Gestational Trophoblastic Disease: When A Pregnancy Becomes A Cancer

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Case Report

26 year old female presents to the ER with a cough for several weeks and heavy vaginal bleeding.

Pregnancy test (Bhcg)- 500,000

Ultrasound shows no fetus in the uterus

Pelvic Ultrasound

Chest X-Ray

Gestational Trophoblastic Disease

Inter-related Diseases

Abnormal Cells or Cancer of Fetus or Placenta

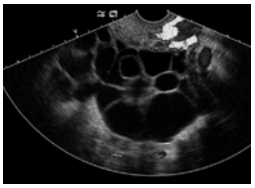
NOT from mother

Can occur in any kind of pregnancy

Highly curable

Signs and Symptoms (Late Diagnosis)

- Vaginal Bleeding
- Theca Lutein Cysts
- Hyperemesis Gravidum
- Pre-eclampsia
- Hyperthyroidism
- Respiratory Difficulty



Work-up

- Type and Screen → Rhogam?
  - For partial moles
- Thyroid profile
- LFTs
- CBC
- Renal function
- CXR but occult mets on CT 40% of time
- Pelvic Ultrasound

Types of GTD

1. Complete Hydatidiform mole
2. Partial Hydatidiform mole
3. Invasive Mole
4. Choriocarcinoma
5. Placental Site Trophoblastic Tumors
6. Epithelioid Trophoblastic Disease

Epidemiology

Incidence
- US 1: 1,500
- Taiwan 1: 125
- Ireland complete 1:1,945; partial 1:695

Vitamin A deficiency

Maternal age, paternal age

History of Infertility/Miscarriage

OCPs

Molecular Genetics

Complete Molar Pregnancy- p53, c-fms

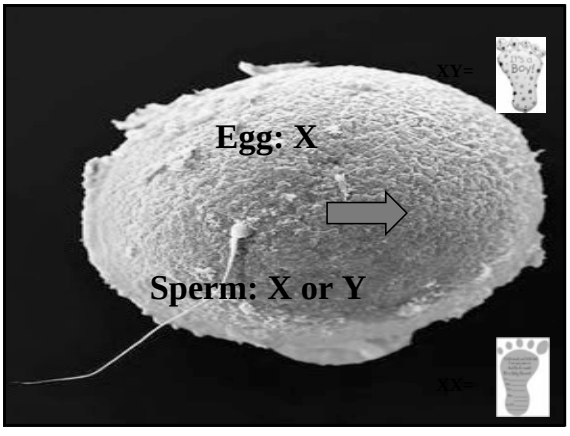
Choriocarcinoma- ras, c-myc

Both increase in EGFR if high expression of EGFR in complete molar pregnancy then more likely to be invasive.

Microarray analysis

Complete Molar Pregnancies

- All chromosomes paternal
- 80 % of GTD cases
- Woman's age
  < 20 years; > 40 years
- Potential for invasive or malignancy
- Any type of pregnancy:
  Miscarriage, abortion, ectopic pregnancy, preterm or term pregnancy
- Bhcg >100,000



Complete Moles

Generalized hydrops and large vesicles

Today, currently evacuated between 6-10 weeks

Absence of p57 (KIP2) immunostaining

Chromosomes all paternal
but maternal mitochondrial DNA

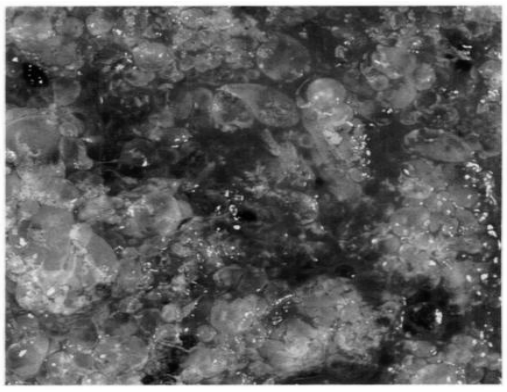
Malignant transformation occurs in 16% of CHM

p57

- Paternally imprinted, maternally expressed
- The decidua comes from mom and if negative, more likely to be complete

