Treatment Outcome of Gestational Trophoblastic Neoplasia

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Abstract: Objective: To assess the outcome of patients with gestational trophoblastic neoplasias (GTN) after treatment, also to analysis the prognostic factors with respect to response to initial chemotherapy (CT) and survival rate. **Methods:** This retrospective study was conducted at Department of Clinical Oncology Tanta University Hospital and Tanta Cancer Center from Jan. 1999 to Dec. 2008. The files of all diagnosed patients with GTN during the study period were reviewed regarding their history, clinical examination, investigations, treatment and follow-up. **Results:** During the study period there were 62 proved patients with GTN. Out of 62 patients, 35 (56.5%) patients treated with single agent initial CT, 27 (43.5%) patients treated with initial multi-agent CT. Suction curettage was applied for 55 (88.7%) patients while total abdominal hysterectomy (TAH) was initially applied for 7 (11.3%) patients. Complete remission (CR) with first-line treatment was achieved in 74.2% of all patients. Complete remission had achieved in 86.5% (32/37) low risk patients and in 56% (14/25) of intermediate and high risk patients. Factors that significantly affecting the response rate were; pathologic type (p>0.001), disease stage (p<0.001), risk score (p<0.007), presence of metastases (p=0.001) and type of CT (p=0.018). The 5-year overall survival rate for all patients was 74.9 % with a mean survival time of 53.2 ± 28.3 months. With multivariable analysis, WHO scoring and disease stage were found to be independent prognostic factors for survival rate (p= 0.008 & 0.004 respectively). The recurrence rate was 11.3% with a median interval of relapse was 7 months (range, 4 to 32 months). **Conclusion:** It is important to individualize treatment for women with malignant GTN based upon known risk factors. WHO scoring and FIGO staging were found to be independent prognostic factors for survival rate. Although GTN was found to be a highly chemosensitive, a significant proportion of patients die of the disease, so more effective therapeutic protocols may be required in such patients to improve the survival rate.
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Key words: Gestational trophoblastic neoplasia**,** Invasive mole, Choriocarcinoma

1. Introduction

GTN are malignant lesions that arise from abnormal proliferation of placental trophoblast. The pathologic conditions that make up this entity include partial and complete hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. GTN often arises after molar pregnancies but can also occur after any gestation including miscarriages and term pregnancies.[(1)]

GTN is highly responsive to CT. Therefore, it is the main modality of treatment in patient with GTN even in its metastatic forms.[(2)] GTN is potentially curable with an overall cure rate reported to be 90-100%.[(3)] GTN is also radiosensitive. Radiotherapy can be used in treatment of some patients with brain, hepatic metastases or in patients who CT is not possible due to medical problems.[(4)]

Several single CT regimens have been used to treat low-risk GTN; weekly methotrexate (MTX)[(5)], MTX daily x 5 days[(6)], 8-day alternating MTX and leucovorin[(7)], MTX continuous infusion[(8)] and dactinomycin biweekly (pulse)[(5)]**.**

The multi-agent CT EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine) has widely become accepted as the treatment of high-risk disease.[(9)] EMA/CO may improve the primary response rate and lower the acute toxicity rate, compared with MAC (methotrexate, dactinomycin, and cyclophosphamide) regimen, especially among patients at high risk, but theoretically may increase the risk of leukemia.[(10)] Twenty-five percent of patients with high-risk disease will have an incomplete response to or relapse from a methotrexate-containing regimen such as EMA/CO. These patients should be treated with salvage CT regimens employing platinum, often in conjunction with surgical resection of sites of persistent tumor in the uterus or lungs.[(11)]

It is strongly recommended that pregnancy be delayed for 1 year or more after CT, due to the genetic damage and teratogenic effects of anti-cancer agents, and 1 year or more after the completion of β-hCG monitoring.[(12)]

2. Patients and Methods

This retrospective study was conducted at the Department of Clinical Oncology, Tanta University Hospital and Tanta Cancer Center. The records of all presented cases with malignant GTN between Jan 1999 and Dec 2008 were analyzed regarding the age, parity, clinical picture, pre-therapy β-hCG, histopathology, radiological investigations, type of trophoblastic disease, type of surgical treatment, CT treatment, response and mortality associated with this disease.

All patients were staged according to current International Federation of Gynecology and Obstetrics (FIGO) classification.[13] Based on the FIGO 2000 scoring system for GTN[14] (Table 1) all patients were classified into three risk groups; 37 patients (59.7%) were low risk (≤4), 19 patients (30.6%) were intermediate risk (5-7) and 6 patients (9.7%) were high risk (>8).

