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RESEARCH ARTICLE

Clinical factors associated with days to hCG remission with low risk gestational trophoblastic neoplasia

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ABSTRACT

Objective: To assess the effect of clinical factors on time to hCG remission and chemo-resistance among women with low risk gestational trophoblastic neoplasia (GTN). **Methods**: This retrospective study compromised of 69 patients diagnosed with low risk GTN. Associations of time to hCG remission with various factors were investigated using odds ratio. Associations of chemo-resistance with above clinical variables were analysed using chi square test. **Results**: The analysis showed that FIGO score >4, hCG $\geq 10^4$ mIU/mL at diagnosis, and need for second line multiagent therapy were associated with statistically significant increased days to remission. For every increase in stage there was increase in days to remission by approximately 17 days. For every one unit increase in FIGO score there was increase of remission by approximately 4 days. Serum hCG > 10000 mIU/mL was associated with the risk of chemo-resistance. **Conclusions**: FIGO score > 4, pre-treatment serum hCG > 10,000 mIU/mL is associated with the risk of chemo-resistance. Prompt identification of risk factors and change of chemotherapy to minimize the exposure of these patients to ineffective chemotherapy is essential. This decreases the morbidity, toxicity and treatment time in these young patients.

Keywords: Gestational trophoblastic neoplasia, chemo-resistance, days to remission.

Gestational trophoblastic neoplasia (GTN) are spectrum of malignant lesions that arise from abnormal proliferation of placental trophoblast. This includes invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumour (ETT).

The international rate of choriocarcinoma has been reported to be as high as 1 in 500-600 pregnancies, in India 1 in 50,000 pregnancies [1]. These malignancies are highly susceptible to chemotherapy and almost all patients with low risk GTN are cured with chemotherapy while preserving the woman's reproductive function.

Various single agent chemotherapy regimens had been used in low risk cases with different effectiveness outcomes and toxicity profiles. Four common drugs reported were methotrexate (MTX) with/without folinic acid rescue, actinomycin D (Act-D), etoposide, and 5-flourouracil [2]. Actinomycin D and MTX regimens are the most widely used drugs [3] and are the treatment of choice for low risk GTN [4]. The first successful treatment of GTN with MTX was described [5] by Li in 1956. Complete remission rates from large studies ranged from 66.8% to 90.2% [6, 7]. Actinomycin D was first reported as a treatment of GTN by Goldstein et al[8] in 1972. It has complete remission rates ranging from 77% to 94% [9]. Only 30% of patients with a 5 - 6 FIGO score can be cured with single agent therapy [10]. Many clinical factors like hCG levels, presence of metastatic disease, history of molar pregnancy have all been associated with either an increased risk of chemotherapy resistance [11-13]. The objective of this study was to identify the clinical factors affecting time to hCG remission and chemo-resistance among women with low risk GTN.

Methods

This retrospective study was conducted by using information on patients diagnosed with GTN in a regional

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cancer institute between 2010 and 2019. The study was granted exemption by the institutional ethics committee as it involved only data collection from files retrospectively and analysing it.

All these patients met the FIGO criteria for GTN[11] i.e. they had an hCG plateau of ±10% over the course of at least 3 weeks, or exhibited a rise of serum hCG >10% over the course of 2 weeks, or showed metastasis before hCG plateau or rise. All patients with evidence of suspected GTN underwent history and physical examination, baseline serum hCG level measurement, chest X-ray and pelvic ultrasound.

Patients with functional abnormalities or regional symptoms underwent CT scan/MRI scan of the brain, thorax, abdomen and pelvis as clinically indicated. A combined anatomic staging and scoring system based on The International Federation of Gynaecology and Obstetrics (FIGO, 2009), and modified World Health Organization (WHO) risk factor scoring system defines low risk GTN as a FIGO stages I - III with a WHO score ≤6, and high risk GTN as either FIGO stage IV or any stage with a WHO score ≥7. The patients were treated with 8 day inj. methotrexate / folinic acid alternate day regimen or inj. actinomycin D 5 - day regimen every two weeks.

