Efficacy and Safety of Chemotherapeutic Management for Gestational Trophoblastic Neoplasia at the Philippine General Hospital: A Retrospective 5-year Review


Presented by
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Gestational trophoblastic disease

- Encompasses the histopathological entities of the benign complete and partial moles, invasive mole, and the malignant choriocarcinoma and placental site trophoblastic tumor;
- Complication of molar pregnancy, fullterm or preterm delivery, abortion, or in general, any form of pregnancy.

**DIAGNOSIS:**
- beta-hCG values reveal a plateau, a rising level or persistently elevated values in the absence of pregnancy.

**MANAGEMENT:**
- Involves a multidisciplinary approach
TREATING MOLAR PREGNANCY: Philippines

- National prevalence rate of H mole in the years 2002-2008: 2.4/1,000 pregnancies
- At the University of the Philippines- Philippine General Hospital: 14/1,000 pregnancies
- Presenting symptoms which were similar to those reported in other countries: varying amounts vaginal bleeding after a period of amenorrhea, uterine size larger than gestational age, absence of fetal heart tones, hyperemesis, toxemia
- Pelvic ultrasound is primarily used to confirm the diagnosis, and correlated with quantitative b hCG levels
TREATING MOLAR PREGNANCY: Philippines

• Histologic confirmation is mandatory in the diagnosis of H mole
• Immunohistochemistry staining with p57kip2 may be done when the histologic diagnosis is in doubt
• Further, cytogenetic studies may be done when both histologic confirmation and immunohistochemistry staining are inconclusive
TREATING MOLAR PREGNANCY: Philippines

• Management:

• Medical complications must be recognized and stabilized/treated before uterine evacuation

• Laboratory work-up: CBC with bloodtyping, urinalysis; thyroid/renal/liver function tests, chest X ray, transvaginal ultrasound, ECG

• Uterine evacuation: Suction curettage is used for those who want to preserve their child bearing capacity. For those with closed cervix, mechanical dilators are used to dilate the cervix pre-operatively;

• hysterectomy can be considered in women with completed family size
TREATING MOLAR PREGNANCY: Philippines

- Chemoprophylaxis is given to patients who are deemed “high risk” of developing GTN and those whose follow-up surveillance are doubtful
- Methotrexate; alternative: actinomycin; the prophylaxis is given only as one course
- Monitoring of hCG after evacuation: levels are taken 1 week after evacuation, then every 2 weeks thereafter. If two consecutive biweekly levels are taken, the monitoring is decreased to every month for 6 months, then discontinued.
- A reliable contraception is advised to the patient the entire time serial hCG monitoring is being done
TREATING MOLAR PREGNANCY: Philippines

- Pregnancy is allowed after 6 months of normal hcg levels. Placenta in subsequent pregnancies should also be submitted for histologic examination.
- In succeeding pregnancies, early ultrasound should be done.
- 6 weeks after delivery of every succeeding pregnancy, hcg levels are determined.

Clinical Practice Guidelines for the Diagnosis and Management of Gestational Trophoblastic Diseases, 3rd edition, 2016, PSSTD, Inc.
Gestational Trophoblastic Neoplasia: PHILIPPINES

- National prevalence have remained constant at 22.4/40,000 pregnancies
- In contrast to H mole, diagnosis of GTN is based on clinical presentation, trend in the hCG levels, and typical ultrasound findings.
- Diagnosis of Post molar GTN is made when there is a rise or plateau of the hCG levels, or a histologic diagnosis or choriocarcinoma.
- Histopathologic diagnosis is not mandatory in the diagnosis of the disease since it may be diagnosed based on clinical, radiologic, and biochemical parameters alone.
Gestational Trophoblastic Neoplasia: PHILIPPINES

• Management:
  • CBC, bhCG, liver/renal/thyroid function tests as well as imaging studies like transvaginal ultrasound, chest X ray, whole abdominal ultrasound.

• Other tests: chest CT scan requested when the chest x ray result is normal or in preparation for removal of a resistant pulmonary nodule.

• Cranial CT scan is requested for those who have lateralizing neurologic symptoms, or in patients whose pulmonary lesions measures at least 3cms.
Gestational Trophoblastic Neoplasia: PHILIPPINES

- Staging and Scoring is done using the FIGO anatomic staging and WHO prognostic scoring system.
- Chemotherapy is started after staging and scoring

- Non metastatic and Low risk metastatic disease are almost always cured with a single agent chemotherapy; methotrexate.

- Alternatively, actinomycin may be used, or is also used for those who develop methotrexate chemoresistance.
Gestational Trophoblastic Neoplasia: PHILIPPINES

- For Metastatic high-risk disease: combination chemotherapy is given: EMACO

- Adjunctive treatment: In a 10-year review: hysterectomy is the most common in 97% of cases followed by lung resection in 2% and excision of liver metastasis in 1%
Gestational Trophoblastic Neoplasia: PHILIPPINES

- Ultra-high risk GTN patients has been identified as any presentation of GTN that might be associated with early death within weeks of starting chemotherapy or poor long term survival.

