease.[5] Factors associated with poorer outcomes include liver and brain metastases, particularly if co-occurring. However, the prognosis for these patients has improved over time.[54-56]

Primary Chemotherapy

EMA/CO, in which EMA and CO are given on alternate weeks, is the most commonly used initial regimen for high-risk disease. Based on existing evidence, this regimen is thought to provide the best combination of efficacy with acceptable toxicity for treating patients with high-risk GTN. Multiple groups have confirmed the efficacy of EMA/CO, reporting complete response rates of 62% to 78% and long-term survival rates of 85% to 94%.[52,53,57-64]

Reports of other regimens that have been used in first-line treatment of high-risk GTN include:

- EMA/EP (etoposide, methotrexate, dactinomycin alternating with etoposide and cisplatin)[65,66] or EP/EMA (etoposide and cisplatin alternating with etoposide, methotrexate, and dactinomycin)[67]
- MEA (methotrexate, etoposide, dactinomycin) [68]
- MAC (methotrexate, dactinomycin, and chlorambucil)[69]
- FA (5-FU and dactinomycin)[70]
- MEF (methotrexate, etoposide, and 5-FU)[71]
- CHAMOCA (methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine)[69]

Due to the lack of RCTs in this setting, systematic reviews have been unable to draw conclusions regarding a superior combination regimen for primary treatment of high-risk GTN.[46,72] EMA/EP (or EP/EMA) is highly active and considered by some to be superior to EMA/CO for ultra-high-risk disease; however, its use as standard initial therapy is limited by increased toxicity and inability to provide adequate salvage chemotherapy if required for persistent/recurrent disease.[4,67]

Induction Chemotherapy for Ultra-High-Risk Disease

Patients with widespread metastatic GTN, as evidenced by prognostic score greater than 12, have a poorer prognosis.[73,74] Initiation of standard combination chemotherapy in these patients can lead to tumor collapse with hemorrhage, metabolic acidosis, septicemia, and/or multiple organ failure, resulting in the potential for early death (ie, within 4 weeks).[18,52,74] Efforts to improve outcomes for this ultra-high-risk population have included induction chemotherapy with etoposide and cisplatin prior to initiating EMA/CO.[52,74] In a case series of 140 patients with high-risk GTN, 33 patients who were determined to have large disease burden (ie, ultra-high-risk GTN) received low-dose induction chemotherapy with etoposide/cisplatin prior to EMA/CO therapy (etoposide 100 mg/m² IV and cisplatin 20mg/m² IV on days 1 and 2, every seven days for 1-3 courses). Overall survival and early death rate were 94.3% and 0.7%, respectively, for the high-risk GTN cohort, representing a considerable improvement over outcomes reported for an earlier cohort who did not receive induction chemotherapy.[52]

Management of CNS Metastases

Additional treatment considerations are recommended for patients with central nervous system (CNS) metastases, who may require emergency intervention to manage intracranial bleeding or elevated intracranial pressure.[4,75] Rates of CNS metastases are low with post-molar GTN, but approximately 20% of patients with choriocarcinoma have CNS involvement.[75] In addition to systemic combination chemotherapy, additional treatment modalities may be employed, including whole brain irradiation, stereotactic radiosurgery, and/or craniotomy with surgical excision.[4,55,76-79] Additionally, EMA/CO should be modified to include high-dose methotrexate dose (1 g/m^2) or the addition of intrathecal methotrexate to encourage sufficient blood brain barrier penetration.[18,78] Reported cure rates with brain metastases range from 50% to 80%, depending on the patient's symptoms as well as number, size, and location of brain lesions.[55,75,76,78,80-83]

Adjuvant Surgery

Adjuvant surgical procedures for chemotherapy-resistant disease may be required to manage high-risk disease. Select patients with isolated disease may be candidates for surgical resection, especially for isolated disease in the uterus or lungs.[84-86] PET/CT imaging may be useful for detecting isolated metastatic sites that are amenable to targeted surgery.[87] Additionally, interventional procedures to prevent or control hemorrhage are important components in the management of high-risk GTN.[4] Selective arterial embolization can be used to manage bleeding from the uterus/vagina or other tumor sites.[88-90] In one case series, nearly 50% of patients with high-risk disease underwent some form of surgical procedure during the course of treatment in order to effect cure.[91]

