Response to Chemotherapy in Patients with Gestational Trophoblastic Neoplasia in Dr. Hasan Sadikin General Hospital

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Abstract

Background: The incidence of gestational trophoblastic neoplasia (GTN) is high in Indonesia. Based on the FIGO prognostic score, GTN is classified into low-risk and high-risk categories. The high-risk group requires multidrug chemotherapy whereas the low-risk group requires single-drug chemotherapy. Response to chemotherapy would reflect the remission rate. The aim of this study was to describe the response to chemotherapy in GTN patients.

Methods: This was a cross-sectional descriptive retrospective study on medical records of patients with GTN treated in Dr. Hasan Sadikin General Hospital during the period of 2016 to 2018. The inclusion criteria were GTN patients who received >3 cycles of chemotherapy while the exclusion criteria were incomplete, inaccessible, or missing data. Data were collected on patient's age, parity, history of previous pregnancy, pregnancy-therapy interval, tumor size, number and location of metastases, and history of failed chemotherapy.

Results: Of the189 medical records of the GTN patient collected, only 88 met the inclusion criteria, (63.6% low risk and 36.4% high risk). Most patients were responsive to chemotherapy (61.4%), aged <40 years old, multiparity, tumor size >5 cm, had 4 month interval from previous pregnancy <4 months, had a history of molar pregnancy, had no metastases, and no previous failed chemotherapy.

Conclusions: The chemotherapy response in gestational trophoblastic neoplasm patients is fairly good with most patients are in the low-risk groups. Specific tumor markers used in early diagnosis of GTN may play a major role.

Keywords: FIGO, prognostic score, gestational trophoblastic neoplasia, remission rate

Introduction

Gestational trophoblastic disease (GTD) is a group of diseases that originate from an abnormal proliferation of placental trophoblast cells, which occur after fertilization.[1,2] Gestational trophoblastic disease consists of partial and complete hydatidiform mole known as a benign tumor and malignant gestational trophoblastic neoplasia (GTN). Based on the histopathological characteristics, GTN is categorized into invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).[1]

Clinical diagnosis of GTN refers to the prognostic score and staging system of GTN.[3] Both of these are necessary to assess the prognosis, risk factors and stage of GTN to optimize therapy. A Prognostic scores can be used to define the severity stages of GTN by using the risk factor of the GTN patient as an indicator. The prognostic score created by the International Federation of Gynecology and Obstetrics (FIGO) is an improved scoring system that combines FIGO anatomical staging (stage I through IV) with the World Health Organization (WHO) prognostic scores (score 1 to 4 for each category).[4,5] Based on the FIGO prognostic score, GTN is classified

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into low-risk and high-risk categories. The low-risk category is defined by stages 1, 2 and 3 GTN and a FIGO score of <7, whereas the high-risk category is defined by stages 2, 3 and 4 GTN and a FIGO score of >7. Low-risk GTN patients should receive methotrexate (MTX) or actinomycin-D as a single-agent chemotherapy regimen, while high-risk GTN patients should receive a multi-agent/ combination regimen consisting of etoposide, methotrexate, folinic acid, cyclophosphamide, and vincristine (EMA-CO) with a multi-agent/ combination regimen consisting of etoposide, methotrexate, folinic acid, cyclophosphamide, and vincristine (EMA-CO) with or without adjuvant therapy such as surgeryor radiation.[6]

Epidemiological studies have showed that the incidence of GTN in Asia is higher than in Europe and North America.[7] Dr. Hasan Sadikin General Hospital has reported yearly that there is 730 existing old cases. Additionally, there are 5 new cases in 2018 and 23 new cases of GTN between 2017 and 2018.[8] The GTN has a high mortality rate in the past, but currently, it is one of the malignancies with the lowest mortality rate due to high recovery rate.[7] The increased recovery rate of GTN is caused by the discovery of specific tumor markers which aids the early diagnosis of hydatidiform mole and GTN. The tumor marker is human chorionic gonadotropin (hCG), a glycoprotein hormone produced by the placenta, and its varying levels provide useful clinical information on GTN diagnosis.[1] The gestational trophoblastic disease produces β-hCG in a longer cycle than normal pregnancy.[2]

The success of the chemotherapy regimen given can be monitored by changes in β-hCG levels. Aside from being a tumor marker, β-hCG is also used to determine the patient's response to the chemotherapy regimen given during a specified cycle (usually 2-3 cycles).[9] This response is determined by measuring serum β-hCG levels that are monitored after chemotherapy.[10] The chemotherapy response to low-risk and high-risk GTNdoes not always produce the same results.