- p57 = Complete
+ p57= Partial or other GTD

Popiolek DA, Yee H, Mittal K, et al. Hum Pathol 2006; 37:1426-1434



Partial Moles

Triploid conceptions

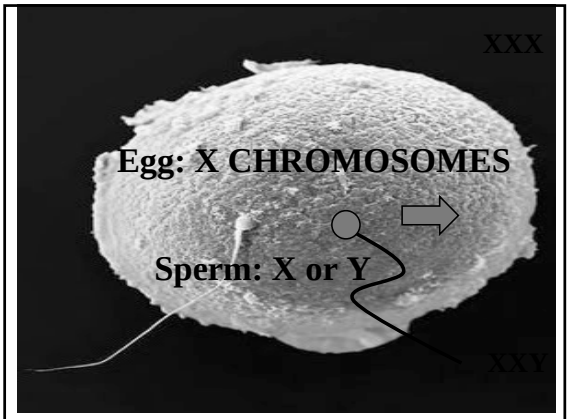
Embryo survives until about the 8th week of gestation

Usually presents as a miscarriage

p57 positive

High α free BHCG, but overall lower BHCG

Infrequently associated with excessive uterine size, ovarian cysts



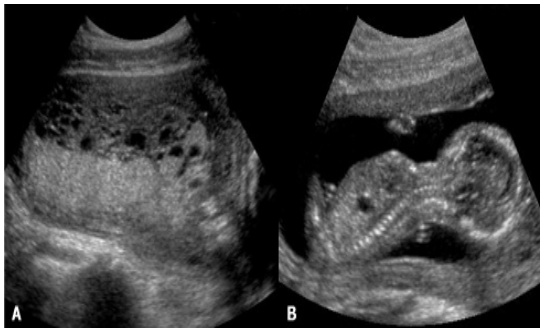
Partial Moles

Only type of GTD with potential:
fetus, amniotic fluid, fetal cardiac activity

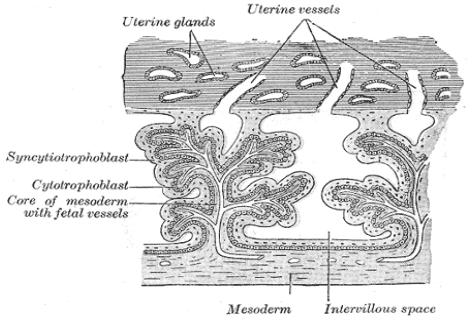
High rate of intrauterine death related to triploidy

Misdiagnosed as an incomplete or missed abortion

Partial Moles

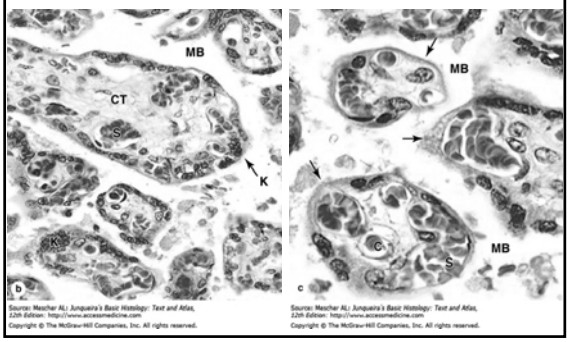


Syncytiotrophoblasts and Cytotrophoblasts



Gray's Anatomy . Secondary chorionic villi. Diagrammatic. (Modified from Bryce.)

Placenta



Intermediate trophoblasts

- Differentiate towards an invasive phenotype
- Leaves the placenta entirely
- Interdigitate through the extracellular spaces of the endo- and myometrium
- The endpoint for this invasive behavior is penetration of maternal spiral arteries

Choriocarcinoma

- Spontaneously from the placenta of a term pregnancy, abortion, or ectopic pregnancy
- Cytotrophoblasts and syncytiotrophoblasts, no chorionic villi
- Approximately
  - 1 in 16,000 normal gestations
  - 1 in 15,000 abortions
  - 1 in 40 complete molar pregnancies.

