The Effects of Induction Chemotherapy in the Management of Ultra High-Risk Gestational Trophoblastic Neoplasia

Agnes L. Soriano-Estrella, MD, MHPEd and Koleen C. Pasamba, RND, MD

Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Objectives. This study aimed to determine the clinical outcomes of ultra high-risk gestational trophoblastic neoplasia (GTN) patients managed with and without induction chemotherapy in the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology, Philippine General Hospital.

Methods. Clinical and demographic data were collected retrospectively from ultra high-risk GTN patients admitted in the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology, Philippine General Hospital from January 2015 to December 2021. Rate of remission and early death of those who received induction chemotherapy were compared to those who did not.

Results. A total of 21 patients with ultra high-risk GTN were included in the study, nine of whom underwent induction chemotherapy while 12 had no induction chemotherapy and was given the standard EMACO regimen. There was no significant difference in the rate of early death as well as the rate and time to achieve remission between those who received induction chemotherapy compared to those who were immediately started on EMACO.

Conclusion. A firm conclusion cannot be drawn from the results considering the small population included in the study. Further studies with larger sample size and prospective study design are recommended.

Keywords: gestational trophoblastic neoplasia, ultra high-risk, induction chemotherapy

INTRODUCTION

Gestational Trophoblastic Neoplasia (GTN) refers to malignant lesions that arise from placental villous and extravillous trophoblasts. It includes four distinct clinicopathologic conditions namely invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.[1] All patients diagnosed with GTN are staged and scored using the International Federation of Gynecology and Obstetrics (FIGO) 2000 Anatomic Staging System (Table 1) and the World Health Organization (WHO) prognostic scoring system, respectively (Table 2).[2,3] Based on the WHO scoring system, a patient is considered low-risk if her score is six or less and is classified as high-risk if her score is seven and above. Treatment is then based on the patient's combined stage and prognostic score. Those with non-metastatic and metastatic low-risk disease are given single agent chemotherapy in the form of methotrexate or actinomycin D. On the other hand, patients with metastatic high-risk disease receive multiple agent chemotherapy, of which the regimen composed of Etoposide,

eISSN 2094-9278 (Online)
Published: June 28, 2024
https://doi.org/10.47895/ amp.v58i11.9127

Corresponding author: Agnes L. Soriano-Estrella, MD, MHPEd
Department of Obstetrics and Gynecology
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: alsorianoestrella@up.edu.ph
ORCiD: https://orcid.org/0000-0003-3038-2532

Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine (EMACO), is the most commonly utilized.

The treatment of GTN is one of the success stories of modern-day medicine. Until the mid 1950's, the prognosis of patients afflicted with this disease was extremely poor. The discovery of Methotrexate as an effective agent in treating patients with GTN by Li and associates in 1957, led to the rapid improvement in the prognosis of patients with this disease.[1] Currently, cure is anticipated in almost all patients with non-metastatic and low-risk metastatic disease while high-risk metastatic disease patients have an over-all survival rate reaching as high as 95%.[3]

Recent reports have shown that patients with a WHO score of 13 or above as well as patients with brain, liver, and extensive metastases do poorly with first line multiple agent chemotherapy regimens.[4] Based on the latest FIGO cancer report, this subgroup of patients is now classified as ultra high-risk GTN.[3] These patients are at risk of early death which may occur within a month of initiating intensive multiagent chemotherapy due to sudden tumor collapse with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure. Alifrangis et al. documented a total of seven early deaths out of 140 patients diagnosed with ultra high-risk GTN.[5] To avert this complication, initial administration of induction chemotherapy composed of etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2, repeated weekly for 1 to 3 cycles has been proposed to be given prior to the initiation of EMACO. It is theorized that initial low doses of chemotherapy will lead to a more gradual reduction in tumor volume, thus decreasing the risk for significant hemorrhage in critical organs affected by the disease.[5] Currently, there are limited studies that have investigated the effectiveness of induction chemotherapy in GTN.[5,6] Due to the rarity of the disease, most of the studies were retrospective cohorts since randomized control trials are usually not recommended or will be difficult to conduct for rare diseases. The Division of Trophoblastic Diseases in the Philippine General Hospital started using induction chemotherapy around 2014 to 2015.

To date, only a few studies have reported on its utility. It is important to look into new strategies that will further improve the survival rate of patients with GTN. Thus, this study aimed to determine the clinical outcomes of ultra high-risk GTN patients managed with and without induction chemotherapy in the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology, Philippine General Hospital.

