TÜRK JİNEKOLOJİK ONKOLOJİ DERNEĞİ
TURKISH SOCIETY OF GYNECOLOGIC ONCOLOGY

## *Gestational Trophoblastic Disease*

# *Management of low - risk Disease*

**Prof. Dr. Mehmet HARMA**
**Dr. Öğr. Üyesi Görker SEL**
Zonguldak Bülent Ecevit Üniversitesi, Jinekolojik Onkoloji Cerrahisi BD, Tr

1. Uluslararası ve 16. Ulusal Jinekolojik Onkoloji Kongresi,
21-25 Kasım 2018, Su Sesi Luxury Resort – Antalya
23 Kasım 2018, Cuma, Salon 1,
Gestasyonel Trofoblastik Hastalıklar, 16.40 - 16.50

# Low Risk GTN

- FIGO Stage I; FIGO Stage II-III:<7

Patients with low risk GTN are typically cured with **a simple intervention** (repeat uterine curettage or single-agent chemotherapy - dactinomycin/methotrexate).

**The few primary treatment failures** are often the result of **rapid transformation** of low-risk disease into more **malignant** histology (**choriocarcinoma**)

- In some reports **WHO Score 5-6** may be at an increased risk of resistance to single agent chemotherapy, with up to **70%** of these patients **require combination chemotherapy** to achieve remission.
- Patients with low risk GTN have an overall excellent prognosis with **survival rates of 100%** after treatment, albeit this may include combination chemotherapy.
- Generally **sequential therapy** is preferred, incase of resistance to first drug.
- The role of second D/C is conflicting.

# Clinical management of Low-Risk Disease Methotrexate Regimens

The first successful chemotherapeutic treatment of this disease in **1956** using methotrexate

**a. 8 day regimen**

**Charing Cross regimen**: Bagshawe reported on the Charing Cross experience with an eight-day alternating methotrexate/leucovorin combination (MTX/LVR) that was repeated every 14 days. (**MTX: 1 mg/kg; 1-3-5-7**)

8-day **Leucovorin (2-4-6-8)** was added as "rescue" from the side effects of methotrexate, a potent anti-metabolite, in particular, the dose-limiting oral mucositis

**Bagshawe protocol** remains the most commonly used regimen for low-risk disease worldwide

# MTX

**b. 5 day regimen:** MTX 0.3-0.5 mg/kg (im, iv); Five consecutive days, every two weeks.

**c. Weekly MTX**: MTX 30-50 mg/$m^2$ weekly, until normal hCG values are attained. Long duration of therapy.

**d. High dose MTX:** Inf of 100 mg/$m^2$, followed by 12 hrs cont. inf at 200 mg/$m^2$; 15 mg FA p.o. begin 24 hrs after initial MTX dose cont every 12 hrs for 6 doses. Short duration of therapy. Lower complete remission rate.

# Clinical management of Low-Risk Disease Methotrexate Regimens

More recently, a number of different MTX regimens have been used to treat low-risk GTN.

- Weekly oral methotrexate
- Weekly intra-muscular methotrexate
- Methotrexate infusion with LVR
- Weekly methotrexate infusion with LVR
- Loading dose of parenteral methotrexate followed by weekly oral drug.
- 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)

# Clinical management of Low-Risk Disease
# Dactinomycin Regimens

Dactinomycin has been successfully used to treat low-risk disease. It binds to DNA and inhibits RNA synthesis. The mechanism of action of dactinomycin is as a Nucleic Acid Synthesis Inhibitor, and Protein Synthesis Inhibitor. Dactinomycin is a chromopeptide antineoplastic **antibiotic** isolated from the bacterium Streptomyces parvulus.

**a.** The original regimen was effective and consisted of a **5-day course of daily intravenous injections (0.4 mg/kg/day; 10-12 mcg/kg/day) Every other week.**

This regimen was associated with significant **toxicity** including; alopecia, severe nausea/vomiting, truncal rash, radiation-recall and gastro-intestinal mucositis.

There was a potential for significant skin slough if interstitial injection occurred.

**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.

# Clinical management of Low-Risk Disease Dactinomycin Regimens

**b. "Pulsed" dactinomycin:**

This dactinomycin regimen (intravenously bi-weekly at 1.25 mg/m2 with each dose was capped at 2 mg) was both more efficacious and more cost effective than existing methotrexate regimens.

