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Predictors of chemotherapy resistance & relapse in gestational trophoblastic neoplasia

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***Background & objectives*: Gestational trophoblastic neoplasia (GTN) is a chemosensitive malignancy with an excellent cure rate. The primary objective of the present study was to determine the predictors of chemoresistance and disease relapse, and the secondary objective was to appraise the WHO/FIGO risk scoring and course of disease in women with GTN.**

***Methods*: In this retrospective study, case records of women treated for GTN from January 2011 to June 2019 were reviewed. For the purpose of comparison, sub-stratification of FIGO/WHO low risk group (≤6) into low (0-4) and intermediate (5-6) risk was done. Similarly, WHO high risk (≥7) group was sub-stratified into high (7-12) and ultra-high risk (≥13) groups.**

***Results*: Case records of 116 patients were included: 51.7 per cent (60/116) were of low risk disease and 48.2 per cent (56/116) were of high risk disease. Chemoresistance developed in 28.4 per cent (33/116) and relapse in 10.3 per cent (12/116) cases. Risk of chemoresistance was higher in low risk (0-6) while risk of relapse was more in high risk (≥7) group. On sub-stratification, chemoresistance was more with intermediate [0-4: 28.5% (10/35), 5-6: 44% (11/25), 7-12: 22.5% (9/40), ≥13: 18.7% (3/16)] and relapse with ultra-high risk score [0-4: 5.7% (2/35), 5-6: 4% (1/25), 7-12:10% (4/40), ≥13: 31.2% (5/16)]. Age, myometrial invasion, serum beta-human chorionic gonadotropin and tumour size were not related to chemoresistance or relapse.**

***Interpretation & conclusions*: WHO risk score and presence of metastatic disease predict the probability of developing chemotherapy resistance and disease relapse. Risk of chemotherapy resistance was higher in women with intermediate-risk score (5-6), and risk of relapse was more in those with ultra-high risk score (≥13).**

Key words Chemoresistance - gestational trophoblastic neoplasia - high risk GTN - intermediate-risk GTN - low risk GTN - pregnancy-related cancer - relapse - ultra-high risk GTN

Gestational trophoblastic neoplasia (GTN) describes pregnancy-related malignant neoplasms, that include invasive mole, choriocarcinoma, placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumours (ETT)[1,2]. This is a heterogeneous disorder, and, owing to its rarity,

there are wide variations in diagnostic and treatment protocols[3]. The management of GTN is guided by the International Federation of Gynecology and Obstetrics/World Health Organization (FIGO/WHO) two-tier risk scoring system[2]. Based on the risk score, patients are stratified into low risk or high risk groups, referring to the probability of drug resistance with single-agent therapy. The chemotherapeutic regimen is decided according to the individual patient score[2]. Cure rate as good as 100 per cent in low risk and 90 per cent in high risk disease[1,2] has been reported, but adverse events such as drug resistance and relapse are often encountered during treatment[2-6]. This complicates the management, and multidisciplinary care is often needed to provide optimum care to such patients. There are additional implications on treatment duration, cost and patient's quality of life. Hence, there is a need to review the factors that may predict the possibility of chemoresistance and relapse. This will be useful to prognosticate patients and reduce the exposure to an ineffective therapy[4-6]. Previous studies have observed an increased threshold for high risk group assignment using the current FIGO/WHO score, leading to erroneous risk categorization for certain patients[4,6,7]. There is an ongoing debate to redefine the cut-off points and to re-stratify the risk groups into low, intermediate, high and ultra-high risk as the course of disease and outcome vary with the disease burden[4,6]. The primary objective of the present study was to determine the predictors of chemoresistance and disease relapse in GTN patients. The secondary objective included appraisal of WHO/FIGO risk scoring system and to analyze the course of disease in women with GTN.

Material & Methods

This retrospective study was carried out in the departments of Obstetrics and Gynaecology and Medical Oncology, (BRAIRCH), All India Institute of Medical Sciences, New Delhi, India. Case records of women who attended the cancer clinic and underwent treatment for GTN, during the period from January 1, 2011, to June 30, 2019, were reviewed. The study was approved by the Institute's Ethics Committee (IEC-661/06.09.2019).

Risk stratification: The FIGO/WHO 2000 scoring system[6] was used, and patients with score ≤6 were categorized as low risk disease and those with ≥7 were labelled as high risk disease. For the purpose of comparison, further sub-stratification within these two risk groups was done and groups were designated as follows: risk score 0-4=low risk; 5-6=intermediate risk; 7-12=high risk and ≥13=ultra-high risk[4,6].

