16
LOW RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA

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16.1 Introduction

Gestational trophoblastic disease (GTD) comprises a number of abnormalities of gestation/placentation that may present clinically as one of a spectrum of conditions ranging from partial or complete mole to choriocarcinoma, placental site tumour (PSTT) and epithelioid trophoblastic tumour (ETT). Each entity has the potential to persist and/or metastasize. The incidence of these trophoblastic diseases ranges from 0.5 to 8.3 cases per 1000 live births worldwide.[1] In many developing countries both the numerator and the denominator may be very difficult to obtain with accuracy. However, in the United Kingdom where reporting of both figures is required, the rate is approximately 1.5 per 1000 live births.[2,3]

A molar pregnancy is diagnosed histologically when the villus trophoblast consisting of cytotrophoblast (CT) proliferates around an hydropic villus and migrates into the anchoring villi where it undergoes metaplasia into implantation site intermediate trophoblast (ISIT) that invades the maternal decidual plate.[4,5] This initial peri-villus proliferation of both CT and ST is characterized immunohistochemically by an increased level of Ki-67 (marker of cell proliferation) and a normal MelCam assay (cell adhesion molecule that specifically identifies IT).[6] The villus undergoes similar hydropic change in early or missed abortion and can present a histologic dilemma.[7]

A complete mole is the result of inactivation or extrusion of the maternal genetic material around fertilization that results in an androgenetic conceptus composed entirely of 2 paternal haploid chromosome sets derived from either one sperm that undergoes a meioisis-1 error (digny) or two sperm (diandry). In a partial mole, usually derived from a triploid conceptus, one

maternal haploid set of chromosomes shares the nucleus with two paternal haploid sets from either one or two sperm. If the triploid conceptus consists of 2 maternal and only one paternal haploid sets then hydropic degeneration occurs without trophoblastic proliferation (nonmolar gestation).[8] Complete moles are more likely to persist than partial moles (5-15 vs 0.5-5 percent).[9,10] Complete moles have a 10 fold higher likelihood of recurrence in subsequent gestations. Partial moles present no increased risk of GTD in subsequent pregnancies.

Very soon after implantation the developing placenta begins to make human chorionic gonadotropin, first, as a primitive hyperglycosylated form of hCG (H-hCG) derived from the cytotrophoblast layer surrounding the primitive villus. Within 4 weeks the terminally differentiated syncytiotrophoblast layer (ST) that has devolved from the villus cytotrophoblast begins to produce typical double-stranded hCG. HCG levels peak at 14 weeks in a normal gestation and then decline as the villus syncytiotrophoblast is gradually lost as the placenta ages. In a normal or aborted nonmolar gestation the hCG level will decline rapidly after the uterus is emptied. Following a term gestation the level will normalize by 14 days in 73 percent of women and in 97 percent by the third week.[4,11]

16.2 Clinical Presentation

The majority of patients who present with a trophoblastic neoplasm, defined as persistent or metastatic trophoblastic disease or choriocarcinoma, have had a preceding molar pregnancy. Increasingly, an abnormal pregnancy screening ultrasound is the first clinical evidence of trophoblastic disease. However, in a review of patients referred with a probable histologic diagnosis of GTD, the sensitivity and specificity of the preceding uss was only 44 and 74 percent respectively. Diagnosis was more accurate for complete rather than partial moles ($p<0.001$) and there was a non-significant trend suggesting that diagnosis was increasingly accurate as the age of the gestation advanced (>14 weeks). Overall screening uss detected less than 50 percent of hydatidiform moles, the majority being reported as either missed or incomplete abortions.[12]

Once diagnosed, at an average gestational age of 10.1 weeks, the uterus is emptied.[13,14] Suction curettage is the preferred method of extraction because of its simplicity and effectiveness and the low probability of uterine perforation.[15] Some investigators have employed operative

hysteroscopy to precisely outline the trophoblastic tissue and ensure completeness of the curettage.[16] Oxytocics are typically used to contract the uterus after curettage but should, in theory, have little effect since the uterus at this early stage of gestation lacks functioning oxytocin receptors. There is some evidence that oxytocin can stimulate proliferation of both normal and abnormal trophoblast in vitro.[17] There was an early suggestion that administration of the drug before the uterus had been fully emptied could potentially increase the likelihood of trophoblastic persistence (GTN) and dissemination.[18] However, in clinical practice, that concern appears unfounded.

Previously, patients with a molar pregnancy typically presented with a uterus more than 4 weeks larger than the presumed gestational age, prolonged vaginal bleeding, anemia, hyperemesis and/or large theca lutein cysts. Occasionally they also exhibited signs of thyrotoxicosis or toxaemia of pregnancy and renal dysfunction. These significant clinical manifestations of trophoblastic disease were the result of a large burden of abnormal trophoblastic tissue as evidenced by a grossly elevated hCG level. Patients were, on average, diagnosed at 11.3 weeks gestation in one recent paper.[13,14] Over the last 2 decades the clinical presentation of GTD has changed as a result of early pregnancy ultrasound screening such that molar pregnancy is now diagnosed about 1-4 weeks earlier, and usually before symptoms other than irregular vaginal bleeding, still the commonest presenting symptom, have appeared.[13] Surprisingly however, the incidence of persistence (GTN) has not declined despite earlier diagnosis and curettage. This suggests that whatever factor(s) that determine whether a molar pregnancy will persist are determined at or very near to conception and are not related to the age of the molar gestation.[14]

16.3 Classification

In 1967 the U.I.C.C. first categorized the different types of gestational trophoblastic disease (GTD) *histologically* as: molar pregnancy, invasive mole/chorioadenoma destruans (CAD) and choriocarcinoma.[19,20] Latterly, the terms CAD and invasive mole have fallen into disuse. Kurman and Shih described a third type of trophoblast cell, intermediate type that invades the maternal decidual plate both in normal and abnormal gestations. In its benign form IT can appear as an *exaggerated placental-site reaction* or, if it escapes normal controls on proliferation/invasion of the decidua, can develop into a malignant entity, *PSTT*. A small

amount of IT is also present in the chorion leave opposite the decidua vera. This IT can form either a benign *placental nodule* or a malignant variant, *ETT*.[5,21,22]

Persistent trophoblastic disease, correctly referred to as trophoblastic neoplasia or GTN, is diagnosed following evacuation of a molar pregnancy if the serum/urine hCG level rises, plateaus or persists according to guidelines posited by F.I.G.O. in 1982 and by both F.I.G.O. and the International Society for the Study of Trophoblastic Diseases (I.S.S.T.D.) in 2000/2002. However, the criteria for a definition of persistence are not universally agreed even today. The current F.I.G.O./I.S.S.T.D. definition of persistent disease is: a static hCG level based on 4 consecutive weekly titres over 3 weeks, a rise based on 3 levels over 2 weeks, failure to reach normal by 6 months or metastatic disease at any time. The magnitude (percentage) of the rise, or the failure to decline for definition of a plateau, was left undefined.[23] Most investigators use 10 percent for both rise and plateau but, particularly at low levels (<100-300 miu/ml), most investigators are content to continue to observe as long as the level continues to decline and there is no new metastatic disease.