Inclusion criteria - All women diagnosed with low risk GTN who received treatment at our regional cancer institute, formed the subjects of the study.

Exclusion criteria - Patient who defaulted to treatment or died during treatment before normalization of hCG.

Resistance was defined using the modified FIGO criteria and included an hCG plateau of ±10% over the course of 3 weeks, an elevation of hCG level over the course of 2 weeks. Time to remission (days) was defined as the interval between initiation of chemotherapy and first normal hCG value (< 5 mIU/mL). Therapy was continued for additional two cycles in low risk GTN after normal hCG values according to institutional protocol. The case files were studied with respect to age, parity, antecedent pregnancy, pre-treatment β hCG, risk score and presence of metastases. Follow up visits were tracked to note any case of relapse. The data was analysed in order to find any risk factors associated with chemo-resistance. All the cases were put on surveillance according to protocol.

Statistical analyses were carried out using Stata 16 statistical software. The odds ratio calculated using logistic regression was used to assess associations between clinical factors and time to hCG remission. A linear regression model was adjusted to estimate the effect of FIGO score and stage on time to hCG remission. Chi square test was used for determining association with the factors associated with chemo-resistance. Significance level was set as p ≤ 0.05.

Results

Out of 147 women diagnosed with GTN, 74 belonged to low risk. After excluding 5 patients (all defaulted for treatment) sixty-nine women with low risk GTN were eligible to be part of the study. General characteristics of the study population are as shown in table 1. Mean patient age was 24.26 years (range: 18–38). History of prior mole was reported by 43 (62.5%) patients. Out of the 69 women, 30 (43.5%) were nulliparous.

Table 1: General characteristics of patient (N=69)

Mean age	24.26 years (18-38 yrs.)		
		Number	**Percentage (%)**
Parity	Nulliparous	30	43.5
	Parous	39	56.5
Previous pregnancy	Molar	43	62.5
	Non molar	26	37.5
Beta hCG (mIU/mL)	<10000	26	38
	10000-1lakh	25	36
	>1lakh	18	26
Metastasis	Non metastatic	65	94
	Metastatic	4	6
FIGO score	≤4	54	78
	>4	15	22
Choriocarcinoma	Yes	10	14.5
	No	59	85.5
Need for further lines of chemotherapy	Yes	21	30.5
	No	48	69.5

Disease was confined to the uterus in 65 (94 %) cases whereas only minority had metastatic disease 4 (6%). Beta hCG level had almost equal distribution among the women with <10000, 10000-100000, >100000 miu/ml levels constituted by 38%, 36%, 26% respectively. Majority 54 (78%) had FIGO score of ≤ 4 and minority 15(22%) had score >4 in the cohort. Ten (14.5%) women had histological diagnosis of choriocarcinoma prior to start of treatment. Stagewise distribution of patients is as shown in table 2 and majority of the women i.e. 64(92.75%) belonged to stage 1.

Table 2: Details of remission in low risk GTN

Categories	Median	Interquartile range
Days to remission	60	44-88
Cycles to remission	3	2.5-4

Methotrexate, actinomycin D, EMACO regimen was used as first line chemotherapy in 56(81%), 2(3%), 11(16%) respectively. The choice of chemotherapy was based on discretion of the treating physician based on patient's risk profile including stage, FIGO score and hCG levels. Overall median (first, third quartile) time to remission was 60 days (44-80) and median cycles to remission was 3 (2.5 - 4). In 20 (29%) of the patients, second line chemotherapy was required to achieve hCG remission. Actinomycin D, EMACO and EMA EP regimen was used as second line chemotherapy in patients as needed. Two patients underwent uterine artery embolization (UAE) for plateauing hCG levels after second line single agent actinomycin D and all achieved remission with second line therapy/ UAE. On analysis of the relationship between the stage of disease and days to remission using linear regression, there was statistically significant association between the two variables (p=0.0052). For every increase in stage there was increase in days to remission by approximately 17 days.

