

Chemo-resistant gestational trophoblastic neoplasia, 5-years experience of Mansoura University Hospital, Egypt

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ABSTRACT

Introduction: Gestational trophoblastic neoplasia (GTN), is recognized as the most curable gynaecologic malignancy. However, many cases are resistant to first line chemotherapy. **Objective:** The aim of the study is to report our 5 years experience in the management of GTN cases with special stress on the chemo-resistant cases. **Methods:** The study was performed through reviewing the records of 51 patients who were diagnosed as GTN during the period from 1/1/2006 to 31/12/2010 in Mansoura University Hospital, Egypt. **Results:** Resistance to methotrexate therapy was reported in 15.15% of low risk cases and received etoposide or cisplatinum/etoposide. Sixty percent of high risk cases were resistant to MAC combination and received salvage chemotherapy or hysterectomy. There was significant correlation between patient response and initial B-hCG, as well as WHO risk score (P value = 0.001 in both) but correlations with age, parity, type of antecedent pregnancy, and histopathology were non significant (p = 0.95, 0.53, 0.47 & 0.83 respectively). **Conclusion:** Low risk GTN cases who were resistant to methotrexate monotherapy received etoposide or cisplatinum/etoposide as a second-line therapy. High risk GTN cases who were resistant to MAC combination received second-line combination chemotherapy and/or hysterectomy. WHO risk score and initial B-hCG were correlated to resistance to first line chemotherapy.

Keywords: Gestational Trophoblastic Neoplasia- Chemotherapy-Resistance

1. INTRODUCTION

Gestational trophoblastic neoplasia (GTN), is the term now commonly applied to persistent or invasive gestational trophoblastic disease [1]. GTN is typically diag-

nosed in asymptomatic women undergoing routine hCG monitoring after evacuation of a complete molar pregnancy. It is recognized today as the most curable gynaecologic malignancy [1]. The reported incidence of GTN is 2/1000 pregnancies in Japan and 0.6 - 1.1/1000 pregnancies in Europe [2]. In Africa, Moodley and colleagues reported that the incidence of GTN was 0.5 /1000 deliveries in South Africa [3].

There are many classifications of GTN, in 1973, Hammond *et al.* classified GTN into non metastatic and metastatic diseases, the later is further subdivided into good prognosis metastatic disease and poor prognosis metastatic disease. In 1976, Bagshawe suggested the use of a prognostic scoring system. The WHO has adopted a modification of Bagshawe's scoring system [1].

Patients scored as low risk (score 0 - 6) receive methotrexate and folinic acid and have a survival rate of about 100%, but a third require second-line chemotherapy, either with single-agent intravenous actinomycin D or with etoposide, methotrexate, actinomycin D alternating with cyclophosphamide and vincristine (EMA/CO) [4-6].

Patients scored as high risk (score ≥ 7) receive EMA/CO as first-line therapy and have a survival rate of 90% but more than 10% of patients fail this therapy [6,7]. To salvage women failing EMA/CO, Newlands *et al.* [8] have previously shown that the addition of cisplatin to etoposide (EP) alternating weekly with EMA (1 day only) with or without surgery salvages a further 75% of cases. El-lamie *et al.* [9], recommended incorporation of paclitaxel in the third-line treatment of resistant GTN. However, Deng *et al.* [10], concluded from a Cochrane systematic review that a MAC regimen was better than other regimens for high-risk GTN because of lower toxicity.

Furthermore, adjuvant surgical procedures could be excellent adjuncts to salvage chemotherapy in removing known foci of chemotherapy-resistant disease in selected patients with persistent GTN [11].

Zhou *et al.* [12], classified refractory GTN as chemo-

resistant GTN group who had never a normal serum beta subunit of human chorionic gonadotropin (β -hCG) level during their previous treatment, relapsed GTN group who had elevated serum β -hCG levels in the absence of the pregnancy after finished treatment 3 months or more, and undetermined GTN group who had elevated serum β -hCG levels in the absence of the pregnancy less than 3 months after completed treatment. They concluded that comparing with the patients with chemo-resistant GTN, the outcome of patients with relapsed GTN was better.