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

# Methotrexate vs. Dactinomycin

- Five-day dactinomycin was determined to be the better treatment for low-risk patients.
- MTX and Act-D are associated with **hematological toxicity**, both excreted by **Kidneys**. **MTX** is **hepatotoxic**.
- 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
- Patient satisfaction was higher among the patients who received first line dactinomycin

# Other First-Line Chemotherapeutic Options
# Etoposide

- 100 mg/$m^2$ iv, Daily for 5 days; every 10 days.
- **Secondary malignancies:** Leukemia, breast-colon cancer, melanoma

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

1-2% dose-dependent risk of late-developing second malignancy, typically acute myelogenous leukemia

# Other First-Line Chemotherapeutic Options
## 5 Fluorouracil

- In 1984 Song reported on the extensive Chinese experience with 5-FU at the Peking Union Hospital.
- 30 mg/kg/day for 10 days.
- The drug was inexpensive and, using a 28-day cycle,
- Song 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.

## Single-agent regimens for low-risk gestational trophoblastic neoplasms (GTN)

| Methotrexate (MTX) regimens* | Primary remission rates (%) |
|---|---|
| 1) MTX five-day regimen: 0.3 to 0.5 mg/kg IV or IM daily for five days every two weeks (maximum 25 mg per dose) | 87 to 93 |
| 2) MTX weekly regimen: 30 to 50 mg/m$^2$ IM weekly | 49 to 74 |
| 3) MTX-Leucovorin¶ eight-day regimen: | 74 to 90 |
| MTX 1 mg/kg IM or IV on days 1, 3, 5, and 7 | |
| Leucovorin¶ 15 mg orally on days 2, 4, 6, and 8 given 24 hours after each MTX dose | |
| 4) High-dose IV MTX-Leucovorin¶ | 69 to 90 |
| MTX 100 mg/m$^2$ IV over 30 minutes followed by | |
| MTX 200 mg/m$^2$ IV infusion over 12 hours | |
| Leucovorin¶ 15 mg every 12 hours in six doses IM or orally beginning 24 hours after starting MTX | |
| **Dactinomycin regimens (Vesicant: If administered peripherally, give through free-flowing IV)** | |
| 1) Dactinomycin 10 to 12 micrograms/kg IV push daily for five days | 77 to 94 |
| 2) Dactinomycin 1.25 mg/m$^2$ IV push every two weeks | 69 to 90 |
| **Sequential chemotherapy** | **100** |

# Therapy-Monitoring

- After complete remission is attained, consolidation therapy is applied to prevent relapse; consisting of 3 courses of the last effective regimen.
- **Monitoring:** Weekly serial hCG measurement.
- **Remission:** 3 consecutive normal hCG values.
- **Persistant disease:** Increase or plateau in 2 consecutive hCG values over a two week interval.
- After remission, hCG values are measured every month for one year.
- Recurrence rate is 5-10%.

# Surgery

**Hysterectomy** decreased the likelihood that patients with non-metastatic low-risk disease would require chemotherapy from 20 to 4%.

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.

# 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.
- Cochrane review on the subject of prophylactic treatment.
- 3 randomized trials in the literature, two involving methotrexate. All the patients in the 3 studies had had a prior complete mole.

# Prophylactic chemotherapy

- **Prophylactic MTX was found to decrease the likelihood of subsequent chemotherapy** (RR 0.37; p< 0.00001)
- The studies were all of *low methodologic quality*.
- 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.
- **Generally speaking, the practice has not found general favor and is currently only offered to the occasional patient at high risk for default**

# Management of Relapsed Low Risk Disease

- Cochrane review on recurrent/resistant low risk GTN
- As long as a patient still had low risk disease, treatment with the alternate drug (ACT-D or MTX) was effective in many patients.
- However, the study did not recommend whether second line regimen should be 1,  5 or 8 days in length.
- Patients treated for relapsed disease should be followed, at least monthly, for a minimum of 12 months.

Osborne R. Low risk gestational neoplasia. in GTD Book, Gestational Trophoblastic Disease 4th ed. 2015, Eds: Hancock BW, Seckl MJ, Berkowitz RS

# Thank You