Chemoresistance: It was defined as <10 per cent fall over two cycles or >10 per cent rise in beta-human chorionic gonadotropin (β-hCG) values after one cycle.

Adverse drug reactions were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[8]; Grade 1: mild symptoms not needing any intervention, Grade 2: moderate symptoms needing local or non-invasive interventions, Grade 3: severe but not immediately life-threatening and needing hospitalization, Grade 4: life-threatening consequence for which an urgent intervention indicated, and Grade 5: death related to adverse events.

Complete remission (CR) & relapse: CR was considered after three consecutive weekly normal β-hCG (beta human chorionic gonadotropin) levels (<2 IU/l). Relapse was elevation of at least two levels of β-hCG after achieving CR in the absence of a confirmed pregnancy.

Data concerning the clinical profile, including age, history of antecedent pregnancy, previous treatment and examination findings, were recorded. Details of available investigations including serum β-hCG, X-ray chest, imaging including pelvic ultrasound, Doppler, computed tomography (CT) scan, magnetic resonance imaging (MRI) if available, complete blood count and liver and kidney function tests were noted. Histopathology report of biopsy or curettage was noted, if available. The FIGO standardized β-hCG diagnostic criteria were used for the diagnosis of GTN[2]. Using this information, the risk score was calculated[6].

Treatment: All patients received treatment as per the standard hospital protocol. Low risk cases were treated with single-agent methotrexate therapy (SAM), and those with high risk disease received combination chemotherapy with etoposide, methotrexate, actinomycin cyclophosphamide and vincristine (EMA-CO) regimen[2]. For the low risk disease, methotrexate was administered at a dose of 1 mg/kg intravenously on days 1, 3, 5 and 7; leucovorin factor was given after 24 h on days 2, 4, 6 and 8. The cycle was repeated every two weeks. Actinomycin-D was administered

as 0.5 mg intravenous push daily for five days in those who had poor tolerance to methotrexate. Serum β-hCG was measured weekly and before the start of a new chemotherapy cycle. The chemoresistant patients with low risk disease received either actinomycin-D (with non-metastatic disease) or EMA-CO. Other chemotherapy regimens used as salvage therapy for chemoresistant disease in women with high risk score were EMA-EP (etoposide, methotrexate, actinomycin-D and etoposide, cisplatin), TP-TE (paclitaxel, cisplatin- paclitaxel, etoposide) and BEP (bleomycin, etoposide and cisplatin), as per the standard protocol[6].

Response assessment: During therapy, patients showing >10 per cent fall in β-hCG value were continued on the same therapy till β-hCG was normal, followed by two more consolidation cycles in low risk and three consolidation cycles in high risk cases. Patients with a resistant or metastatic disease, not responding to therapy, were subjected to appropriate surgical procedures. Factors affecting resistance and relapse were analyzed. Response rate, progressive disease while on chemotherapy and relapse were the key outcome measures.

Follow up: After the last chemotherapy cycle, patients remained on regular follow up using regular β-hCG monitoring as per the standard guidelines. Patients were also advised standard contraceptive measures. During follow up, the course and outcome of new pregnancy were recorded. Serum β-hCG level was measured at 6-8 wk after the end of any pregnancy to exclude disease recurrence.

Statistical analysis: Data were analyzed by STATA 14.0 (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: Stata Corp LP). To test the normality assumptions of continuous data, Kolmogorov–Smirnov test was carried out. Normally distributed data were presented as mean, standard deviation and range values. Mean values between the two groups were tested by the Student's independent t test. Non-normal/skewed data were presented as median and interquartile range (IQR) values. Median values were compared using Mann–Whitney U-test. Categorical variables were presented as frequency and percentage values. Frequency data by categories were compared using the Chi-square test/Fisher's exact test as appropriate. Unadjusted odds ratios with 95 per cent confidence intervals were calculated.

