Gestational Trophoblastic Neoplasia

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KEYWORDS

• Trophoblastic disease • Neoplasm • Gestational • Choriocarcinoma

KEY POINTS

- Origin
  Trophoblastic disease is an allograft of fetal tissue consisting of paternally-derived tissue that invades the maternal decidual plate in an uncontrolled manner.
- GTN
  Trophoblastic neoplasia is defined by the F.I.G.O. (2002) definition of persistent disease (a rise or plateau in the quantitative β-hCG titer.
- Treatment
  The type of treatment is determined by the W.H.O. risk score (low risk 0-6 and high risk $>$6). Patients with the former receive single-agent, and the latter, combination chemotherapy.
- Prognosis
  Low risk disease is almost universally curable and most high risk disease is also successfully treated unless there are liver (and brain) metastases.
- Regionalization
  Since this is a very rare but potentially curable disease, treatment should be centralized in tertiary centers, by oncologists with particular knowledge and expertise in the management of trophoblastic neoplasia.

Trophoblastic neoplasms are a truly fascinating set of diseases that arise from a failed gestation. A molar pregnancy is an allograft of fetal tissue typically containing only paternal chromosomes that may invade the maternal decidua following a failed gestation that may have arisen up to decades earlier. Choriocarcinoma (CCA), the most common malignant form of trophoblastic disease, represented the very first

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medical cure of a solid cancer in 1956[1–3] following an observation by pathologist M.C. Li in 1954 that the urine human chorionic gonadotropin (hCG) level declined in a woman undergoing treatment for melanoma. Dr Roy Hertz then used this anecdotal information to successfully treat trophoblastic disease using a drug called amethopterin, a less toxic form of the drug aminopterin first used by Lucy Willis in 1930 to treat pernicious anemia of pregnancy.[4,5]

PATHOLOGY

These tumors are derived from the fetus/conceptus and not from the mother. With the single exception of partial mole (PHM), all of these lesions will be composed, in whole or in part, of paternal genetic material, a process called androgenesis.

Trophoblastic Function and Differentiation

Human trophoblast is derived from trophectoderm, the outermost layer of the blastocyst. The earliest cell layer of the trophectoderm, cytotrophoblast, lines the blastocyst and serves as the stem cell for the other layers of the developing trophoblast. Cytotrophoblast also makes a primitive hCG molecule called hyperglycosylated hCG (H-hCG; ITA or invasive trophoblast antigen) for the first 14 days after conception that seems to promote blastocyst adhesion and the earliest invasion by the syncytiotrophoblastic mass beneath the blastocyst at the implantation site. Immediately after implantation (day 7), cytotrophoblast, in its function as the trophoblast stem cell, differentiates into a syncytial mass (previllous trophoblast).[6]

Early cytotrophoblast, also referred to as the Langhans cell layer, is the germinative layer that proliferates and differentiates along two distinct pathways. First, on the incipient villus surface it fuses into syncytiotrophoblast cells (ST), a terminally differentiated cell line that loses its proliferative capability but secretes hormones/proteins including human placental lactogen (hPL), hCG, and other paracrine proteins. These proteins regulate the microenvironment of the implantation site and establish the villus interface with maternal blood permitting fetomaternal oxygen/carbon dioxide transfer as well as nutrition and metabolic product exchange.[6]

Second, the extravillus trophoblast, cytotrophoblast, differentiates into intermediate trophoblast (IT). IT is a heterogenous cell population that can be subcategorized based on its anatomic location. In the intravillus mesenchyme, the so-called anchoring columns, cytotrophoblast evolves imperceptibly into implantation site IT (ISIT). ISIT loses its proliferative ability (low Ki-67 assay) but is now able to invade the maternal decidua and myometrium, dissecting between the smooth muscle fibers. By tropism, ISIT migrates to and invades the maternal spiral arteries (high MelCAM assay) leaving their overall structure intact. ISIT coats the vascular endothelial surface with extracellular matrix resulting in incompetence of the arterial valves that in turn results in a very low resistance environment that facilitates oxygen and waste transfer between mother and fetus. ISIT makes hPL, whereas chorion-type IT (CTIT) does not. ISIT also loses its proliferative capability and does not invade the decidua parietalis. In normal early pregnancy, the ISIT invades the maternal decidual plate but is tightly controlled both spatially and temporally, involving only the decidua and, at most, the inner 30% of the myometrium solely beneath the implantation site. Later, in normal pregnancy, the ISIT cells fuse into multinucleated cells with accompanying loss of both their migratory and invasive characteristics.[6]

Gestational Trophoblastic Diseases

The gestational trophoblastic diseases (GTDs) include all molar gestations, both complete and partial, even though over 90% will resolve without treatment following

uterine evacuation. The term *GTD* also includes persistent moles that are not completely expelled after curettage and go on to require active management, and its malignant analogue, CCA. The definition also includes the malignant variant of exaggerated placental site reaction (EPS), placental site trophoblastic tumor (PSTT) that arises from the ISIT, and the malignant variant of benign placental nodule (PN), and epithelioid trophoblastic tumor (ETT) that arises from CTIT of the chorion laeve. As would be expected from its pathologic characteristics, PSTT extensively invades myometrium and its vascular structures. CCA, ETT, PSTT, and persistent mole all require active management and are referred to collectively as gestational trophoblastic neoplasia (GTN).[6]

The several forms of GTD are related to discrete pathologic errors that occur at different stages of differentiation of the trophoblast. Some of these lesions are neoplasms (CCA, ETT, PSTT), whereas their benign counterparts (EPS, PN, and molar pregnancy, respectively) are best described as abnormal placentas with the potential to develop malignant placental lesions. The cytogenetics of molar pregnancy are well-understood, but the pathogenesis of these other trophoblast lesions is not, in part because of the rarity of these abnormalities and the absence of an experimental model.