FIGO SCORING	0	1	2	4
Age	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4 – <7	7 – <13	≥ 13
Pre-treatment serum hCG (IU/L)	$<10^3$	10^3 – $<10^4$	10^4 – $<10^5$	≥ 10^5
Largest tumor size (including uterus) cm	<3	3 – <5	≥ 5	-
Site of metastases	Lung	Spleen, Kidney	Gastro-intestinal	Liver, Brain
Number of metastases	-	1 – 4	5 – 8	> 8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

Table 16.1. W.H.O. risk scoring system 2000/2002

Hammond at the Southeast Regional Trophoblastic Center, Duke University described a clinically based *risk scoring system* to segregate patients with GTN into good and poor prognostic categories. It was later adopted by the American National Cancer Institute (N.C.I.) and came into widespread use in North America.[24] Women with good prognosis disease were offered single agent treatment, typically methotrexate, while those with poor prognosis disease (serum hCG titer >40,000 miu, brain or liver metastases, treatment interval > 4 months, histologic evidence of choriocarcinoma or late maternal age) were offered a first line multi-agent regimen, initially MAC and later EMA-CO.[25,26]

More recently, GTN is categorized clinically as either low or high-risk based on a W.H.O. risk scoring system that evolved from a 12-criterion, 3-category prognostic score first described in 1976 by Bagshawe.[18] This risk score initially included several items that on review were dropped as the scoring system matured following its adoption by the W.H.O. in 1982.[23,27,28,29] The excluded factors included parity, parental ABO blood group incompatibility, and a subjective evaluation of the histologic immune response and degree of lymphocytic infiltration. Following

the publication of the Charing Cross risk criteria in 1976, F.I.G.O. enunciated an 8-criterion risk scoring system in 1982 that was revised again in 2000/2002.[23] Patients with a risk score of 0-4 (0-6 in the 2000/2002 version) were determined to have "low-risk" disease and were candidates for single agent (less toxic) chemotherapy.

The risk score is still undergoing critical review. There is current controversy as to whether patients with a risk score of 5 or 6 should be considered low-risk and treated initially with only a single-drug regimen.[30,31] Generally, both vaginal and lung metastases have been managed conservatively although Bagshawe did suggest that patients with pulmonary disease >2 cm should not be included with the low-risk category. Several authors have recently questioned whether lung metastases should be counted on the basis of a CT lung or, as has classically been the case, by simple chest x-ray.[32] There are also conflicting views as to whether CXR-negative, CT-positive lung disease adversely affects prognosis and whether it is an independent prognostic factor important enough to be included in the risk score proper. There are no clear risk factors for the development of pulmonary micro-metastases[33,34]

Patients with low risk GTN are typically cured with a simple intervention, either repeat uterine curettage or single-agent chemotherapy (dactinomycin or methotrexate). The few primary treatment failures are often the result of rapid transformation of low-risk disease into more malignant histology; choriocarcinoma, PSTT or rarely, ETT. The latter two lesions are generally not chemotherapy-sensitive but fortuitously they rarely present as extra-uterine disease.

Finally, there is also an *anatomic* classification of GTN espoused by F.I.G.O. that may be appended to the risk score to add further clarity to the extent and severity of the disease. Its role is to permit broad comparisons of disease between units, regions and countries. It is not terribly useful from the clinical perspective.[23]

The likelihood that a patient will receive chemotherapy is approximately 15 percent in North American Trophoblastic Disease units where there is more rigid adherence to the F.I.G.O. definitions and universal pathology review. In the United Kingdom hCG levels are often observed for longer periods of time, particularly at lower levels, as long as the titre continues to decline. Gillespie looked at patients in the Sheffield unit who were treated more than 6 months

after initial curettage "according to Centre policy". One of the 28 women in the report was treated 56 weeks after initial evacuation of the uterus. All the women had LR disease and 17/18 were cured with 8-day methotrexate.[35] For both logistic and economic reasons the U.K. units do not routinely review the initial curettage pathology on patients referred with a community-based diagnosis of GTD. This likely results in some missed abortions being included in their incidence rates.

The reported likelihood of a patient being treated for persistent disease (GTN) in the Sheffield and Charing Cross units is 4-7 percent and 15-20 percent in North America.[2,36,37]
The difference is the greater comfort in the United Kingdom observing hCG levels that may exceed the F.I.G.O. strict definitions but that continue to decline longitudinally in the absence of clinical symptoms.

16.4 Differential diagnosis

Morphologic examination, although subjective, is still the primary diagnostic tool in the differential diagnosis of GTD, however, there is considerable inter-observer variation.[38] With earlier uterine evacuation and diagnosis, the ability of ultrasound to differentiate moles from nonmolar placentation such as *missed or incomplete abortion* has declined. The $p57^{KIP2}$ gene (CDKN1C) can be used to assist in the diagnosis of molar pregnancy. It is strongly paternally imprinted and expressed from the maternal allele. It can reliably differentiate between a complete mole containing only paternal genes and partial moles and nonmolar gestations that contain both maternal and paternal genetic material.[38]

Very unusually, small islands of cytotrophoblast or terminally differentiated syncytiotrophoblast may remain in the myometrium and secrete low-level hCG and some H-hCG. These patients may present so-called *quiescent hCG syndrome*, a condition that neither requires nor benefits from treatment and typically regresses spontaneously within several months. A very small number, currently estimated at between 7 and 20 percent, may go on to develop active proliferative disease and require chemotherapy.[39,40] Cole has also described another lesion, also chemo-refractory, *minimally-aggressive gestational trophoblastic neoplasm* that can apparently be identified either by H-hCG assay (<40 percent of the total hCG level) and an hCG doubling time of > 14 days.[42]

Low-level "false positive" hCG levels are another potential diagnostic problem sometimes referred to as *phantom hCG syndrome*. Heterophile antibody, often a remnant of childhood immunization, may result in an apparent low-level hCG assay. This large molecule does not easily cross into the urine so the diagnosis may be made with paired serum (+) and urine (-) hCG titres, or serial dilutions or use of a different assay (rabbit vs mouse). False positive assay levels up to 800 miu/ml may also occur due to serum anti-mouse antibodies (HAMA) or by non-specific serum protein interference.[43,44,45]

There is always a risk that a trophoblastic neoplasm may not be of gestational origin. *Non-gestational tumours* are quite rare but contain only maternal genes whereas in gestational neoplasms paternal genetic material is present This can be reliably determined using DNA restriction fragment length polymorphism analysis (RFLP).[46]

16.5 Clinical Considerations

16.5.1 Implications of "low-risk"

The management of low-risk disease has, in many respects, been the most controversial aspect of the clinical management of GTN. Low-risk would seem to imply that there is little chance of extra-uterine dissemination, a high probability of cure with simple first-line treatment and minimal treatment-related side effects. The term also seems to imply rapid resolution of disease with quick return to normal reproductive capability for these typically young, anxious women who are typically keen to begin their reproductive careers. Regimens for low-risk disease should also be cost and resource-efficient and be accompanied by high patient acceptance/preference.[47,48,49,50]

16.5.2 Quality of the evidence

Until quite recently, the majority of the literature on the clinical management of trophoblastic disease consisted of single-institution case series from either tertiary referral Centres or from the population-based referral Centres in the United Kingdom. The U.K. data originated from either of the two supra-regional Trophoblastic Centres at Charing Cross, London and latterly in

Sheffield. An hCG collection hub was also established for Scotland at Dundee.[2,51] This population-based data represented the largest data sets and the methodologically best available information on the management of GTN. However, although population-based, the data was still open to local bias. There was no attempt to prospectively test alternative regimens against the "in-house" regimens. All patients with a diagnosis of GTD were registered in one of the sites, but the pathology from the initial curettage was only reviewed centrally if the patient developed persistent or metastatic disease. Furthermore, early treatment decisions for patients with "presumed" GTD were made by the local Gynecologist prior to referral to one of the two supra-regional units.

