CASE REPORT:

Characteristics of gestational thropoblast tumor in Dr. Soetomo Hospital, year 2015-2017

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ABSTRACT

Objectives: To report the characteristics of the patients of Gestational Trophoblastic Neoplasia (GTN) and its management at Dr. Soetomo Hospital, Surabaya, Indonesia.
Case Report: There were 41 cases GTN at dr. Soetomo hospital within 3 years, data were collected from January 2015 to December 2017, which are 11 cases develop drug resistance.
Conclusion: GTN is a chemosensitive neoplasia but can also experience resistance to chemotherapy. It is important to monitor the levels of beta-HCG for at least 12 months before the patient can get pregnant again.

Keywords: Gestational Trophoblastic Neoplasia; Gestational Trophoblastic Disease; Hydatidiform Mole; Choriocarcinoma; Placental Site Trophoblastic Tumor; Epitheloid Trophoblastic Tumor; beta-HCG

ABSTRAK

Tujuan: Melaporkan karakteristik pasien Tumor Trofoblas Gestasional (GTN) dan tatalaksananya di RSUD Dr. Soetomo, Surabaya, Indonesia.
Laporan Kasus: 41 kasus GTN di rumah sakit umum daerah (RSUD) dr. Soetomo dalam kurun waktu 3 tahun (Januari 2015 – Desember 2017), dimana didapatkan 11 kasus GTN yang resisten kemoterapi.
Simpulan: GTN merupaka neoplasia yang bersifat kemosensitif akan tetapi dapat juga mengalami resistensi pada pemberian kemoterapi. Pemantauan kadar beta-HCG penting untuk dilakukan minimal selama 12 bulan sebelum pasien boleh hamil kembali.

Kata kunci: Tumor Trofoblas Gestasional; Penyakit Trofoblas Gestasional; Mola Hidatidosa; Koriokarsinoma; Placental Site Trophoblastic Tumor; Epitheloid Trophoblastic Tumor; beta-HCG

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INTRODUCTION

Gestational Trophoblast Tumor (GTN) is a malingnant form of Gestational Trophoblast Disease (GTD). GTD is a disease in pregnancy characterized by abnormal proliferation of the placenta and hydrophic changes in the corialis villi. Based on the course of the disease, GTD is divided into two namely premalignant and malignant.[1-5] This premalignant form of GTD is called GTN, which includes Invasive Mola, Choriocarcinoma, Trophoblastic Tumor Site (PSTT), Trophoblastic Tumor Epitheloid Tumor (ETT), and persistent or elevated levels of beta-HCG in the Hydatidiform Mole. While complete and partial hydatidiform mola are included in the premalignant GTD category. The incidence of hydatidiform mole and choriocarcinoma differs between in Asia and western countries where the incidence of Mola and Coricarcinoma is more common in Asia, which is 63-202 per 100,000 pregnancies. The incidence of choriocarcinoma in America is 19 per 100,000 pregnancies.[5-9]

In 1969 there was a high mortality due to GTN due to unknown diagnosis and therapy, but at this time GTN is included in chemosensitive neoplasia so that the cure rate is high and also the reproductive function of GTN patients can return again. Based on data in Dr. Soetomo from January 2015 to December 2017, there were 41 cases of GTN where resistance was found in 11 cases. In this report we will discuss the characteristics of GTN patients and their management in Dr. Soetomo.

CASE REPORT

In this case report, the number of deliveries between January 2015 to December 2017 was 2,876 deliveries. Thus the case of Gestational Trophoblast Tumor has a percentage of 1.6%. In the table below we attach the characteristics of each GTN patient. Data based on maternal age shows that the most age of GTN is between 30-39 years with a total of 19 (46.3%) cases. The distribution of parity in GTN cases was 9 (22%) nulliparous and 32 (78%) multiparous. In the case of GTN, it was more common in multiparas (table 2).

