Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Nov 12; 10(B):1446-1449.
https://doi.org/10.3889/oamjms.2022.9983
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Gynecology and Obstetrics*

Risk Factors That Correlate with Resistance to First-Line Chemotherapy on High-risk Gestational Trophoblastic Neoplasia

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Kurniadi A, Zulvayanti Z, Suardi D, Mantilidewi K, Irsyad BI, Reswari A, Purwara BH, Nyarumenteng Adhipurnawan Winarno GNA. Risk Factors That Correlate with Resistance to First-Line Chemotherapy on High-risk Gestational Trophoblastic Neoplasia. Open Access Maced J Med Sci. 2022 Nov 12; 10(B):1446-1449.https://doi.org/10.3889/oamjms.2022.9983
Keywords: High-risk gestational trophoblastic neoplasia; EMCO; Chemotherapy resistance
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Received: 27-Apr-2022
Revised: 28-Oct-2022
Accepted: 02-Nov-2022

Funding: This study was supported by institutional grant from Universitas Padjajaran No. 1959/UN6.3.1/PT.00/2021
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Gestational trophoblastic neoplasia (GTN) is a condition arising from abnormal proliferation of the trophoblastic cells. GTN incidence in Indonesia, precisely in Hasan Sadikin General Hospital, as many as 730 cases are reported per year. GTN is generally highly sensitive to chemotherapy, and multiagent chemotherapy regimens are recommended for high-risk GTN. Multiagent chemotherapy regimens for GTN treatment at Hasan Sadikin General Hospital are EMCO, with no other literature study describing chemotherapy resistance with EMCO today.

AIM: This study aimed to identify risk factors associated with first-line chemotherapy resistance at Hasan Sadikin General Hospital.

METHODS: In this cross-sectional study, medical records of 81 patients with high-risk GTN presented in the period from January 2018 to June 2021 who received EMCO chemotherapy at Hasan Sadikin General Hospital were retrieved from the archives, and medical data were reviewed and analyzed. Bivariate analysis was performed using the Chi-square test with Fisher's exact alternative, and multivariate analysis using the binary logistic regression test. $p < 0.05$ was considered statistically significant.

RESULTS: From 81 samples that received EMCO chemotherapy, 15 (18.5%) cases were resistant to EMCO, and 66 (81.5%) cases were responsive to EMCO. The risk factors associated with EMCO resistance were histopathological features and appropriate with EMCO chemotherapy interval ($p < 0.05$). Variables of age, previous pregnancy, GTN stage, FIGO prognostic score, stage, beta-hCG level, and side effects of EMCO did not significantly correlate with resistance to EMCO ($p > 0.05$).

CONCLUSION: Histopathological features and appropriate chemotherapy intervals were associated with the incidence of resistance to EMCO in Hasan Sadikin General Hospital.

Introduction

Gestational trophoblastic neoplasia (GTN) is a type of gestational disease group of pregnancy-related malignancies [1]. GTN incidence in developed countries is approximated to be one case per 40,000 pregnancies; meanwhile, in Indonesia, precisely in Hasan Sadikin General Hospital, as many as 730 cases are reported per year [2], [3]. GTN is generally highly sensitive to chemotherapy with a high cure rate of up to 90−100% [2], [4], [5]. Chemotherapy options depend on the risk classification according to the International Federation of Gynecology and Obstetrics (FIGO) prognosis scoring system. Multiagent chemotherapy regimens are recommended for high-risk GTN; by definition is GTN with a FIGO prognosis score of ≥ 7. The survival rate of high-risk GTN patients treated with multiagent chemotherapy regimens is higher than that of single-agent regimens (65−70% vs. 14−39%, respectively) [2].

Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine (EMA-CO) are the first-line chemotherapy regimens for high-risk GTN, with a remission rate of 90.6% [2], [6], [7]. In addition to EMA-CO, EMA-EP (Etoposide, Methotrexate, Actinomycin-D, Etoposide, and Cisplatin) is also reported as a second-line chemotherapy regimen with a remission rate of up to 82% [4]. A retrospective study in Korea examined the efficacy of multiagent chemotherapy regimens in 227 high-risk GTN patients. The study showed that EMA-CO had the highest remission rate and required fewer chemotherapy cycles for remission compared to other multiagency regimens. Remission rates for the other chemotherapy regimens are 63.3%, 67.5%, and 76.2% for MFA (Methotrexate, Folinic acid, and Actinomycin-D), MAC (Methotrexate, Actinomycin-D, and Cyclophosphamide), and CHAMOCA (Cyclophosphamide, Hydroxyurea, Doxorubicin, Actinomycin-D, Methotrexate, Melphalan, and Vinstine), respectively [2].

