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Original Research Article

Chemo-resistant gestational trophoblastic neoplasia: a review of cases at a tertiary cancer centre

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ABSTRACT

Background: Gestational trophoblastic neoplasia (GTN) was earlier a dreaded malignancy with high mortality rates. GTN is now considered to be one of the most curable solid tumours in women with cure rates greater than 90% even in the presence of metastases. Despite the high chemo sensitivity, treatment failure or drug resistance has been described in both groups.

Methods: In this study, available records of GTN cases over 6 years were reviewed with emphasis on those who were resistant to the first line of chemotherapy. Of these, 37(34.58%) were resistant to the first line of chemotherapy. These cases were studied with respect to age, parity, antecedent pregnancy, interval from antecedent pregnancy, pretreatment β hCG, risk score and presence of metastases. The data was analyzed in order to find any risk factors associated with chemo-resistance.

Results: Total number of cases of GTN was 107. Out of these 107 cases, 63 (58.88%) were low risk and 44 (41.12%) were high risk according to FIGO scoring system. Complete response was achieved with first line chemotherapy in 70 (65.42%) patients. The remaining 37 (34.57%) were resistant to first line chemotherapy. In the low risk group, 30 (47.62%) cases, and in the high-risk group, 7(15.91%) were resistant to first line of chemotherapy.

Conclusions: Despite the high chemo sensitivity of GTN, resistance to first line chemotherapy may be encountered in up to 40% of cases. It is important to identify the patients who are at risk to develop resistance, early identification of resistance and change of chemotherapy so as to minimize the exposure of these patients to ineffective chemotherapy.

Keywords: Chemoresistance, Chemotherapy, Gestational trophoblastic neoplasia

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) was earlier a dreaded malignancy with high mortality rates. This changed in 1956 when Li et al reported the first complete remission using injection methotrexate (MTX) in a patient with metastatic choriocarcinoma.¹ GTN is now considered to be one of the most curable solid tumours in women with cure rates greater than 90% even in the

presence of metastases.² This is mainly due to the chemosensitivity of this tumor and the availability of a sensitive tumor marker β hCG (beta subunit of human chorionic gonadotropin).

The FIGO prognostic scores are used to classify the patients into low risk (score 0-6) and high-risk groups (score \geq 7). Despite the high chemo sensitivity, treatment failure or drug resistance has been described in both groups. According to a recent Cochrane systematic

review, resistance to first line chemotherapy is seen in about 45% of women with low risk GTN and 30%-40% of those with high risk GTN.³ A multi-modality approach with multiple lines of chemotherapy, surgical intervention or radiation may sometimes be required. Treatment of patients who develop drug resistance remains a key challenge.

In this study, available records of GTN cases over 6 years were reviewed with emphasis on those who were resistant to the first line of chemotherapy.

METHODS

This is an observational retrospective study. A total of 107 cases of GTN managed at our regional cancer centre from 2009 till 2016 were reviewed. Of these, 37 (34.58%) were resistant to the first line of chemotherapy. These patients required second or third line of chemotherapy, some also required surgical intervention.

Inclusion criteria

- Cases of GTN which failed to achieve remission with first line of chemotherapy with either a plateau of β hCG.
- Rising β hCG or an inadequate log fall and required second or third line of chemotherapy or surgical intervention.

Exclusion criteria

- Those patients who went into remission with the first line of chemotherapy and did not require any further treatment with no relapse.

The cases files were studied with respect to age, parity, antecedent pregnancy, interval from 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. Patients were followed till December 2018.

RESULTS

Total number of cases of GTN was 107. Out of these 107 cases, 63 (58.88%) were low risk and 44 (41.12%) were high risk according to FIGO scoring system. Complete response was achieved with first line chemotherapy in 70 (65.42%) patients.

The remaining 37 (34.57%) were resistant to first line chemotherapy. In the low risk group, 30 (47.62%) cases, and in the high-risk group, 7 (15.91%) were resistant to first line of chemotherapy as shown in Table 1.

Table 1: Number of resistant cases of the total GTN patients (total number n=107).