Most of the GTN cases were referral cases in which as many as 39 (95%) cases. From 41 cases, there were 21 (51%) cases of low risk GTN and 20 (49%) cases (table 2). Anatomical Pathology Results of GTN patients at RSUD Dr. Soetomo was mostly complete hydatidiform mole in 21 (53%) cases, partial hydatidiform mole in 5 (13%) cases, invasive mola in 6 (24%) cases, and choriocarcinoma in 8 (20%) cases (table 1).

Table 1. Distribution of Anatomical Pathology Results for GTN Patients

AP Outcome	Total	(%)
Complete mola	21	53%
Parrial mola	5	13%
Invasive mola	6	24%
Coriocarcinoma	8	20%

Table 2. Characteristics of GTN patients in RSUD dr. Soetomo

Variabel	Jumlah	%
Age		
< 20	3	7.3%
20-29	10	24.3%
30-39	19	46.3%
≥ 40	9	21.9%
Mean : 32.17 ± 8.3 th		
β-HCG		
< 100	1	2%
100 -<1.000	0	0%
1000 -<10.000	6	15%
10.000 -<100.000	6	15%
100.000 -1.000.000	26	63%
>1.000.000	2	5%
Mean : 365.603 ± 411.119.15 IU/ml		
Length of treatment		
< 4 weeks	1	2%
4- <8 weeks	0	0%
8- <12 weeks	2	5%
12 -<16 weeks	7	17%
16 -<20 weeks	13	32%
20 -<24weeks	6	15%
24 -<28 weeks	5	12%
28 -<32 weeks	5	12%
32 -<36 weeks	1	2%
≥ 36 weeks	1	2%
Mean :19.5 ± 7.2 weeks		
Parity		
Nulliparous	9	22%
Multiparous	32	78%
Pregnancy history		
Mola	3	10%
Abortion	11	34%
Aterm pregnancy	18	56%
AP outcome		
Complete mola	21	51.2%
Partial mola	5	12.2%
Invasife mola	6	14.6%
Coriocarcinoma	8	22%
WHO scores		
< 7	21	51%
≥ 7	20	49%
Therapy		
Single agent chemotherapy	21	51.2%
Combined chemotherapy	9	22%
Resistant	11	26.8%
Line 2+ chemotherapy	5	45.4%
Histerectomy	6	54.6%
Line 2 chemotherapy		
Contraceptives		
Oral	5	12%
DMPA	18	44%
IUD	3	7%
No contraceptives	15	27%

The distribution of initial complaints in TTg patients was vaginal bleeding by 32 (78%), no menstruation by 6 (15%), and decreased consciousness in 3 (7%) cases (table 3). All TTg patients who were referred from outside RSUD Dr. Soetomo had been curetted or laparotomy in the initial referral hospital. Most underwent mole curettage 1 time in 33 (92%) cases and 3 (8%) cases had 2 mole curette. The referred GTN patients had a reason to refer to that? Levels of beta-HCG were persistent in 28 (78%) cases and increased in 8 (22%) cases. In the case of referral that has been carried out by laparotomy as many as 2 (67%) cases were not examined levels of -HCG.

Table 3. Distribution of Initial Complaints of GTN Patients

Complaints	Total	(%)
Bleeding	32	78%
No menstruation	6	15%
Decreased consciousness	3	7%

-HCG levels of GTN patients in Dr. Soetomo has the most between 100,000-1,000,000 IU / ml in 26 (63%) cases and found 1 patient with complete hysterectomy Mola Hidatidosa with a level of beta-HCG <100 IU / ml (table 4).

Table 4. Distribution of beta-HCG levels

β-HCG level	Total	(%)
<100	1	2%
100-<1.000	0	0%
1000-<10.000	6	15%
10.000-<100.000	6	15%
100.000-1.000.000	26	63%
>1.000.000	2	5%

From 41 GTN cases we got 4 (10%) cases with metastasis, 3 (75%) cases with pulmonary metastases and 1 (25%) with vaginal metastases (table 5).