Optimization of treatment strategies for patients who develop drug resistance remains a key challenge. We tried to clarify factors that were linked to resistance to first-line chemotherapy and management of the chemo-resistant cases during the last 5 years in our university hospital

2. PATIENTS AND METHODS

The study was performed through reviewing the records of 51 patients who were diagnosed as gestational trophoblastic neoplasia during the period from 1/1/2006 to 31/12/2010 in the departments of Gynaecology and Clinical Oncology, Mansoura University Hospital, Egypt.

The cases were diagnosed as GTN after persistent positive hCG more than 6 months, plateauing, or rising serum level of β -hCG after evacuation of molar pregnancy or after histological diagnosis of choriocarcinoma, invasive mole, or placental site trophoblastic tumour (PSTT).

The patients were evaluated with respect to age, parity, type of antecedent pregnancy, clinical presentation, and presence of metastasis. The level of serum β -subunit of hCG at diagnosis, and its level on follow up visits were studied. Uterine re-curettage and pathological findings were evaluated. All women were classified as low-risk or high-risk disease using FIGO and WHO scoring systems [1].

The first line chemotherapy treatment for these cases was studied regarding its type (single or multiple agent), number of courses, and the response rate. Patients needed second, third lines of combination chemotherapy as well as performing hysterectomy or other surgical procedures were also analyzed.

3. STATISTICAL ANALYSIS

The statistical analysis of data done by using *excel* program for figures and SPSS program (SPSS, Inc, Chicago, USA) statistical package for social science version 16.

To test the normality of data distribution K-S (Kolmogorov-Smirnov) test was done only significant data revealed to be nonparametric. The description of the data done in form of mean (+/-) SD for quantitative data and Frequency & proportion for qualitative data.

The analysis of the data was done to test statistical significant difference between groups. For quantitative data student t-test was used to compare between two groups.

Paired sample t-test was used to compare one group at different times. Chi square test was used for qualitative data. P is considered significant if less than or equal to 0.05 at confidence interval 95%.

4. RESULTS

This retrospective study included 51 cases who were diagnosed as GTN. The mean follow up duration was 28.45 months (range: 3 - 54). Thirty-six cases (70.6%) were low risk and 15 cases (29.4%) high risk according to WHO scoring system. The mean age was 28.7 years (range: 17 - 50 years). The mean parity was 1.29 (range: 0 - 5). Mean β -hCG level on admission was 52705.8 mu/ml (range: 60.0 - 500,000). The mean time since the last pregnancy was 6.15 months (range: 1 - 72).

The history of the previous pregnancy was shown in **Table 1**, as can be seen from the table, 30 cases (58.8%), followed complete hydatidiform mole.

The initial clinical presentation of the studied cases was post molar bleeding in 24 cases (47.05%), non-normalization of hCG after molar evacuation in 10 cases (19.60%), abnormal vaginal bleeding in 16 cases (31.38%), and one case (1.97%), was presented to the emergency unit by internal haemorrhage with elevated hCG (1000 mu/ml) and diagnosed after laparotomy as ruptured hepatic metastasis of choriocarcinoma.

Dilatation and curettage was done in 36 cases (70.6%), the histopathology of these cases was shown in **Table 2**. There were 8 cases (15.68%) with distant metastases, the sites of metastasis are shown in **Table 3**.

Forty-eight patients received first line chemotherapy for 2 - 15 cycles, 3 low risk cases (5.9%) did not receive chemotherapy due to spontaneous decline of β -hCG after uterine re-curettage (a total of 51 cases). Complete response was achieved in 34 patients (70.83%), while 14 cases were resistant to chemotherapy (29.17%).

Regarding first-line treatment, 33 low-risk cases received methotrexate in a dose of 1 mg/kg in days 1, 3, 5, and 7 alternating with oral folinic acid 0.1 mg/kg in days 2, 4, 6, and 8. Mean number of courses was 5.09 (range: 2 - 15). Twenty-eight cases (84.85%) achieved remission, while 5 cases (15.15%) needed second line therapy in the form of etoposide (3 cases) and cisplatin/etoposide (2 cases) with a complete response.