Beginning in the late 1980's the Gynecologic Oncology Group of the N.C.I. through its Trophoblastic Subcommittee of the Corpus Committee undertook the first randomized phase II and phase III multi-centered trials in both low and high-risk GTN. Consequently, the quality of the evidence around the management of GTN has improved substantially during the last 15 years. Unfortunately, to date, that has not yet translated into widespread evidence-based change in clinical practice.

Randomized data is vastly preferable to single-institution data because the process of randomization obviates the effect of both overt and inadvertent bias. Unfortunately, randomized trials are expensive to conduct and typically require large patient cohorts. Large Clinical Trial Groups that might be interested in asking important questions in rare diseases such as GTN are increasingly employing alternatives to phase III randomized trials (RCT) such as randomized phase II or adaptive phase II trials that require smaller patient samples but 2-4x the patient sample as single-arm studies. They are also faster to complete and cheaper to conduct but are generally lower powered.[52,53,54]

The value of randomized (phase III) trials in the study of GTN can be seen on inspection of the reports on bi-weekly dactinomycin for low-risk disease. The initial reports on the regimen were all single-institution case series. All reported at least a 90 percent response rate.[55,56,57,58] However, when several recent RCT's were reported the effectiveness of the same regimen in a randomized setting was between 69 and 79 percent depending on the risk score cutoff and whether patients with choriocarcinoma were included in the analysis.[30,59,60,61]

Finally, it is very difficult to compare earlier single-armed studies with contemporary studies because there is lack of uniformity in the cohorts: different definitions of persistence, different W.H.O. risk score cutoffs (4 vs. 6), inclusion of patients with choriocarcinoma and/or patients with and without metastatic disease (lung lesions <2 cm or vagina).

16.6 Clinical management of Low-Risk (LR) Disease

Li and Hertz reported the first successful chemotherapeutic treatment of this disease in 1956 using methotrexate.[61,62] It was only later realized that the disease spanned a clinical spectrum ranging from benign (hydatidiform mole) to highly malignant (choriocarcinoma). In 1976, Bagshawe first advanced his concept of a GTD prognostic score that segregated the disease into low, intermediate and high-risk categories that was used to determine the most suitable primary drug regimens and gave a clearer indication of prognosis. The premise behind the accompanying treatment recommendations was that more malignant tumours would respond more successfully to combinations of drugs, each with different modes of action. Low-risk disease was treated with an 8-day alternating methotrexate and folinic acid (leucovorin) regimen repeated every 14 days.[18] Intermediate-risk disease was treated with the CHAMOMA regimen and high-risk with the 7-drug CHAMOCA regimen. Over time intermediate-risk disease came to be managed with a variety of 2 or 3-drug regimens. In 2000/2002, F.I.G.O. and the I.S.S.T.D. determined that the outcomes for intermediate-risk disease were not materially different from low-risk disease so they were combined into a single "low-risk" category treated with either single agent methotrexate or dactinomycin.[23,27,28,29] High-risk disease that was originally treated with the MAC regimen in North America and CHAMOCA in the United Kingdom and the rest of the world is now treated universally first-line with the EMA-CO regimen. MAC fell into disfavor when a phase III G.O.G. study had to be terminated prematurely because of several treatment-related deaths due to neutropenic sepsis.[25] Along with the discovery of VP16-213 (etoposide) in the mid 1970's the more complicated CHAMOCA regimen evolved into the EMA-CO regimen.[26]

6.6.1. Methotrexate Regimens

A parenteral methotrexate regimen reported in 1956 was the very first successful chemotherapy regimen for low-risk disease.[62] In 1976, Bagshawe reported on the Charing Cross experience with an eight-day alternating methotrexate/leucovorin combination (MTX/LVR) that was repeated every 14 days.[3] Leucovorin was added as "rescue" from the side effects of methotrexate, a potent anti-metabolite, in particular, the dose-limiting oral mucositis. In the 1976 report, the reported effectiveness of the regimen was 68 percent and 80, 69 and 75 percent respectively in subsequent reports from Charing Cross.[3,18,31,36,64,65] On the other side of the ledger though, ten percent of the patients experienced mucositis severe enough to require a change in regimen. While the 8-day regimen has not changed, the Charing Cross low-risk patient cohort has undergone re-definition such that their low-risk patients are not perfectly matched to patients in reports from other centres. The differences include use of an in-house risk scoring system that roughly equates to the WHO risk score. Low-risk patients with evidence of pulmonary metastases receive prophylactic intra-thecal methotrexate in addition to the 8-day parenteral methotrexate and low-risk patients with a registration hCG level >400,000 miu/ml are treated with first line combination chemotherapy not methotrexate/LVR.[65] These subtle differences in management strategy make intra-institutional comparisons challenging. Regardless, the Bagshawe protocol remains the most commonly used regimen for low-risk disease worldwide.

Hancock published the Sheffield results with the same *8-day methotrexate/LVR*. From 1987 to 2000 some 5613 women were registered. During the period 250 women were determined to have low-risk disease requiring treatment, 178 (71 percent) had stage 1 disease and 72 women (29 percent) had stage 3 disease (all had lung metastases only). Primary cure was observed in 72 percent (81 percent of the stage 1 patients and 60 percent of the women with stage 3 disease.[2]

More recently, a number of different methotrexate regimens have been used to treat low-risk GTN. Weekly *oral methotrexate* was reported by LaPolla et al to be effective first-line treatment for 60 percent of 24 patients studied and Barter et al reported on 15 patients, 13 of whom were cured with the same oral regimen.[66] Holmseley tested *weekly intra-muscular methotrexate* in a phase II G.O.G. sponsored study, initially at @ 30 mg/m^2 and then with rapid escalation to 50 mg/m^2. He reported primary cures of 76 and 81 percent of patients in the two G.O.G. studies. Since the

outcomes in the two studies were not statistically different he concluded that the dosages were equivalent. Side effects were minimal. In particular, mucositis was minor and no patient required a change in regimen.[67,68] Accordingly, weekly parenteral methotrexate at 30 mg/m^2 became the standard arm in the subsequent phase III G.O.G. study (#174) that compared bi-weekly dactinomycin @ 1.25 mg/m^2 (dose capped at 2 mg) against weekly methotrexate @ 30 mg/m^2.[30]