CCA arises from a prior molar pregnancy in 50% of cases as evidenced by the fact that most are homozygous (85% of complete moles have an XX karyotype) because they have arisen through diandry; duplication of a single X sperm in an empty ovum. Approximately 95% of PSTT and ETT lesions arise after a term pregnancy or a nonmolar abortion. Based on histopathologic studies, PSTT and ETT are believed to arise from distinct subpopulations of extravillous IT (ISIT and CTIT, respectively). Recent molecular evidence confirms both their fetal (trophoblastic) origin and the presence of paternal genes.[7]

Partial moles are nonrecurring and have a very low risk of persistence (.5%–2%). Partial moles are typically, but not invariably, triploid. Triploid gestations only demonstrate trophoblastic proliferation (GTD) when there are at least two paternal haploid chromosome sets arising either by dispermy (fertilization by two sperm) or diandry (one sperm that duplicates through a meiosis-1 error), plus a maternal haploid set. When the extra haploid set is maternal the gestational villi are hydropic but there is no trophoblastic proliferation, the hallmark of trophoblastic disease. Such gestations are not a GTD but usually consist of a nonviable fetus and a hydropic but nonproliferative placenta.

Complete moles have a 10-fold risk of recurrence in the next gestation and a further 10-fold risk with a third pregnancy. Partial moles have no increased risk of persistence in follow-on gestations because they are due to nonrecurring errors of fertilization. A very few families seem to have a predisposition to repeated GTD. The defect is thought to be on chromosome 7 at the NLRP locus. In one recent report, the NLRP7 mutation was present in 60% of patients with two hydatidiform moles (HMs), 13% with one HM, and 8% of patients with three or more spontaneous abortions. If the patient had two defective alleles, reproductive wastage was even higher.[8]

The diagnosis of a complete mole is sometimes difficult, particularly in very early pregnancy. Classically the diagnosis is based on histologic and genetic criteria, but the former, based on morphology, is highly subjective and prone to significant interobserver variability.[9] The unique genetic features of CHM (androgenetic diploidy), PHM (diandritic triploidy), and hydropic abortus (biparental diploidy) permit the use of certain molecular discriminators. The immunohistochemical expression of the $p57^{kip2}$ gene, a cell cycle inhibitor and tumor suppressor that is strongly paternally imprinted and maternally expressed, has been shown to reliably differentiate CHM from PHM

and hydropic abortus. The villous cytotrophoblast cells of CHM lack the maternal genome and stain negatively for the gene, whereas PHM and hydropic abortus stain strongly positive for the gene regardless of gestational age.[10,11] Recent evidence suggests that a second marker gene PHLDA2 may also accurately differentiate CHM from PHM and other gestational mimics.[12] Whereas p57 expression can identify CHM, because of the absence of maternal DNA, fluorescence in situ hybridization can determine the genetic identity of PHM and abortus by determining their ploidy status. By allowing accurate subclassification of moles and unusual products of conception, more accurate prognostic information can be obtained.[13,14]

TUMOR BIOMARKERS

Human Chorionic Gonadotropin

HCG is a near-perfect biomarker. Each trophoblastic cell makes a relatively finite amount of hCG per day (10^{-5} mIU/mL), and the assay result provides an accurate indication of the trophoblastic cell burden. The most primitive trophoblast cell, cytotrophoblast, makes hyperglycosylated hCG for only the first few weeks of the gestation. This autocrine hormone likely plays an active role in establishment of both the implantation site and the fetomaternal circulation and also evolves into syncytiotrophoblast that makes regular hCG of normal pregnancy. Production of hCG increases logarithmically from implantation (day 7) and peaks at 10 weeks at a median level of about 60,000 mIU/mL, then declines between the 10th and 20th weeks and remains stable at around 12,000 mIU/mL until term.[15,16]

The hCG molecule is not a single biological molecule. Regular hCG is produced by differentiated syncytiotrophoblast cells and consists of a common 92 amino acid glycopeptide chain, with asparagine-linked mono- and biantennary sugar moieties and a unique 145 amino acid beta (β) chain with both asparagine and serine linked disaccharide moieties, the latter attached to the C-terminal peptide of the chain. The hCG molecule acts to maintain the vascular supply of the placenta in normal gestation by stabilizing the myometrial and decidual spiral arteries.[17] The molecule, particularly the β chain, often becomes fragmented, particularly when malignant transformation occurs. In normal pregnancy, the free β fragment comprises less than 1% of the total hCG assay, the nicked β fragment less than 10%, and there may be a very small amount of H-hCG. The β core fragment, a terminal degradation product of β chain metabolism, is only detectable in the urine. The more common fragments, β core, nicked β, and hyperglycosylated free β, are produced in varying amounts. Hyperglycosylated free β also functions as an autocrine hormone (acts on its tissue of origin) by independently promoting growth and invasion in GTN.[18]