Treatment protocols

Sixty-two patients were included in this retrospective study. Therapeutic methods in this study as shown in Table (2) were: Suction curettage with single agent CT [methotrexate MTX daily for 5 days (0.4 mg/kg, maximum 25 mg) IV or IM daily for 5 days; recycle every 14 days until β-hCG normal for 3 consecutive weeks, or weekly MTX (30-50 mg/m^2 IV; recycle weekly until β-hCG normal for 3 consecutive weeks) for 23 patients or, actinomycin-D (0.5 mg/day for 5 days repeated every 2 weeks) for 11 patients] for 34 low risk patients (score ≤ 4), total abdominal hysterectomy (TAH) with adjuvant single agent methotrexate with for only one low risk patient. Suction curettage with multi-agent CT [MAC regimen (methotrexate 0.3 mg/kg IM daily, actinomycin-D 8-10 microgram/kg IV daily and cyclophosphamide 250 mg IV daily) days 1-5 repeated every 14 or 21 day] for 19 intermediate and high risk patients (score > 4) and 2 low risk patients, TAH with adjuvant MAC regimen for 6 intermediate and high risk patients. Indication of hysterectomy was emergency presentation with heavy bleeding.

After the first undetectable β-hCG level, 2 additional CT courses are administered to reduce the risk of relapse. Second line CT was used for 16 patients (5 low risk patients and 11 intermediate / high risk patients) resistant to initial CT in form of: (1) EMA/CO protocol for 12 patients [EMA; (day1: etoposide 100 mg/m^2 IV over 30 minutes, methotrexate 100 mg/m^2 IV bolus and 200 mg/m^2 over 12 hours and actinoomycin-D 0.5 mg IV bolus, day 2: etoposide 100 mg/m^2 IV over 30 minutes, actinomycin-D 0.5 mg IV bolus and folinic acid 15 mg PO bid for 2 days commencing 24 hours after start of methotrexate), CO; (vincristine 1 mg/m^2 IV bolus and cyclophosphamide 600 mg/m^2 IV alternating weekly with EMA)], (2) MAC regimen for 4 patients initially treated with single agent CT. Routine surveillance during treatment included complete blood counts, chemistry profiles, and β-hCG levels before each course of treatment.

Table (1): Modified WHO prognostic scoring system for GTN as adapted by FIGO[13]

Prognostic factor	Score			
	0	1	2	4
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy [a]	<4	4-<7	7-<13	≥13
Pre-treatment serum β-hCG (IU/mL)[b]	$<10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size (cm)	-	3-<5	≥5	-
Site of metastases	Lung	Spleen, Kidney	Gastro-intestinal	Liver, Brain
Number of metastases	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

a) Interval = time (months) between end of antecedent pregnancy and start of chemotherapy.
b) Immediate pre-therapy plasma β-hCG level.
Risk groups: ≤4 low-risk group, 5 to 7 intermediate-risk group, >8 high-risk group

Table (2): Types of initial therapeutic treatment.

Surgery	Chemotherapy			
	Single agent		Multi-agent	Total
	Methotrexate	Actinomycin-D		
Suction curettage	23 (65.7%)	11 (31.4%)	21 (77.8%)	55 (88.7%)
TAH	1 (2.9%)	-	6 (22.2%)	7 (11.3%)
Total (%)	35 (100%)		27 (100%)	62 (100%)

TAH; Total abdominal hysterectomy

Response evaluation

Complete response (CR) was defined as a minimum of three consecutive weekly β-hCG levels were within normal range (<5 mIU/ml). At this point, CT was stopped and patients entered the post-treatment screening programme. Refractory (resistant) disease is defined as increased β-hCG, or failed to decrease >5% below the preceding β-hCG level (plateau) on CT. Patients were given at least 3 cycles of CT before a diagnosis of refractory disease could be made. Patients with persistent GTN received one or more additional courses of the same primary CT or crossed over to a second line multi-agent CT. Relapse was defined as two elevated and increasing serum β-hCG levels, in the absence of a normal pregnancy, after achieving complete serological remission with CT.[15]

Post-treatment Follow-up

Patients with CR were followed-up with monthly β-hCG titers until they had six consecutive months of normal β-hCG titers and were then followed-up every two months for another six months. All patients had completed β-hCG follow-up for 6 months or more after treatment. Patients were strongly advised not to conceive for at least 1 year after completion of CT as a rise in β-HCG from a pregnancy will confuse the situation.