Results

The characteristics of 116 patients are depicted in Table I and Fig. 1. Post-molar GTN was seen in 61.2 per cent (71/116) and histologically confirmed choriocarcinoma in 11.2 per cent (13/116) cases, while none of the cases had features of PSTT and ETT. Metastatic GTN was seen in 31 per cent (36/116) and non-metastatic GTN was seen in 68.9 per cent (80/116) instances. Of the 116 cases, 51.7 per cent (60/116) were of WHO low risk and 48.2 per cent (56/116) were of WHO high risk. Among the 60 low risk patients, 59 received SAM therapy and one patient received actinomycin-D due to methotrexate intolerance. Among the 56 high risk patients, 41 received EMA-CO as first-line therapy and the other 15 received incomplete chemotherapy before referral. They were started on

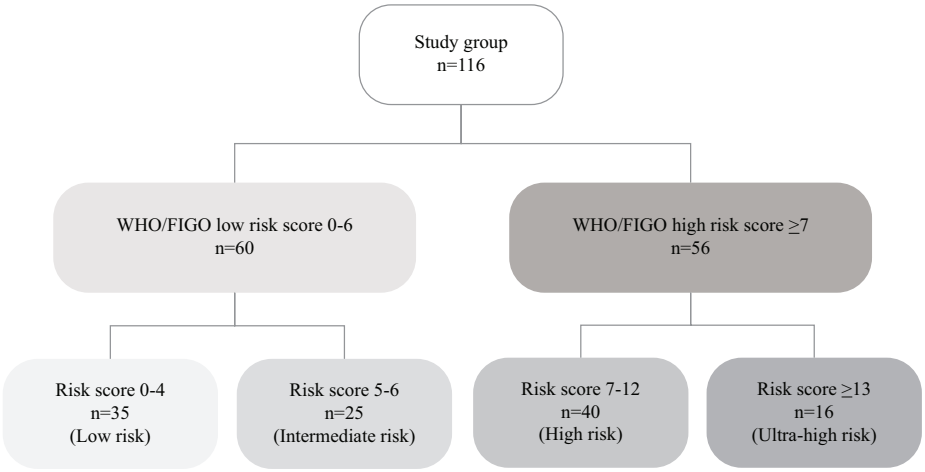

Fig. 1. Distribution of the study participants according to the risk stratification.

Table I. Characteristics of the study participants (n=116)

Variable	Median/frequency	Range (minimum, maximum)/per cent
Age (yr)	28.0	(20, 51)
Parity	1.0	(0, 8)
Abortions	1.0[#]	(0, 5)
Interval from antecedent pregnancy (months)	3.0	(1, 42)
Pre-treatment serum β-hCG (IU/l)	58158	(200, 1,200,000)
Number of evacuations prior to diagnosis	1.0	(0, 5)
Marital status		
Married	111	95.7
Unmarried	5	4.3
Religion		
Hindu	95	81.9
Muslim	21	18.1
Age (yr)		
<40	101	87.1
≥40	15	12.9
Size of largest tumour (cm)		
<3	30	25.9
3-5	26	22.4
>5	60	51.7
Antecedent pregnancy		
Mole	71	61.2
Abortion	35	30.2
Term pregnancy	8	6.9
Ectopic pregnancy	2	1.7
Pre-treatment β-hCG (IU/l)		
<1000	9	7.8
1000-10,000	16	13.8
10,000-100,000	39	33.6
>100,000	52	44.8
Metastasis		
Present	36	31.1
Absent	80	68.9
Sites of metastasis		
Lung	28	-
Liver	5	-
Others[*] (spleen, mesentery, brain, vagina)	4 (1, 1, 2, 2)	-
FIGO stage		
I	72	63.2
II	6	5.1
III	28	24.6
IV	10	8.7

Contd...

Variable	Median/frequency	Range (minimum, maximum)/per cent
WHO risk score		
0-6	60	51.7
≥7	56	48.3

[$]Values are expressed as median (minimum, maximum) or frequency (%), [*]Multiple sites were involved in three patients, [#]The total number of abortions in the study was 131, and were distributed as follows; 0=23 patients, 1=65 patients, 2=15 patients, 3=8 patients, 4=4 patients, 5=1 patient. hCG, human chorionic gonadotropin; FIGO, International Federation of Gynaecology and Obstetrics

Table II. Characteristics of patients who developed chemoresistance (n=33) and relapse (n=12) at baseline and at the time of outcome