Other investigators have reported their experience with still other methotrexate regimens. Among them, the New England Trophoblastic group has used a *methotrexate infusion with LVR* to treat low-risk (LR) patients @ 300 mg/m^2. The regimen consists of an initial 100 mg/m^2 loading dose over 30 minutes followed by a 12-hour infusion @ 200 mg/m^2 with leucovorin rescue @ 24 hours (15 mg iv q12h x 4 doses) repeated every 14 days. The authors reported that 74 percent of their low-risk patients were cured with the regimen but that, in addition to the 20 percent who developed drug resistance, a further 6 percent had to change regimen because of mucositis.[37] In a later report on the same regimen involving 192 women with LR NMTD and MTD, 124 (64.6 percent) were cured primarily but tellingly, 81 percent of those cured required only 1 cycle of treatment.[69] This suggests that many of those women would likely have experienced spontaneous remission if the hCG levels had been observed for a longer period. Wong reported on the same methotrexate infusion regimen given without LVR unless the serum methotrexate level at 24 hours exceeded 10 micromoles/L. The group observed a 91.5 percent primary response rate in a small number of patients (59) with both stage 1 and stage 3 disease. Toxicity was not severe and, in fact, the dose of methotrexate received with this protocol was roughly twice that given with the 8-day regimen.[70]

In a 2001 report, Kwon et al described 22 patients with low-risk disease treated with weekly methotrexate infusion with LVR @ 100/m^2. The response rate was only 45.5 percent.[71] In 1994, Elit described the Toronto MTX/LVR experience and reported a primary cure rate of 84 percent in 78 patients with NCI-defined low and intermediate-risk disease (including 13 with metastases). Patients received a uniform dose of 1000 mg administered intravenously with sodium bicarbonate over 16 hours followed by folinic acid rescue at 24 hours repeated every 14 days.[72] This high dose parenteral methotrexate regimen was well tolerated (no grade 3/4 toxicity and no dose reductions or treatment delays) but did not result in a significantly higher cure rate when compared to a 50 mg/m^2 weekly dosing without rescue.[67,68]

The Brewer Trophoblastic Diseases Unit at Northwestern University, Chicago has long used a *5-day intramuscular methotrexate* injection @ 0.4 mg/kg daily IV/IM (daily dose capped at 25 mg) x 5 days without folinic acid rescue repeated every 14 days. The reported cure rate was 81 percent but the 10 percent risk of mucositis sufficient to require a change in regimen was similar to the 8-day Charing Cross regimen that employed a higher daily dose of methotrexate/LVR.[73] In a case series spanning 1962-90 the same authors reported a failure rate of 15.4 percent in 253 women with NCI-defined low risk disease including choriocarcinoma (resistance 10.7 percent and stomatitis requiring a regimen change 4.7 percent respectively). They concluded, somewhat enthusiastically, that the 5-day regimen was "extremely" well tolerated.[74] In a recent report from the Brewer unit, 358 patients treated between 1979 and 2009 experienced drug resistance in 18 percent (64/358) and drug toxicity requiring a change in regimen in 4 percent (16/358).[75] Using 5-day methotrexate without LVR Soper reported similar outcomes and side effects.[76] Diaz has also reported on the same 5-day regimen but using a 21-day cycle in an attempt to limit the significant mucositis. His group reported on a sample of 31 patients and observed an 83 percent cure rate but their patients still experienced a 26 percent incidence of at least grade 2 stomatitis.[77]

Barter et al reported a case series of low risk patients who were given a loading dose of *parenteral methotrexate followed by weekly oral drug.* They reported response/cure in 31 of 39 patients (84 percent) and determined that the regimen was safe, effective and caused minimal side effects.[78]

In a non-randomized study from 1997-2000 Kang et al compared 59 patients with low risk disease treated with 8-day MTX/LVR against 48 women treated with weekly parenteral MTX @ 50 mg/m^2 and reported equivalent effect (69.5 vs 70.8 percent) but more toxicity on the 8-day regimen (13.6 vs 2.1 percent required a regimen change). The authors concluded that weekly MTX was preferred because of lower toxicity and improved ease of administration and convenience. Successful treatment with primary MTX/LVR was also more prolonged (8.1 vs 6.4 weeks).[79]

16.6.2. Dactinomycin Regimens

Dactinomycin, also an anti-metabolite, has been successfully used to treat low-risk disease. The original regimen was effective and consisted of a *5-day* course of daily intravenous injections @ 0.4 mg/kg/day.[80] However, the regimen was associated with significant toxicity including; alopecia, severe nausea/vomiting, truncal rash, radiation-recall and gastro-intestinal mucositis. In addition, there was a potential for significant skin slough if interstitial injection occurred. Not unexpectedly, patients and physicians preferred 8-day methotrexate (or a variant thereof) as first line treatment for low risk GTN and 5-day dactinomycin fell into disuse except as salvage treatment for patients who failed first line methotrexate.[81]

In 1990, Schlaerth reported on a variation of the original dactinomycin 5-day regimen. He described and tested what he referred to as "pulsed" dactinomycin.[55] Several additional case series using pulsed dactinomycin followed, all suggested an effectiveness of 86-94 percent.[55,56,57,58] Twiggs published work that concluded the dactinomycin regimen was both more efficacious and more cost effective than existing methotrexate regimens.[82] The drug was administered intravenously bi-weekly at 1.25 mg/m^2 with each dose was capped at 2 mg.[55,56] This change in the method of administration was accompanied by a significant improvement in the incidence of nausea/vomiting and rash, and only minor (ECOG grade 1) hair loss in 10 percent of patients as determined prospectively in G.O.G. #174.[30]

16.6.3 Methotrexate vs Dactinomycin: Data from Randomized Trials

Many phase III trials fail to confirm an expected significant difference when preceding hypothesis-generating case series and phase II trials have reported highly interesting, positive results. Approximately 50 percent of follow-on randomized trials fail to confirm a statistically positive phase II trial result, and further, 20 percent of the follow-on randomized trials actually report a negative association. The literature on the bi-weekly dactinomycin regimen demonstrates a 20 percent difference between the results from the several 1985-95 case series and the later randomized datasets that illustrate this specific phenomenon in GTN.[30,59,60,61] While useful for hypothesis generation, case series, large population-based data sets and phase II studies should never be mistaken for incontrovertible evidence of true effect. The latter can only be imputed from randomized studies.[52,53,54]

In 1993 Gleeson published the results of a randomized trial comparing weekly methotrexate @ 50 mg/m^2 to the 8-day regimen. The study reported that the weekly protocol produced a better outcome with fewer side effects and the authors concluded that, as a result, the weekly regimen was preferred.[83]