Statistical Analysis

The association between response to treatment and following factors; initial serum β-hCG (mIU/ml), pathology, WHO scoring system, disease stage, presence of metastases, duration of disease and CT type were determined with Chi-Square as appropriate. The Kaplan-Meier method provided estimates of overall survival rate.[16] The log-rank test was used for univariate analysis of prognostic factors affecting survival. Overall survival was defined as the time from diagnosis until either death or last follow up for patients. The forward stepwise Cox regression hazard model was used for multivariate analysis.[17] Statistical analysis was performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL). Significance was prespecified as $p<0.05$.

3. Results

The clinical characteristics of the patients are shown in Table (3). The mean age was 27±8 years (range 18-53) and the median duration of symptoms was 4 months (range 1-12). Nulliparous women were the majority of the population in this study represented with 54.8%. Forty-seven patients (75.8%) were presented with early stage of disease (stage I). The median pre-therapy β-hCG level was 10151 mIU/mL. Median courses of given CT were 5 courses (range, 3-9). Out of 62 patients, 45 (72.6%) had invasive mole, 17 had choriocarcinoma (27.4%), 15 (24.2%) had metastatic disease, and the lung was the most common site of metastases 12/15 (80%). No patient had placental site trophoblastic tumor.

Table 4 shows response to initial CT according to the patients' characteristics. Complete remission was achieved in 46/62 patients (74.2%). Patients with invasive mole were more likely to respond to initial CT compared with choriocarcinoma (86.7% and 41.2% respectively, $p<0.001$). With regard to FIGO staging system, a significant higher response was observed among patients with stages I-II compared with those with stages III–IV, 85.7% vs. 30.8% respectively ($p<0.001$). Remission rate of low vs. intermediate and high-risk patient was 86.5% and 56% respectively ($p=0.007$). Patients with no metastatic disease at presentation showed a significant higher response rate than patients presenting with metastatic disease 85.1% vs. 40% respectively ($p=0.001$). Patients treated with single agent CT showed a significant higher response rate compared to those treated with combined CT 85.7% vs. 59.3% respectively ($p=0.018$).

The 5-year overall survival rate for all patients enrolled in this study was 74.9 % (Figure 1) with a median time of follow-up for the all patients was 55 months (range 6-115). Univariate analysis of the patients characteristics affecting the survival rate of the studied patients as shown in Table (5) revealed that; pathology ($p<0.0001$), WHO scoring system ($p<0.0001$), disease stage ($p<0.0001$), presence of metastases ($p<0.0001$) and type CT treatment ($p<0.0001$) were significantly affecting the 5-year survival rate. Factors found to have a significant effect on survival rate in the univariate analysis were included in the multivariable analysis. WHO scoring and FIGO staging were found to be independent prognostic factors ($p= 0.008$ & 0.004 respectively).

In the present study the recurrence rate was 11.3% (7/62), the median interval of relapse was 7 months (range, 4 to 32 months). Three relapsed patients initially treated with single agent CT had treated with EMA/CO regimen and one of them had achieved CR again, 2 patients previously achieved CR with second line EMA/CO regimen was received salvage chemotherapy with EP/EMA regimen (EP: etoposide 150 mg/m^2 and cisplatin 75 mg/m^2 alternating weekly with EMA) and none of them had achieved CR and 2 patients had underwent TAH.

Table (3): Characteristics of 62 patients with malignant GTN.

Characteristics		N	%
Age (year)	<40	53	85.5
Mean 27±8	≥40	9	14.5
Median 24.5 (range 18-53)			
Duration of symptoms (months)	Mean 3.9±2.4 months		
	Median 4 months (range 1-12)		
FIGO Stage	I	47	75.8
	II	2	3.2
	III	6	9.7
	IV	7	11.3
Initial serum β-hCG (mIU/ml)	<1000	35	56.4
	1000-<10,000	7	11.3
	10,000-<100,000	13	21.0
	≥100,000	7	11.3
Parity	Nulliparous	29	46.8
	1-3	29	46.8
	≥4	4	6.4
WHO scoring system	Low risk	37	59.7
	Intermediate risk	19	30.6
	High risk	6	9.7
Pathology	Invasive mole	45	72.6
	Choriocarcinoma	17	27.4
Metastasis	Non-metastatic	47	75.8
	Metastatic	15	24.2
	Lung	12	80
	Brain	4	26.7
	Liver	2	13.3
	Pelvis	5	33.3

Table (4): Factors affecting response to initial CT according to the patients' characteristics.