Placental-Site Trophoblastic Tumor (PSTT)

Rare, slowly-growing malignant tumors from the placenta

<0.2 percent of all cases of GTD

Months to years after a term gestation

Intermediate trophoblasts

Compared to the other GTDs, the serum hCG concentration in PSTT is relatively low relative to the tumor volume

More than 30 % metastatic disease at presentation

Epithelioid Trophoblastic Tumor (ETT)

Rare variant of PSTT

Can present many years after full term delivery

Gestational Trophoblastic Neoplasia

NOT GTD
Persistent, invasive, or metastatic moles
Gestational choriocarcinomas
Placental-site trophoblastic tumors (PSTT)

Criteria for the Diagnosis of Gestational Trophoblastic Neoplasia*

4 values or more of plateau of hCG over at least 3 weeks (days 1, 8, 15, 22)

A rise of hCG of 10% or greater for 3 values or longer over at least 2 weeks (days 1, 8, 15)

Persistence of hCG 6 months after mole evacuation

Choriocarcinoma or PSTT

*rule out new IUP

More Stringent Criteria in US

Lost to follow-up:

80% do not comply with follow-up
15% lost to follow-up prior to remission

Invasion

15 % invasive disease after evacuation of a molar pregnancy

Characteristics that increase the likelihood of GTN:

- Large theca lutein cysts (≥6 cm)
- Excessively enlarged uterus for dates
- Age over 40
- Previous GTD
- Initial hCG >100,000 mIU/mL
- Presence of hyperplasia or atypia on histology

Uterine Invasion

AV Malformations

GTD lesions are highly vascular

associated with arterial-venous malformations (AVM)

Thus, hemorrhage is common

Metastases

4 percent have metastatic disease

Sites of Metastases:

- Pulmonary
- Liver
- Brain
- Vagina
- Other: Spleen, GI

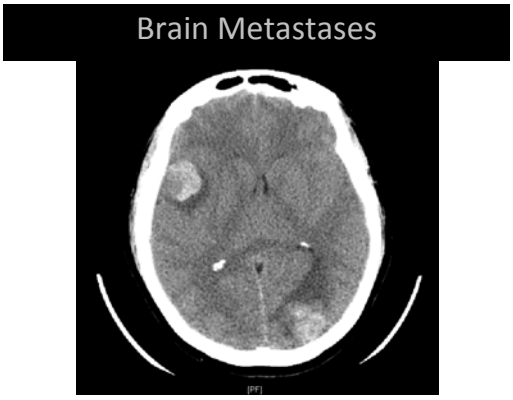
Pulmonary Metastases

Liver Metastases

Splenic Metastasis

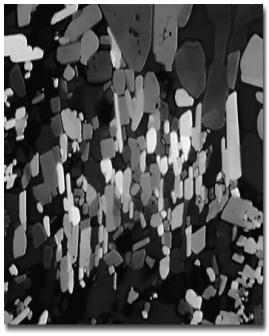
Brain Metastasis

Brain Metastases



Vaginal Metastases

- Bleeding from vaginal metastases can be controlled by vaginal packing
- Wide local excision if necessary.
- Arteriographic embolization of the vaginal branch of the hypogastric artery



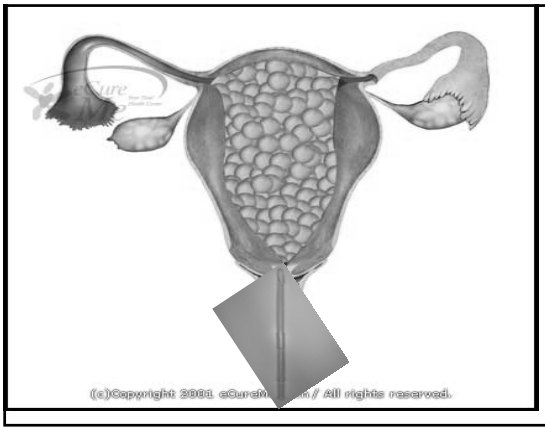
Management of GTD

Surgical evacuation
- D&C
- Hysterectomy
- Removal of Metastatic Disease

Close monitoring of the postevacuation hCG levels
- baseline within 48 hrs of evacuation
- weekly until normal

Role of Surgery

1. Uterine Evacuation
2. Excise bulky and/or resistant tumor
3. Treat complications of the disease (hemorrhage or bowel obstruction)



Prophylactic Chemotherapy

Kim et al.
- In high risk tumors, reduced the risk from 47% to 14%
- No change in outcome in low risk tumors

Limpongsanurak et al.
- Act-D with high risk reduced from 50% to 13.8%

Berkowitz et al.
- 11% of high risk complete moles developed post-molar tumor

FIGO Anatomic Staging of GTD

Stage I	Disease confined to uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lung, with or without genital involvement
Stage IV	All other metastasis

Imaging in Staging

- Post-molar GTN
  - HCG
  - CXR/Pelvic ultrasound
- Choriocarcinoma/PSTT/relapsed or drug resistant disease
  - CT scan of chest, abdomen, pelvis
  - MRI of brain
  - Role of PET scan?