Variables	Median (minimum, maximum)	
	Chemoresistance (n=33)	Relapse (n=12)
Baseline characteristics		
Age (yr)	29 (22, 50)	28 (20, 34)
Parity	1 (0, 4)	2 (0, 3)
Abortions	1 (0, 3)	1 (1, 2)
Time interval from antecedent pregnancy (months)	3 (1, 42)	3 (1, 13)
β-hCG (IU/l)	42,687 (579, 1,000,000)	162,500 (200, 1,000,000)
WHO score	6 (2, 15)	10 (2, 13)
Tumour size (cm)	4.8 (2, 15)	NA
Initial chemotherapy regimens	Low risk: Mtx, Act- d High risk: EMA-CO	Low risk: Mtx High risk: EMA-CO, EP-CO[**]
Number of initial chemotherapy cycles	6 (3, 11)	4.5 (3, 13)
At the time of chemoresistance, relapse		
Time to chemoresistance or relapse (months)	2.5 (0.25, 5.50)	5.5 (0.50, 41)
Serum β-hCG at relapse/resistance diagnosis (IU/l)	1580 (67.2, 700,000)	400.5 (63.4, 15,000)
Methods for diagnosis	Surveillance	Surveillance (n=11), abdominal pain and bleeding PV (n=1) after 41 months of CR
Site of disease at the time of outcome[*]	NA	Uterus: 9, Lung: 4, Liver: 2, Adnexa: 1
Follow up (months) after CR	13 (1, 96)	6.5 (3, 37)
Outcome	Alive and disease free	Alive and disease free

[*]Three patients had multiple sites of disease at the time of relapse. [**]EP-CO regimen was given to one patient with brain metastasis. Mtx, methotrextae; Act-D, actinomycin D; EMA-CO, etoposide, methotrexate; actinomycin-D, cyclophosphamide, vincristine; EMA-EP, etoposide, methotrexate, actinomycin-D, etoposide, cisplatin; hCG, human chorionic gonadotropin; CR, Complete remission; PV, per vaginum

EMA-CO therapy after recalculating the risk score. The median follow-up time (n=116) was 18 months (range 1-96).

The overall CR rate after the first-line chemotherapy was 71.5 per cent (83/116); low risk (0-6): 65 per cent (39/60), high risk (≥7): 78.5 per cent (44/56). On further sub-stratification of WHO low risk group (n=60), CR rate was 71.4 per cent (25/35) for scores 0-4 and 56 per cent (14/25) for intermediate-risk score (5-6). In the high risk (n=56) group, CR rate was 77.5 per cent (31/40) for scores 7-12 and 81.2 per cent (13/16) for score ≥13. The remission rates after second-line chemotherapy were 75 per cent (34/45). Second-line chemotherapy included actinomycin-D, EMA-CO, EP-CO, BEP, TP-TE and EMA-EP. Third-line chemotherapy included BEP, EMA-EP, EMA-CO and oral etoposide; it was given to 11 patients, and CR rates were 71.4 per cent (8/11). Only one patient received oral etoposide; she had a risk score of 5 and received three cycles of SAM but developed chemoresistance. She was started on EMA-CO therapy, but after the second cycle of EMA-CO, she developed fever and

Table III. Comparison of demographic and clinical variables of patients who had a remission after first-line chemotherapy with those who developed chemoresistance

Variables	Remission with first line chemotherapy (n=83), frequency (%)	Chemoresistance (n=33), frequency (%)	$P^{\$}$	Odds ratio (95% CI)
Age (yr)[#] Mean±SD	29.5±7.3	30.7±7.4	0.41[*]	-
<40	72 (86.7)	29 (87.8)	0.80	0.9 (0.26-3.06)
[†]40	11 (13.2)	4 (12.1)		1.0
Myometrial invasion				
Present	22 (40.7)	11 (45.8)	0.60	0.7 (0.24-2.23)
Absent	32 (59.2)	13 (54.2)		1.0
Adverse events				
Present	20 (24.1)	5 (15.1)	0.33	0.5 (0.19-1.65)
Absent	63 (75.9)	28 (84.8)		1.0
Serum β-hCG (IU/l)				
<1000	6 (7.2)	3 (9.1)		1.0
1000-10,000	11 (13.2)	5 (15.2)	0.60	0.9 (0.15-5.19)
>10,000-100,000	26 (31.3)	13 (39.4)		1.0 (0.21-4.65)
>100,000	40 (48.2)	12 (36.4)		0.6 (0.13-2.76)
Size of tumour (cm)				
<3	19 (27.7)	6 (21.2)	0.70	1.0
3-5	14 (22.9)	7 (21.2)		1.5 (0.43-5.75)
>5	37 (49.4)	16 (57.6)		1.3 (0.46-4.06)
Risk score				
Low risk (0-4)	25 (30.1)	10 (30.3)	0.20	1.0
Intermediate risk (5-6)	14 (16.9)	11 (33.3)		1.9 (0.66-5.77)
High risk (7-11)	31 (37.3)	9 (27.3)		0.7 (0.25-2.06)
Ultra-high risk (≥13)	13 (15.7)	3 (9.1)		0.5 (0.13-2.46)
Metastasis				
No	60 (72.3)	20 (60.6)	0.20	1.0
Yes	23 (27.7)	13 (39.4)		1.6 (0.7-3.9)
Initial chemotherapy cycles				
Mean±SD	5.1±1.9	6.6±2.4	0.009[*]	1.4 (1.12-1.65)

