Trophoblastic tumours

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Conflicts of interest: none to declare
GTD spectrum

**Pre-Malignant**
- Complete Hydatiform Mole
- Partial Hydatiform Mole
- Atypical placental site nodule

**Malignant**
- Invasive Mole
- Choriocarcinoma
- Placental site trophoblastic tumours/ETT

References:
- Kaur et al Int J Gyn Pathol 2015
- Sarwar et al ISSTD Toronto 2019

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Scoring to determine therapy

<table>
<thead>
<tr>
<th>FIGO SCORING</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 40</td>
<td>≥ 40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td>-</td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt; 4</td>
<td>4 – &lt;7</td>
<td>7 – &lt;13</td>
<td>≥ 13</td>
</tr>
<tr>
<td>Pre-treatment serum hCG (IU/L)</td>
<td>&lt; 10³</td>
<td>10³ – &lt;10⁴</td>
<td>10⁴ – &lt;10⁵</td>
<td>≥ 10⁵</td>
</tr>
<tr>
<td>Largest tumor size (including uterus) cm</td>
<td>&lt; 3</td>
<td>3 – &lt;5</td>
<td>≥ 5</td>
<td>-</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen, Kidney</td>
<td>Gastro-intestinal</td>
<td>Liver, Brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>-</td>
<td>1 – 4</td>
<td>5 – 8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>-</td>
<td>-</td>
<td>Single drug</td>
<td>2 or more drugs</td>
</tr>
</tbody>
</table>

Low Risk 0-6, High Risk >6 Ultra Hi Risk > 12

Kohorn et al Int J Gynecol Cancer 2000, Seckl et al Annals Oncol 2013
Low Risk Rx

Methotrexate 50mg IM noon d1,3,5,7
Folinic acid 15 mg PO 6pm d2,4,6,8

or

Actinomycin D 1.25mg/m² IV

GOG 0275 study closed early

Seckl et al Annals Oncol 2013, Schink et al ISSTD 2017, 2019
Low Risk Therapy

6 weeks consolidation

Lybol et al Gynecol Oncol 2012
Low Risk
Methotrexate/Folinic Acid  
n = 485

- hCG normalised for 6 weeks  
  n = 324
- MT X resistance or toxicity  
  n = 161

Hi Risk

- EMA/CO

67%
33%

- 300 IU/L = same  
  Sita-Lumsden et al BJC 2012
- 1000 IU/L = same  
  Seckl et al ISSTD 2017

Single agent actinomycin D

- hCG normalised for 6 weeks  
  n = 58
- hCG greater than 100 IU/L  
  n = 94

87%
13%

~100% cure rate

McNeish et al JCO 2002

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<table>
<thead>
<tr>
<th>High Risk</th>
<th>Ultra-high Risk</th>
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</thead>
<tbody>
<tr>
<td>FIGO score 7-12</td>
<td>FIGO score ≥ 13</td>
</tr>
<tr>
<td>No early deaths</td>
<td>Risk of early death</td>
</tr>
<tr>
<td>Low risk of late death</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Interval &lt; 2.8 yrs</td>
<td>Interval &gt; 2.8 yrs</td>
</tr>
<tr>
<td></td>
<td>Liver ± brain mets</td>
</tr>
<tr>
<td></td>
<td>Advanced disease</td>
</tr>
</tbody>
</table>

Low dose Etop 100mg/m2 + cisplat 20mg/m2 d1-2 wkly x 1-3
Consider adapted on-going therapy

A dental visit

May ‘09

Aug ‘09

Woman childbearing age + unexplained mets = measure hCG
High Risk Investigations

- CT chest/abdo
- MRI brain/pelvis and spine
- Doppler ultrasound pelvis
- LP to assess CSF hCG: serum hCG
- FDG-PET scan
- Histopathology (not mandatory)
- Genetics
EMA/CO

**EMA**

**Day 1**
- Dactinomycin 0.5 mg IV bolus
- Etoposide 100 mg/m² over 30 minutes
- Methotrexate 300 mg/m² over 12 hours

**Day 2**
- Dactinomycin 0.5 mg IV bolus
- Etoposide 100 mg/m² over 30 minutes
- Folinic acid 15 mg PO bid for 2 days commencing 24 hours after start of methotrexate

**CO**
- Vincristine 0.8 mg/m² (maximum 2 mg) bolus
- Cyclophosphamide 600 mg/m² over 30 minutes
- EMA and CO alternate weekly
Overall survival: EMA/CO 1995-2010
Non-gestational tumors do badly

20% relapse: how do we salvage them?

