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OPERATIONAL RESEARCH

Hospital Based Clinical Protocol for the Management of Gestational Trophoblastic Disease at Maternity and Women's Hospital

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Abstract

An operational research has been carried out to fill up gap in the practice of managing gestational trophoblastic disease within the hospital. Literature review, hospital practice record and series of focus group discussions were the primary mode of methodology. A simplified flow chart form of clinical practice protocol has been prepared.

Key words: Gestational trophoblastic disease, Clinical protocol, Operational research

Introduction

Gestational Trophoblastic Disease (GTD) is a major bulk of gynecological oncology cases admitted in the hospital. This is the only tumor which can be cured by simple and cheap drug regimen. Patients with malignant nonmetastatic or metastatic low-risk gestational trophoblastic neoplasia have an almost 100% probability of cure with chemotherapy. The probability of cure after chemotherapy for patients with metastatic high-risk gestational trophoblastic neoplasia is approximately 75%. The probability of a late recurrence after the patient has been in remission (normal serum β-hCG titers) for 1 year is less than 1%. Despite this fact the management pattern at the study site was not uniform and not matched from one unit to another due to lack of definite institutional protocol. For every case and type of gynecological cancer we need to have discussion for optimal management, follow up and referral of the patient. Oncological case management always runs with the series of intervention packages for fairly long duration of treatment period. It's ongoing by cycles of treatment for months to years. If we do not have a uniform working guideline in the hospital, it will be very difficult for further management and to identify the place of improvement as well as for the comparison purpose among different institution. This gap was sufficient base to prompt an operational research at the workplace.

Rationale: Optimal care for the gestational trophoblastic tumor, as in other types of cancers, needs multidisciplinary intervention at some steps of sequential management modalities. Diagnostic facilities are not available at a single institution. Treatment options like surgery, chemotherapy, radiotherapy and palliative care sites are also scattered. Outpatient consultation schedule is fixed day for each unit at the hospital. Getting serum tumor marker (β-hCG) reports and then getting consultation will usually result in a lag of one or two weeks. These all practical obstacles justify us to make a client friendly protocol without contradicting standard practice of resourceful set up. Burden of GTD was 3.2 and 5.1 per thousand live births at this hospital 12 and 5 years ago respectively. The magnitude of disease detection has been increasing annually. Continuity of treatment was not there, many of the defaulters noted and detail records available were limited.

Expected outcome: - A clinical management protocol has been developed with consensus from gynecologic oncology group and tumor board of the hospital. Even

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during the process the upcoming protocol has been started to follow with intra hospital referral and opinion sharing. This research project has come out with a practical, simple and cost effective treatment protocol to be followed by all in hospital practice. Serum tumor marker (β-hCG) testing has been started in the hospital but yet to make more frequent.

Methodology

Paropakar Maternity and Women's Hospital was the site of research at Thapathali, Kathmandu, Nepal. Existing records of hospital practice were surveyed. The existing guidelines in the country (like NESOG protocol) and abroad (like FIGO, RCOG, SOGC protocols) were studied. Series of meetings and focus group discussions were held with the radio-oncology department of Bir Hospital and the tumor board of this hospital. Tumor board comprises of oncology group of the hospital, pathologist, medical oncologist and radio/medical-oncologist. Management steps were modified as relevant to our population and based on available investigation and treatment modalities. There were altogether five meetings for focus group discussion with the same group for every steps of management beginning from 2009 November to 2010 May. Finally the result was disseminated in a regular CME (continuing medical education) schedule at the hospital for final endorsement. Research protocol was approved by hospital research committee (institutional review committee) and hospital director. There was no any ethical violence and anything to declare financially till the end of process.

Result

The first edition of hospital based clinical management protocol has been developed. Protocol has been abbreviated as 'MtyProtocol-GTD.V-2010'. It is ready to use and publish for regular practice in the hospital. WHO Scoring System Based on Prognostic Factors, FIGO staging system and WHO classification of trophoblastic disease as pre-malignant (Partial and Complete Molar Pregnancy) and malignant (Invasive mole, Choriocarcinoma and Placental site trophoblastic tumors) forms were adopted. All protocol steps are illustrated in the flow chart form so that it would be easy to adopt clinically.