Pulse dactinomycin has been compared to low dose parenteral methotrexate, and to both 5 and 8-day methotrexate in randomized trials. GOG #174 demonstrated that bi-weekly dactinomycin was statistically superior to weekly methotrexate @ 30 mg/m^2 while papers from Mousavi (not randomized) and Yarandi have reported that pulse dactinomycin was superior to both 5-day methotrexate and methotrexate at 30 mg/m^2 (90 versus 68 percent; p=0.018 and 90 vs 48 percent respectively). Major side effects were not observed in the Iranian studies but in the GOG report, ECOG grade 1 alopecia was seen in 10 percent, grade 1 and 2 nausea was slightly more common in the dactinomycin group while mucositis was observed in approximately 10 percent of the both patient groups.[30,59,60,61] The mean number of courses to cure in GOG #174 was 4.2 courses of pulse dactinomycin and 5.6 courses with weekly parenteral methotrexate. Following the change to the W.H.O. risk score in 2000/2002, in 2004 this randomized study was amended to include patients with a risk score of 5 or 6 and patients with choriocarcinoma, patients that had not previously been included in low-risk studies. When the pulse dactinomycin regimen in G.O.G. #174 was scrutinized post hoc, the success rate was found to be 70 percent for patients with a risk score of 0-6 and 73 percent for patients with the more commonly reported risk score limits of 0-4 and excluding patients with a diagnosis of choriocarcinoma. In the same study, weekly IM methotrexate was effective in only 53 and 58 percent of patients respectively, a statistically significant difference. Five patients in each arm actually failed treatment based on a strict post hoc evaluation of the hCG levels. However, the treating physicians did not recognize this fact and continued the allocated treatment onto cure resulting in a complete response in an additional 5 percent of patients per arm.[30]

In a small but similar randomized study of 30 women with LR disease, Shahbazian reported that 86.7 percent (13/15) of patients who received bi-weekly dactinomycin were cured with first line treatment but only 53.3 percent (7/15) of the women who received weekly methotrexate @ 40 mg/m^2 were cured (p<0.04). The dactinomycin patients had a shorter mean number of treatment cycles to cure (4.3 vs 6.5) and the mean duration of treatment was shorter (9.6 vs 13

weeks). Toxicity was somewhat different in the 2 groups but statistically similar. Overall, patient satisfaction was higher among the patients who received first line dactinomycin.[84]

In another randomized trial, Lertkhachonsuk et al compared 5-day dactinomycin and 8-day MTX/LVR in 49 women with nonmetastatic low-risk disease. They observed a 100 percent response in the dactinomycin arm and a 73.6 percent response in the MTX/LVR patients. They also had to switch 6/22 of the methotrexate patients to dactinomycin because of rising liver enzymes. Grade 1 and 2 alopecia and stomatitis was reported in the dactinomycin patients. Five-day dactinomycin was determined to be the better treatment for low-risk patients.[85]

16.6.4. Methotrexate and Dactinomycin doublets

In an effort to maximize the primary response rate several authors have combined both methotrexate and dactinomycin into a single first line regimen. In a 20-year retrospective study, Eirrickson and Hoskins et al combined methotrexate and 2-day dactinomycin in a 14-day regimen for patients with selected "low-risk" disease (hCG < 60,000 miu and no extra-pulmonary metastases). They employed dactinomycin @ 0.6 mg/m2 on days 1 and 2 plus methotrexate @ 100 mg/m2 on day 8 of a 14 day cycle. Their primary cure rate was 97 percent in 100 patients who required a median of 3 cycles for cure. The authors stated that toxicity was "modest" but grade 3-4 hematologic toxicity was observed in 30 percent and grade 2-3 stomatitis was seen in 47 percent.[86] Smith et al obtained the same exceptional outcomes in a 1975 report when he reported the results from the M. D. Anderson Hospital, Houston. Rose and Piver also reported on a doublet regimen used in 9 patients with 100 percent success but with universal, moderate degree stomatitis.[87]

Most investigators are loath to consider more than single drug treatment for these low-risk, highly curable, typically young reproductive-aged women since similar outcomes can be obtained in a high proportion of patients with single agent therapy alone.

16.6.5. Other First-Line Chemotherapeutic Options

16. 6.5.1 Etoposide

In the mid-1970's a novel new drug appeared that was initially referred to as VP16-213 and was first used on GTN patients at the Charing Cross Hospital by Bagshawe et al. It became recognized as a highly effective drug particularly in failed high-risk disease patients. It was later tested on low-risk women with excellent results but the nausea and complete alopecia were deemed unacceptable toxicities for patients with low-risk disease.[26,88] Wong et al reported 95 percent primary cure in 60 patients treated with oral etoposide @ 100 mg/m^2 q2 weekly, some with choriocarcinoma and 20 percent with extra-uterine disease. They did not recommend routine use of the drug for low-risk disease because of the complete alopecia and severe nausea observed.[89] In addition, in 1998, Rustin and Newlands reported that patients treated with etoposide experienced a 1-2 percent dose-dependent risk of late-developing second malignancy, typically acute myelogenous leukemia.[90] That observation has recently been revisited and the revised data suggests the incidence of AML is slightly higher and the rates of lung and breast cancer slightly lower resulting in no overall increase in second malignancy.[91] There was no observed increase in second tumours using 8-day methotrexate /LVR.[92]

16.6.5.2 5 Fluorouracil

In 1984 Song reported on the extensive Chinese experience with 5-FU at the Peking Union Hospital. The drug was inexpensive and, using a 28-day cycle, he and his colleagues reported a surprisingly high response rate. They did note significant gastro-intestinal side effects that has precluded use of this drug as primary treatment for low-risk disease in Europe and the Americas.[93]

16.6.6. Surgery

In 1982, Clayton et al reported that hysterectomy decreased the likelihood that patients with non-metastatic low-risk disease would require chemotherapy from 20 to 4 percent.[92] However, since the majority of these women are still of reproductive age, extirpation of the uterus as primary treatment is usually reserved for older women, for patients who present with life-

threatening uterine rupture and hemoperitoneum or for women with drug-resistant uterine disease.[95,96]

Tidy has looked at the mode of evacuation as a potential risk factor for persistence. The Sheffield group determined that suction curettage was preferred over medical methods of uterine evacuation since the latter resulted in a higher rate of persistence likely due to incomplete evacuation.[15]

Initial second curettage, rather than immediate chemotherapy, has been used by community gynecologists in both Europe and North America to manage persistent disease or excessive uterine bleeding from slow-resolving trophoblastic disease but without clear evidence in support of that approach.[97,98,99,100,101,102] The older reports are retrospective reviews and case series but several contemporary reports, one from the Netherlands and 2 from the United Kingdom, suggest that the potential for chemotherapy-sparing curettage may be between 9 and 60 percent. The authors of the Charing Cross and Sheffield studies determined that patients with hCG levels above 5000 and/or 1500 miu/ml respectively were unlikely to benefit from initial second curettage. These studies all reported only a 1-2 percent risk of uterine rupture requiring simple conservative management.[65,103,104,105] Schlaerth reported an 8 percent rate of rupture in a 1990 paper but not all the patients had low-risk disease.[101] Uterine infection appeared insignificant but the potential risk of infertility from repeat curettage was not examined longitudinally in any of the studies.[65,103,104,105] In another report, Berkowitz reported that second curettage did decrease in the likelihood of persistent disease.[106] Finally, in a 1989 report Gao et al suggested that second curettage was of little value since only 3.3 percent of the repeat curettage specimens actually contained residual molar tissue.[107]

The Gynecologic Oncology Group has recently completed a prospective phase II trial of initial second curettage for persistent low-risk, non-metastatic disease and has observed that 38.6 percent (23/59) of patients were saved the need for chemotherapy. The authors also observed 2 of the 64 patients had PSTT in the second curettage specimen. Although these women all went on to curative but fertility-ending hysterectomy, they were saved the several cycles of what would surely have been ineffective, standard single-agent chemotherapy. The G.O.G. study concluded that second curettage actually benefited 42 percent (27/64) of the study population. They also observed that the benefit from the procedure was relatively independent of the hCG level, tumor

size, volume or depth of myometrial invasion although the small numbers precluded statistical evaluation. However, little benefit was seen in patients older than 39 or in patients with a risk score of 5 or 6. The authors concluded that second curettage should not be offered to these women.[108]