After molar evacuation, patients should be monitored with weekly determinations of a-subunit hCG levels until these levels are normal for three consecutive weeks, followed by monthly determinations until the

levels are normal for six consecutive months. Good response (complete remission) to chemotherapy is defined as a log fall in serum β-hCG levels after each course of chemotherapy [4]. In our protocol, patients were measured for biweekly serum β-hCG levels until they were detected as a normal levels for three evaluations. There are several definitions of refractory or progressive disease: An increased serum β-hCG levels for 2 weeks after β-hCG measurement of more than three separate intervals, failure to achieve normal serum β-hCG titers after consolidated chemotherapy, or there are new metastases [4], [6]. Chemoresistance occurs when (1) four or more plateaued hCG concentrations over 3 weeks; (2) increase of hCG concentrations for three or more consecutive measurements for at least 2 weeks; (3) if there are a histologic diagnosis of choriocarcinoma; and (4) elevated hCG concentrations for 6 months or longer [8]. Sinaga *et al*. stated that factors affecting the development of GTN post-molar pregnancy include patient age, serum levels β-hCG, the uterine size larger than expected age, and the presence of lutein theca cysts [9].

Multiagent chemotherapy regimens for GTN treatment at our center Hasan Sadikin General Hospital are different from the previous studies; Etoposide, Methotrexate, Cyclophosphamide, and Vincristine (EMCO) omit Actinomycin-D (EMCO) in the therapy regimens. There has been no other literature study describing chemotherapy resistance with EMCO today. However, this research can be a breakthrough in evaluating the therapy of EMCO at Hasan Sadikin General Hospital. This study aims to identify risk factors associated with first-line chemotherapy resistance at Hasan Sadikin General Hospital.

Methods

In this cross-sectional study, medical records of 81 patients with high-risk GTN presented in the period from January 2018 to June 2021 who received EMCO chemotherapy at Hasan Sadikin General Hospital were retrieved from the archives, and medical data were reviewed and analyzed. Patients were classified according to age, previous pregnancy history, GTN stage, FIGO prognosis score, histopathology, chemotherapy side effects, pre-treatment beta-hCG level (IU/mL), and appropriate chemotherapy interval. The dependent variable in this study was chemotherapy response. Bivariate analysis was conducted using the Chi-square test with the exact fisher alternative, and multivariate analysis was performed using a binary logistic regression test. From this analysis, we will get a p-value, which defines as significant if $p < 0.05$. Research Ethics Committee Hasan Sadikin Hospital approved this study with approval number LB.02.01/X.6.5/59/2022.

Results

Table 1 describes the characteristics of patients who received EMCO chemotherapy. Among 81 patients who received chemotherapy, 15 (18.5%) were resistant to EMCO chemotherapy, and 66 (81.5%) were complete response cases. In both groups, other characteristics such as age showed similar distribution, of which group with <39 years old and that of ≥39 years old. The previous pregnancy history in both groups was majority molar pregnancy, followed by aborted pregnancy and term. Of the 15 patients with resistant EMCO chemotherapy, seven were Stage I (46.7%), two were Stage II (13.3%), five were Stage III (33.3%), and one was Stage IV (6.7%). Most patients in both groups had FIGO scores of 7−12, and a small number had FIGO scores of 13. GTN histopathology with complete response is most with partial hydatidiform mole (42.4%), followed by complete hydatidiform mole (28.8%), choriocarcinoma (24.2%), and the most negligible response was the invasive hydatidiform mole (4.5%). In resistance groups, the histopathology type from most common to the least found is choriocarcinoma (66.7%), complete hydatidiform mole (20.0%), and partial hydatidiform mole (13.3%). In contrast, an invasive mole was not found in this group. Histopathology type significantly differs from resistance response and complete response ($p < 0.05$). In both groups, most patients did not show side effects due to EMCO chemotherapy, patients with EMCO chemotherapy resistance (46.7%) and patients with complete EMCO chemotherapy (78.8%).