FIGO 2000 Scoring

	0	1	2	4
Age	≤39	>39	-	-
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	-
Interval	<4	4-6	7-12	>12
hCG	$<10^3$	10^3-10^4	$>10^4$-10^5	$>10^5$
Largest tumor size	3-4cm	5cm		-
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
No. of metastases	0	1-4	5-8	>8
Previous failed Chemotherapy	-	-	Single drug	2 or more

Total score 0-6 = low risk
≥7 = high risk
PSTT excluded

Kohorn EI Int J Gynecol Cancer 2001, 11, 73-77

Management of Low-Risk GTD

• Initial therapy	Single-agent methotrexate Dactinomycin
• Salvage therapy	Single-agent dactinomycin Multi-agent chemotherapy Hysterectomy in selected patients

Single-Agent Therapies

METHOTREXATE

GOG 174

DACTINOMYCIN

GOG 174

MTX 30 mg/m2 IM wkly	Dactinomycin 1.25 mg/m2 IVP biweekly
CR: 53%	CR: 70%
RR Score 0-4: 58%	RR Score 0-4: 73%
RR Score 5-6: 9%	RR Score 5-6: 42%

Single-Agent Therapies

Chemotherapy regimen	Primary remission rate, %
1. MTX 0.4 mg/kg (maximum 25 mg)/d IV or IM for 5 d; repeat every 14 d	87–93
2. MTX 30-50 mg/m² IM weekly	49–74
3. MTX 1 mg/kg IM d 1, 3, 5, 7; folinic acid 0.1 mg/kg IM d 2, 4, 6, 8	74–90
4. MTX 100 mg/m² IVP, then 200 mg/m² in 500 mL D5W over 12 h; folinic acid 15 mg IM or PO q 12 h for 4 doses beginning 24 h after start of MTX;	69–90
5. Act-D 10-13 µg/kg IV qd for 5 d; repeat every 14 d	77–94
6. Act-D 1.25 mg/m² IV every 2 wk	69–90
7. Alternating MTX/Act-D regimens 1 and 5	100

Lurain. Am J Obstet Gynecol. 2011 Jan;204(1):11-8.

Single-Agent Therapies

METHOTREXATE

A) Methotrexate 1mg/kg IM days 1, 3, 5,and 7
Leucovorin 15 mg PO days 2, 4, 6, and 8 (30 hrs after the methotrexate dose)

Recycle every 14 days

B) Methotrexate 30-50 mg/m^2 IM weekly

C) Methotrexate 0.4 mg/kg/daily IM x 5 days
Recycle every 14 days

MTX

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
			CYCLE #1	D1 MTX	D2 LV	D3 MTX
D4 LV	D5 MTX	D6 LV	D7 MTX	D8 LV		
			CYCLE#2	D1	D2	D3

Single-Agent Therapies

DACTINOMYCIN

A) Dactinomycin 0.5 mg IVP daily x 5 days
Recycle every 14 days

B) Dactinomycin 1.25 mg/m^2 IVP (Pulse)
Recycle every 14 days

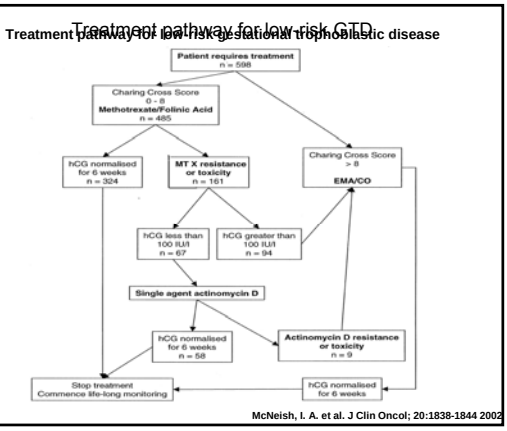
Pulse Dactinomycin

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
				CYCLE #1A D1 Act-D	D2	D3
D4	D5	D6	D7	D8	D9	D10
D11	D12	D13	CYCLE #1B D14 Act-D			