FIGO Anatomic Staging of Gestational Trophoblastic Tumors:

- Stage I (a, b, c): - Disease confined to the uterus
- Stage II (a, b, c): - GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
- Stage III (a, b, c): - GTN extends to the lungs, with or without known genital tract involvement
- Stage IV (a, b, c): - All other metastatic sites (brain, liver)

N.B.

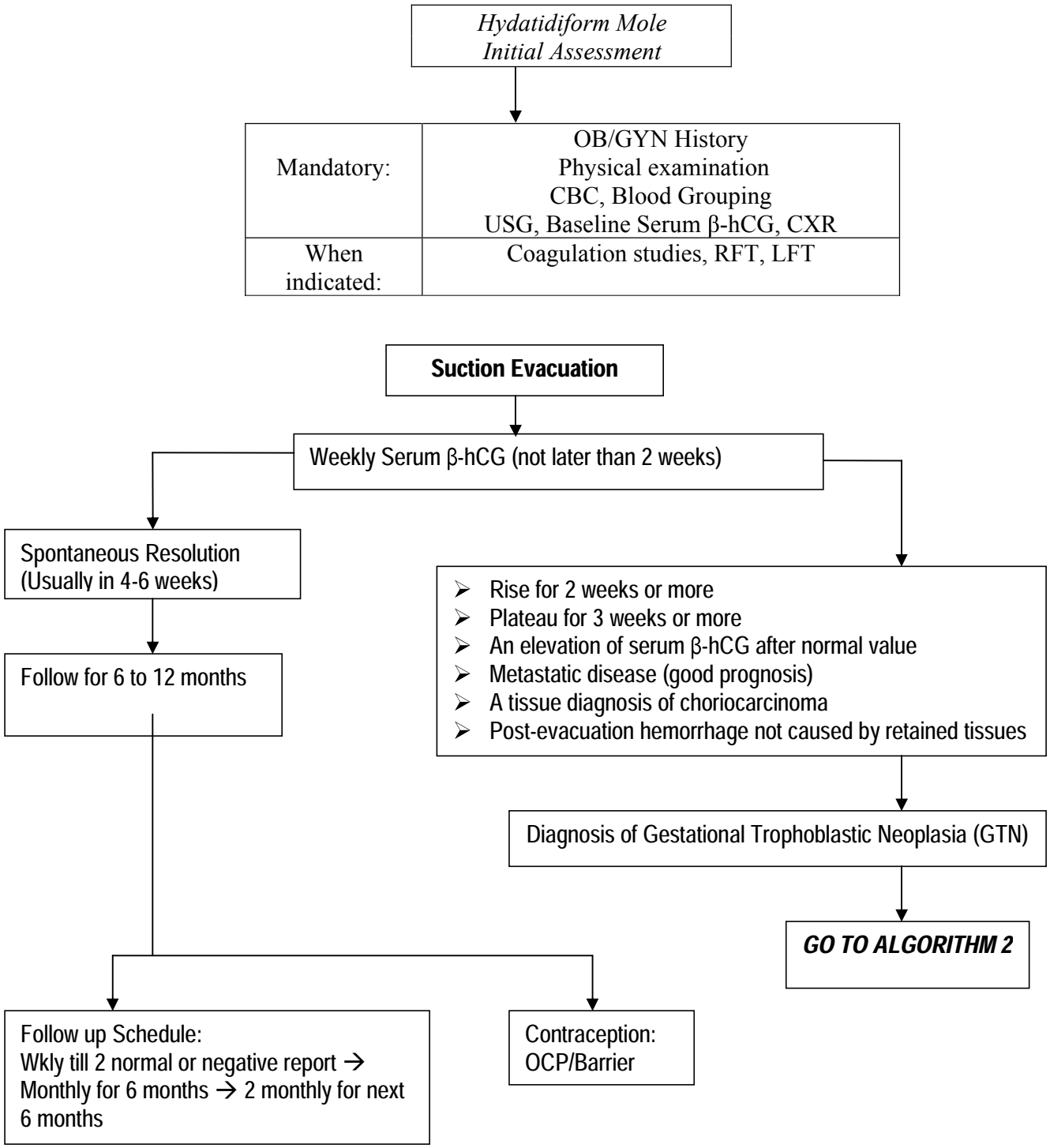
- a= without risk factors, b= with one risk factor, c= with two risk factors.
- Risk factors affecting staging include the following: (i) human chorionic gonadotrophin >100, 000 mIU/ml and (ii) duration of disease longer than 6 months from termination of antecedent pregnancy.
- The following factors should be considered and noted in reporting: (i) prior chemotherapy has been given for known gestational trophoblastic tumor, (ii) placental site tumors should be reported separately, and (iii) histologic verification of disease is not required.