Hyperglycosylated hCG

H-hCG, also called ITA or invasive trophoblast antigen, is regular hCG with double-sized, tri- and tetrasaccharide O-linked sugars and is made by undifferentiated extravillous cytotrophoblast. H-hCG functions as an autocrine hormone by facilitating ordered trophoblast invasion at the implantation site in normal gestation and supporting disordered malignant invasion in GTN.[16] A hyperglycosylated free β subunit is produced by a high proportion of GTN and other malignancies.[17] H-hCG functions as an autocrine and has the ability to signal normal placental cytotrophoblast to grow and invade, whereas hCG promotes uterine vascularization. Insufficient H-hCG levels are associated with pregnancy loss and preeclampsia.[18]

It is very important to use an assay that can detect not only the intact hCG molecule but also H-hCG and H-free β, as well as all their degradation products (hCG β radioimmunoassay and the Siemens Immulite assay), because most automated

commercial laboratory tests (12 are currently on the market) detect only regular hCG with accuracy.[19] In the same study, when the same sera were tested against other hCG assays, there was as much as a 58-fold variation in the assay titer results. When the same assay was retested with the same sera there was a 1.4-fold difference using pregnancy sera and a 2.2-fold difference with GTN sera. This discordance was related to differences in assay recognition of nicked hCG, free β, and other hCG variants.[20] H-hCG and its degradation fragments may be significantly overproduced, particularly in early pregnancy, CCA, and germ cell malignancies. A nonquantitative hCG assay therefore may not accurately reflect the true disease burden.[18]

Free β and the β Core Fragment

The free β assay is the biomarker of choice for detecting/following PSTT, a neoplasm characterized by intermediate cell invasion of the myometrium. Because there is very little syncytiotrophoblast present, the amount of hCG present is very low and is not a useful marker of response for PSTT. The free β assay is also part of early pregnancy serum screening for Downs syndrome (2 fold increase in free b and 9 fold increase in H-hCG). ETT tumors make low level hCG and are best monitored with the urinary β core fragment assay.[6,17]

Clinical syndromes involving hCG assay

Quiescent hCG syndrome. Some patients continue to make small amounts of real hCG in the absence of any radiologic evidence of GTN. Typically the titer is only double-digit and remains stable for months or up to 16 years.[21,22,23] It seems that a small focus of, or perhaps individual, dispersed, differentiated syncytiotrophoblast cells are present, sometimes after prior chemotherapy. These slow growing cells make small static amounts of hCG and do not have invasive potential so long as there is no cytotrophoblast or IT present. These syncytiotrophoblast cells do not respond to chemotherapy, and hysterectomy does not normalize the hCG titer. H-hCG is usually absent but may constitute no more than 6% of the total hCG assay result. Cole and Khanian[22] have reported that 7% of these patients will begin to secrete increased H-hCG within 5 years, weeks to months before the hCG titer begins to rise and before there is clinically detectable GTN.

Phantom hCG. About 2% of reproductive aged women will have a low level positive conventional hCG test without trophoblast seemingly present ($<$ 300 mIU/mL). This is a false-positive test result due to the presence of nonspecific heterophile antibody in the patient's serum usually due to childhood (smallpox) immunization. The term *heterophile antibody* implies the presence of a cross-species antibody. HCG tests involve two animal antibodies, one that is specific for binding one molecular site on hCG and one specific for binding a distant site on hCG. This second site has a dye, enzyme, chemoluminescence, or tracer attached that will identify the amount of hCG present. The hCG molecule is sandwiched between the immobilized antibody and the tracer antibody. Antibodies are always bivalent and, when heterophile antibody (human antianimal antibody) is present, it binds the animal antibodies used in the hCG assay and causes a false-positive or "phantom" result.[24,25] The large heterophile molecule does not enter the urine because of its size. True elevated hCG will produce a positive serum and urine assay for hCG, but in this syndrome the urine hCG assay is usually nondetectable (and never $>$50 mIU/mL). The diagnosis can also be made with serial dilution of the sample (false titers are not affected by dilution) or use of a second commercial assay that will often result in a marked fluctuation in the titer (most will be negative). Occasionally the false report is related to the reagent, so

repeating the assay with an assay from a different species (sheep vs rabbit) will strip off the heterophile antibody. No treatment is required if the hCG result is a false-positive, because no abnormal trophoblast is present.[22]

Menopausal elevation of the hCG assay. A small number of perimenopausal and postmenopausal women will be found to have a low level positive hCG test result. One percent of perimenopausal and 7% of postmenopausal women have a serum hCG concentration above the conventional cutoff level of 4 to 5 mIU/mL. Both serum follicle-stimulating hormone (FSH) and hCG are known to increase with age. In one study it was suggested that women over 55 years of age should have a reset hCG cutoff value of 14 mIU/mL to minimize the possibility of such a false-positive assay result. These false results are due to elevated pituitary FSH and luteinizing hormone and/or benign low level pituitary hCG production.[26] If truly pituitary in origin, the hCG titer can be suppressed with a small dose of an oral contraceptive tablet over as few as 7 days.[27]