High risk patients (15 cases) received methotrexate - actinomycin D-cyclophosphamide (MAC) combination as first-line chemotherapy, 6 cases (40%) responded to this treatment while 9 cases (60%) were resistant. According to our tumour discussion panel, 6 of the resistant cases received cisplatin/etoposide as second-line

Table 1. The type of antecedent pregnancy.

	Count	Percentage
Abortion	10	19.6%
Partial mole	9	17.6%
Complete mole	30	58.8%
Term pregnancy	2	3.9%
Total	51	100.0%

Table 2. Histopathology of the studied cases.

	Count	%
No endometrial biopsy*	15	29.4%
Choriocarcinoma	20	39.2%
Molar tissues	10	19.6%
Invasive mole	3	5.9%
PSTT**	3	5.9%
Total	51	100.0%

*: Diagnosis of GTN was done by non-normalization of B-hCG after evacuation of hydatidiform mole; PSTT**: Placental site trophoblastic tumor.

Table 3. Sites of distant metastases.

Percentage	Number	
62.5%	5	Lungs
12.5%	1	Lungs and brain
12.5%	1	Bone and brain
12.5%	1	Liver
100 %	8	Total

therapy, where 4 of them achieved remission by this salvage chemotherapy and the other 2 cases did not respond and had hysterectomy. The remaining 3 cases were not given second line chemotherapy; 2 cases had hysterectomy as they refused salvage chemotherapy and they had no distant metastasis while the last case died during the first line therapy after rapid progress with lung and brain metastasis.

Radiotherapy was used in two cases (3.92%) with brain and/or bone metastasis. Surgical treatment was done in 5 high risk cases (9.8%). Hysterectomy was done in 4 cases (7.84%); as a second line in 2 cases and as a third line in 2 further cases. Hepatic resection was done in one case who presented by internal haemorrhage due to rupture of hepatic metastasis.

The overall survival of GTN cases in our study was 98.04% and was found to be 100% for low risk patients.

Table 4 shows the correlation of age, parity, and initial B-hCG to patient response to first-line chemotherapy. As can be seen from this table, patient response was not

Table 4. Correlation of age, parity, and initial B-hCG to patient response to first-line chemotherapy.

	Response	N*	Mean	S D**	P value
Age	Responders	37	28.73	7.85	0.953 (NS)***
	Non responders	14	28.57	9.97	
Parity	Responders	37	1.38	1.497	0.534 (NS)
	Non responders	14	1.07	1.73	
Initial hCG	Responders	37	27533.65	46849.297	0.001 (Sig.)****
	Non responders	14	119232.14	1.40103.5	

N*: Number of patients; SD**: Standard deviation; (NS)***: Non significant; (Sig.)****: Significant.

significantly correlated to age and parity but there was significant correlation to initial B- hCG.

Table 5 shows the correlation between type of antecedent pregnancy and patient response to first-line chemotherapy, P value was 0.74 (non significant).

Table 6 shows the correlation between histopathology and patient response to first-line chemotherapy, again, there was no significant correlation. **Table 7** shows the correlation between WHO risk score and patient response to first-line chemotherapy, there was significant correlation (P value = 0.001).

5. DISCUSSION

Gestational trophoblastic neoplasia is highly responsive to chemotherapy and prognosis is excellent following treatment, especially in low-risk patients [13]. However, resistance to first line chemotherapy was reported to occur in 33% of low risk cases and about 10% of high risk cases (4,8). There is a need to find out the factors that linked to chemo-resistance as well as to reach the ideal treatment strategies for these patients.

This retrospective study was performed through reviewing the records of 51 patients who were diagnosed as gestational trophoblastic neoplasia during the period from 1/1/2006 to 31/12/2010 in the departments of Gynaecology and Clinical Oncology, Mansoura University Hospital, Egypt.