Table 5. Metastasis Distribution of GTN Patients

Metastasis	Total	(%)
Lung	3	75%
Vagina	1	25%
Liver	0	0%
Brain	0	0%

Symptoms of hyperthyroidism often accompany GTN because the receptor subunit a on beta-HCG resembles a TSH receptor. In the case of GTN we got 7 (17%) cases of hyperthyroid symptoms. Symptoms of hyperthyroidism can be followed by severe preeclampsia in 2 (29%) cases of hyperthyroidism and severe preeclampsia (table 6).

Table 6. Symptoms of Hyperthyroidism in GTN Patients

Hyperthyroid symptoms	Total	(%)
Yes	7	17%
No	34	83%

Management of GTN patients at RSUD Dr. Soetomo found 21 (51%) received MTX chemotherapy, 9 (22%) cases received EMACO, and 5 patients underwent hysterectomy after chemotherapy. (table 7).

Table 7. Distribution of GTN Patient Therapy

Therapy	Total	(%)
MTX LD	21	51%
MTX LD-EMACO	3	7%
MTX LD-EMACO-EP EMA	1	2%
EMACO	9	22%
EMACO-EP EMA	2	5.5%
EMACO-Histerectomy	2	5.5%
EMACO-EP EMA-Histerectomy	3	7%

We found 11 cases of GTN that had resistance so they had to get second-line chemotherapy or operative measures in the form of hysterectomy. After getting chemotherapy we got 6 cases of GTN successfully being pregnant again, namely 2 (33%) high risk GTN cases and 4 (67%) low risk GTN cases (table 8).

Table 8. Post-GTN Pregnancy

GTN type	Total	(%)
High risk GTN	2	33%
Low risk GTN	4	67%

Diagnosis

The diagnosis of GTN is done by taking an history and the initial symptoms of a GTN patient are vaginal bleeding or no menstruation. On physical examination found signs of pregnancy with uterine enlargement does not match the period of pregnancy. From the results of supporting examinations, it was found that the levels of beta-HCG were increased and the results of ultrasound that showed a mass in the uterine cavity resembled a wasp's nest ("Honey Comb"). In 2002, FIGO (International Federation of Gynecology and Obstetric) grouped GTN by stadium and scoring. This grouping is important in the management of GTN patients.

Table 9. GTN Staging

FIGO anatomic staging for gestational trophoblastic neoplasia

GTN	Gestational trophoblastic neoplasia
Stage I	Disease confined to the 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 lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

GTN patients with modified WHO FIGO scores <7 are categorized as low risk and scores> 7 are categorized as high risk GTN.

Table 10. GTN Scoring

Table 4
Modified WHO prognostic scoring system as adapted by FIGO

Scores	0	1	2	4
Age	<40	>40	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4	4–7	7–13	>13
Pretreatment serum hCG (IU/L)	<1000	<10,000	<100,000	>100,000
Largest tumor size (including uterus)	–	3–<5 cm	>5 cm	
Site of metastases	Lung	Spleen/kidney	GI	Liver/brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy			Single drug	2 or more drugs

Management

The management of GTN patients is carried out based on WHO scores whether including low risk or high risk. In low risk GTN patients, single agent chemotherapy is given, namely low dose MTX (Methotrexat) or Actinomycin D. Whereas in high risk GTN patients, multi agent chemotherapy is given with EMACO (Etoposide-Methotrexat-Actinomycin and Cyclofosfamide). If the MTX administration is found to have resistance marked by elevated or persistent ß-HCG levels, chemotherapy replacement is carried out as in the high risk GTN. And if there is resistance to the administration of EMACO then chemotherapy is replaced using EP-EMA where Cyclofosfamid is replaced by Cisplatin.[10-12]

Operative action on GTN patients is done by looking at the amount of parity and level of patient compliance. Hysterectomy is only performed on patients who have sufficient parity and it is important to remember that hysterectomy does not eliminate the risk that GTN will reappear. There is still a risk of 3.5% in GTN patients who have had a hysterectomy. For GTN with cerebral metastasis, craniotomy and radiation can be performed. Monitoring of ß-HCG levels in GTN patients is continued until a minimum of 12 months where ß-HCG levels are examined every 1 month in the first 6 months and every 2 months in the second 6 months. The use of combined oral contraceptive pills is also a contraceptive choice in GTN patients.[13,14]