Table 1. WHO Scoring System Based on Prognostic Factors

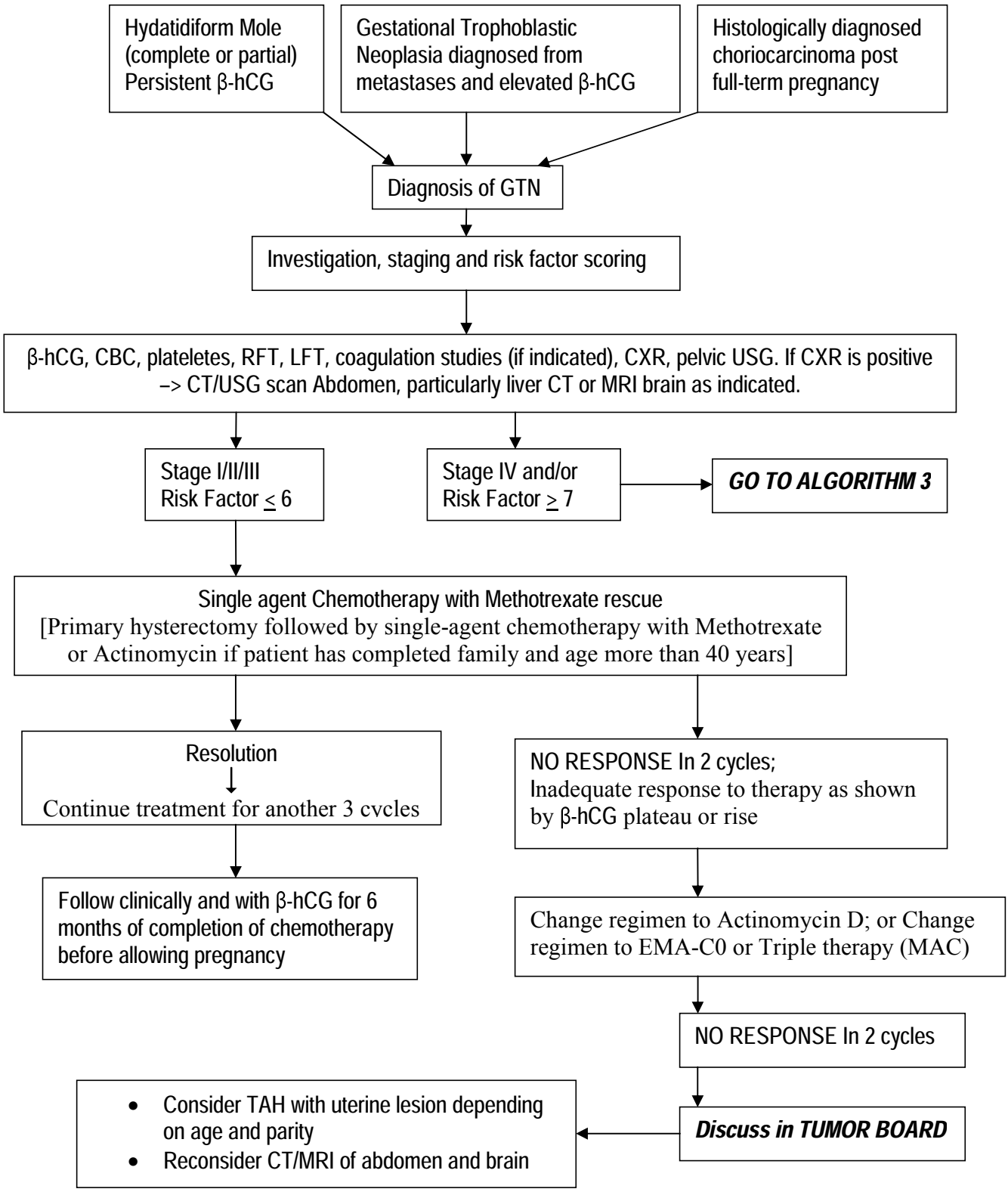
SN	*Prognostic Factors*	0	1	2	4
1	Age (in years)	<40	≥40	-	-
2	Antecedent Pregnancy	H.Mole	Abortion	Term	-
3	Interval months from index pregnancy	<4	4-6	7-12	>12
4	Pretreatment hCG (mU/ml	$< 10^3$	10^3 - 10^4	$> 10^4$ - 10^5	$> 10^5$
5	Largest tumor size including uterus	-	3 - 4 cm	≥ 5 cm	-
6	Site of metastases	Lung	Spleen, Kidney	GIT	Brain, Liver
7	Number of metastases identified	-	1-4	5-8	>8
8	Previous chemotherapy	-	-	Single drug	≥2 drugs