Salvage Chemotherapy

Despite the use of multiagent primary therapy, approximately 30% to 40% of high-risk patients will have an incomplete response to first-line therapy or experience relapse from remission.[92,93] Most of these patients have multiple metastases to sites other than the lung and vagina and many will have received inadequate initial therapy.[94,95] Salvage chemotherapy with drug regimens employing etoposide and a platinum agent, often combined with surgical resection of persistent tumor, will result in cure of about 80% to 90% of patients with high-risk disease.[96]

The EMA/EP or EP/EMA regimens are considered the most appropriate therapy for patients who have responded to EMA/CO but have plateauing low hCG levels or have developed re-elevation of hCG after a complete response to EMA/CO.[97,98] The rate of complete response/remission with EMA/EP for disease resistant to EMA/CO has been reported between 75% and 85%.[63,97-100]

Additional drug combinations containing etoposide and a platinum agent have been effective in patients who have developed disease resistant to methotrexate-containing regimens. These include TP/TE (paclitaxel and cisplatin alternating weekly with paclitaxel and etoposide), BEP (bleomycin, etoposide, and cisplatin), VIP (etoposide, ifosfamide, and cisplatin), and ICE (ifosfamide, carboplatin, and etoposide).[46,96,99,101,102] Additionally, TIP (paclitaxel, ifosfamide, and cisplatin) has been used as a salvage chemotherapy regimen in germ cell tumors, including those with choriocarcinoma components.[103-106]

These etoposide-platinum containing regimens require the use of granulocyte colony-stimulating factor (G-CSF) support to prevent neutropenic complications and treatment delays.[96,101,107] The overall success of salvage therapy in this group of patients is about 80%. Factors associated with worse survival outcomes include high hCG at the start of salvage therapy, greater number of metastatic sites, metastases to sites other than the lung and vagina (stage IV), and FIGO score >12.

Additional Agents/Regimens with Potential Activity in Treatment-Resistant GTN

Several additional treatment regimens have been shown to have some activity when treating resistant GTN, including high-dose chemotherapy (HDC) with peripheral stem cell transplant, immunotherapy, and other chemotherapy regimens. For a subset of patients with resistant disease despite multidrug chemotherapy, HDC with autologous stem cell support has been reported to produce sustained complete responses.[108-112] A retrospective study of 32 patients with refractory choriocarcinoma or poor-prognosis PSTT/ETT who underwent HDC with peripheral blood stem cell support reported a sustained complete response in 7 patients, with 13 of 32 patients remaining disease free at the time of analysis following HDC with or without additional therapy.[110]

Pembrolizumab is a monoclonal antibody that inhibits programmed cell death protein 1 (PD-1), which functions as a checkpoint protein for regulation of various immune cells, including T cells with potential antitumor activity.[113-115] Programmed death ligand 1 (PD-L1) is strongly expressed by GTN.[116,117] Outcomes were recently reported for 4 patients with drug-resistant GTN who received pembrolizumab, including 2 cases of metastatic choriocarcinoma and 2 cases of metastatic PSTT or mixed PSTT/ETT.[118] All patients had tumors with high levels of PD-L1 expression. Durable response to pembrolizumab was observed in three of the four cases. The patient whose disease did not respond to pembrolizumab had strong PD-L1 tumor expression but an absence of tumor-infiltrating lymphocytes.[118]

Gemcitabine, capecitabine, and fluorouracil may also have potential for treating GTN in this setting. Limited data have suggested activity of gemcitabine, administered with or without a platinum agent.[119] Additional support for the potential activity of these regimens in GTN can be found in the data for treating germ cell tumors. Successful use of capecitabine as single-agent salvage chemotherapy has been reported.[120,121] Groups in Asia have also reported on fluorouracil, primarily in combination with dactinomycin.[70]