	No. of cases	%	Resistant cases	%
Low risk	63	58.88	30	47.62
High risk	44	41.12	7	15.91
Total	107			34.58

The mean age of patients was 27.64 years (19 to 47 years). The mean pre-treatment β -hCG was 1,93,006 IU/L (113- 12,00,000 IU/L). The mean follow up duration was 17.04 months. Antecedent pregnancy was vesicular mole in more than half of the patients (53.85%). The history of antecedent pregnancy is shown in Table 2.

Table 2: Antecedent pregnancy in the two groups (n= 107).

Antecedent pregnancy	Responders	Non-responders	Total
Vesicular mole	36	20	56
Abortion	18	14	32
Term pregnancy	16	3	19
Total	70	37	107

The mean interval between the antecedent pregnancy and diagnosis of GTN was 8.37 months. Of the total 107 patients, 36 (33.64%) had metastases. Metastases in the two groups are shown in table 3. (Responders- responded to first line chemotherapy; non-responders- resistant to first line chemotherapy).

Table 3: Site of metastasis (n=36).

Site of metastasis	Responders	Non-responders	Total
Only lung	17	9	26
Vagina	1	1	2
Lungs and vagina	5	0	5
Lungs and liver	0	1	1
Lungs and brain	1	0	1
Vagina, lungs, liver, brain	1	0	1
Total	25	11	36

All low risk patients (63) received methotrexate/folinic acid (MTX/FA) initially. Thirty of these did not respond adequately, with plateauing of β hCG in 17 and rising β hCG in 13 patients. Of these 30 cases, 20 were given actinomycin D (Act D) as second line chemotherapy. Eight responded and achieved remission with Act D. The remaining 12 patients did not have an adequate log fall with multiple cycles of Act D and were given etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA CO) as the third line chemotherapy. Eleven achieved remission with EMA CO and are on surveillance. One patient who was started on EMA CO,

had severe gastrointestinal toxicity and grade IV neutropenia. She succumbed after the first cycle.

Ten patients were given EMA CO directly after MTX. Of these, 8 achieved remission and are on follow up. One patient had plateauing of β hCG and was given etoposide, methotrexate, actinomycin D, etoposide, cisplatin (EMA EP), she achieved remission after 2 cycles of EMA EP. One patient was lost to follow up. One non-metastatic low risk case, started on MTX, took irregular treatment and developed resistant disease with pulmonary metastasis. She received multiple lines of chemotherapy and surgical intervention in the form of total hysterectomy and pulmonary resection. She did not achieve remission. All high-risk patients (44) received EMA CO as initial treatment. Seven of them did not show adequate response to first line chemotherapy, with rise in β hCG in 3 and plateauing in 4 patients. Two were given bleomycin, etoposide, cisplatin (BEP) as second line and both achieved remission after 2 cycles and are on surveillance. Two were given EMA EP, one achieved remission while the other was lost to follow up.

In two patients, after receiving 7 and 8 cycles of EMA CO, there was plateauing and rise in β hCG. A repeat metastatic workup revealed disease limited to the uterus. Abdominal hysterectomy was done in both following which there was an immediate fall in β hCG. Both of them achieved remission after two more cycles of EMA CO. One patient who was resistant to multiple lines of chemotherapy underwent surgical intervention-hysterectomy and pulmonary resection and is in remission. The patients who required multiple lines of chemotherapy were further studied to find any factors responsible for the initial chemo-resistance. Authors found a high rate of chemo-resistance in our low risk group- 47.62%. The characteristics of the low risk chemo-resistant patients were analysed. Table 4 shows the pre-treatment β hCG levels in the low risk chemo-resistant group.

Table 4: Pre-treatment β hCG level in low risk chemo-resistant cases (n=30).

β hCG (IU/L)	Number of patients
< 1000	None
1000-<10,000	6
10,000-<1,00,000	19
\geq 1,00,000	5

Table 5: Risk scores in low risk chemo-resistant cases (n=30).

Risk score	Number of patients
2	9
3	9
4	2
5	4
6	6

All low risk chemo-resistant cases had β hCG more than 1000 IU/L and in 24 (80%) patients, it was more than 10,000 IU/L. The FIGO risk scores of low risk chemo-resistant cases are shown in Table 5.

Thus, ten patients had a risk score of 5 or 6 (corresponding to intermediate risk group of earlier classification). History of antecedent pregnancy in the low risk chemo-resistant patients is shown in Table 6.