- Low dose chemotherapy is given before starting standard chemotherapy is recommended for ultra-high risk GTN.

- Stage IV with brain metastasis is treated with high dose EMACO with concurrent whole brain radiation. Initial reports of success of this treatment protocol in UP-PGH showed much lower remission rate of 35% for patients initially presenting with brain metastasis and 15% in those who developed brain metastasis during or after.
Gestational Trophoblastic Neoplasia: PHILIPPINES

• Intrathecal methotrexate may be given instead of irradiation as alternative adjunctive treatment for Stage IV with brain metastasis.

• Salvage chemotherapy: EP-EMA, for those who have plateauing or rising hCG values or those with appearance of new metastasis.

• Other salvage therapy used locally: paclitaxel-cisplatin/paclitaxel-etoposide; bleomycin, etoposide and cisplatin combination.

• Consolidation courses are given after the first normal b hCG. For low risk GTN: 2 consolidation courses are given; for high risk GTN: three consolidation courses are given.
METHODS:

A descriptive retrospective study to review the chemotherapeutic outcome and drug toxicities of patients diagnosed of GTN who underwent chemotherapy admitted from January 2008 to December 2012 at Philippine General Hospital.
### 224 Cases of GTN admitted in the Philippine General Hospital (2008-2012)

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included as subjects for the study (152 cases)</td>
<td>68%</td>
</tr>
<tr>
<td>Not included as subjects for the study (72 cases)</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Incomplete chemo treatment</strong></td>
<td>18%</td>
</tr>
<tr>
<td>Home against medical advice</td>
<td>5%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>12%</td>
</tr>
<tr>
<td>Requested to transfer to other health facility</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Admitted without chemo treatment</strong></td>
<td>14%</td>
</tr>
<tr>
<td>Home against medical advice</td>
<td>4%</td>
</tr>
<tr>
<td>Mortalities</td>
<td>7%</td>
</tr>
<tr>
<td>Under remission</td>
<td>2%</td>
</tr>
<tr>
<td>Requested to transfer to other health facility</td>
<td>1%</td>
</tr>
<tr>
<td>Regimen</td>
<td>First Line</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>MTX</td>
<td>100 (88)*</td>
</tr>
<tr>
<td>ACT</td>
<td>6 (5)**</td>
</tr>
<tr>
<td>EA</td>
<td></td>
</tr>
<tr>
<td>MEA</td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td></td>
</tr>
<tr>
<td>EMACO</td>
<td>46 (45)***</td>
</tr>
<tr>
<td>EMA-PT</td>
<td></td>
</tr>
<tr>
<td>EMA-EP/EP-E MA</td>
<td>6</td>
</tr>
<tr>
<td>ETOPOSIDE</td>
<td></td>
</tr>
<tr>
<td>EACO</td>
<td></td>
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Chemotherapy Regimens Used in the Treatment for GTN
*12 patients had drug toxicities to MTX, **1 patient developed drug toxicity to ACT, ***1 patient developed EMACO toxicity.
Adverse Effects and Toxicity associated with Chemotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number of Cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>82</td>
<td>78</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>Hepatic</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Infections (Immunocompromised)</td>
<td>27</td>
<td>26</td>
</tr>
</tbody>
</table>

- Of the 152 patients included in this study, 69% (105/152) experienced adverse drug reactions at some point during their chemotherapy with their respective regimens.
Gestational Trophoblastic Neoplasia: PHILIPPINES

• Follow-up: after biochemical remission, serum b hCG is done every month for 6 months, every 2 months for another 6 months, every 3 months for the next year, then every 6 months thereafter.

• Serial radiographic/sonologic imaging is done if residual lesions are present at the end of treatment.

• Adequate contraception should be in place to avoid pregnancy during the first year following biochemical remission.
Conclusion

• These good survival rates can be attributed to three clinical characteristics of the disease:
  • very responsive to chemotherapy in almost all cases
  • very reliable tumor marker in the form of β-hCG which gives the clinician a measure of the burden of the disease;
  • risk factors that determine the response to chemotherapy have already been identified.

• Therefore, despite the spectrum of potential adverse drug reactions or toxicities that comes with chemotherapy, benefits of remission and cure will always be optimum over the accompanying risks.
Changes over the past 2 decades

- National trophoblastic society is actively educating generalists regarding prompt diagnosis of patients via holding of regular conferences

- Better support from government regarding financial assistance to indigent patient
  - Access to chemotherapeutic agents
  - Management of complications of disease and treatment
Thank you!