		Response (%)	*P*
Responding patients		46/62 (74.2%)	
Initial serum β-hCG (mIU/ml)	<10.000	33/42 (78.6%)	0.254
	≥10.000	13/20 (65.0%)	
Pathology	Invasive mole	39/45 (86.7%)	<0.001*
	Choriocarcinoma	7/17 (41.2%)	
WHO scoring system	Low risk	32/37 (86.5%)	0.007*
	Intermediate & High risk	14/25 (56%)	
Stage	I & II	42/49 (85.7%)	<0.001*
	III & IV	4/13 (30.8%)	
Metastases	Yes	6/15 (40.0%)	0.001*
	No	40/47 (85.1%)	
Duration of disease	≤4 months	36/48 (75.0%)	0.788
	>4 months	10/14 (71.4%)	
Chemotherpy	Single agent	30/35 (85.7%)	0.018*
	Multi-agent	16/27 (59.3%)	

**P* significant <0.05

Table (5): Univariate and multivariate analysis of the prognostic factors affecting overall survival rate.

		Univariate	Multivariate analysis	
		P	*P*	HR (95% CI)
Initial H-BCG	<100.000	0.397	NS	
	≥100.000			
Pathology	Invasive mole	<0.0001*	0.079	
	Choriocarcinoma			
WHO score	Low	<0.0001*	0.008*	7.97 (1.45-43.71)
	Intermediate & High			
Stage	1 & 2	<0.0001*	0.004*	2.22 (1.24-3.98)
	3 & 4			
Metastases	Yes	<0.0001*	0.634	
	No			
Duration of disease	≤3 months	0.248	NS	
	> 3 months			
Chemotherpy	Single	0.0001*	0.669	
	Multi-agent			

**P* significant <0.05; CI : Confidence interval; HR: Hazard ratio

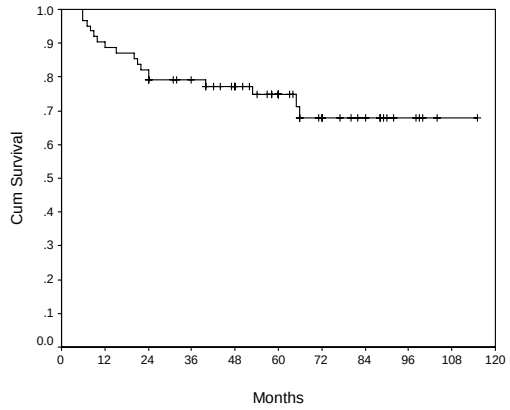

Figure (1): Overall survival rate

4. Discussion

Gestational trophoblastic disease (GTD) is extremely responsive to CT. Therefore, in addition to achieving long-term cure, minimizing both long and short-term toxicity must be an important factor in evaluating the treatment. It is difficult to compare treatment results for persistent GTD across the world because of the heterogeneity of patient groups selected for single or multi-agent CT, and because of the wide varieties in CT regimen used.[7]

In our study 24.20% presented with metastatic disease and the lung was the most common metastatic site represented with 80% of patients followed by brain metastases (26.7%). Berkowitz & Goldstein[18] reported that, the most common metastatic sites are the lung (80%), vagina (30%), brain (10%), and liver (10%) and interestingly, Garner[19] had found that, 40% of patients with presumed non-metastatic disease have occult pulmonary nodules on CT scan .

In our study the overall response rate for initial CT was 74.2%. The overall response rate of low and intermediate risk patients together was 80.4% this percent was more than the percents that reported with previous studies; Khan et al.[20], Roberts & Lurain[21] and Berkowitz et al.[22] reported an overall response rate of low and intermediate risk GTN patients whose initial treatment with methotrexate and folinic acid was 72%, 65.6% and 68.2%, respectively. When the response rate of low and intermediate risk GTN patients were considered separately, the response rate was 86.5%, and 68.4% respectively. Compared to a previous study, Goldstein et al.[23] reported that single agent CT produced remission 87% and 76% of low and intermediate risk patients respectively. Other authors have also reported remission rates of over 80% for this group of patients.[24-26] Intermediate risk patients could be treated with both single and multi-agent CT.[27] In the present study, intermediate risk patients (score 5-7) are treated in the same way as those who were high risk.