Posttreatment low level hCG elevation. In a report from Sheffield, a small percentage of women (.05%) had a low level persistent hCG assay following apparent successful treatment of GTN where the titer either reached normal then rose slightly or plateaued at a very low level. The hCG titer did not respond to a change in treatment, or remained static for a protracted period, without any clinical sign or disease. The test result was rarely higher than 40 mIU/mL. The presumed cause was either a small residual focus of syncytiotrophoblast or a false-positive assay due to elevated gonadotropin or heterophile antibody.[28]

DIAGNOSIS AND STAGING

Tumors of Cytotrophoblasts and Syncytiotrophoblasts

When a molar pregnancy is first detected, the following basic investigations are indicated: pelvic ultrasound (if not already performed), quantitative hCG, complete blood count (CBC), creatinine, thyroid function tests, and a chest radiograph. The diagnosis of GTD is typically made by pelvic ultrasound that demonstrates a snowstorm-like appearance within the uterine cavity. Current ultrasound can resolve down to hydropic placental vesicles as small as 2 mm. A partial mole usually is found with an accompanying nonviable gestation present in addition to an enlarged hydropic placenta. Most molar gestations are nowadays identified at the time of the early pregnancy screening sonogram in the absence of symptoms. Previously, patients usually presented with vaginal bleeding, an enlarged uterus, or occasionally signs of hyperthyroidism or early toxemia. Surprisingly, the incidence of persistent disease has not changed despite earlier diagnosis, suggesting that the likelihood of developing neoplasia is determined at a very early developmental stage. Complete moles may also occasionally be found as the second gestation in a twin pregnancy where the other fetus is normal and potentially viable. Other diagnoses to consider based on a hydropic uterine mass are Beckwith-Wiedemann syndrome, viral placentitis, and syphilis or Rh isoimmunization.

Ultrasound will provide information on the type of molar gestation, whether the disease involves the endometrial cavity or if it is partial or wholly intramyometrial (suggesting that second curettage may not be useful), the potential risk of uterine perforation, and the presence of theca lutein cysts or adnexal/vaginal metastases. There is also recent information that a uterine artery pulsatility quotient may be able to differentiate patients at higher risk of developing persistent and resistant disease at an earlier time point.[29]

A simple chest radiograph is obtained when persistence is diagnosed, but imaging of the brain or abdomen is not performed unless the chest film demonstrates pulmonary disease. The chest radiograph will resolve disease of at least 10^9 cells, whereas a computed tomographic or magnetic resonance (MR) scan will detect 10^7 cells and a positron emission tomography scan as few as 10^6 cells. However, a computed tomographic lung scan is the dose equivalent of 100 chest films (roughly the equivalent of a single long-haul air flight).[30] The value of a computed tomographic lung scan for disease staging remains controversial.

Once a molar pregnancy is found, the uterus is emptied. The mode of uterine emptying is important. Typically patients undergo a suction curettage, but medical methods of evacuation are sometimes used. The evidence suggests that the latter results in a higher likelihood of incomplete emptying and a higher rate of persistence and subsequent chemotherapy. As a result, medical evacuation should be discouraged.[31]

Following evacuation of a molar gestation, the hCG titer is monitored weekly until it either returns to normal (80%–95%) or persists (a rise or plateau as defined by the World Health Organization [WHO] and International Federation of Gynecology and Obstetrics [FIGO] criteria) requiring active management. The diagnosis of persistent disease GTN is also made if there is extrauterine disease not including vagina, adnexa, or lung if no single pulmonary lesion exceeds 2 cm. The definitions of a rise or plateau are contained in the WHO and FIGO guidelines for GTN but are purposely imprecise. These definitions are, at best, surrogate measures of GTN. This imprecision is a major reason why it is very difficult to compare results from different trophoblastic disease units (TDUs), given the differing institution-specific diagnostic criteria, risk scoring differences, and different regimens and reporting criteria.

Some patients may be falsely labeled as having GTN when in fact, the titer would return to normal with further observation alone. Historically, centers in the United Kingdom and Europe have tended to observe these patients for a longer period (up to 6 months as long as the titer continues to decline) than have most North American centers, accounting for the geographic discrepancy in persistence rates (5%–7% vs 15%–30%).[32]

Rarely, abnormal trophoblast may be found in the fallopian tube, where it usually presents as a typical ectopic gestation with abdominal pain and/or vaginal bleeding, or it may be diagnosed on an early pregnancy ultrasound. The abnormality may equally be PHM, CHM, or CCA. Treatment is usually removal of the abnormal tissue, but only 25% persisted and required chemotherapy in a series from Sheffield.[33]

Tumors of Intermediate Trophoblast

Tumors of IT have only recently been identified and described, so long-term clinical data are lacking. These tumors include EPS and PSTT and PN and ETT.

PSTT typically presents with abnormal vaginal bleeding. The tumor invades and destroys myometrial smooth muscle. As a result, the mass is poorly defined both clinically and radiologically. The assay for free β is the best biomarker for following PSTT.