Intermediate Trophoblastic Tumors

Whereas molar pregnancies and choriocarcinoma are derived from villous trophoblast (ie, cytotrophoblast and syncytiotrophoblast), ITTs (including PSTT and ETT) develop from extravillous trophoblast (ie, intermediate trophoblast). ITTs comprise approximately 1% of GTN cases, and as such, their biologic behavior and treatment are less well established. These tumors typically develop months to years following normal pregnancies, but can occur after any pregnancy event. A recent series of 62 cases of ITT suggested that interval between antecedent pregnancy and disease onset may be longer for ETT than PSTT.[122]

PSTT and ETT are generally slow-growing tumors that can metastasize months or years after the initial primary has developed and often present with abnormal uterine bleeding or amenorrhea. The vast majority of ITTs secrete hCG, but at significantly lower levels compared with other types of GTN. As such, hCG is a less reliable tumor marker for these subtypes of GTN. At diagnosis, metastases are noted in 30% to 50% of cases, most commonly to the lungs. Unlike other GTNs, these have a greater propensity for lymphatic spread. Data are currently being collected in a global database of PSTTs and ETTs through the efforts of the International Society for the Study of Trophoblastic Disease (ISSTD).[10,123-128]

ITTs can be differentiated from other types of GTN via their histopathologic characteristics.[10] In PSTT, immunohistochemical (IHC) staining reveals the diffuse presence of cytokeratin, Mel-CAM, and human placental lactogen (hPL), whereas hCG staining is only focal. Cytogenetic studies have revealed that PSTTs are more often diploid than aneuploid.[129] Serum hPL measurements are not clinically useful in monitoring disease course or guiding clinical management.[126,127,130,131] ETT is distinguished from PSTT by its smaller, fairly monomorphic cells and a nested, nodular, well-circumscribed growth pattern. IHC reveals strong expression of p63, but only focal to weak expression of Mel-CAM and hPL.[132] It frequently involves the lower uterine segment and endocervix, and because of its epithelioid histologic appearance and expression of p63 and cytokeratins, ETT can be confused with squamous cell carcinoma.[10,132,133]

Due to the rarity of these tumors, generally small cohort sizes preclude rigorous statistical analysis of risk factors in ITT. The FIGO prognostic scoring system for GTN does not correlate well with outcomes in PSTT and ETT.[10] Based on findings from the largest existing database, PSTT and ETT accounted for 125 of 54,743 cases of GTD (0.23%), with post-treatment 5- and 10-year survival estimates of 80% and 75%, respectively. The most important prognostic factors include advanced disease stage and interval from last known pregnancy event of ≥48 months.[124,127,128,134] Additional risk factors associated with less favorable outcomes are advancing age, deep myometrial invasion, tumor necrosis, large tumor size, and mitotic index.[10,128,135]

Treatment Approach

ITTs are relatively chemoresistant and thus follow a somewhat different treatment paradigm than invasive mole and choriocarcinoma, with surgical intervention playing a more critical role. Treatment of PSTT and ETT is determined mainly based on presence or absence of metastatic disease with some consideration given to high-risk factors. Hysterectomy with lymph node dissection is the recommended treatment for localized disease. Metastasectomy should be employed for isolated distant disease, especially in the lungs. Chemotherapy is given to patients with metastatic disease and should be considered for patients with nonmetastatic disease who have any of the adverse prognostic factors noted above.[136]

Although the optimal chemotherapy regimen for PSTT and ETT remains to be defined, the current clinical impression is that a platinum/etoposide-containing regimen, such as EMA/EP or TP/TE, is the treatment of choice. The survival rate is approximately 100% for nonmetastatic disease and 50% to 60% for metastatic disease. Increased use of platinum-based and HDCT over time has led to improved overall survival for the subset of patients with ITT who have an overall poor prognosis (ie, interval ≥48 months from last known pregnancy event).[124,126-128]

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