The response rate of our high risk patients was 16.7 %, out of the six high risk patients, 5 of them presented with metastatic disease and all high risk patients treated initially with MAC regimen. Many studies had reported that, MAC is inadequate as primary treatment for high-risk, metastatic GTN as it induces remission in only half the patients. [24,28,29] EMA/CO is the first-line regimen used to treat high-risk GTN since it has the best effectiveness to-toxicity ratio. Goldstein et al.[23] reported that at New England trophoblastic disease center EMA/CO induced complete remission in 100% of patients with high-risk stage II GTN and in 97.3% of patients with high-risk stage III GTN. At other centers, Bower and Bolis reported that EMA/CO induced remission in 86% and 76% of patients with high-risk metastatic GTN, respectively.[30, 31]

Although EMA/CO is the most commonly used multi-agent CT, other regimens have been used in the management of high-risk GTN. In a retrospective analysis of four chemotherapeutic regimens, Kim et al.[32] compared the effectiveness of MFA (MTX, folinic acid, ACT-D), MAC, CHAMOCA (cyclophosphamide, hydroxycarbamide, doxorubicin, ACT-D, MTX, melphalan, and vincristine) and EMA/CO. They reported remission rates of 63%, 68%, 71%, and 91%, respectively. These results support EMA/CO effectiveness as primary therapy for patients with high-risk disease.

Factors that significantly affecting the response rate to the initial CT among our patients were; pathological type (choriocacinoma vs. invasive mole), risk score (low vs. intermediate & high risk), disease stage (stages I & II vs. III & IV), presence of metastases (yes vs. no) and type of CT (single agent vs. multi-agents).

Hoekstra et al.[33] reported that factors determined to significantly influence resistance to initial chemotherapeutic treatment for 804 patients with GTN on multivariable analysis were; presence of metastases compared with nonmetastatic disease (41% vs.12%; 95% CI 0.13– 0.35); metastatic site other than the lung or vagina (76% vs. 31%; 95% CI 0.02– 0.13) and duration of disease greater than 4 months compared with ≤4 months (35% vs. 17%; 95% CI 0.21– 0.66). In another study reported with Roberts'[34], patients in whom initial therapy failed tended to be older, had higher pretreatment β-hCG levels and higher WHO scores than those successfully treated, but the only statistically significant finding was disease staging.

The 5-year overall survival rate for all patients enrolled in this study was 74.9 % with a median follow-up 55 months (range 6-115). Univariate analysis of the patients characteristics significantly

affecting the survival rate were; pathology (p<0.0001), WHO scoring system (p<0.0001), FIGO stage (p<0.0001), presence of metastases (p<0.0001) and CT regimen (p<0.0001). Factors found to have a significant effect on survival rate in the univariate analysis were included in the multivariable analysis. WHO scoring and FIGO stage were found to be independent prognostic factors (p= 0.008 & 0.004 respectively).

Lurain et al.[35] reported that the overall survival rate for 396 GTN patients was 89% (100% for nonmetastatic and 78% for metastatic disease). Factors found to significantly influence survival were clinicopathologic diagnosis of choriocarcinoma, time greater than 4 months from pregnancy event to treatment, pretreatment β-hCG level more than 100,000 mIU/ml, metastases to sites other than the lung and vagina, antecedent term pregnancy and prior failed CT.

Pietrzak et al.[36] through a retrospective analysis of 1259 patients with GTN recorded a 5-year survival rate of 96.5% and the survival of patients depends on clinical stage and risk factors.

The recurrence rate among our patients represented with 11.3%, the median interval of relapse was 7 months (range, 4 to 32 months). Women with history of GTN have a potential risk of disease recurrence that is largely dependent on their initial stage.[1] Mutch et al.[37] reported recurrence rates of 4% in patients with low-risk, metastatic GTN, and 13% in patients with high-risk, metastatic disease. At the New England trophoblastic disease center, the reported recurrence rates were 2.9% in patients with stage I disease, 8.3% in stage II, 4.2% in stage III, and 9.1% in patients with stage IV GTN and the mean time from the last undetectable β-hCG level to documented recurrence was 6 months, irrespective of the FIGO stage.[23] Similarly, Ngan et al.[38] reported that the median recurrence time in women from Hong Kong with GTN was 6.5 months .

5. Conclusion

It is important to individualize treatment for women with malignant GTN based upon known risk factors, using less toxic therapy for patients with low-risk disease and aggressive multi-agent therapy for those with high-risk disease. WHO scoring and FIGO staging were found to be independent prognostic factors for survival rate. Although GTN was found to be a highly chemosensitive, a significant proportion of patients die of the disease, so more effective therapeutic protocols may be required in such patients to improve the survival rate.

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