A small number of women may present with, or develop, persistent or life-threatening vaginal bleeding due to a-v malformations that may or may not be tumour-related. Furthermore, a few patients will develop false a-v malformations as a result of aggressive curettage. These vascular abnormalities may persist well after successful completion of chemotherapy. Hysterectomy is typically curative, however, most of these women are reproductive-aged and wish to retain fertility. Arterial embolization has been successfully used to control significant bleeding although an occasional patient may require a second embolization to effect control. Postoperative pelvic pain similar to that seen following embolization of uterine fibroids is the only significant potential adverse effect. The procedure does not appear to affect subsequent fertility.[109]

16.6.6. Prophylactic chemotherapy

There was an earlier suggestion that prophylactic chemotherapy might actually increase the number of chemotherapy cycles required for women who went on to develop persistent disease.[110]

Prophylactic treatment has been reported to decrease the likelihood of persistent disease from 14 to 4 percent. In a report from the New England Trophoblastic Disease Unit at Brigham and Womens' Hospital, Boston, patients received one course of parenteral methotrexate @ 300 mg/m^2 with leucovorin rescue and were then followed longitudinally for a rise or plateau in their hCG level.[111,112]

There are also reports on the use of prophylactic single-dose dactinomycin given prior to the initial curettage. In a non-randomized study, Uberti et al observed a significant decrease in the need for chemotherapy in 163 women who were at increased risk for developing persist disease compared to cohort of 102 similarly at-risk women to whom prophylactic chemotherapy was not offered. In the treated group 18.5 percent required treatment whereas 34.3 percent required

treatment when prophylactic dactinomycin was not given, a statistically significant difference.[113,114]

Fu et al completed a Cochrane review on the subject of prophylactic treatment. The authors identified 3 randomized trials in the literature, two involving methotrexate. All the patients in the 3 studies had had a prior complete mole. Prophylactic methotrexate was found to decrease the likelihood of subsequent chemotherapy (RR 0.37; $p< 0.00001$) but the authors determined that the studies were all of low methodologic quality. A smaller study that looked at prophylactic dactinomycin also demonstrated a significant decrease in the need for further chemotherapy (RR 0.28; $p=0.01$) but this study was also deemed to be of low quality. The authors concluded that, given the low quality of the studies, prophylactic chemotherapy could not be recommended in part because of the possible negative effects including; potential drug resistance, treatment delay and unnecessary exposure to anti-metabolite drugs and related toxicity.[117]

Generally speaking, the practice has not found general favor and is currently only offered to the occasional patient at high risk for default.[106,11,115.116]

16.6.8 Consensus First-Line Treatment ?

There is a dearth of randomized data on which to determine a "best" first-line regimen for low-risk disease. Should the oncologist follow the lead of one of the several large referral Centres such as the Brewer or Charing Cross and use their particular, time-tested regimen? Should they continue to use their institution's preferred regimen, should they use collated data like the Cochrane reviews to inform their decision or should they refer to one of the few randomized trials (RCT's) that have comparatively tested a few of the available regimens.[118] The available RCT's seem to suggest that bi-weekly dactinomycin is at least as effective as either weekly methotrexate, and 5 or 8-day methotrexate.[119,120]

There are a number of thoughtful *economic evaluation and patient preference* studies that address the issue of a "best" regimen for low-risk disease. Some of the studies have prospectively assessed patient QOL and some have used decision analysis software to perform sensitivity analyses around the more important outcome measures.[121] Reade reported that pulse dactinomycin was

favoured over 5 and 8-day methotrexate both from an economic perspective and based on a prospective patient preference study.[122]

Going forward, the G.O.G., newly renamed as the N.R.G., has begun an international phase III trial comparing 5 and 8-day methotrexate and bi-weekly dactinomycin.[123] The study is ongoing and several years from completion. In the absence of better information it would seem reasonable to use one of these 3 options, with a bias in favour of pulse dactinomycin, given its lower side effect profile, equivalent outcomes, ease of administration, lower resource consumption/cost and higher patient preference.[118]

16.6.9 Other Management Issues

16.6.9.1. Treatment Consolidation

The most common approach has been to recommend 2 further courses of the same regimen after the first normal titre. In the two-armed, phase III G.O.G. #174 trial the observed risk of relapse after a patient had attained a normal hCG level, for both low dose methotrexate and bi-weekly dactinomycin was only 1 percent (1/102 and 1/101) at 10 and 22 months respectively after only one consolidation course.[30] In the phase II GOG second curettage study, patients were followed for only 6 months and no late recurrences were observed.[108]

The longtime policy at the 2 supra-regional Centres in the U.K. has been to offer patients six to eight weeks of consolidation following the first normal titre (equivalent to 3-4 additional full cycles of the 8-day regimen).[9,36,64,65] However, a retrospective, non-randomized comparison of relapse rates from the Netherlands Trophoblastic Working Party and Charing Cross has suggested that, at least for the 8-day methotrexate/leucovorin regimen, three additional courses might be superior to two (risk of relapse 8.3 versus 4.0 percent; p=0.006). The two patient

cohorts were not equivalent; the diagnosis of persistent disease was not identical, the Dutch patients had a higher average hCG titre at registration ($p<0.001$) and more patients with metastatic (pulmonary) disease ($p=0.012$). However, the average number of courses to a normal titre was not statistically different ($p=0.375$).[124,125,126,127]

In the absence of prospective randomized data it would seem perfectly reasonable to offer low risk patients 1 or 2 consolidation courses unless the slope of the regression curve is particularly flat and the number of courses to reach a normal titre is not excessive in which case a third or fourth course may be indicated.

Patients successfully treated for low-risk disease should be followed, at a minimum, weekly x 4 then monthly for 12 months following the first normal hCG level. In the U.K., patients who require second line treatment are followed indefinitely thereafter.[9] There is evidence that this close surveillance and prolonged interdiction of pregnancy does have a negative psychological impact on young women (fear of recurrence, infertility and risk to subsequent conceptions) but it also appears to offer positive reassurance and the level of patient anxiety declines in surveillance as opposed to active management. These anxieties appear inversely correlated with patient age.[128]

16.6.9.2. Prediction of First-Line Failure

The diagnosis of GTN is imprecise and subjective. The hCG level is used as a surrogate marker for the diagnosis of neoplasia and as an indication of tumor burden. In fact, some, if not many women who strictly speaking meet the F.I.G.O. criteria for persistence, if observed for a few more weeks, likely would achieve a normal titre spontaneously without the need for chemotherapy.

Several authors have attempted to predict early failure to first line chemotherapy in the hope of decreasing the number of cycles of an ineffective regimen. However, since a gold standard for the diagnosis of GTN has not yet been identified any alternative approaches to early identification of persistence are also only surrogate measures and not incontrovertible evidence of true neoplasia.