[$]Chi-square/fisher exact test applied, [*]*t*-test applied, [#]Age structure of patients who developed chemoresistance (n=33); 20-24 yr (6 cases), 25-29 yr (12 cases), 30-34 yr (5 cases), 35-39 yr (6 cases), 40-44 yr (1 case), [†]45 yr (3 cases). SD, standard deviation; hCG, human chorionic gonadotropin

thrombocytopenia. Considering the low disease burden (β-hCG: 54.15 IU/l), she was given oral etoposide for two months before achieving CR. Two patients received fourth-line chemotherapy; one achieved CR with TP-TE and the other one received gemcitabine and docetaxel along with thalidomide, but two months later, she relapsed and eventually required a hysterectomy.

Chemoresistance was seen in 28.5 per cent (33/116) and relapse was seen in 10.3 per cent (12/116) cases. The baseline characteristics of patients who developed resistance and relapse are shown in Table II. Variables affecting the development of chemoresistance and relapse were analyzed (Tables III and IV). Age, myometrial invasion, antecedent pregnancy and pre-treatment serum β-hCG were not associated with resistance (Table III). Fig. 2 depicts the distribution of chemoresistance and relapse, according to WHO risk-score. A numerically higher proportion of chemoresistance was present in the low risk (score 0-6) than high risk GTN (score ≥7), but this difference was not significant (35.0 vs. 21.4%; *P*=0.10).

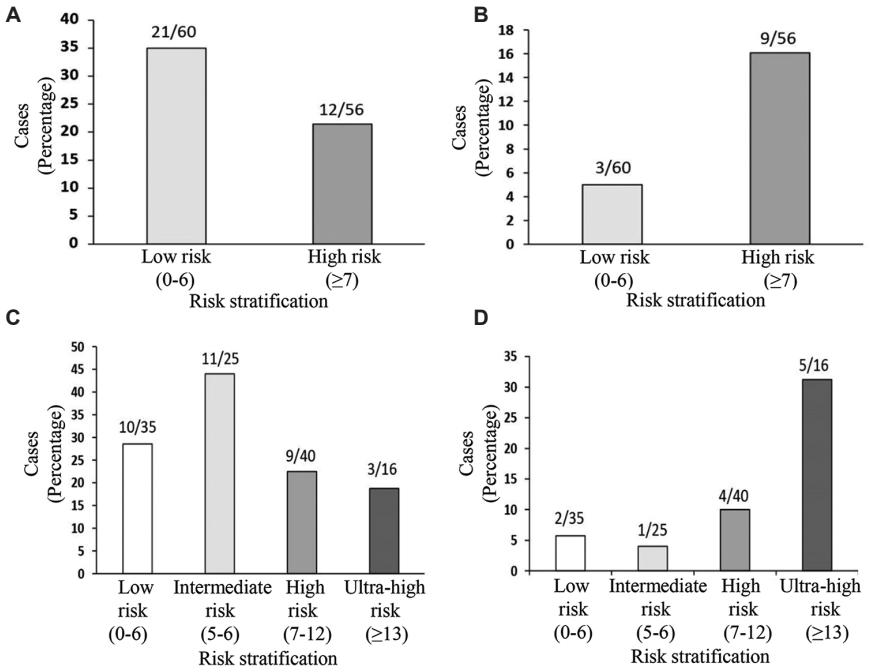

Fig. 2. Distribution of chemoresistance, relapse according to risk stratification. (**A**) Chemoresistance stratified according to two-tier FIGO/WHO risk score. (**B**) Relapse stratified according to two-tier FIGO/WHO risk score. (**C**) Chemoresistance sub-stratified according to four-tier risk score. (**D**) Relapse sub-stratified according to four-tier risk score.