ETT is typically a disease of reproductive aged women that follows a term pregnancy in 70% of patients (15% after either molar pregnancy or spontaneous abortion). The interval from the index gestation to diagnosis is an average of 6.2 years (range 1 to 18). It is typically a discrete nodule composed of hyalinized extracellular matrix and necrosis measuring as much as 5 cm in size. Blood vessel structure within the tumor is preserved, and intratumor hemorrhage is atypical. Patients usually present with abnormal vaginal bleeding. Metastases are unusual ($<$25%) but typically

involve lung. The serum hCG level is elevated but usually remains below 2500 mIU/mL. This lesion is best followed with the β core fragment assay.[17]

The best treatment for both PSTT and ETT is hysterectomy. However, in young reproductive aged women, these lesions are occasionally managed by localized, hysteroscopic resection.

PRIMARY TREATMENT

When GTD persists, or if the curettings contain CCA (or PSTT or ETT), the patient's disease is staged (FIGO criteria) and a risk score (WHO criteria) assigned that determines the primary treatment regimen. The FIGO stage is an anatomic staging that has no bearing on the clinical management of disease. The risk score is composed of eight distinct criteria that are each assigned a score from 0 to 4. Initial disease staging includes CBC, creatinine, liver and thyroid function tests, pelvic ultrasound, and chest radiograph. There is little likelihood that a patient will have metastatic disease (brain, liver, or gastrointestinal tract) if the chest radiograph is negative (no lung lesion $\geq$ 1 cm); therefore, further investigation of the brain or liver is not indicated at that point.

The hCG titer, an excellent measure of the burden of disease, independently predicts for the failure of low-risk regimens. The hCG titer is assigned a risk score value of between 0 and 4 but, in the absence of other risk factors, even patients with a titer greater than 10^6 can have a low-risk score. In a report from the United Kingdom, if the initial titer exceeds 400,000 mIU/mL most patients will eventually require combination therapy that should be commenced at the outset of treatment. If the titer is between 100,000 and 400,000 mIU/mL, 30% of patients will be cured with a low-risk dose regimen. The remaining 70% will require a change in regimen, but with no loss of curability, and with only an additional 2 weeks of treatment.[34]

Chemotherapy for Low-Risk Disease

WHO determined "low-risk" disease (risk score 0–6) is treated with single agent chemotherapy using one of several published methotrexate regimens, with or without folinic acid rescue, or using dactinomycin, usually as a biweekly parenteral injection. Both drugs have relatively low side effect profiles; methotrexate produced mucositis and marrow depression in multiple single-institution reports, whereas dactinomycin resulted in grade 1 alopecia in 15% and grade 1 nausea in 40% in the phase III Gynecologic Oncology Group (GOG) study.[35]

The specific single drug regimen chosen is unfortunately both institution- and/or continent-specific. Europeans generally prefer an 8-day methotrexate regimen (Charing Cross TDU) that includes alternate-day folinic acid. North Americans typically prefer either a 5-day methotrexate regimen without folinic acid rescue or biweekly "pulse" dactinomycin. These regimens are very difficult to compare because of the paucity of prospective randomized studies.

The very large Charing Cross TDU data set, and collaborative single-institution results, have all reported an approximately 78% likelihood of cure using the 8-day methotrexate regimen, and a 2% to 26% chance that the patient will require a change in protocol because of toxicity (mucositis or marrow depression).[36]

The other commonly used methotrexate treatment is the 5-day methotrexate regimen (without folinic acid rescue) developed by the Brewer TDU at Northwestern University, Chicago. The Brewer regimen recently reported an 81% primary response rate and a 6% incidence of regimen change due to toxicity.[37]

There are two randomized trials comparing pulse dactinomycin and methotrexate at 30 mg/m^2 that included randomized data on response and toxicity.[35,38] In the GOG

study, biweekly dactinomycin was 71% effective using strict definitions and failure criteria, rising to 75% if the "failure" was statistically correct but clinically trivial (and had gone unrecognized by the treating physician). Furthermore, in the GOG study, if only patients with a risk score of 0 to 4 were counted (all previous studies excluded harder-to-cure patients with risk scores of 5 or 6) the outcome was 79%.[35]

Gleeson and colleagues[39] published a phase III study that compared weekly methotrexate at 40 mg/m^2 and 8-day methotrexate/folinic acid. His group found no difference in response rate between the regimens, although the former was better tolerated and was preferred by patients.[39] Two other large TDUs have reported nonrandomized comparisons of low-risk treatment options. Kang and colleagues[40] compared weekly methotrexate at 50 mg/m^2 and 8-day methotrexate and folinic acid. Each regimen was approximately 70% effective as first line treatment. Mousavi and colleagues[41] compared biweekly dactinomycin and 5-day methotrexate and found the former to be 90% effective and the latter only 68% effective ($P = 0.018$). Both reports favored dactinomycin based on treatment outcome, toxicity, and ease of use.

We know from several large data sets, and from the GOG study, that a risk score of 5 or 6 confers a much lower chance of primary response/cure. Some investigators now question whether the inclusion of risk score 5 and 6 patients and the collapsing of the separate intermediate risk category into the low-risk group were in error.[42]

Several other regimens have been tested on patients with low-risk disease, all in nonrandomized, single-institution studies. Ng and colleagues and others have reported on the effectiveness of methotrexate infusion at 150 mg/m^2, and a dose of 1000 mg/cycle has also been studied.[43,44] Single agent etoposide has been used for low-risk disease at 100 mg/m^2.[45] It is a very effective regimen, but the alopecia, nausea, and risk of second malignancy have prevented its use as a primary treatment for all but high-risk patients. Methotrexate and dactinomycin in tandem have also been reported for low-risk disease. The investigators reported a 98% primary response rate, but there was a 10% likelihood of grade 3 or 4 toxicity.[46] The question arises whether so-called low-risk disease should be treated with two of the three most active agents and whether the toxicity of this regimen is acceptable for so-called low-risk patients.