Schlearth was one of the first to examine the normal regression line in responding patients. He determined that if a patient's hCG level fell outside the 95 percent confidence limits they were going to eventually fail that regimen.[129] Later investigators have made similar observations but the regression curve did not find general acceptance possibly because the standard F.I.G.O. criteria for static or rising hCG levels were easy to use and clinically efficient.[130,131,132,133,134,135]
More recently, Van Trommel has re-visited the same issue and determined that, using an ROC curve, an hCG level cutoff value of 737 IU/L can be used to predict subsequent failure to first line 8-day methotrexate in 52 percent of women before their 4th cycle with a very high specificity (97.5 percent). If true this would reduce first line treatment by 2.5 cycles of 8-day methotrexate.[134,135]

Charing Cross has looked at the low-risk patients and determined that if a normal hCG is achieved by 50 days after evacuation the risk of persistence is negligible but that if the titre exceeded 500 miu/ml at the same point in treatment, was an accurate predictor of methotrexate resistance.[36,91] The trophoblastic group at Brigham and Womens' and others have also determined that once undetectable hCG levels are achieved recurrence risk is very small.[126]

Sebire tried to identify histopathologic and immunohistochemical markers that might predict persistence at an earlier stage but their research did not yield any helpful clinical markers of treatment failure.[136]

16.6.9.3. Risk of first line failure

Some patient groups are more likely to fail first-line single agent treatment regardless of the choice of drug or regimen. The risk of first line failure is low with most of the commonly used regimens since most will cure between 70 and 80 percent in the first instance. And there is near universal success if the few primary treatment failures require a salvage regimen and/or surgery. In the Sheffield experience, of 250 women treated for LR disease, 8/250 (3.2 percent) recurred, 3 within 12 months, 4 in 24 months and 1 within 36 months.[2] In the G.O.G. #174 study only 1/107 and 1/107 recurred in the dactinomycin and methotrexate arms, at 4 and 22 months respectively.[30]

Charing Cross has looked at the response/cure rate for women with LR disease (0-6) who have an *initial hCG level* of >100,000 and >400,000 miu/ml. The study determined that only 29.7 percent (11/37) and 0.0 percent respectively were cured with first-line 8-day methotrexate. However, they did offer that patients with an initial titre between 100,000 and 400,000 miu/ml should still receive first line 8-day methotrexate since the regimen was substantially less toxic than EMA-CO and only added an additional 13 days to the treatment time for failed patients.[65] They have also determined that patients with a titre >20,000 miu/ml 4 weeks post-evacuation have a much higher likelihood of requiring treatment and both they and the Sheffield Trophoblastic Unit now use this additional parameter as a determinant of persistent disease (GTN). Other authors have suggested that initial titre is a risk factor for first-line single agent treatment failure.[74,76,137] Taylor et al found that patients with an hCG titre <100,000 miu/ml when persistence was diagnosed were significantly more likely to respond to first line 8-day methotrexate than those whose titre exceeded 100,000 miu/ml. (84 versus 34 percent: $p< 0.0001$).[64]

The histologic diagnosis of *choriocarcinoma* in the initial curettage specimen does not currently affect the risk score calculation but many investigators are loath to treat these patients with first-line single agent therapy. Charing Cross and Sheffield together have looked at patients with a diagnosis of choriocarcinoma and LR disease (not all pathologically reviewed) and found that 37 percent (24/65) normalized spontaneously without treatment. Of 23 with histologically confirmed choriocarcinoma only 8 (35 percent) were cured with 8-day methotrexate alone. None of 2 choriocarcinoma patients with a risk score of 6, or the 1 patient with extra-pelvic disease, responded to first line treatment but all patients were successfully salvaged.[31]

The New England group at Brigham and Womens' looked at the *pretreatment curettage* as a potential predictor of the risk of persistence but were unable to develop a clinically useful association between curettage material and outcome.[138]

Women who have disease confined to the uterus (*F.I.G.O. stage 1*) have a higher likelihood of cure than those with lung lesions (stage 3). In the Sheffield results the chance of cure was 81 and 60 percent respectively.[2]

There is controversy regarding the clinical significance of *micro-metastatic pulmonary disease*. The risk score mandates that only a chest x-ray can be used to identify and count lung lesions. Since the resolution of a chest film is approximately 6 mm, smaller lung lesions are not routinely identified. Some investigators stage patients with a CT lung and alter the patient's risk score and treatment plan accordingly. A paper from Sheffield suggests that patients with stage 3 disease do not do as well. However, there are several reports suggesting that patients with a negative chest film and a positive CT lung (10-20 percent) do as well as patients with no lung disease.[2,30,32,34]

In a review of the Charing Cross data, 76 patients with an abnormal chest x-ray were reviewed after successful completion of first line chemotherapy. Eleven percent (8/76) had a residual abnormality on chest x-ray while 19 percent (15/76) had a residual lung lesion on chest CT scan. Only 2 patients (2.6 percent) actually relapsed and required salvage treatment. The authors determined that residual pulmonary abnormalities on chest imaging do not require excision.[139]

Other investigators have unsuccessfully looked at ultrasound-defined *lesion size* and hCG titre in an effort to predict failure to first line drug.[140]

Seckl et al have examined whether *uterine artery pulsatility* (UAPI) might predict for persistence/first line failure. Their premise is that with more vascular, larger uterine tumor mass uterine artery blood flow should be increased. Since tumor burden and high registration hCG level both appear to predict for persistence and first line treatment failure, a high UAPI as measured on the staging ultrasound may be useful. Preliminary evidence from Charing Cross appears to support the hypothesis and the issue is being tested as an ancillary question in the multi-national 3-armed low-risk study, G.O.G. #275.[123,141]

Patients with gestational trophoblastic neoplasia previously classified as having *intermediate-risk* disease (W.H.O. risk score 5 and 6) have been subjected to greater variation in treatment. In the 2000/2002 revision of the F.I.G.O. guidelines for trophoblastic disease, patients with a risk score of 5 or 6 were included in the low-risk category since they were easier to cure than high-risk patients (risk score ≥ 7) and there was a desire to simplify GTN treatment protocols.[23] There is now greater clinical experience with the new classification and there is data from randomized studies demonstrating that these women are significantly more difficult to cure with first-line

single agent regimens.[141,142] The G.O.G. phase III trial observed that only 12 and 44 percent respectively were cured with either methotrexate or dactinomycin alone as opposed to a cure rate of almost 80 percent for patients with risk scores of 0-4.[30] The Sheffield and Charing Cross experience was similar.[65,109] Taylor et al reported that 29/36 women (81 percent) with a risk score of 6 failed first line 8-day methotrexate compared to 87/253 (34 percent) with a score of 0-5.[31,64] Sita-Lumsden et al have studied UAPI in women with a risk score of 5 or 6 and determined that, for "high vascularity" uterine tumors (UAPI >1), the test may be an independent predictor of resistance to 8-day methotrexate.[141,143]

There is no consensus as to which regimen, single agent or combination chemotherapy, these women with "intermediate-risk" disease should receive. Patients presenting with a risk score of 6 (and probably 5 as well) might be an opportunity to study an innovative 2-drug regimen but negate patient exposure to platinum and etoposide ie. EMA-CO.[86]