Risk of relapse was more in the high risk than low risk GTN (16 vs. 5%; *P*=0.05). On further sub-stratification into the four-tier categorization, among the low risk GTN, numerically higher risk of chemoresistance was seen in patients with scores 5-6 (intermediate-risk) than lower scores 0-4 [44 vs. 28.5%; odds ratio (OR)=1.9, 95% confidence interval (CI)=0.66-5.77; *P*=0.2] (Fig. 2 and Table III). Among the high risk group, risk score of ≥13 had more risk of relapse than those with the scores 7-12 (OR 7.5, 95% CI =1.26-44.30; *P*=0.02) (Fig. 2 and Table IV). In the current study, all patients except one were eventually cured.

Five patients had liver metastasis, four were treated with EMA-CO and one received EP-CO therapy. Among the four cases who were treated with EMA-CO as the first-line therapy, one was cured, two had chemoresistance and one had relapse. The two patients with chemoresistance subsequently received second-line therapy with TP-TE followed by third-line therapy with EMA-EP before CR. One patient who had a co-existent brain and liver metastasis received EP-CO regimen followed by stereotactic radiation therapy for residual brain metastasis. Another patient with brain metastasis was treated with whole-brain radiation and was cured.

Adverse drug reactions of any grade were seen in 21.5 per cent (25/116) cases and 12 of them also showed multiple adverse effects. The need for hospitalization or change of chemotherapy due to adverse drug reactions (grade 3/4) was required in six (5.1%) patients and one patient had grade 5 adverse event. Other 19 patients only had grade 1/2 events. The commonly observed adverse effects were mucositis (n=18), bone marrow depression (n=11), febrile illness (n=5), dermatological reactions (n=4), hypersensitivity (n=3) and peripheral neuropathy (n=2). One patient who died was a 25 yr old woman, who presented with serum β-hCG of 1,000,000 IU/l and risk score of 16. She was started on EMA-CO therapy but had severe myelosuppression, hepatitis, respiratory failure and sepsis and succumbed despite supportive measures.

In our study, six patients required surgical procedures, including hysterectomy and pulmonary wedge resection as part of their GTN management (Table V). Uterine artery embolization was performed in one case because of irregular bleeding and highly vascular tumour. This patient achieved CR after chemotherapy and did not require further surgical management.

Table IV. Comparison of demographic and clinical variables of patients who had a complete remission after chemotherapy with those who developed relapse

Variables	Remission after completing the chemotherapy (n=104), frequency (%)	Relapse (n=12), frequency (%)	$P^{\$}$	Odds ratio (95% CI)
Age (yr)[#] Mean±SD	30.2±7.5	27.3±4.1	0.20[*]	-
<40	89 (78.0)	12 (100)	0.36	1.0
≥40	15 (14.4)	0		--
Myometrial invasion				
Present	30 (42.8)	3 (25)	1.00	0.8 (0.17-3.61)
Absent	40 (57.1)	5 (41.7)		1.0
Adverse events				
Present	24 (23.0)	1 (8.3)	0.45	0.3 (0.03-2.46)
Absent	80 (77.0)	11 (91.7)		1.0
Serum β-hCG (IU/l)				
<1000	8 (7.7)	1 (8.3)	0.48	1.0
1000-10,000	16 (15.4)	0		--
>10,000-100,000	35 (33.7)	4 (33.3)		0.9 (0.08-9.32)
>100,000	45 (43.3)	7 (58.3)		1.2 (0.13-11.52)
Size (cm)				
<3	21 (23.9)	4 (36.4)	0.50	1.0
3-5	20 (22.7)	1 (9.1)		0.2 (0.02-2.55)
>5	47 (53.4)	6 (54.5)		0.6 (0.17-2.62)
Risk score				
Low risk (0-4)	33 (31.7)	2 (16.7)	0.02	1.0
Intermediate risk (5-6)	24 (23.1)	1 (8.3)		0.6 (.05-8.02)
High risk (7-11)	36 (34.6)	4 (33.3)		1.8 (.31-10.67)
Ultra-high risk (≥13)	11 (10.6)	5 (41.7)		7.5 (1.26-44.30)
Metastasis				
Yes	29 (27.9)	7 (58.3)	0.04	3.6 (1.06-12.32)
No	75 (72.1)	5 (41.7)		1.0
Initial chemotherapy cycles				
Mean±SD	5.8±2.7	5.5±2.1	0.65[*]	1.1 (0.82-1.39)

"--" Odds ratio cannot be calculated due to zero value in one cell, [$]Chi-square/Fisher exact test applied, [*]t test applied, [#]Age structure of patients who developed relapse (n=12); 20-24 yr (4 cases), 25-29 yr (4 cases), 30-34 yr (4 cases). SD, standard deviation; hCG, human chorionic gonadotropin.