Table 1. FIGO 2000 Staging System for GTN[2]

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	Lung metastasis
IV	All other distant metastases

MATERIALS AND METHODS

This is a cohort study, which was done to investigate the remission as well as early mortality rate of ultra-high risk GTN patients with or without induction chemotherapy in the Division of Trophoblastic Diseases, Department of Obstetrics and Gynecology, Philippine General Hospital. Ethics approval was obtained prior to the conduct of the study from the University of the Philippines-Manila Research Ethics Board (UPM-REB) and the study was registered in the Research Grants and Administration Office (RGAO) with reference number RGAO-2023-0514. The authors adhered to the principles of good clinical practices of the WHO, with the 1964 Helsinki declaration as well as its amendments and other comparable standards.

Data were collected retrospectively from patients admitted from January 2015 to December 2021. All patients who were diagnosed with ultra high-risk GTN, defined as those with WHO prognostic score of 13 or above, who were able to receive at least 1 cycle of chemotherapy at the said institution were included in the study. Patients who received induction chemotherapy using etoposide and cisplatin were identified and compared with those who were not given induction chemotherapy prior to the usual regimen of EMACO. Patients were followed-up until remission or death, whichever happened first. Due to the retrospective nature of the study, the choice of regimen was based on the

Table 2. Modified WHO Prognostic Scoring System as Adapted by FIGO[3]

Risk Factor	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval (months)	4	4 to 6	7 to 12	>12
Pretreatment serum βhCG (mIU/mL)	<10^3	10^3 to 10^4	10^4 to 10^5	>10^5
Largest tumor (including uterus)	<3 cm	3 to 4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	–	1 to 4	5 to 8	>8
Prior failed chemotherapy	–	–	Single drug	≥2 drugs

clinical judgement of the physicians attending to the patients upon admission. Patients excluded were those who were not able to receive chemotherapy, those with incomplete data, and those who were still undergoing treatment at the end of the study period. The following data from each patient were collected and tabulated using Microsoft Excel 365: age, histopathology result if available, FIGO stage, WHO score along with its components namely: last pregnancy prior to diagnosis of GTN, interval from last pregnancy to GTN diagnosis, baseline beta-hCG level, largest tumor size, location of metastases, chemotherapy toxicities, remission, and early death. Remission in cases of GTN refers to three consecutive normal beta-hCG titers (normal ≤5 mIU/mL). Early death was defined as mortality within four weeks after treatment initiation as a result of hemorrhage, sepsis or organ failure. Toxicities, specifically liver toxicity, anemia, neutropenia, and thrombocytopenia, experienced by patients were documented and classified based on the WHO grading for chemotherapy toxicity (Table 3).[7]

Descriptive statistics were computed to analyze the characteristics of the patients. To identify significance between the group who had induction chemotherapy compared to patients who did not receive induction chemotherapy, t test and Fisher's test were done using STATA version 10.0 with a *p* value set at ≤0.05 as the level of significance and confidence interval at 95 %. To determine the difference between the remission rates of the two groups, Kaplan-Meier and log-rank test were done.

RESULTS

A total of 26 ultra high-risk patients were admitted during the study duration. Of these, four were excluded due to death prior to initiation of chemotherapy while one was excluded since the patient was still undergoing treatment at the end of the study period. A total of 21 patients with ultra high-risk GTN were thus included in the study, nine of whom underwent induction chemotherapy while 12 had no induction chemotherapy and was given the standard EMACO treatment for metastatic, high-risk GTN patients. The baseline characteristics and profile of patients are shown in Table 4 based on whether patients were given induction chemotherapy or not.

Patients who underwent induction chemotherapy were significantly younger compared to those who were not given induction chemotherapy. There was also a significant difference between the GTN stage of patients between those who had induction chemotherapy to those who had no induction chemotherapy. Two patients who underwent induction chemotherapy were classified as stage 1. These two patients were cases of recurrent GTN. The average largest tumor size was around 9 centimeters for both groups. There were no significant differences between the two groups for the other parameters included in the study.

Out of the 21 patients included in the study, there were a total of seven early deaths. Two patients had acute respiratory failure secondary to pulmonary hemorrhage, three patients had intracranial bleeding, and one had gastrointestinal bleed. One patient died secondary to sepsis. Table 5 shows the clinical outcome as well as toxicities of patients who underwent induction chemotherapy versus those who received EMACO outright. For the patients who underwent induction chemotherapy, four patients died while five had remission. On the other hand, out of the 12 patients who did not receive induction chemotherapy, three achieved remission while three had early mortality. There was no statistically significant difference between the rate of remission as well as early deaths between the two groups.