Finally, there are reports from China and the Peking Union Hospital (Song) stretching back several decades on the use of high dose 5-fluoruracil for these patients. This regimen, although quite cost-effective, is toxic (nausea and gastrointestinal symptoms) and has not found favor in Western countries to date.

Single agent methotrexate and dactinomycin have both been used as prophylactic single dose treatment for low-risk patients and, whereas the likelihood of a patient requiring full treatment is decreased, this approach does result in unnecessary treatment for a very many patients whose disease would likely have resolved spontaneously.[47,48,49]

Low-risk metastatic disease, as defined by the older National Cancer Institution criteria for low-risk disease, has been successfully treated with sequential 5-day methotrexate and dactinomycin. The success rate in this harder-to-treat low-risk group in the Brewer series was 67%, but drug resistance was reported in 22% and drug toxicity in another 11%, suggesting that, although effective, this regimen is likely too toxic for general use.[50]

It is very difficult to compare the available regimens on outcome and toxicity because of the differences in patient selection, risk scoring criteria, and rigid institutional preference for specific regimens. Therefore, there is no international consensus about a" best" primary regimen for low-risk disease.[51–53]

Follow-Up

Given the significant loss-to-follow-up rates in the United States where 3% to 13% of patients do not complete treatment and 40% are lost before follow-up is completed, Goldstein and colleagues[54] have suggested that prompt introduction of single agent chemotherapy for persistent disease may be prudent in some circumstances.[54,55]

In the United Kingdom, if the titer normalizes with 50 days (7 weeks), there is scant chance of recurrence. This finding was confirmed by a report from the Dutch Central Registry of Hydatidiform Mole where only 1 out of 265 patients developed recurrence after as few as two normal titers.[56]

Management of Low-risk Primary Treatment Failure

Early diagnosis of resistance to low-dose single agent chemotherapy is highly desirable in order to limit the number of ineffective treatment cycles before a switch is made to a curative regimen. Several investigators have used a regression graph to predict need for treatment. These investigators have graphed the slope of normal postevacuation hCG regression and applied 95% confidence limits to the curves. If the patient's titer falls outside the confidence intervals, the patient is deemed to have persistent disease requiring active management. Rotmensch and colleagues[57] designed a 90th percentile log-exponential regression curve based on a small number of patients successfully treated with methotrexate. Shigematsu and colleagues[58] developed a receiver operating characteristic curve with an hCG cutoff value that identifies refractory patients at an earlier point in their treatment. More recently, von Trommel and Kerkmeijer[59] collaborated to develop a cutoff value (737 mIU/mL) that predicted resistance to 8-day methotrexate in 50% of patients who eventually did not respond to methotrexate a full 2.5 cycles earlier than with conventional definitions. A very high test specificity is essential so that very few patients are switched unnecessarily to combination chemotherapy, and in this study, a 97.5% level of specificity was obtained.[59]

Between 17% and 36% of patients initially treated with low-dose methotrexate regimens will require a change in treatment because of drug resistance. When this requirement occurs, the patient's disease is restaged and the risk score is recalculated. If the score is still low-risk (0–6), patients may be retreated with 5-day methotrexate or dactinomycin. The Sheffield group has also reported that a combination of etoposide and dactinomycin (EA regimen) has a very high (97%) chance of cure in these patients without significant toxicity and no observed second malignancy risk.[60] If the hCG titer is less than 150 mIU/mL, the two UK sites would offer 5-day or biweekly dactinomycin. This has proven to be an excellent regimen in this circumstance (cure rate of 94% and no observed grade 3–4 toxicity). Given the success of the regimen, the Sheffield and Charing Cross groups have recently increased the hCG assay threshold to 300 mIU/mL.[61]

If the recalculated risk score exceeds 6, the EMACO regimen is used. If the chest radiograph is now positive, the liver (computed tomography of abdomen) and brain should be imaged (MR brain) to rule out metastatic disease.

Chemotherapy for High-risk Disease

If the curettings contain CCA, the patient may be treated with a single agent regimen if the risk score is 0 to 6, but if it is 7 or higher, the patient should receive a first line multiagent regimen, usually EMACO. This protocol contains not only methotrexate and dactinomycin but, in addition, etoposide, vincristine and cyclophosphamide. The regimen is repeated every 14 days and is more emetogenic and marrow-toxic than

the single agent protocols. In addition, use of etoposide confers a small (2%) but dose-dependent lifetime risk of late-developing acute myelogenous leukemia.[62]

The Sheffield group has studied treating these women with methotrexate, etoposide, and dactinomycin (MEA) and omitting the much less active CO part of EMACO with good effect (75%).[60]