Research providing data about the response of GTN chemotherapy and the characteristics of GTN patients in Indonesia is scars. Therefore, this study was conducted to describe the chemotherapy response and the characteristics of GTN patients in Dr. Hasan Sadikin General Hospital, that served as a referral hospital in West Java. The result of this study was expected to assist clinicians in predicting the prognosis of GTN patients and to adjust the chemotherapy regiment.

Methods

This research was a descriptive study with a retrospective cross-sectional study design. Secondary data were obtained from patients' medical records at Dr. Hasan Sadikin General Hospital during 2016–2018. Data of patients diagnosed with gestational trophoblastic neoplasia were collected. Inclusion criteria were patients who received three cycles of chemotherapy. The exclusion criteria in this study were medical recordsof patients with incomplete or less than 3 cycles of chemotherapy and medical records that were inaccessible or data missing.

This study used total sampling as the sample collection method. The variables inquired in this study were the type of GTN based on the FIGO score (low-risk and high-risk). The data on demography and clinical characteristics i.e. age, parity, tumor period, previous pregnancy, metastatic location, number of metastases, history of failed chemotherapy were noted, including the chemotherapy response which was categorized as responsive, partial, and unresponsive. Responsive chemotherapy response was defined by serum β-hCG levels of <5 mIU/ml, the partial response when serum β-hCG levels decreased by 50% from baseline, and unresponsive when serum β-hCG levels remained at baseline or even increased.

This study protocol was approved by the Research Ethics Committee Universitas Padjadjaran with the number 764/UN6. KEP/EC/2019 as well as the Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung no. 283/UN6.KEP/EC/201 8LB.02.01/X.2.2.1/11572/2019. After ethical approval was obtained, medical records were selected according to inclusion and exclusion criteria. Data were then presented in tables and figures to infer a conclusion.

Results

A total of 189 patients with diagnosis of gestational trophoblastic neoplasia (GTN) was collected of whom only 88 patients met the inclusion criteria. Diagnosis and management of GTN were determined based on the FIGOprognostic score, whereas distinguishing specific types of GTN was designated through histopathological examination. The included patients were diagnosed based on the FIGO prognostic scores of whom 19 were diagnosed based on the results of histopathological examination. There were 56 (63.6%) patients were included in the low-risk category and

Table 1 Clinical Characteristics of Patients with Gestational Trophoblastic Neoplasia

Characteristics	N	%
Age		
< 40 years	57	64.8
> 40 years	31	35.2
Parity		
Primi	21	23.9
Multi	57	64.8
Grande	10	11.4
Previous Pregnancy History*		
Mole	60	80.0
Term Birth	13	17.3
Abortion	2	2.7
Pregnancy-Therapy Interval *		
< 4 months	37	58.7
4–6 months	10	15.9
7–12 months	7	11.1
>12 months	9	14.3
Tumor Size*		
<3 cm	8	12.5
3–4 cm	14	21.9
>5 cm	42	65.6
Metastasis Location		
Lung	17	19.3
Kidney	1	1.1
Gastrointestinal Tract	1	1.1
Liver/Brain	-	-
No Metastasis	65	73.8
Number of Metastatic Tumors		
1–4	21	91.3
5–8	2	8.7
Previous History of Failed Chemotherapy		
Singledrug	4	4.5
Multidrugs	2	2.3
None	82	93.2

Note: *incomplete data

32 (36.4%) patients were in the high-risk category.