Table 3: Stagewise distribution

Stage	Number (%)	Days to remission (median days)
1	64(92.75%)	60
2	1(1.5%)	90
3	4(5.75%)	93

Table 4: Time to remission for clinical factors and associated odds ratio and test p-value.

Clinical variables		Days to remission (median)	Odd ratio (95 %CI)	p value
Previous pregnancy	Molar	60	1.0091	0.3932
	Non molar	65	[0.9893-1.0305]	
Parity	Nulliparous	56.5	1.0086	0.4086
	Parous	60	[.9882-1.0294]	
Beta hCG (mIU/mL)	<10000	44	1.0513	0.00005
	≥10000	72	[1.0223-1.0811]	
Metastatic disease	No	60	1.0233	0.3668
	Yes	90	[0.9724-1.0767]	
Chemo-resistance	Yes	90	0.9242	0.0001
	No	50	[0.8892-0.9605]	
FIGO score	≤4	56.5	1.0381	0.0043
	>4	75	[1.0096-1.0673]	
Choriocarcinoma	Yes	63.5	0.9852	0.2758
	No	60	[0.9590-1.0122]	

Table 5: Characteristics of patients with low risk chemo-sensitive & resistant GTN

Clinical variables		Chemo-resistance	No resistance	P value
Parity	Nulliparous	8	22	0.79
	Parous	12	27	
Beta hCG mIU/mL	<10000	3	22	0.02
	>10000	17	27	
Metastasis	Non metastatic	18	46	0.62
	Metastatic	2	3	
FIGO score	≤ 4	16	38	1
	> 4	4	11	
Choriocarcinoma	Yes	5	6	0.2759
	No	15	43	

Analysis of relationship between clinical factors and days to hCG remission was made using logistic regression and odds ratio was derived from it and details are presented in table 3. The analysis showed that FIGO score > 4, hCG ≥ 10^4 mIU/mL at diagnosis, and need for second line multiagent therapy were associated with statistically significant increased days to remission. On analysis of the relationship between the FIGO score and days to remission using linear regression, there was statistically significant association between the two variables (p=0.025). For every one unit increase in FIGO score there was increase of hCG by 4 units. On analysis of time to remission for clinical factors, FIGO score (p=0.0043), hCG >10000 mIU/mL (p=0.00005) and chemo-resistance (p=0.0001) was associated with increased days to remission. Whereas previous molar/non molar gestation (p=0.393), metastatic disease (p=0.366), parity (p=0.408) and choriocarcinoma (p=0.2758) was not associated with increased days to remission. The details of the clinical factors have been shown in table 4.

On further analysis of clinical variables affecting chemo-resistance in low risk GTN, only hCG levels >10000 mIU/mL was associated with increased risk of chemo-resistance whereas other factors like FIGO score (p=1) previous molar/ non molar gestation (p=0.393), metastatic disease (p=0.62 and parity (p=0.79). Overall choriocarcinoma (p=0.275) was not associated with increased risk of chemo-resistance. However, on excluding patients who received primary EMACO regimen for choriocarcinoma, choriocarcinoma was associated with increased resistance to single agent methotrexate / actinomycin D (p=0.038). Detailed information about the clinical variables has been shown in table 5.

Discussion

GTN although a rare malignancy in women it affects women in their reproductive age which is the vital time for her professional and personal life. The course of disease, chemotherapy, and hospitalisation has significant impact on the productivity and quality of life of these young women [12]. The psychological, social, and sexual consequences of gestational trophoblastic neoplasia can be reduced by decreasing side effects and duration of chemotherapy by monitoring the response to chemotherapy[13]. Response of the disease to treatment can be assessed by time to remission which reflects the duration of chemotherapy and which in turn has a great impact on the quality of life of patients.

Complete remission rates from large studies ranged from 66.8% to 94% [6, 9] from first line single agent chemotherapy in low risk GTN. From previous studies, 16-20% of low risk GTN resisted first line treatment (single agent chemotherapy) [14].

In our study, the mean age of low risk GTN patients was 24.26 years which was similar to another study by Mousavi AS et al [15].