Patients with a primary diagnosis of PSTT should be treated with a different regimen, the EPEMA regimen, which contains biweekly platinum and weekly etoposide. Some investigators would also use this regimen as primary treatment for "very high-risk" CCA (risk score ≥12). This regimen is quite marrow-toxic and typically requires granulocyte-stimulating factor support by the third cycle. Other possible first line options are MEA[60] that contains a higher dose of etoposide (300 vs 200 mg/m^2) or methotrexate, actinomycin, cyclophosphamide, which was an effective regimen in the 1980s but one that was associated with potentially life-threatening myelosuppression.[32]

Management of High-risk Primary Treatment Failure

If treatment with EPEMA fails, the treatment options are quite limited. Taxol may have a role to play at this stage. Several centers have successfully used a doublet containing etoposide/Taxol and etoposide/platinum, and there is evidence that this regimen may be less toxic than EPEMA as second line therapy.[63]

Other regimens are largely salvage treatments that are unlikely to result in cure and are typically marrow-suppressive and toxic. These additional protocols include cis-platin, etoposide, bleomycin, ifosfamide, cis-platin, etopiside, high dose 5-flurorouracil, gemcitabine, and ultra high dose etoposide with autologous bone marrow transplantation.

PSTT and ETT are easily cured by hysterectomy when the disease is confined to the uterus. However, metastatic PSTT and ETT are relatively chemotherapy-insensitive, and cure when the disease is extrauterine is problematic.

Postchemotherapy Fertility

Once cured, regardless of regimen, chemotherapy patients are normally fertile, although after chemotherapy, menopause typically occurs about 3 years earlier than normal.[64]

METASTATIC DISEASE

Pulmonary Disease

Approximately 10% of patients will have a positive chest radiograph at presentation. Unless individual lesions are greater than 2 cm they can be observed as long as there is no other sign of metastatic disease and the hCG titer continues to decline appropriately. Patients with lesions larger than 2 cm are unlikely to spontaneously resolve and therefore should be treated. The chest film may remain radiologically positive for as long as several years after the hCG titer has normalized. If the chest film is normal, there is very little likelihood that there is disease elsewhere, specifically brain or liver. Therefore, in the absence of specific symptoms to suggest metastatic disease, imaging of brain or abdomen is not indicated when the chest radiograph is normal.

A computed tomographic scan of the lung is positive in 10% to 25% of asymptomatic patients who have a negative chest film. Several studies have suggested that these micrometastatic lesions do not confer a higher risk of distant disease, presumably because this small-volume disease can still be cleared by

maternal immune surveillance mechanisms.[65] On the other hand, a recent report from Sheffield revealed that, of 192 patients with GTN, 52 had a normal chest radiograph and a positive computed tomographic scan. Of those whose risk score remained low-risk, even when the computed tomographic scan result was incorporated into the risk score, 27% failed first line treatment. Additionally, of 20 patients whose disease became high-risk when the computed tomography findings were incorporated into the risk score, 70% needed a regimen change, suggesting that computed tomographic lung scanning may indeed predict outcome. If this finding is confirmed, computed tomographic scanning of the lung may need to replace simple chest radiograph in the scoring system in the future.[66]

Central Nervous System Disease

Most patients who develop brain metastases had an antecedent term pregnancy or a long interval after the last pregnancy. Patients who present with evidence of intracranial disease and an elevated hCG titer (typically headache, nausea, or visual disturbance) need to be managed aggressively. Most of the deaths from central nervous system metastases occur in the first 14 days after presentation.[67,68] A neurosurgeon should assess the patient as soon as an MR brain scan is completed because some isolated superficial lesions can be effectively treated by surgical resection.[69] Patients need to receive immediate parenteral steroids to minimize cerebral edema that might result in coning if there is bleeding from the lesion(s). Chemotherapy is begun as soon as possible, usually with single agent etoposide at 100 mg/m^2. Seven days later full dose EMACO can be started.[68]

Radiotherapy for acute intracranial disease is controversial. Some TDUs treat these women with 24 to 30 cGy to the whole brain with or without stereotactic boost.[70] However, there is theoretic concern about the long-term neurologic effects.[71] Furthermore, radiation-induced tumor vessel sterilization usually requires up to 14 days to be effective, so rapid control of potential intracranial bleeding is problematic. Stereotactic radiotherapy has been successfully used to treat brain metastases, particularly when the disease is in areas of the brain that cannot be accessed neurosurgically. There was longstanding concern that the blood-brain barrier was relatively impervious to chemotherapeutic drugs, but that may not entirely be the case.[72] Charing Cross, in particular, has used prophylactic intrathecal methotrexate in patients who have a positive chest film on the assumption that these women are most at risk of developing intracranial disease. At Charing Cross, cranial irradiation is not used for patients with brain metastases. Instead, intrathecal methotrexate is given in addition to systemic multiagent chemotherapy for patients with documented brain disease. Based on data from Charing Cross, it seems that if patients survive the initial 14 days after diagnosis, their outlook is substantially better with cure rates in the order of 80%.[68]

Liver/Gastrointestinal Disease

Liver metastases are very uncommon (2.7%). Two-thirds of liver lesions follow a term pregnancy, often over 12 months earlier. Synchronous lung metastases are very common (93%), and concomitant brain metastases are found in 33% of the women. Almost all patients fall into the high-risk category based on the WHO criteria. Liver disease often presents as right upper quadrant pain due to bleeding into the liver parenchyma and distention of the hepatic capsule. These areas cannot be safely treated with radiotherapy, so chemotherapy is the preferred treatment. Regional chemotherapy of the liver and occasionally selective resection have been used but with little success. The curability of patients with liver metastases is approximately