The characteristic of the patients was, however, not all listed on the medical record. Fifty-six patients had complete characteristics, whereas the data of previous pregnancy history, pregnancy-therapy interval, and tumor size were incompletein 32 patients. The age of patients with GTN was mostly <40 years old, with the age group of 21 to 35 years old was

Table 2 Chemotherapy Response among Patients with Gestational Trophoblastic Neoplasia Based on Low-risk and High-risk Category

Category	Chemotherapy Response					
	Responsive		Partial		Unresponsive	
	n	%	N	%	N	%
Low-risk	38	70.4	16	50	2	100
High-risk	16	29.6	16	50	-	-
Total	54	100	32	100	2	100

the most prevalent (64.8%). The patients were mostly multiparous (64.8%) and had a history of molar pregnancy (80%) as shown in Table 1. The majority had a pregnancy-therapy interval of <4 months (58.7%) with a tumor size of >5 cm (65.6%). Most of them had no metastases (65 of 88). Those with metastases had lung metastases (19.3%). Most patients had no history of failed chemotherapy (93.2%).

Furthermore, of those GTN patients who received chemotherapy, 54 patients (61.4%) were responsive to chemotherapy, 32 patients (36.4%) had a partial response and 2 patients (2.3%) were unresponsive as depicted in Table 2. Most of the responsive patients (70.4%) were categorized as low-risk GTN.

Of those GTN patients who were responsive to chemotherapy were mostly aged <40 years (70.4%), were multiparous (64.9%), had a history of previous molar pregnancy (84.1%), had a pregnancy-therapy interval of<4 months (56.4%), had a tumor size of >5 cm (62.5%), had no metastases (75.6%) and had no history of failed chemotherapy (91.1%). The characteristic of GTN patients who were responsive to chemotherapy was shown in Table 3.

The percentage of chemotherapy responses was 50% in both the single drug regimen and multidrug regimen. The chemotherapy response among GTN patients based on the type of chemotherapy regimen was presented in Table 4.

Discussion

This study has recruited patients with GTN, diagnosed with FIGO prognostic score, of whom 63.6% has been categorized as a low-risk GTN and 36.4% as a high-risk GTN. Most low-risk GTN patients in this study have a FIGO score of 4. This result is consistent with previous study that has reported the majority of GTN patients are low-risk.[11] Gestational trophoblastic neoplasm is a malignant tumor that can be treated completely with chemotherapy, and surgery is only considered when indicated. Moreover, surgery is not recommended in high-risk GTN patients who have high FIGO scores because of the risk of bleeding.[12] The FIGO prognostic scores have been determined by the characteristics of GTN patients. By knowing the characteristics of patients, the risk level of GTN can be predicted earlier.[3]

In this study, most of the GTN patients are under the age of 40 years. This is consistent with the results of other studies that showed that GTN often appears at reproductive age.[6,13] Furthermore, our study shows that that most patients are multiparous, have a history of molar pregnancy, and havea pregnancy-therapy interval of <4 months (Table 1). Patients with a history of molar pregnancy, multiparous, and have a pregnancy-therapy interval of <4 months have a higher risk to develop invasive moles.[9] Other types of GTN can arise from various types of pregnancy. Choriocarcinoma occurs in 50% of molar pregnancies, 25% of abortions, and 25% of term births. The average choriocarcinoma has a pregnancy-therapy interval of >12 months.[14,15] In placental site trophoblastic tumour (PSTT) and epitheloid trophoblastic tumour (ETT), the pregnancy-therapy interval of patients varies greatly from 6 months to 20 years.[12]

This study has also shown that most patients have a tumor size of >5 cm, metastasize in the lungs, have several metastatic tumors between 1 to 4, and have no history of failed chemotherapy. This is similar to research on the pathology of the GTN type which reports that patients with choriocarcinoma often experience metastasis, that occurs in the lungs (80%), in the vagina (30%)as well as in the brain and liver (10%).[14]

Patients with GTN who have undergone history taking, physical examination, laboratory and supporting examinations

Table 3 Chemotherapy Response among Patients with Gestational Trophoblastic Neoplasia Based on Clinical Characteristics (1)