At the end of 2 yrs, all women were under remission without relapse after primary treatment. Among sixty-nine patients, 57 patients, 2 patients, 11 patients received methotrexate, actinomycin D, EMACO regimen respectively as first line chemotherapy. In our study median time to hCG remission (60 days) which was similar to those observed in other study [16]. Median number of cycles to remission was 3 (range: 2.5-4).

Majority of the women were parous (56.5%), but didn't have significant effect on days to remission (p=0.40). Low risk GTN had predominantly molar gestation (62.5%) compared to non-molar gestation preceding the diagnosis of GTN. However prior molar pregnancy didn't affect the remission (p=.39).This result was similar to study by Mousavi AS et al[14] which found no significant association with prior molar gestation.

Beta hCG levels >10000 mIU/ml at diagnosis was seen in 62% of women and had significantly more days to remission compared to levels > 10000 mIU/ml.

Low risk GTN with metastatic disease took more median number of days (90 days vs 60 days) to remission compared to non-metastatic GTN, but it didn't reach statistically significant levels. This was in contrast to the results of Maesta I et al and this may be due to the difference in treatment as 3 out of 5 women with metastatic LR GTN received EMACO regimen as primary chemotherapy in our study [17].

Patients with FIGO score > 4 required significantly more days for normalisation of hCG (75 vs 56.5 days) compared to FIGO score $\leq$ 4 (p=0.0043). Similar results were seen in a study by Maesta I et al. On regression analysis, it was estimated that for every one unit increase in FIGO score there was increase by approximately 4 days to remission which was statistically significant.

There was no significant effect of histological diagnoses of choriocarcinoma (p=0.2758) on remission, and was in contrast with study by Hoekstra AV et al [18] which had impact on remission due to chemo-resistance, however this is difficult to interpret as we did not take routine biopsy of everyone.

Need for 2nd line chemotherapy due to chemoresistance reflected in statistically significant increased duration of remission of hCG (p=0.0001), this was similar to study by Maesta I et al. All patients (n=20) who developed chemo-resistance had received methotrexate single agent as first line therapy amounting to methotrexate resistance of 35%, whereas both patients who received actinomycin D as primary therapy achieved cure. Out of twenty who developed chemo-resistance, eighteen women received actinomycin D and two received EMACO regimen as second line therapy. All achieved remission except three. Among three, one received EMACO regimen as third line who had plateauing at 300 mIU/mL and rest two patients had plateauing of hCG at 15 and 22 mIU/mL for which uterine artery embolization was done (as they had AV malformation on USG) and hCG normalised. All patients were under remission at 2 year follow up. The cochrane review in 2012, including 513 patients in five randomized controlled trials, showed that actinomycin D (Act-D) appeared to be superior to methotrexate (MTX) (risk ratio [RR] 0.64; 95% confidence interval, [CI] 0.54–0.76) [19].

On analyses of the relationship between chemo-resistance to first line chemotherapy and clinical variables our study found that only pre-treatment serum hCG > 10000 mIU/mL was significantly associated with the risk of resistance to first line chemotherapy. Other variables like prior mole, metastasis, FIGO score and parity were not significantly associated with resistance. Choriocarcinoma was significantly associated with chemo-resistance after excluding patients who received EMACO regimen as primary chemotherapy (p=.038).

Hoekstra et al studied the attribute of resistance in 408 GTN patients and found that a history of prior unsuccessful treatment and metastatic site, other than the lung or vagina, were associated with an increased risk of resistance in low risk GTN [17].

Conclusion

Our study showed that risk factors of increased days to remission in the low-risk GTN patients was risk score >4, β-hCG > 10000 mIU/mL and presence of chemo-resistance. Further study showed increased risk of chemo-resistance in patients with β-hCG level higher than 10000 mIU/mL and choriocarcinoma. Patients with these risk factors can be identified and treated with actinomycin D or EMACO as primary therapy on case by case basis. This approach is more cost-effective and decreases the morbidity of unnecessary chemotherapy and improves the quality of life.

Conflict of interest: None. **Disclaimer:** Nil.

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