There was also no significant difference in terms of toxicities secondary to chemotherapy between the groups. However, there was a higher total percentage of occurrence of anemia among those who had no induction chemotherapy (33.9%) compared to those who had induction chemotherapy (10%). Among those who had grade 4 neutropenia, all had febrile neutropenia except for two patients who had induction chemotherapy.

Figure 1 shows the Kaplan-Meier curve generated to illustrate the remission rates of the two groups. The log rank test performed after showed no statistically significant difference between the two groups (*p* value = 0.515). The mean estimates in months and confidence interval of the remission rates are shown in Table 6.

Table 3. WHO Common Toxicity Criteria Grade[7]

Toxicity	0	1	2	3	4
Bone Marrow					
WBC (cells/mm^3)	>4	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	<1.0
Platelet	WNL	75.0 – normal	50 – 74.9	25 – 49.9	<25.0
Hb (g/dl)	WNL	10 – normal	8.0 – 10.0	6.5 – 7.9	<6.5
Granulocytes/bands (cells/mm^3)	>2.0	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	<0.5
Lymphocytes (cells/mm^3)	>2.0	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	<0.5
Liver					
Transaminase (SGOT, SGPT)	WNL	<2.5 x N	2.5 – 5.0 x N	5.1 – 20 x N	>20 x N

Table 4. Characteristics and Profile of Ultra High-risk GTN Patients who Underwent Induction Chemotherapy versus those who had no Induction Chemotherapy

	With induction chemotherapy Mean ± SD n=9 (%)	Without induction chemotherapy Mean ± SD n=12 (%)	*p* value
Age in years (mean ± SD)	29.3 ± 9.6	39.6 ± 8.5	0.0182[a]
Interval in months from last pregnancy to GTN (mean ± SD)	12.1 ± 11.8	27.5 ± 38.6	0.2647
Beta-hCG in mIU/mL	970559.4 ± 401591.6	903886.3 ± 467132.6	0.7353
Largest tumor size (n, %)			0.686
<3 cm	0 (0)	0 (0)	
3–4 cm	1 (11.1)	1 (8.3)	
≥5 cm	8 (88.9)	11 (91.7)	
Failed chemotherapy (n, %)			0.686
None	8 (88.9)	11 (91.7)	
Single drug	1 (11.1)	0 (0)	
Multiple drugs	0 (0)	1 (8.3)	
Location of metastases (n, %)			0.192
Lung	2 (22.2)	6 (50.0)	
Spleen/Kidney	2 (22.2)	0 (0)	
GI tract	0 (0)	0 (0)	
Brain/Liver	5 (55.6)	6 (50.0)	
Number of metastases (n, %)			0.087
1–4	1 (11.1)	5 (41.7)	
5–8	0 (0)	2 (16.7)	
>8	8 (88.9)	5 (41.7)	
Antecedent pregnancy (n, %)			0.076
Mole	7 (77.8)	4 (33.3)	
Abortion	2 (22.2)	3 (25.0)	
Term	0 (0)	5 (41.7)	
Histopathology results (n, %)			0.122
None	8 (88.9)	7 (58.3)	
Invasive mole	1 (11.1)	1 (8.3)	
Choriocarcinoma	0 (0)	4 (33.3)	
WHO score (mean ± SD)	15.8 ± 2.2	15.0 ± 2.1	0.4413
Stage (n, %)			0.011[a]
1	2 (22.2)	0 (0)	
2	0 (0)	0 (0)	
3	0 (0)	6 (50.0)	
4	7 (77.8)	6 (50.0)	

[a] *Significant P value at ≤0.05, continuous variables were analyzed using T test while categorical variables were analyzed using Fisher's test*

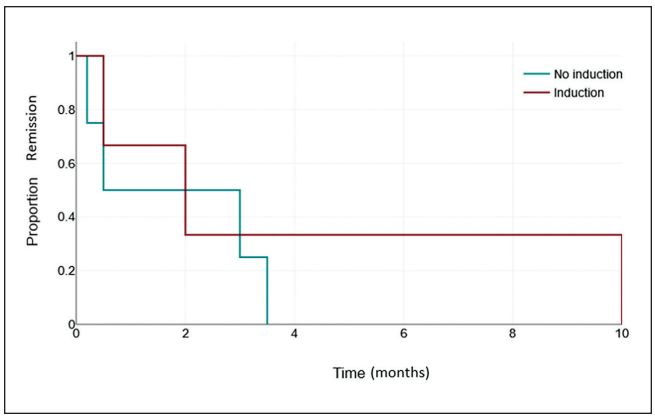

Figure 1. Kaplan-Meier curve of remission rates.