Log-rank p < 0.001
Median follow-up 4.2 years

Alifrangis et al J Clin Oncol 2013
Salvage approaches

• EP/EMA vs TE/TP: both salvage 75-80% but TE/TP less toxic
• Hi dose: salvages ~40%
• Gemcitabine/pemetrexed/capecitabine
• Surgery
• Radiotherapy - stereotactic in brain
  - whole brain is toxic
• New agents?
  - TKIs: Erlotinib/gefitinib
  - Anti-vascular: Bevasuzimab
  - Anti-hCG antibodies/vaccine
  - Anti-endoglin
  - Immune checkpoint inhibitors

Seckl et al Annals Oncol 2013, Frijstein et al Eur J Can 2019
Worley et al Gynae Oncol 2018
Pembrolizumab is active

75% (9/12) CRs incl: PSTT & ETT
All PD-L1 +ve and TIL +ve, non-responders few TILs

Ghorani et al Lancet 2017 and Seckl et al ISSTD Toronto 2019
Which GTN for immunotherapy?

TROPHIMMUN trial: cohorts A and B

- Low-risk
  - Single agent regimen (MTX, ACT-D)
  - hCG normalization
  - Resistance
  - Cohort A

- High-risk
  - Polychemotherapy EMA-CO; EMA-EP
  - hCG normalization
  - Resistance
  - Cohort B

Benoit You et al in Lyon, France trial using anti-PD-L1 antibody atezolizumab

Cohort A: 15 patients  Cohort B: 6 patients

Results expected for ASCO 2020
What about combinations?

Balancing toxicity vs efficacy vs cost

Ipilimumab
Pembrolizumab
Long-term outlook

Chemotherapy

Remission

hCG follow-up for 10 yrs

83% successful pregnancies

4% relapse

EMA/CO - hastens menopause ~ 3 yr
- No increased risk 2nd tumours

Early pregnancy
- no increase in abnormal fetus
- no increase in relapse rate

Woolas et al BJOG 1998
Bower et al Eur J Cancer 1998
Blagden et al Brit J Cancer 2002
Williams et al J Reprod Med 2014
Savage et al J Clin Oncol 2015
Tranoulis et al Int J Gynecol Cancer 2019
When to stop hCG monitoring after Rx

<table>
<thead>
<tr>
<th></th>
<th>Low risk = 3507</th>
<th>High risk = 694</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses:</td>
<td>154 (4.4%)</td>
<td>44 (6.3%)</td>
</tr>
<tr>
<td>Year 1</td>
<td>112 (73%)</td>
<td>34 (86%)</td>
</tr>
<tr>
<td>Year 2</td>
<td>19 (12%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Year 3</td>
<td>17 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Year 4</td>
<td>2 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Years 5 &amp; 6</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Year 7</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>&gt; Year 7</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Balachandran et al. Gynae Oncol 2019
Summary

• 16% CHM and 0.5-1% PHM need chemo
• Registration, pathol review and hCG essential
• Low risk: ~100% survival
• High risk (HR): >94% survival
  • Ultra HR: low dose induction EP avoids early deaths consider EP/EMA vs EMA/CO
    CNS disease: 1g/m² MTX EMA(1day)/CO ± iT MTX
• Salvage: surgery vs immunotherapy vs hi dose
• Fertility outcomes are excellent
• Stop follow-up between 3-10 years
PSTT/ETT

Compared to Choriocarcinoma:

- Slow growing
- Metastases late
- LN involvement more common
- Less chemosensitive
- Arises from intermediate trophoblast
- Less hCG
- OS ~ 80%

Schmid et al Lancet 2009, Horowitz et al Gynae Oncol 2017
Froeling et al. Br J Cancer 2019
PSTT/ETT management summary

• Diagnosis: Pathology essential
• Prognostic markers
  – > 48 months and Stage IV most important
  – < 48 months excellent outcomes
  – Others such as mitosis may become important
• Current recommended treatment
  – Local disease: hysterectomy >> focal resection
  – Metastatic disease: EP/EMA + resect residual lesions
  – > 48 months or stage IV: EP/EMA followed by immunotherapy or high dose + surgery

Support the international PSTT/ETT database: www.pstt.shef.co.uk
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PSTT/ETT Investigations

- CT chest/abdo with contrast
- MRI brain/pelvis ± spine with contrast
- Doppler ultrasound pelvis
- FDG-PET CT scan?
- Histopathology (mandatory)
- Genetics: gestational + causative pregnancy