The socio-demographic criteria of GTN patients may differ according to the geographic distribution. The mean age of our cases was 28.7 years which agreed with findings of other authors [8,12] but did not agree with data published by Kaye [14], from Uganda who reported that most of his cases occurred below 20 years or above 35 years. The mean parity of patients in our study was 1.3 which did not agree with Kaye [14] as 68% of his patients had 5 or more deliveries. This may be explained by different community criteria.

Most of our GTN cases occurred after complete molar

Table 5. Correlation of type of antecedent pregnancy to patient response to first-line chemotherapy.

	Response		Total
	Responders	Non responders	
Abortion	6 (60%)	4 (40%)	10
Partial mole	8 (88.89%)	1 (11.11%)	9
Complete mole	22 (73.33%)	8 (26.66%)	30
Term pregnancy	1 (50%)	1 (50%)	2
Total	37	14	51

P value : 0.47 (non significant).

Table 6. Correlation of histopathology to patient response to first-line chemotherapy.

	Response		Total
	Responders	Non responders	
Endometrial biopsy not done	13 (86.67%)	2 (13.33%)	15
Choriocarcinoma	13 (65%)	7 (35%)	20
Molar tissues	9 (90%)	1 (10%)	10
Invasive mole	1 (33.33%)	2 (66.67%)	3
PSTT	1 (33.33%)	2 (66.67%)	3
Total	37	14	51

P value : 0.083 (non significant).

Table 7. Correlation of WHO risk score to patient response to first-line chemotherapy.

	Response		Total
	Responders	Non responders	
Low risk (score 0 - 6)	31 (86.11%)	5 (13.99%)	36
High risk (score \geq 7)	6 (40%)	9 (60%)	15
Total	37	14	51

P value: 0.001 (Significant).

pregnancies (58.8%), as can be seen from **Table 1**, this was in agree with other authors [15,16]. **Table 2** shows the histopathology of the cases who had been performed uterine curettage. Twenty of thirty-six cases (55.56%), were found to be choriocarcinoma this finding was agreed with other authors [17,18]. Distant metastases were shown in **Table 3**, lung metastasis was the commonest, a similar finding was reported by Kumar *et al.* [19].

Low risk GTN cases received Methotrexate/folinic acid but there was 15.15% of patients fail to respond to this monotherapy. Resistance to methotrexate therapy was reported also by other authors [5,6].

High risk cases received MAC combination chemo-

therapy, however, 60% of them were resistant to this protocol. This figure was higher than reports of other authors [10,12], this can be explained by smaller number of patients in the current study.

In this study, we tried to determine whether there were any factors linked to resistance to first line chemotherapy during initial treatment of GTN. **Tables 4-7**, showed that there was significant correlation of chemotherapy response to initial B-hCG and WHO score ($p = 0.001$ in both). These findings were supported by other author [20,21]. No significant correlation of age, parity, type of antecedent pregnancy, and histopathologic type ($p = 0.95, 0.53, 0.47$ & 0.83 respectively). This was supported by the results of Wang *et al* [22] but did not agree with Bagshawe [20]. This discrepancy may be as result of small number of patients who performed endometrial biopsy (36 cases).

Surgical procedures may be good adjuncts to chemotherapy in properly selected cases as the majority of women with GTN are young and wish to preserve their fertility. Hysterectomy was done in 4 high-risk cases who failed to respond to first line chemotherapy as a second or third line therapy. This findings was also supported by other authors [12,17,23].

We have to report that this retrospective study represented a single center experience and had relatively small number of cases. A large multicenter prospective trial is recommended.

6. CONCLUSIONS

Low risk GTN cases were found to be resistant to methotrexate monotherapy in 15.15%, these cases received etoposide or cisplatinum/etoposide as a second-line therapy. High risk GTN cases received MAC combination but 60% were resistant and needed second line combination chemotherapy or hysterectomy. WHO score and initial B-hCG were significantly correlated to resistance to first-line chemotherapy.

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