Management of High-Risk GTD

Initial therapy	EMA/CO chemotherapy Aggressive management of brain and liver metastases
Salvage therapy	EP/EMA chemotherapy Other individualized combination chemotherapy Surgical resection of solitary chemotherapy-resistant disease

Treatment pathway for low-risk GTD



McNeish, I. A. et al. J Clin Oncol; 20:1838-1844 2002

Combination Chemotherapy

MAC

EMA-CO

EP-EMA

Combination Chemotherapy

EMA-CO current favored regimen

- Favorable response rates
- Favorable toxicity profile
- Theoretical benefit of dose intensity of MTX and dactinomycin
- Inclusion of etoposide
- Ability to treat brain metastases without the use of RT

EMA-CO

EMA

Day 1

Dactinomycin	0.5 mg IVP
Etoposide	100 mg/m^2 IVPB
Methotrexate	300 mg/m^2 IVCI over 12 hrs*

Day 2

Dactinomycin	0.5 mg IVP
Etoposide	100 mg/m^2 IVPB
Leucovorin	15 mg po/IM every 12 hrs x 48 hrs, 24 hrs after start of methotrexate

CO

Day 8

Vincristine	0.8 mg/m^2 IVP
Cyclophosphamide	600 mg/m^2 IVPB

EMA-CO

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
			CYCLE #1	D1 EMA	D2 MTX	D3 LV
D4 GSF	D5 GSF	D6 GSF	D7	D8 CO		GSF
GSF	GSF	GSF	CYCLE #2	D1 EMA	D2 MTX	D3 LV

EMA-CO for High-Risk GTD

N= 272

No prior therapy (N= 151)		Prior therapy (N= 121)	
N= 140	High Risk	N= 86	Failed prior Tx
N=11	Intermediate Risk	N= 35	Relapse

Bower M, Newlands ES, et al. JCO 15(7), 1997

EMA-CO for High-Risk GTD: Response

272 consecutive high-risk patients treated

N= 12	Early deaths	5%
N= 213	Complete Response	78%
N= 16	Relapsed	8%
N= 47	Developed Drug Resistance	17%
N= 33	Salvaged with cisplatin-based	70%

Bower M, Newlands ES, et al. JCO 15(7), 1997

EMA-CO for High Risk GTD: Outcomes

- The last death due to GTD occurred 2.1 years after the start of EMA-CO
- Median time to relapse following completion of chemotherapy was 4 months

Bower M, Newlands ES, et al. JCO 15(7), 1997

EMA-CO for High-RISK GTD: Outcomes

5 year survival rate: 86.2%
(95% confidence interval, 81.9% to 90.5%)
Bower M, Newlands ES, et al. JCO 15(7), 1997

Survival: 93%
n=30
Lurain JR et al. J Reprod Med. 2006 Oct;51(10):767-72.

A single-center experience of EMA/CO chemotherapy for high-risk gestational trophoblastic neoplasia: Induction low-dose cisplatin and etoposide chemotherapy improves outcome

Objectives: After EMA/CO was 87% between 1979-1995. Determine if survival improved

Methods: GTD 1994 and 2010.

The introduction in 1994 and use of low-dose etoposide 100mg/m^2 and cisplatin 20mg/m^2 (EP) on days 1 and 2 repeated weekly as induction chemotherapy for 1-2 weeks before commencing EMA/CO was noted.

C. Alifrangis, 2011 ASCO Annual Meeting, J Clin Oncol 29: 2011 (suppl; abstr 5024)

Induction Chemotherapy

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
			CYCLE #1	D1 EP	D2 EP	D3
D4 GSF	D5 GSF	D6 GSF	D7	D1 EP	D2 EP	GSF
GSF	GSF	GSF	CYCLE #2	D1 EMA	D2 MTX	D3 LV

A single-center experience of EMA/CO chemotherapy for high-risk gestational trophoblastic neoplasia: Induction low-dose cisplatin and etoposide chemotherapy improves outcome

Results:

OS (median follow-up 4.29 years) was:

98% (9 deaths / 442 pts; 95% CI : 96.6-99.3%) in the modern

compared to:

87% (95% CI : 81.9 - 90.5%) in our previous cohort

Difference in early deaths

C. Alifrangis, 2011 ASCO Annual Meeting, J Clin Oncol 29: 2011 (suppl; abstr 5024)

A single-center experience of EMA/CO chemotherapy for high-risk gestational trophoblastic neoplasia: Induction low-dose cisplatin and etoposide chemotherapy improves outcome

Conclusions:

Overall survival following EMA/CO for GTN has improved significantly from 87% to 98% in our recent patient cohort.