16.6.9.4. Modeling and Early Prediction of Relapsed LR Disease

At recurrence, patients are often re-staged and a new W.H.O. risk score determined. If the patient still has low risk disease they may be treated in a variety of ways. Other Centres may follow the Charing Cross lead and treat based on the hCG titre without re-scoring.[65]

A number of investigators have attempted to limit the number of unnecessary first-line cycles with a drug that will fail by attempting to identify that likelihood as early as possible. This may be possible by modeling hCG regression in responding patients. Early attempts at rapid identification of patients unlikely to be cured by primary first-line chemotherapy utilized a normal regression curve. If a patent's own curve deviated by more than 2 standard deviations they were deemed very likely to fail their current drug and so an early change in treatment was implemented. More recently investigators have modeled hCG regression and identified an early clinical intervention point. In an article by You et al using 2 different data sets and two different methotrexate regimens (Charing Cross 8-day and G.O.G. 50 mg/m^2) kinetic modeling of hCG measurements was found to be an excellent discriminator of methotrexate resistance with an optimal hCG cut-off value of 20 IU/L (AUC 0.87; sensitivity 0.91 and specificity 0.83)[144]

Charing Cross has reported successful use of 5-day dactinomycin for 8-day methotrexate failures if the hCG level at recurrence is quite low (low tumour burden). Initially the hCG limit was ≤100 miu/ml, then ≤400 and as the effectiveness of the regimen has been further observed, most recently ≤1000 miu/ml. If the hCG level exceeds the threshold patients are treated with the EMA-CO regimen that is significantly more time and labor intensive and is associated with more clinical toxicity.[64] Using a regression model Van Trommel et al demonstrated that an hCG cutoff value of 737 IU/L before the fourth course predicted for resistance to 8-day methotrexate/LVR with a sensitivity of 53 percent and a specificity of 97.5 percent.[129] That finding was strengthened when a confirmatory study involving the Charing Cross data was performed.[135]

16.6.9.5 **Management of Relapsed LR Disease**

The Sheffield group has had success treating relapsed LR patients with a 2-weekly regimen consisting of etoposide and dactinomycin. In a 2000 report they reported a 75 percent rate of cure. Alopecia was universal and patients experienced grade 2/3 neutropenia and stomatitis.[145]

The Brewer group at Northwestern University, Chicago has reported that overall 75 percent rate of secondary cure for patients who had failed 5-day methotrexate patients. Seventy-one percent of patients with drug resistance and 88 percent of patients with severe methotrexate toxicity requiring regimen change were salvaged with 5-day dactinomycin. However, a W.H.O. score ≥3 or a histologic diagnosis of choriocarcinoma adversely affected outcome ($p=0.025$).[75] In an earlier report from the Brewer unit Roberts suggested that 5-day methotrexate then 5-day dactinomycin, or vice versa, for relapsed patients was 99 percent effective but 24 percent of the women in the report also underwent "adjuvant" hysterectomy. Additionally, 10.9 percent of the patients had to change their regimen because of stomatitis.[73]

The New England group reviewed their methotrexate failures and found that 80 percent (27/37) were cured if the hCG titre 1 week after the initiation of first-line methotrexate was <600

miu/ml again suggesting patients with low tumour burden do better. Most of the primary methotrexate failures were rescued with 5-day dactinomycin and only 7 percent of the 150 women with low-risk GTN required combination chemotherapy to achieve cure.[138]
A phase II G.O.G. study observed that 85 percent of patients who had failed low-dose methotrexate @ 30 mg/m^2 were subsequently cured with bi-weekly dactinomycin.[146]

Finally, Alazzam published a Cochrane review on recurrent/resistant low risk GTN and concluded that as long as a patient still had low risk disease, treatment with the alternate drug (dactinomycin or methotrexate) was effective in many patients. However, the study did not recommend whether second line regimen should be 1, 5 or 8 days in length.[147]

Patients treated for relapsed disease should be followed, at least monthly, for a minimum of 12 months. Some centres, Charing Cross among them, continue to follow these women 6-monthly indefinitely.

16.7 Conclusions

In summary, there are a number of clinical uncertainties with respect to GTN. Firstly, we do not possess a gold standard to diagnose this condition with complete assurance. Rather we typically rely on surrogate measures of neoplasia to determine who has the disease of interest such as the hCG level or its regression characteristics. Sometimes we get it wrong and patients receive treatment that if withheld for a few additional weeks might not be needed. There really is no consensus as to a *best* management of low-risk GTN. There are a number of choices based on either methotrexate or dactinomycin or surgery. However, historically there has been very little effort to test the more common chemotherapy regimens prospectively and in a randomized setting where bias could be minimized and equally distributed between treatment arms. Historically, institution-based unwillingness to prospectively test other regimens in a competitive clinical setting has hampered the implementation of best practice based on sound non-biased prospective evidence.

The problem of choosing a best regimen has been exacerbated by the relatively high curability of this disease and the paucity (and declining) incidence of GTN worldwide, which is in turn related to greater geographic mingling of at-risk populations and vastly improved nutrition in at-risk geographic regions. The Gynecologic Oncology Group/N.R.G. has attempted to address these issues with its current international phase III trial that will test the 3 commonest choices for primary treatment, specifically, bi-weekly dactinomycin, 5-day methotrexate without LVR and 8-day methotrexate with LVR. However, it will be, at a minimum, several years until this trial is completed. It will report not only clinical outcomes but also quality of life data that will expand on and increase the external generalizability of the results.[123]

Since the more widely used regimens, 8-day methotrexate with leucovorin rescue, 5-day methotrexate and bi-weekly "pulse" dactinomycin all result in a primary cure rate approximating 70-80 percent, based on available evidence, the choice of a *best* regimen should probably be determined on patient preference, cost and resource consumption. This type of analysis has been reported on several occasions and would appear to favor "pulse" dactinomycin because of the lower cost, fewer factor inputs and higher patient preference for a bi-weekly 1-injection therapy versus a more complicated bi-weekly 5 or 8-day regimen.

The G.O.G. study (242) on second curettage suggested that a primary repeat curettage, rather than immediate chemotherapy, could be safely and effectively used for patients except those aged 39 or older and patients with a risk score of 5 or 6. The authors reported that 42 percent of the patients benefited from second curettage with negligible side effects and complications.[108] It would seem that an initial second curettage is a useful therapeutic option for many patients that is currently underutilized.

Optimal primary treatment for the harder-to-cure older patients, patients with intermediate-risk disease, and women who fail second curettage, is still not well defined but probably should be based on a generally more aggressive management strategy.

Outcomes are much better in specialized regional Trophoblastic Units than in community or even tertiary hospitals that lack dedicated supra-regional expertise in the trophoblastic diseases. Without question, the United Kingdom GTD service, first begun at Charing Cross and later

expanded to Sheffield with a sample collection unit at Dundee is the clearest example of just what can be accomplished from the perspective of optimizing patient outcomes, research and teaching.[51] Sheffield has also demonstrated that a strong nursing component vastly improves communication and patient support.[148]

Several of the more pressing issues going forward include defining the precise role of H-hCG, discovering a gold standard for diagnosis, increased regionalization and much more profitable external collaboration and organized trial design and implementation..

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