Twenty one conceptions occurred in 29 women during the follow up; 16 pregnancies resulted in successful term deliveries with no obstetric complications, three had missed abortion and one had repeat molar pregnancy and required suction evacuation, while one underwent medical termination of pregnancy for an unplanned pregnancy. The contraceptive details were available for 68 patients only; 72 per cent (49/68) used barrier contraception, 14.7 per cent (10/68) used oral contraceptive pills, 7.4 per cent (5/68) used an intrauterine device (IUCD) and only 5.9 per cent (4/68) patients had tubectomy during follow up. None of the patients had repeat GTN.

Discussion

GTN is an uncommon, heterogeneous disorder with diagnostic and management challenges[9,10]. Several countries have established centralized trophoblastic disease centres for standardized care[4,6,11]. GTN is a chemosensitive malignancy with response rates as good as 50-100 per cent[4,11]. The probability of developing chemoresistance after

Table V. Characteristics of cases requiring surgical management for gestational trophoblastic neoplasia

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yr)	45	48	30	32	29	34
Interval since antecedent pregnancy (months)	24	9	2	5	9	17
Pre-treatment β-hCG (IU/l)	4343	19,950	100,000	397,600	300,000	15,000
Initial FIGO stage	I	III	II	IV	IV	I
Site of metastasis	None	Lungs	none	Lung, liver	Lung, liver	None
WHO Risk score	10	12	11	13	10	4
Number of prior Chemotherapy cycles	First line	First line	Two lines	Four lines	Three lines	Two lines
Adverse event during chemo	Bleeding per vagina	Resistance	Resistance	Relapse	Resistance	Resistance
Surgical procedure	TAH	TAH	TAH	Pulmonary wedge resection	TAH	TAH
Indication for surgery	Heavy vaginal bleeding	Resistant disease	Relapse with uterine mass	Persistent disease in lung	Relapse with uterine mass	Chemo resistant disease with bleeding PV and uterine mass
Histopathology	Invasive mole	GTT	Chorio-carcinoma	Metastatic choriocarcinoma	Chorio-carcinoma	Invasive mole
Post-operative chemotherapy	Yes, (EMA-CO)	Yes, (EMA-EP)	Yes (BEP)	None	None	Yes (EMA-CO)
Duration of follow up (months)	30	54	60	LFU	LFU	4 months

TAH, total abdominal hysterectomy; GTT, gestational trophoblastic tumour; LFU, lost to follow up; EMA-CO, etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine; EMA-EP, etoposide, methotrexate, actinomycin-D, etoposide, cisplatin; BEP, bleomycin, etoposide, cisplatin; PV, per vaginum

first-line chemotherapy is 20-40 per cent[7,9,12-14]. The probability of chemoresistance is reportedly higher in the low risk patients (0-6), especially those with the intermediate-risk score (5-6)[4,7,15,16]. Mousavi *et al*[17] observed 14-fold higher risk of chemoresistance in women with a score of 5-6 than with a score of 0-4 (OR=14.28, 95 per cent CI=5.54-36.81). We also observed a numerically increased probability of resistance in the intermediate-risk (5-6) than lower risk (0-4) patients, but significance could not be established due to smaller sample size. Mousavi *et al*[17] observed increased probability of chemoresistance in patients with large tumour size (OR=7.73; 95% CI=1.93-30.91), high β-hCG >100,000 IU/l (OR=5.86, 95% CI=1.07-32.02), less than four months interval since antecedent pregnancy (OR=3.30, 95% CI=1.08-10.02) and metastatic disease (OR=8.42, 95% CI=2.44-29.07). While some authors linked chemoresistance with intermediate-risk scores[15], pre-treatment β-hCG[14], others did not find association with variables such as age[12,14], interval since antecedent pregnancy[14], metastasis[12], high β-hCG[12,14], FIGO stage[14] and tumour size[12,13]. We observed an association of chemoresistance in patients with the intermediate-risk score who had metastasis than those with no metastasis. The inconsistency regarding risk factors among different studies can be explained by variations in sample size and chemotherapy used[16].