30% but falls to 10% if there are synchronous cerebral metastases. None of the various high-risk chemotherapy regimens seem to offer a significant outcome advantage.[73]

SURGERY FOR GTN

Initial management of GTD should always include uterine curettage rather than medical evacuation (prostaglandin, an antiprogestin, or oxytocin), regardless of the size of the uterus. There is a higher likelihood of incomplete emptying with a nonsurgical approach and an associated 1.7- to 1.9-fold increased risk of persistence requiring chemotherapy.[31] In a small percentage of perimenopausal and postmenopausal women, hysterectomy may be curative and/or may decrease the likelihood that the patient will need chemotherapy, or it may reduce the number of chemotherapy cycles needed to achieve cure.[74]

Reports from the Netherlands, Charing Cross, and the Sheffield TDU suggest that a second therapeutic uterine curettage is of as yet undetermined value. The report from van Trommel and colleagues[75] concluded that 9.4% of women were saved chemotherapy but with an accompanying 2.5% likelihood of uterine perforation. The investigators concluded that second curettage was not useful.[75] In contrast, the Sheffield group determined that, for persistent low-risk disease, patients with an hCG titer between 1500 to 5000 mIU/mL, second curettage rather than immediate chemotherapy was curative for 60% of women. The Sheffield group used a much less rigid definition of persistence that might explain their higher observed cure rate.[76] In another study, the Charing Cross group observed that, if the preevacuation titer exceeded 5000 mIU/mL, 70% of patients went on to require chemotherapy. If the titer exceeded 100,000 mIU/mL the potential benefit was quite small, whereas the risk of uterine perforation and hemorrhage was significant.[34] A phase II trial has been mounted by the GOG to prospectively study the utility of second curettage and the significance of the depth of uterine infiltration.[77]

Selected patients with drug-resistant foci of disease in the uterus, lung, brain, or liver may be cured by hysterectomy or by partial lung, liver, or brain resection.

A small number of women will experience significant vaginal bleeding either during or after treatment. If the blood loss originates from a vaginal or uterine mass, hysterectomy may be required. Selective arterial embolization of a symptomatic residual arteriovenous malformation after normalization of the hCG assay is often curative.[78,79,80,81] This minimally invasive approach preserves fertility in younger aged women and should be offered whenever possible.

DISCUSSION

This disease is very uncommon and is often highly complicated, particularly if the disease is high-risk with or without extrapelvic metastases. In addition, the incidence of the disease is declining, presumably as the nutrition of women in underdeveloped countries improves. It seems that the mortality rate from this disease is greatly improved if the disease is treated in regional TDUs where experience and expertise can be centralized. Such an arrangement also fosters better research, because the number of cases seen in noncentralized areas can be very low. The United Kingdom has had a centralized system for both hCG testing and treatment for 30 years, and they remain the world leaders in clinical and basic science research in this disease. The Netherlands has mandated the “rule of 20,” implying that if a clinician manages fewer than 20 cases of a given condition per year they may not have the required expertise to manage specific diseases, and as a result there is regionalization

of GTN management.[82] Several European centers have recently formed a collaborative group to standardize data collection, clinical expertise, and research into one common entity, European Trophoblastic Diseases Group. In North America, there are three well-known regional centers: the Brewer TDU at Northwestern University, New England Trophoblastic Disease Center at Brigham and Women's in Boston, and the South East Trophoblastic Disease Center at Duke University, North Carolina, but the clinical material in most centers is declining as more gynecologic oncologists are trained and enter community-based practice. Trophoblastic disease is a very interesting disease and is typically both low-risk and easily cured, so many of these community-based oncologists will treat GTN without registration or referral to a regional center. As a result, there is evidence that high-risk patients are referred regionally later than should be the case and, as a result, outcomes may be less than optimal.

There are incipient efforts to foster international cooperation to ask relevant clinical questions about this rare disease. Particularly for high-risk and recurrent disease, few centers, if any, have the necessary patient volumes to ask important clinical questions in a prospective and randomized setting. So much of the existing literature on the management of GTN is based on single-institution reports that are nonrandomized and therefore open to a variety of potential methodologic biases. What is needed is prospective unbiased data on the effectiveness of the various regimens, particularly for low-risk disease, and randomized information on toxicity and side effects. The term *low-risk* implies easy to cure, cost-efficient, and safe. Several of the current low-risk regimens are both toxic and resource-intense, and their place in the GTN armamentarium needs to be reexamined in prospective, multiinstitution studies.

Another area where progress may occur is in the field of biomarkers. What is the clinical value of hyperglycosylated hCG testing (H-hCG or ITA)? Does an increase in this marker above a threshold value represent impending invasive disease? Can a simple, reliable assay be developed to test for this biomarker? Is hyperglycosylated hCG, with its invasive potential, the reason that hemochorial placentas developed, and is this the primary reason why homo sapiens were able to develop a larger, better oxygenated brain that allowed this species to predominate and flourish above all others?[83,84] The answers to these and other questions await the results of prospective international clinical trials.

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