DISCUSSION

The incidence of gestational trophoblastic neoplasia varies across the globe and is generally rare. Choriocarcinoma, which is the most common type of GTN, has an estimated worldwide incidence of 0.02-0.07 per 1,000 pregnancies.[8] Due to the rare occurrence of the disease, the incidence and rates of ultra high-risk gestational trophoblastic neoplasia is difficult to establish.

Currently, with early detection and appropriate treatment of low-risk GTN, cure rate approaches 100%.[3,9] Patients classified as high-risk commonly have metastases to other organs. Nonetheless, these patients still have an over-all survival rate reaching as high as 95%.[3]

In 2015, the WHO scoring and classification system was updated, which further subclassified high-risk GTN into ultra high-risk GTN for WHO score of 12 and above.[10]

Table 5. Rates of Remission, Early Mortality and Toxicities among Ultra High-risk Patients with or without Induction Chemotherapy

	With induction chemotherapy n=9 (n,%)	Without induction chemotherapy n=12 (n,%)	*p* value[a]
Remission			0.319
Yes	4 (44.4)	3 (25.0)	
No	5 (55.6)	9 (75.0)	
Early Mortality			0.319
Yes	4 (44.4)	3 (25.0)	
No	5 (55.6)	9 (75.0)	
Liver Toxicity (Grade)			0.092
None	6 (66.7)	6 (50)	
1	0 (0)	5 (41.7)	
2	2 (22.2)	1 (8.3)	
3	1 (11.1)	0 (0)	
4	0 (0)	0 (0)	
Anemia (Grade)			1.000
None	8 (88.9)	9 (75.0)	
1	0 (0)	1 (8.33)	
2	1 (11.1)	2 (16.7)	
3	0 (0)	0 (0)	
4	0 (0)	0 (0)	
Neutropenia (Grade)			0.597
None	3 (33.3)	5 (41.7)	
1	0 (0)	1 (8.3)	
2	2 (22.2)	2 (16.7)	
3	0 (0)	2 (16.7)	
4	4 (44.4)	2 (16.7)	
Thrombocytopenia (Grade)			0.686
None	8 (88.9)	11 (91.7)	
1	0 (0)	0 (0)	
2	0 (0)	1 (8.33)	
3	1 (11.1)	0 (0)	
4	0 (0)	0 (0)	

[a] *Significant P value at ≤0.05, continuous variables were analyzed using T test while categorical variables were analyzed using Fisher's test*

Table 6. Remission Rate of Patients with and without Induction Chemotherapy

	Mean Estimate (months)	95 % CI
No induction	1.80	0.2 – 3
With induction	4.17	0.5 – 2

It was updated again in 2021 where ultra high-risk GTN include those with WHO score of 13 as well as patients with liver, brain, or extensive metastases.[3] In general, ultra high-risk patients were observed to do poorly when treated with first-line multiple agent chemotherapy.[3] In the study done by Kong et al., ultra high-risk GTN patients were observed to have lower survival rate and poor prognosis with a 5-year overall survival rate of 67.9%.[4] Due to the rarity of the disease, most of the studies were retrospective cohorts since randomized control trials are usually not recommended or will be difficult to conduct for rare diseases. This study was thus undertaken to contribute to our knowledge regarding the clinical outcome of ultra high-risk patients who received induction chemotherapy compared to those who were given outright EMACO in terms of remission and early mortality.

Baseline Characteristics

Age, as part of the WHO FIGO scoring, has been seen as a prognostic factor that can determine survival rate of patients diagnosed with GTN. The age cut off in a single center retrospective study done by Hou et al. was 40 years old (HR 2.094; 95 % CI 1.327-3.305).[11] In the current study, there was statistically significant difference between the age of the patients who received induction chemotherapy versus those who did not, although the average age of both groups was less than the cut off age of 40 years old. The difference in the age might have been a random effect given the small sample size of the study.

Other than the age, there was also statistically significant difference in the stage of the disease between those who received induction chemotherapy and those who did not. This is expected because a higher stage connotes a higher tumor burden and wide spread disease which put the patient at risk of early mortality upon initiation of chemotherapy. Hence, these patients are candidates for induction chemotherapy.