Table 1: Comparison between study subject characteristics with EMCO chemotherapy response

Variable	Response		p value
	Resistance	Complete	
	N = 15	N = 66	
Age (years)			0.899
<39	7 (46.7%)	32 (48.5%)	
≥39	8 (53.3%)	34 (51.5%)	
Previous pregnancy			1.000
Term	1 (6.7%)	4 (6.1%)	
Hydatidiform mole	11 (73.3%)	50 (75.8%)	
Aborted	3 (20.0%)	12 (18.2%)	
Stage			0.202
I	7 (46.7%)	51 (77.3%)	
II	2 (13.3%)	2 (3.0%)	
III	5 (33.3%)	12 (18.2%)	
IV	1 (6.7%)	1 (1.5%)	
FIGO Score			0.307
7–12	13 (86.7%)	62 (93.9%)	
≥13	2 (13.3%)	4 (6.1%)	
Histopathology			0.039*
Invasive mole	0 (0.0%)	3 (4.5%)	
Choriocarcinoma	10 (66.7%)	16 (24.2%)	
Complete hydatidiform mole	3 (20.0%)	19 (28.8%)	
Partial hydatidiform mole	2 (13.3%)	28 (42.4%)	
Side effect			0.160
Leukopenia	3 (20.0%)	8 (12.1%)	
Leukopenia; anemia	3 (20.0%)	3 (4.5%)	
Leukopenia; Thrombocytopenia	0 (0.0%)	1 (1.5%)	
Anemia	2 (13.3%)	2 (3.0%)	
No side effect	7 (46.7%)	52 (78.8%)	
Beta-hCG level			0.759
<100.000	10 (66.7%)	47 (71.2%)	
>100.000	5 (33.3%)	19 (28.8%)	
Appropriate with chemotherapy interval			0.004*
Yes	11 (73.3%)	65 (98.5%)	
No	4 (26.7%)	1 (1.5%)	

p value categorical data are determined based on Chi-square test with Kolmogorov–Smirnov test as an alternative test and exact fisher test if Chi-square requirements are not met. Statistically significant value is based on $p < 0.05$. *showed a statistically significant value ($p < 0.05$).

Beta-hCG level in patients with EMCO chemotherapy resistance and complete EMCO chemotherapy in both groups was majority < 100,000 mIU/mL. Moreover, in both groups, the characteristics of patients appropriate with chemotherapy interval showed a significant difference ($p < 0.05$).

Table 2 described a multivariate analysis with binary logistic regression to evaluate which risk factors showed greater magnitude toward EMCO chemotherapy resistance. The result showed that patients appropriate with chemotherapy interval affects chemoresistance.

Table 2: Multivariate analysis with binary logistic regression

Model	B	Df	p value	CI	95%	
					Lower	Upper
Initial model						
Histopathology	0.793	1	0.039*	2.210	1.039	4.701
Side effect	0.216	1	0.311	1.241	0.817	1.884
Appropriate with chemotherapy interval	–2.720	1	0.030*	0.066	0.006	0.763
Stage	–0.479	1	0.160	0.619	0.317	1.208
Final model						
Histopathology	0.785	1	0.035*	2.192	1.055	4.556
Appropriate with chemotherapy interval	–3.080	1	0.009*	0.046	0.005	0.465

Independent variables included in logistic regression model are independent variables in bivariate analysis with $p < 0.25$.

Discussion

In our result, most high-risk GTN patients showed complete responses to EMCO (81.5%). A study that evaluated EMACO chemotherapy results seemed to have higher complete response cases (90.9%) [5]. Although, a different study by Sato *et al.* showed a lower complete response to EMACO (78−79.7%) [10]. It is also known that MEA chemotherapy (without Cyclophosphamide and Vincristine) is also effective, with a 74.4% of remission rate and 20.5% of resistance cases [11].