Low dose EP induction chemotherapy should be routinely considered for patients with a FIGO score >8 and metastasis score >6 to minimize the risk of early deaths.

EMA-CO for High-Risk GTD: Adverse Prognostic Factors

Adverse Prognostic Factors on Multivariate Analysis

- Liver metastasis (P< .0001)
- Interval from antecedent pregnancy (P<.0001)
- Brain metastasis (P= .0008)
- Term delivery of antecedent pregnancy (P=.045)

Bower M, Newlands ES, et al. JCO 15(7), 1997

EMA-CO for High-Risk GTD: Adverse Outcomes

Secondary Malignancies

- 2 AML [one with t(9:11)(p:q23)]
- 2 Cervical cancers
- 1 gastric cancer

FUTURE LEUKEMIA 1.5%

Bower M, Newlands ES, et al. JCO 15(7), 1997

Secondary Malignancies

- 39 second tumors diagnosed
  (expected number 24.45)
- Incidence ratio 1.51 (p=.001)
- No increase in second tumors in patients treated with single agent methotrexate

Rustin GJS et al. JCO 14(10), 1996

Secondary Malignancies

• 1-4 years after Tx-	myeloid leukemia	16.6%
• 5-9 years after Tx-	colon cancer	4.6%
• 10-14 years after Tx-	melanoma	3.4%
• >25 years after Tx-	breast cancer	5.8%

Rustin GJS et al. JCO 14(10), 1996

EMA-CO

- Menstruation usually returns within 2-6 months after completing therapy
- Age at menopause decreased to 47 years
  Compared to 52 to 53 years in patients with molar pregnancies not receiving chemotherapy

Bower M, et al. Eur J Cancer 34, 1998

Management of PSTT

- Hysterectomy
- Primary chemotherapy with EP-EMA if Stage II-IV

EMA-EP Regimen

EMA

Etoposide	100 mg/m^2 IVPB
Methotrexate	300 mg/m^2 IVCI over 12 hrs
Dactinomycin	0.5 mg IVP
Leucovorin	15 mg po/IM every 12 hrs for 48 hrs, beginning 24 hrs after the start of the methotrexate infusion

EP

Etoposide	150 mg/m^2 IVPB
Cisplatin	75 mg/m^2 IVPB

Repeat EMA alternating weekly with EP to serologic remission plus a further 6-8 weeks therapy

Treatment of Brain Mets

A) Methotrexate of 1 g/m2 as an intravenous infusion over 24 hours

B) Intrathecal infusion

C) Radiation

5 year survival rate:
86.2% (95% confidence interval, 81.9% to 90.5%)

Future Pregnancy

- IF GTD, no pregnancy for 6 months.
- IF GTN, pregnancy should be avoided for 12 months?
- Recurrences are most common within the first year
- Pregnancies that occur within six months of completing chemotherapy may be at increased risk

Pregnancy Rates

97% of women who desired fertility after receiving MTX conceived,

80% if MTX-CO

46% pregnancy rates for EMA-CO

If Become Pregnant

- U/S early during the pregnancy to confirm that the pregnancy is normal.
- A serum hCG level should be obtained 6 weeks after delivery of a subsequent pregnancy to exclude repeat GTN.

Prognosis

Non-metastatic GTN has a cure rate of close to 100% with chemotherapy treatment.

Metastatic low-risk GTN has a cure rate of close to 100% with chemotherapy treatment.

Metastatic high-risk GTN has a cure rate of approximately 75% with chemotherapy treatment.

Why are outcomes so good?

- Curability because of paternal antigens on trophoblastic cells
- HLA system may be important

Follow Up

- Serum HCG levels
- Contraception !!! Cross reactivity with LH?
- Anticipate normal future pregnancies
- Evaluate all future pregnancies early with US
- Psychosocial consequences of GTD

Conclusions

- Low-risk disease can frequently be cured with methotrexate and leucovorin
- The methotrexate and leucovorin regimen has no known carcinogenic potential for inducing second tumors
- Patients with high-risk disease or those resistant to single-agent therapies need combination chemotherapy