In this study, recurrent GTN cases were included in the study population. For patients diagnosed with GTN, stage is based on the 2000 FIGO staging system while the prognostic score is based on the WHO prognostic scoring system.[3]

In cases of recurrence, patients' diagnosis would still reflect the original stage and score with an annotation of the word recurrence.[3,12] Treatment, however, is determined based on the current status of the patient, that is, the current extent of disease. In order to do so, the WHO score is re-assessed. The inclusion of recurrent GTN in the study, which would reflect the original stage and score upon first diagnosis, could have affected the wide range and statistically significant difference in terms of GTN stage between the patients.

Aside from age and stage of GTN, the other baseline characteristics of the patients that can affect prognosis of GTN were not statistically different between the groups. Randomization and prospective data collection can decrease chances of difference between groups in future studies.

Mortality, Remission, and Toxicities

Alifrangis et al. was one of the first to report on the utility of induction chemotherapy using cisplatin and etoposide to improve clinical outcomes.[5] Compared to the other reports, they used induction chemotherapy to treat high-risk GTN and those who were clinically assessed to be at high-risk of early death due to a large disease burden. There was no early death among the 33 out of 140 patients who received induction chemotherapy. They also compared the results of this study to the previous cohort done in 1995 which showed the earlier cohort to have a higher death rate. Induction therapy also did not increase the risk of subsequent resistance to EMA/CO.[5]

The prospective study of Bolze described the mortality rate among the different stages and classifications of GTN.[6] A total of 29 patients had FIGO score of more than or equal to 13 of which six underwent induction chemotherapy.[6] A total of 11 deaths from the 29 ultra high-risk patients were observed, three of whom received induction chemotherapy. However, there was no separate analysis or comparison of the outcome of ultra high-risk GTN patients who underwent induction chemotherapy.[6]

Khadraoui et al. reported on two cases of high-risk GTN who were at risk of pulmonary or brain hemorrhage on whom induction chemotherapy was administered.[13] Both patients however received adjuvant therapy in the form of surgery or embolization. Remission was achieved in both patients.[13]

Patel et al. did a retrospective study on high-risk GTN patients who underwent induction chemotherapy.[14] They noted a higher percentage of patients who achieved remission among those who received induction chemotherapy compared to those who did not (71.4 % versus 58.8 %).[14] In the current study, there was a larger proportion of patients who achieved remission among those who did not receive induction chemotherapy although the difference did not reach statistical significance. Analysis of the Kaplan-Meier curve showed a longer time to achieve remission for those who received induction chemotherapy. This was expected since additional time was spent for the administration of the induction chemotherapy prior to giving the usual recommended chemotherapy regimen. Nonetheless, log-rank test showed no statistically significant difference in the time required to achieve remission. This is in agreement with that of Patel's in that there was no significant difference in early mortality and eventual remission in those who received induction chemotherapy compared to those who did not.[13]

The study of Patel et al. showed a decrease in the proportion of patients with adverse events if initial low dose induction chemotherapy is administered. The current study showed a slightly higher proportion of thrombocytopenia and neutropenia among those who received low dose induction chemotherapy.[14] In both studies however, the difference in toxicities and remission rates were not statistically significant.[14]

The differences in the results by Patel et al. and the current study can be explained by the difference in the patient characteristics.[14] In the current study, there were no statistically significant difference in the patients' characteristics in terms of tumor load based on site of metastasis and serum beta-hCG. Around 55% of patients who received low dose induction chemotherapy had liver/brain metastasis compared to 50% among those who received primary EMACO treatment. The beta-hCG was similar at around 970,000 mIU/ml versus 903,000 mIU/ml in the induction chemotherapy and the primary EMACO group, respectively. In contrast, 42.8 % of the patients who received induction chemotherapy in the study of Patel et al. had brain and/or liver metastasis. Only 5.8% of patients who received primary EMACO had liver metastasis and none had brain metastasis.[13] Average beta-hCG level of patients who received induction chemotherapy was around 874,000 mIU/ml versus 693,000 mIU/ml in those who received primary EMACO treatment.[14]

CONCLUSION

The current study showed no significant difference in the rate of early death and remission between those who received induction chemotherapy compared to those who were immediately started on EMACO. However, a firm conclusion cannot be drawn from the results considering the small population included in the study. Additionally, the retrospective nature of the study prohibited the authors from selecting patients who will receive induction chemotherapy.