Characteristic	Chemotherapy Response					
	Responsive		Partial		Unresponsive	
	n	%	n	%	N	%
Age						
< 40 years	38	70.4	18	56.2	1	50
> 40 years	16	29.6	14	43.7	1	50
Total	54	100	32	100	2	100
Chemotherapy Response						
Primi	12	22.2	8	25.0	1	50
Multi	35	64.8	21	65.6	1	50
Grande	7	13.0	3	9.4	-	-
Total	54	100	32	100	2	100
Previous Pregnancy History*						
Mola	37	84.1	21	72.4	2	100
Abortus	7	15.9	6	20.7	-	-
Aterm	-	-	2	6.9	-	-
Total	44	100	29	100	2	100
Pregnancy-Therapy Interval*						
<4 months	22	56.4	15	68.18	-	-
4–6 months	9	23.1	-	-	1	50
7–12 months	3	7.7	3	13.6	1	50
> 12 months	5	12.8	4	18.2	-	-
Total	39	100	22	100	2	100
Tumor Size*						
<3 cm	5	12.5	3	13.6	-	-
3–4 cm	10	25.0	3	13.6	1	50
>5 cm	25	62.5	16	72.7	1	50
Total	40	100	22	100	2	100
Metastasis Location						
Lung	9	16.7	8	25.0	-	-
Kidney	1	1.8	-	-	-	-
Gastrointestinal Tract	-	-	1	3.1	-	-
Liver/Brain	-	-	-	-	-	-
NoMetastasis	41	75.9	22	68.7	2	100
Total	54	100	32	100	2	100

Table 3 Chemotherapy Response among Patients with Gestational Trophoblastic Neoplasia Based on Clinical Characteristics (2)

Characteristic	Chemotherapy Response					
	Responsive		Partial		Unresponsive	
	n	%	n	%	N	%
Number of Metastatic Tumors						
1–4	13	100	8	80	-	-
5–8	-	-	2	20	-	-
>8	-	-	-	-	-	-
Total	13	100	10	100	-	-
Previous History of Failed Chemotherapy						
Singledrug	3	5.4	1	3.1	-	-
Multidrug	2	3.6	-	-	-	-
None	51	91.1	31	96.9	2	100
Total	56	100	32	100	2	100

such as increased β-hCG levels, and a history of resistant chemotherapy will then be assessed by FIGO prognostic scores to decide the treatment.[3] β-hCG levels in patients are monitored every week until consecutively reaching a normal level for three times.[2,7] If β-hCG levels are within normal limits, patients will be monitored every month for 12 months for low-risk patients and 18 months for high-risk patients. Six months afterward, β-hCG levels are monitored once a year. Monitoring is recommended for 5 years.[12] This need to be performed to categorize the chemotherapy response of the given regimen.

The responsiveness of chemotherapy has been shown that 61.4% of patients is responsive, 36.4% have partial chemotherapy responses, and 2.3% is unresponsive (Table 2). Furthermore, 38.6% have received chemotherapy for at least three cycles but have not recovered and did not continue treatment. In our study, the patients who are responsive for chemotherapy is from low-risk GTN (70.4%), whereas from high-risk GTN is accounted for 29.6%. Interestingly, other studies have shown that low-risk GTN has a remission rate of 93–100%, of which the high-risk GTN has a remission rate of 86–94%.[12] In contrast, other study shows that GTN remission rate is quite low, which is 75–100% for low-risk GTN and 67–88% for high-risk GTN.[16]

The result of this study has shown that the remission rate of GTN patients in Dr. Hasan Sadikin General Hospital is relatively lower compared to various studies from other countries, especially in high-risk GTN category patients. Asian people are susceptible to an aggressive disease progression that may be caused by several biological factors and

Table 4 Chemotherapy Response among Patients with Gestational Trophoblastic Neoplasia Based on The Type of Chemotherapy Regimen

Chemotherapy Regimen	Chemotherapy Response						Total
	Responsive		Partial		Unresponsive		
	n	%	n	%	n	%	
Singledrug	27	50	14	43.5	2	100	43
Multidrug	27	50	18	56.2	-	-	45
Total	54	100	32	100	2	100	88

irregular chemotherapy. This is shown by patients who initially have a low-risk GTN then have been progressing into high risk GTN and it thus requires a second-line regimen to achieve the remission.[6,13] Patients with β-hCG levels of >100,000 mIU/ml, history of metastasis, high FIGO scores, and age of >40 years often experience resistance to chemotherapy and require more time to achieve remission.[13]