Table 6: Antecedent pregnancy in low risk chemo-resistant cases (n=30).

Antecedent pregnancy	Number
Vesicular mole	18
Abortion	11
Term pregnancy	1

Metastases in low risk chemo-resistant patients is shown Table 7.

Table 7: Metastases in low risk chemo-resistant cases (n=30).

Site of metastases	Number
Lungs	6
Vagina	1
None	23

The age of patients in the low risk chemo-resistant group is shown in Table 8.

Table 8: Age in low risk chemo-resistant cases (n=30).

Age	Number of patients
<20-24	14
25-30	13
>30	3

The risk factors present in the low risk chemo-resistant patients are shown in Table 9. Resistance to initial chemotherapy may be attributed to one or more of these.

Table 9: Risk factors in low risk chemo-resistant patients (n=30).

Risk factor	No. of patients
Intermediate risk score (5 and 6)	10
Scores 2, 3 and 4	20
β hCG>10,000	8
Metastases (lungs and vagina)	4
Age >30 years	3
Previous incomplete treatment	2
No other risk factors	3

Of the 30 low risk patients who were resistant to first line chemotherapy (MTX/FA), 27 (90%) had some high-risk factor, 10 had risk scores 5 or 6 (intermediate risk), 4 patients had metastases (lungs and vagina), 8 had high

pre-treatment β hCG (>10,000). In 6 of these, it was more than 50,000 IU/L. Three patients were around 35 years old (34, 36 and 37). Two patients had received incomplete treatment outside and were then referred. Clinical and biochemical features of high risk GTN patients resistant to initial chemotherapy are shown in Table 10.

Table 10: Characteristics of patients with high risk chemo-resistant GTN (n=7).

Risk factor	No. of patients	
Pre-treatment β hCG (IU/L)	< 1,00,000	1
	1,00,000- 5,00,000	3
	5,00,000- 10,00,000	2
	>10,00,000	1
Antecedant pregnancy	Vesicular mole	1
	Abortion	5
	Term pregnancy	1
FIGO score	8	2
	9	1
	10	1
	11	1
Site of metastases	Lung	6
	Lung + liver	1

Characteristics of high-risk chemo-resistant cases as shown in table 10-all patients had β hCG> 1,00,000 IU/L. All had pulmonary metastases, one patient had pulmonary and hepatic metastases. Two patients had FIGO risk score of 8, in others it was more than 9.

DISCUSSION

GTN is highly responsive to chemotherapy. The cure rate of low risk cases approaches 100% and that of high-risk cases is more than 90%.² Despite the high chemo sensitivity, resistance to first line chemotherapy is sometimes encountered, requiring second or third line salvage chemotherapy. In some cases, surgical excision of isolated chemo-resistant disease may be required.

According to a recent Cochrane systematic review, resistance to first line chemotherapy is seen in about 45% of women with low risk GTN and 30%-40% of those with high risk GTN.³

In present study, resistance to initial chemotherapy was seen in 37 (34.58%) patients. MTX/FA was the initial chemotherapy in all low risk patients and resistance was seen in 47.62%. All high-risk patients were initially treated with EMA CO and resistance was seen in 15.91% of cases.

More than half cases (52.34%) had antecedent vesicular mole. This is also seen in majority of the studies.^{4,5}

Metastases were present in 33.64% of cases and the most common site was lungs (72.22%).

Low risk GTN

Resistance to first-line chemotherapy has been reported in up to 45% of women with low-risk GTN, depending on the regimen used.^{3,6} Hemida et al reported resistance to first line chemotherapy (MTX) in 15.15% of low risk cases.⁴ In another study by Mousavi et al, resistance to first line single agent chemotherapy was reported in 43% of low risk patients.⁷ In present study, similar results were obtained and resistance to first line chemotherapy was seen in 47.62% of low risk cases.