NB: *- Vaginal metastasis should be noted though not included in scoring.*
-The incidence of choriocarcinoma increases with age and is 5-15 times higher in women 4 years and older than in younger women.

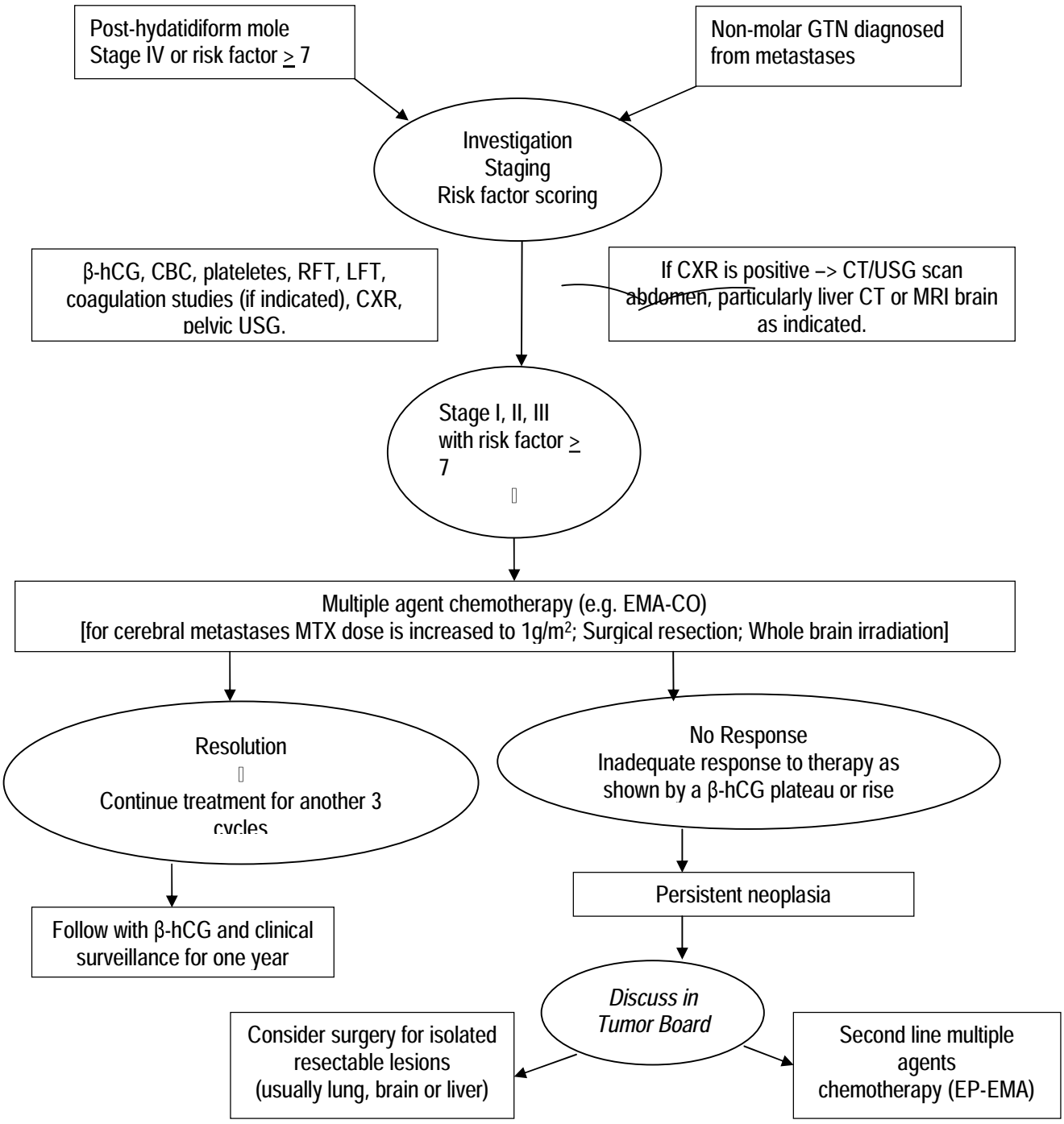
Algorithm 1: Protocol for the management of Gestational Trophoblastic Disease:



Algorithm 2: Guidelines for the Management of Trophoblastic Neoplasia:



Algorithm 3: Guidelines for the management of Trophoblastic Neoplasia:



Placental site trophoblastic disease (PSTT):

When the disease is limited to the uterus, curative treatment can be achieved with hysterectomy alone. For patients with disseminated disease treatment with EP/EMA chemotherapy, this is continued for 6-8 weeks after the normalisation of the β-hCG level. Following successful chemotherapy treatment, hysterectomy is usually recommended.

Chemotherapy Regimens

A. Single-agent chemotherapy for low risk trophoblastic neoplasia (Score ≤ 6).

1. Methotrexate-Citrovorum Factor Rescue Protocol (repeated every 2 weeks).

DAY	THERAPY
1,3,5,7	MTX, 1 mg/kg, IM
2,4,6,8	Folinic acid, O.1 mg/kg, IM

2. Actinomycin-D, 12 micrograms/kg IV daily for 5 days, repeated every 2 weeks.

B. Current multi-agent chemotherapy for high-risk GTN, EMA-CO (Score ≥ 7).

Etoposide (VP-16), Methotrexate, Actinomycin D, alternating weekly with Cyclophosphamide and Oncovin (vincristine) EMA-CO is administered on a weekly basis with anticipated cycling between each course of 14 days.

Day 1 (A)	Actinomycin D	500 micrograms IV push IV.
	Etoposide	100 mg/m^2 over 30-50 minutes
	Methotrexate	100 mg/m^2 IV infusion over 1 hour and then
	Methotrexate	200 mg/m^2 IV infusion over 12 hours by pump.
Day 2 (A)	Actinomycin D	500 micrograms IV push IV
	Etoposide	100 mg/m^2 over 30-50 minutes
	Folinic Acid	15mg IV push Q 6 hours for 8 doses beginning 24 hours after Methotrexate bolus. Some physicians administer the Folinic acid Q 12 hours for 4 doses orally 15 mg commencing 24 hours after Methotrexate.
Day 8 (B)	Vincristine (Oncovin)	1 mg/m^2 IV
	Cyclophosphamide	600 mg/m^2 IV.

NOTE

1. Filgrastim may be administered if needed. Note that this must be started 24 hours after chemotherapy and then be stopped 24 hours before Chemotherapy.

2. If the creatinine is greater than 2.0, creatinine clearance should be done prior to therapy and should be 50 or more.

3. Cycles are repeated on day 15 of cycle.

4. Chemotherapy is administered when WBC is greater than 3000 per cc. Granulocytes are greater than 1500 per cc. Platelets are greater than 100,000 and a Grade 3 gastrointestinal infection and mucositis morbidity has cleared. If toxicity necessitates a delay in course B for longer than 6 days, course A is recycled.

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