At present, there is very limited data on the effect of induction chemotherapy using the low dose cisplatin and etoposide regimen, on remission and mortality rate. Current studies are based on retrospective studies with limited number of patients showing varying results. While a randomized control trial may be the best study design to show the true effect of induction chemotherapy in the management of ultra high-risk disease, this may not be feasible due to the rarity of the disease. A prospective case control or cohort study may then be the best option to gain more robust conclusions.

Acknowledgment

The authors would like to acknowledge Dr. Emmanuel P. Estrella for doing the statistics of this study.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

Funding Source

None.

REFERENCES

1. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematol Oncol Clin North Am 2012 Feb;26(1):111-31. doi: 10.1016/j.hoc.2011.10.007. PMID: 22244665.
2. Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. Int J Gynecol Cancer. 2001 Jan-Feb;11(1):73-7. doi: 10.1046/j.1525-1438.2001.011001073.x. PMID: 11285037.
3. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynaecol Obstet. 2021 Oct;155 Suppl 1(Suppl 1):86-93. doi: 10.1002/ijgo.13877. PMID: 34669197; PMCID: PMC9298230.
4. Kong Y, Yang J, Jiang F, Zhao J, Ren T, Li J, et al. Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: a retrospective cohort study. Gynecol Oncol. 2017 Jul;146(1):81-6. doi: 10.1016/j.ygyno.2017.04.010. PMID: 28461032.
5. Alifrangis C, Agarwal R, Short D, Fisher RA, Sebire NJ, Harvey R, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J Clin Oncol. 2013 Jan 10;31(2):280-6. doi: 10.1200/JCO.2012.43.1817. PMID: 23233709.
6. Bolze PA, Riedl C, Massardier J, Lotz JP, You B, Schott AM, et al. Mortality rate of gestational trophoblastic neoplasia with a FIGO score of ≥13. Am J Obstet Gynecol. 2016 Mar;214(3):390.e1-8. doi: 10.1016/j.ajog.2015.09.083. PMID: 26433171.
7. WHO Toxicity Grades [Internet]. 2020 [cited 2023 Oct]. Available from: https://redbook.streamliners.co.nz/5802.pdf
8. Brown J, Naumann RW, Seckl MJ, Schink J. 15 years of progress in gestational trophoblastic disease: scoring, standardization, and salvage. Gynecol Oncol. 2017 Jan;144(1):200–7. doi: 10.1016/j.ygyno.2016.08.330. PMID: 27743739.
9. Soper JT. Gestational trophoblastic disease: current evaluation and management. Obstet Gynecol. 2021 Feb 1;137(2):355-70. doi: 10.1097/AOG.0000000000004240. PMID: 33416290; PMCID: PMC7813445. Erratum in: Obstet Gynecol. 2022 Jan 1;139(1):149. doi: 10.1097/AOG.0000000000004589. PMID: 34915535.
10. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet. 2015 Oct;131 Suppl 2:S123-6. doi: 10.1016/j.ijgo.2015.06.008. PMID: 26433668.
11. Hou YM, Li PP, Yu H, Feng F, He XY, Chen BH, et al. Clinical features and demographic characteristics of gestational trophoblastic neoplasia: Single center experience and the SEER database. Biomol Biomed. 2024 Jan 3;24(1):176-87. doi: 10.17305/bb.2023.9092. PMID: 37485958; PMCID: PMC10787625.
12. Hu S, Lin X, Yin R, Wang W, Li Q. Recurrent choriocarcinoma complicated with leprosy during chemotherapy: a case report and literature review. Medicine (Baltimore). 2023 Aug 11;102(32):e34548. doi: 10.1097/MD.0000000000034548. PMID: 37565881; PMCID: PMC10419345.
13. Khadraoui H, Herzog TJ, Jackson A, Billingsley C. Acute pulmonary complications in the setting of high risk gestational trophoblastic neoplasia and induction of chemotherapy. Gynecol Oncol Rep. 2023 Jun 10;48:101224. doi: 10.1016/j.gore.2023.101224. PMID: 37346459; PMCID: PMC10279533.
14. Patel SM, Arora R, Tiwari R, Poddar P, Desai A, Mankad MH, et al. Management of "Ultra-High Risk" Gestational Trophoblastic Neoplasia at a Tertiary Center in India. Indian J Med Paediatr Oncol. 2020 May-Jun 27;41(3):345-50. doi: 10.4103/ijmpo.ijmpo_235_18.