Most patients with high-risk GTN were at Stage I. Subject age groups comprise patients equally distributed aged <39 years old and ≥39 years old. The previous pregnancy history consists primarily of molar pregnancy, followed proportionally by term and aborted pregnancy. Most had FIGO scores of 7−11, and a small number had FIGO scores ≥12. In a study by Jareemit *et al*., the characteristics of patients who received EMA chemotherapy were compared to that receiving EMACO chemotherapy. Patients receiving EMACO chemotherapy had significantly higher GTN stadium (stadium III and IV: 61.6 vs. 45.4%, p=0.008), higher WHO median prognostic risk score (8 vs. 4, p = 0.001), higher risk of previous non-molar pregnancy (59 vs. 27.3%, p = 0.014), higher time interval incidence than previous pregnancy ≥7 months (38.5 vs. 2.3%, p = 0.001), more tumors measured ≥3 cm (46.1 vs. 4.6%, p = 0.001), further metastasis (64.1 vs. 47.7%, p = 0.017), and a higher incidence of metastasis (46.2 vs. 15.9%, p = 0.002) than that of EMA group. There were no statistical differences in age, pathological diagnosis, beta-hCG serum levels before treatment, or previous unsuccessful chemotherapy between the two groups [2].

During the evaluation of side effects, most patients receiving EMCO chemotherapy did not report any side effects. The side effects reported post-chemotherapy were leukopenia, leukopenia and anemia, anemia, leukopenia, and thrombocytopenia. Jareemit *et al*. similarly mentioned that the highest side effects of EMACO chemotherapy are neutropenia and oral mucositis [2]. The highest incidence of EMA regimen side effects was leukopenia (82.5%) and anemia (77.6%) [10]. Dobson *et al*. compared side effects between EMACO chemotherapy regimen and MEA chemotherapy regimen, in which EMACO is associated with a higher incidence of anemia, neutropenia, and thrombocytopenia (5%, 13%, and 3%, respectively) compared to MEA (0.5%, 13%, and 0.3%, respectively) [12].

Pre-treatment beta-hCG levels did not show significant results in patients with resistance and complete EMCO chemotherapy ($p > 0.05$). In this study, patients with low beta-hCG levels (<100,000 mIU/ml) responded to complete EMCO chemotherapy but not patients with EMCO chemotherapy resistance. Bagshawe *et al*. showed significant results between chemotherapy response to initial beta-hCG level ($p = 0.001$) [13].

In this study, the two characteristics in the two subject groups that showed significant statistical difference were that almost all patients comply with the protocol of EMCO chemotherapy every three weeks. Furthermore, the GTN histopathology showed a different proportion. Most patients in the chemoresistance group had choriocarcinoma, while the responsive group showed partial hydatidiform mole. Turan *et al.* mentioned that the termination methods in the previous pregnancies, liver metastases, and histopathology might reduce chemotherapy response [5]. Different studies found that EMACO chemotherapy resistance or relapse was not statistically significant (20% vs. 19.2%), $p = 0.45$. Consolidation was also found to be not statistically significant (75% vs. 65.5%), $p = 0.6$. There was no association between the patient's age ($p = 0.899$), previous pregnancy history ($p = 1,000$), FIGO prognosis score ($p = 0.307$), GTN stadium ($p = 0.202$), and EMCO chemotherapy side effects ($p = 0.160$) with EMCO chemotherapy regimen resistance [6].

Table 2 illustrated the risk factors associated with EMCO chemotherapy resistance, which showed compliance affects more than histopathology results. These data were similar to a study by Kim *et al*. that mentioned three main factors were significantly causing resistance to EMACO chemotherapy, among others: (1) Tumor presence of more than 12 months, (2) metastasis to more than two organs, and (3) inadequate previous therapy (loss of follow-up) [14]. In a different study, chemotherapy-resistant patients have a more extended

treatment duration than the complete response to EMACO. In that particular study, there was no significant difference between the initial beta-hCG levels between the resistant and the non-resistant groups [15], [16].

This study is a pioneer study of risk factor analysis affecting EMCO resistance among high-risk GTN patients at Hasan Sadikin General Hospital Bandung. There is no clear evidence to eliminate Actinomycin-D in the treatment of high-risk GTN at Hasan Sadikin General Hospital. To the best of our knowledge, no literature studies explained the outcome of EMCO chemotherapy response, thus making it difficult for authors to compare the results from the previous studies. More research must be performed to evaluate chemotherapy response, including long-term EMCO side effects.

Conclusions

Histopathology result and appropriate with EMCO chemotherapy interval are related to EMCO chemotherapy resistance at Hasan Sadikin General Hospital. This cross-sectional study represented single center with small number of cases so large multicenter trial is recommended.

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