Patients with GTN who are responsive to chemotherapy are mostly from the age group of <40 years (70.4%), multiparous (64.8%), have a previous history of molar pregnancy (84.1%), have a pregnancy-therapy intervals of <4 months (56.4%), have atumor size of >5 cm (62.5%), have no history of metastasis (75.9%) and have no history of chemotherapy failure (91.1%). The GTN patients with pulmonary metastases (16.7%) are responsive to chemotherapy. These results are similar to a study in Iran[17] on the characteristics of GTN patients who have received chemotherapy with methotrexate for the first time. Patients with an age of >40 years tend to have a lower survival and remission rate. Patients who have a resistant response to chemotherapy have often been found in patients with pregnancy-therapy intervals of >4 months.[12] The risk of developing a chemotherapy resistance is increased up to four times in these patients.[17] Furthermore, patients with partial and unresponsive chemotherapy responses are mostly in the age of <40 years old (Table 3). It should be noted that these patients have not yet recovered and are at risk of developing metastasis. It is therefore necessary to monitor patients who have partial or unresponsive responses to maintain their treatment.

The percentage of responsive chemotherapy patients in the single-drug regimen group and multi-drug regimen group are similar, showing that the treatment decisioning GTN patients in Dr. Hasan Sadikin General Hospital is in accordance with the risk category (Tabe 4). Most low-risk GTN patients at Dr. Hasan Sadikin General Hospital have been given MTX for a period of 5 days every 14 days as the first line therapy. A study has shown that patients who are given actinomycin-D as their second line therapy are easier to develop resistance compared to patients with a combined regimen (EMA-CO) as their second line therapy. Patients who have a low-risk FIGO score of 5 and 6 need special attention because their remission rate are lower and tend to be resistant to single regimen chemotherapy.[11]

High-risk GTN patients should receive EMA-CO combination chemotherapy with or without adjuvant therapy such as surgery or radiation.[2,18] This regimen is given on 1st day, 2nd day, and 8th day.[3] High-risk GTN patients who have resistance should be given EMA/EP combination chemotherapy regimen (etoposide, methotrexate, folinic acid, etoposide, and cisplatin). The remission rate of the EMA/EP regimen reaches up to 75–80%. The regimen which is often used to treat high risk GTN patients with chemotherapy resistance in Dr. Hasan Sadikin General Hospital is TE/TP combination chemotherapy regimen (paclitaxel and etoposide alternating with paclitaxel and cisplatin every two weeks).[11] Research on the level of remission of the TE/TP regimen has not been done, however, this regimen is as effective as the EMA/EP regimen with lower toxicity.[11,17] Chemotherapy response at Dr. Hasan Sadikin General Hospital is not as high as in developed countries (86–94%) especially in high-risk GTN patients (29.6%), therefore, it is necessary to examine various risk factors that might affect it, including the type of therapeutic regimen.[17]

The limitation of this research is the design of this study, which was retrospective and descriptive. Further study should be conducted with a prospective study design to assess the chemotherapy response of GTN patients and the risk factors that influence it. Follow-up and education for patients also need to be conducted correctly, considering the number of GTN patients with incomplete chemotherapy and patients with partial and non-responsive responses who are lost to follow up. This study was considered a weak evidence to prove any causal relationship between the variables. The number of incomplete medical record data had made this study difficult to maintain its accuracy.

To conclude, most GTN patients in Dr. Hasan Sadikin General Hospital are responsive (61.4%) and most of them are categorized as low-risk groups (70.4%). Gestational trophoblastic neoplasm patients with responsive chemotherapy response were mostly from the age group of <40 years, multiparous, had a history of previous molar pregnancy, the pregnancy-therapy interval of <4 months, tumor size of >5 cm, have no history of metastases and no history of previously failed chemotherapy. Patients with a responsive chemotherapy response to a single drug regimen and multidrug regimen have similar results, indicating that selection of the therapy regimen based on the respective risk groups is effective.

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