The relapse rates in low risk GTN were reported as 2.6 per cent (6/230) by Matsui *et al*[12] and 3.1 per cent (18/579) by Sita-Lumsden *et al*[4]. Kong *et al*[18], reported an increased risk of relapse in high risk than low risk GTN (6.9 vs. 1.6%). A significant association was observed between metastasis, higher FIGO scores and relapse, but age, β-hCG and interval since antecedent pregnancy were not associated with relapse[12], in accordance with our findings. An association with chemoresistance and relapse was observed by Matsui *et al*[12] (50%; 3/6) and in the current study also, 25 per cent patients who relapsed had prior chemoresistance.

El-Helw *et al*[7] observed that with the introduction of current two-tier WHO risk scoring system, the need for second-line chemotherapy increased by 38 per cent. In their study, 63 per cent of patients with a score of 6 required second-line chemotherapy[7]. Sita-Lumsden *et al*[4] observed that the remission rates with SAM therapy in low risk GTN reduced with increasing scores; >75 per cent with risk score 0-1, 50 per cent with score 3-5 and 31 per cent with score 6. The combination therapy (actinomycin-D and methotrexate) for the low risk disease was found to be more effective in reducing resistance and relapse, but it led to increased dose reductions[13,19]. The efficacy of single-agent was the same as combination therapy for score 0-4 but was inferior for score 5-6[19]. The poor response in lower risk patients (score 0-4) could be due to the short exposure time of trophoblastic cells to chemotoxic agents and not because of actual drug resistance[12,20]. Hence, if the patients do not respond to the initial single agent, alternative single-agent chemotherapy would be sufficient[12,20]. Therefore, the grey zone between 5 and 6, which respond poorly to single-agent therapy, may be separately stratified, and initial combination chemotherapy may be justified to avoid exposure to ineffective toxic treatment.

GTN patients with risk score ≥13 are at increased risk of adverse outcome with the standard combination therapy[6]. In the current study, 31 per cent of ultra-high risk cases developed relapse, 37.5 per cent developed chemotoxicity and one patient died. Another study reported higher mortality in patients with risk-score ≥13 than with score <13 (38.4 vs. 4.9%)[5]. The only patient who died in our study had a risk-score of 16 and died while receiving the first cycle of EMA-CO. Such a death could be avoided by using low-dose induction chemotherapy initially for 1-2 cycles and later giving combination chemotherapy to avoid tumour lysis syndrome[2]. Low-dose EP induction followed by full-dose combination chemotherapy when compared with full-dose combination therapy is associated with better remission (71.4 vs. 58.8%)[21] and reduced mortality (7.2 vs. 0.7%)[15]. Hence, it would be useful if ultra-high risk GTN be stratified separately and managed in specialized multidisciplinary centres[5].

Chemotherapy for GTN is well tolerated, and the incidence of grade 3/4 toxicity is 4-15 per cent[12,16,22]. Surgical treatment is not a routine, except for resection of the resistant, relapsed or septic focus of disease[23,24]. In a previous study, only 0.3 per cent cases needed hysterectomy[4], whereas 4.3 per cent needed surgery in our study. GTN is a disease of young women, and future reproductive performance remains a concern. Pregnancy rates and term live birth rates as good as 86.7 and 75.8 per cent have been reported[25], while in our study, the pregnancy rate was 72.4 per cent and live birth rate was 67 per cent.

The current study highlights the difference in the outcome of women with intermediate (5-6) and ultra-high risk score (≥13) than other counterparts with risk score 0-4 and 7-12, reflecting the variations within the same WHO risk group. Our study supports the concept to re-stratify the WHO score from two to four-tier system so that appropriate chemotherapy and follow up can be instituted for select cases. It was limited by small sample size and retrospective design and therefore accurate, CTCAE grading of each drug-induced adverse event was not possible. Prospective studies with larger sample size are needed to evaluate the individual effect of each prognostic determinant and to provide evidence to recommend a change in risk stratification from two-tier to four-tier scoring.

In conclusion, our study confirms that the overall prognosis of patients with GTN needing chemotherapy is good. Patients with risk score 5-6 (intermediate), who otherwise are categorized as WHO low risk group have a higher risk of developing chemoresistance with the current standard of care single-agent chemotherapy. Similarly, the patients with risk score ≥13 (ultra-high risk) have a higher risk of relapse with standard combination chemotherapy.

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