DISCUSSION

Characteristics of GTN Patients in RSUD Dr. Soetomo in 2015-2017

Based on the characteristics we get, it can be concluded that the most cases of GTN were obtained at the age of 30-39 years, this is in accordance with the theory proposed by Altieri, 2003. We did not get a significant relationship between the types of GTN and the patient's age. Patients aged <20 years or> 40 years increase the risk of GTN although it is not significant. A history of term pregnancy has a strong relationship with the occurrence of hydatidiform mole where a history of term pregnancy reduces the risk of complete hydatidiform mole. We also did not get a significant relationship between pregnancy history with partial hydatidiform mole, invasive mole, and choriocarcinoma. In addition, it was found that GTN was more common in multiparas

Management of GTN Patients in RSUD Dr. Soetomo

Management of GTN patients at RSUD Dr. Soetomo is the same as that stated in the literature, namely GTN is grouped based on WHO scores. At low risk GTN given low dose MTX therapy. At the RSUD Dr. Soetomo is not used in high doses of MTX because of its large side effects on the liver and bone marrow. At high risk GTN given EMACO combination chemotherapy and if resistant to EMACO given EP-EMA. Hysterectomy operative measures are only performed if the patient has enough parity and low levels of adherence. Therapy for PSTT hysterectomy is the first choice at an early stage and at an advanced stage where metastasis is obtained, eating chemotherapy is the first choice. The chemotherapy used is EMACO and EP-EMA.

Characteristics of GTN Resistant Patients

Found 11 cases of GTN that experienced resistance at RSUD Dr. Soetomo in 2015-2017. The characteristics of resistant GTN patients can be seen in table 11 below.

Table 11. Characteristics of Resistant GTN

Variables	Values
Age	Mean : 33 ± 8,9 th
β-HCG	377.833,72 ± 341.186,24 IU/ml
Length of treatment	25,64 ± 9,6 minggu

We conducted a statistical test whether there was a significant difference between the levels of beta-HCG and the length of stay in GTN patients who had resistance or not, the results showed that there was a significant difference between the length of treatment of GTN patients who had resistance and not ($p < 0.001$) where GTN patients who had resistant had a longer treatment period, and no difference was found between initial levels of beta-HCG between resistant and not GTN ($p = 0.479$). In resistant GTN performed hysterectomy had a shorter treatment duration ($p = 0.004$) with a median length of treatment of 18 (4) weeks. No difference was found between initial levels of beta-HCG in resistant GTN performed by histectomy and second-line chemotherapy (table 12).

Table 12. Comparison of Types of GTN Therapy

Variables	Resistant		P value
	Yes (n=11)	No (n=30)	
β-HCG level (IU/ml)	377.833.72 ± 341.186.24	361.119.54 ± 439.216.75	0.479
Length of treatment (weeks)	25.64 ± 9.6	17.33 ± 4.5	0.001*

GTN Patient Fertility

We got 6 patients from 41 GTN patients who managed to get pregnant again after getting chemotherapy. Of the 6 patients, 2 (33%) were low risk GTNs and 4 (67%) were high risk GTNs. This is consistent with the theory put forward by Vargas that as many as 68.4% of GTN patients in the United States can get pregnant again after getting chemotherapy.

Use of oral contraceptive pills combined with GTN

From the data we collected obtained 5 patients using a combined oral contraceptive pill for 5 years before the occurrence of GTN. We conducted a statistical test to determine the relationship between the use of combined oral contraceptive pills and the incidence of GTN. We found the following results: There was no significant relationship between the use of combined oral contraceptive pills with the occurrence of complete, partial, invasive, and choriocarcinoma Mola hydration ($p > 0.005$). In addition, the use of a combined oral contraceptive pill reduces the risk of developing choriocarcinoma and complete hydatidiform mole although it is not statistically significant.

CONCLUSION

GTN is a chemosensitive neoplasia but can also experience resistance to chemotherapy. It is important to monitor the levels of beta-HCG for at least 12 months before the patient can get pregnant again.

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