Risk factors for drug resistance in low risk GTN include a high pre-treatment β hCG (>1,00,000 IU/ L), intermediate risk scores (5 or 6), non-molar antecedent pregnancy and a histological diagnosis of choriocarcinoma.^{3,6,8,9,10} A study from Charring Cross hospital concluded that the cure rate with single agent chemotherapy (MTX) in low risk GTN with β hCG level >1,00,000 IU/L was only 30% and it was much lower in those with higher levels.⁸ Drug resistance to primary chemotherapy is also associated with higher relapse rates.¹¹

In present study, among the resistant low risk cases, one or the other risk factors (FIGO score 5 or 6, β hCG>10,000, metastases, age >30 years and previous incomplete treatment) was present in 90% as given in Table 9. Ten patients had risk scores 5 or 6 (intermediate risk). Mousavi et al reported that the resistance to first line chemotherapy was 11% in those with a score of <4, while it was 63% in those with score \geq 4, which was 14 fold higher.⁷

Seckl et al, reported only 30% of intermediate risk score patients can be expected to be cured with first line chemotherapy.¹² ESMO (European society of medical oncology) guidelines suggest a refinement of the FIGO scoring system so that 70% of women in intermediate risk group who develop resistance to MTX/FA, could be identified initially for more intensive therapy.¹³

In present study methotrexate/ folinic acid (MTX/FA) regimen was used as the first line chemotherapy in all low risk patients. The MTX/FA regimen is effective, well tolerated, does not induce hair loss and in most cases can be taken even from a general practitioner.

Hence MTX/FA is most widely accepted as the first line drug.¹⁴ After resistance to first line chemotherapy either a second line single agent therapy or a multi agent regimen is given.

Multi agent chemotherapy is indicated in case of significant elevation of β hCG, development of metastases or resistance to sequential single agent chemotherapy.²

In spite of risk factors, chemo-resistance and use of multiple modalities of treatment, the salvage rate in low risk GTN approaches 100%.^{2,7}

High risk GTN

High risk patients are treated more aggressively with multi agent chemotherapy with or without radiation or surgery. EMA/ CO is the most widely used primary combination therapy. However, it has been reported that about 30% to 40% of women will develop resistance or will relapse after remission and need salvage chemotherapy.^{3,15} In present study, resistance was seen in 7 patients that is in 15.91% of high-risk cases. Hemida et al reported resistance in 60% high risk patients. However, they had MAC regimen as first line therapy and their study population was small.⁴ Ngu et al reported resistance in 25% of high risk cases.¹⁶ The various salvage regimens used are EMA EP, BEP, EP, VBP (vinblastine, bleomycin, cisplatin), VIP (vinblastine, ifosfamide, cisplatin) among others. Salvage chemotherapy with the EMA-EP regimen is most widely used. This regimen is highly toxic and usually requires granulocyte colony stimulating factor support by the third cycle.¹⁷

Risk factors for resistance to treatment in high-risk GTN include high FIGO score, the number and sites of metastases, incomplete previous treatments, and the stage of the tumour.^{3,18} Metastases to brain, liver, gastrointestinal tract are associated with worse prognosis.^{3,19} In present study 6 of the 7 high risk chemo-resistant patients had score of ≥ 9 . All patients had pulmonary metastasis and one patient had hepatic metastasis. All except one had a pre-treatment β hCG above 1,00,000 IU/L (Table 10). Two patients, after 7 and 8 cycles of EMA CO had rise in β hCG. A repeat metastatic work up revealed disease limited to the uterus. Total hysterectomy was done in both patients, after which there was a fall in β hCG. Both achieved remission after two more cycles of EMA CO and are on surveillance. One patient achieved remission after multiple lines of chemotherapy as well as surgical intervention in the form of total hysterectomy and pulmonary resection. Salvage therapy is more likely to fail in heavily pre-treated patients.²⁰

CONCLUSION

Despite the high chemo sensitivity of GTN, resistance to first line chemotherapy may be encountered in up to 40% of cases. However, most patients achieve cure with salvage treatment. It is important to identify the patients who are at risk to develop resistance, early identification of resistance and change of chemotherapy so as to minimize the exposure of these patients to ineffective chemotherapy. All GTN patients must be managed at tertiary care centres with a multidisciplinary team approach. Individualization of treatment is most important while managing such chemo-resistant cases. Several salvage chemotherapeutic regimens are used for

treating resistant or recurrent GTN. It is important to identify those regimens which are most effective and least toxic. Future clinical trials and cost-effectiveness studies are needed to determine a better choice of treatment in the intermediate risk group (FIGO score 5-6 – old WHO prognostic scoring system).

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