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ORIGINAL ARTICLE

Gestational Trophoblastic Neoplasia: Experience from a Tertiary Care Center of India

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Abstract

Aims Gestational trophoblastic neoplasia (GTN) comprise a spectrum of interrelated conditions originating from the placenta. With sensitive assays for human chorionic gonadotropin (β-hCG) and current approaches to chemotherapy, most women with GTN can be cured with preservation of reproductive potential. The purpose of this analysis was to address the outcome of GTN in patients from a tertiary care center of India.

Materials and Methods We undertook a retrospective and prospective review of GTN cases treated at our center over a period of 7 years from 2008 to 2014. Patients of GTN were assigned to low-risk or high-risk categories as per the FIGO scoring system. The low-risk group was treated with combination of actinomycin-D and methotrexate and the high-risk group received the Etoposide, Methotrexate, Actinomycin-D/ Cyclophosphamide, Vincristine (EMA/ CO) regimen. Salvage therapy was Etoposide, Paclitaxel / Paclitaxel, Cisplatin (EP/TP). Treatment was continued for three cycles after normalization of β-hCG level, after which the patients were followed up regularly.

Results In total, 41 GTN patients were treated at our institution during the above period; 17 were in the low-risk and 24 were in the high-risk category. The lung was the most common site of metastasis. All low-risk patients achieved complete remission. Among high-risk patients, one patient died while receiving first cycle chemotherapy, one patient relapsed, and 22 patients achieved complete

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remission. The single relapsed patient also achieved remission with second-line chemotherapy.

Conclusion Risk-stratified treatment of GTN was associated with acceptable toxicity and resulted in outcome that was comparable with international standards. The use of two-drug combination in low-risk patients is a better option especially in developing countries.

Keywords Gestational · Trophoblast · Neoplasia

Introduction

It is just 100 years since Marchand identified choriocarcinoma as a tumor arising from placental villous trophoblast. Earlier description of similar tumors failed to identify their tissue of origin. Gestational trophoblastic disease (GTD) is the terminological umbrella now used to describe the spectrum of cellular proliferations ranging from villous forms of hydatiform mole through invasive mole and choriocarcinoma to placental site tumors. Each form of GTD presents its own particular set of problems ranging from social to therapeutic.

GTD is still an important reproductive health problem worldwide. The problem is that much information of GTD has come from less-developed countries, where proper diagnostic tools and up-dated treatment cannot be employed.

GTD can be benign or malignant. Histologically, it is classified into hydatidiform mole, invasive mole (chorioadenoma destruens), choriocarcinoma, and placental site trophoblastic tumor (PSTT). Those that invade locally or metastasize are collectively known as gestational trophoblastic neoplasia (GTN). Hydatidiform mole is the most common form of GTN. While invasive mole and choriocarcinoma are malignant, a hydatidiform mole can behave either in a malignant or benign fashion. We report the clinical profile, management, and outcome of GTN patients treated at our center over a 7-year period.

Materials and Methods

The data were extracted by retrieving all case records of GTN patients registered during the study period. The abstracted information included history and examination findings: chest X-ray; pelvic ultrasound; computed tomography (if carried out); MRI Brain; CSF (as and when required); serum human chorionic gonadotropin (β-hCG); and histopathological evaluation of biopsy or curettage specimen, if available. Using this information, patients were categorized as low risk or high risk according to the FIGO scoring system. Patients with a score of $\leq$6 were treated with methotrexate (MTX) and Actinomycin D combination. The MTX was given at a dose of 300 mg/m^2 over 4 h with calcium leucovorin rescue and Actinomycin D at a dose of 0.5 mg on day 1. The cycles were repeated once in 2 weeks. Serum β-hCG levels were measured once every week, including before the start of every chemotherapy cycle; any patient who had two static or one increasing value on treatment was defined as having drug-resistant disease. Patients with a score $\geq$7 were classified as high risk and started on the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen. Patients who relapsed were subsequently treated with EP/TP regimen. The patients with CNS disease received EMA–CO with higher dose of MTX (1 g/m^2) (Table 1). Treatment was continued for three cycles after normalization of Serum β-hCG in high-risk group and for two cycles in low-risk group. After the last chemotherapy cycle, patients were kept on regular follow-up using regular β-hCG monitoring as per standard guidelines [1, 2]. Specifically, β-hCG level was measured at 6–8 weeks after the end of any pregnancy to exclude disease recurrence [3, 4]. Patients were also advised standard contraceptive measures [5]. The response to therapy was defined as follows: complete response as β-hCG values in the normal range for three consecutive weeks; a partial response as more than 50 % decline in β-hCG levels compared with baseline; no response as less than 50 % decline over baseline values. Progressive disease was defined as an increase of at least 25 % in the size of any measurable lesion or appearance of any new lesion with the increasing β-hCG levels. Recurrence was defined as elevation of β-hCG level after more than three normal values in the absence of a confirmed pregnancy [6]. All patients irrespective of age with a diagnosis of GTN were included in the study.

Results

Of the 41 patients diagnosed with GTN, diagnosis was based on histopathological evidence in six, and elevated serum β-hCG and history were consistent with GTN in 36 patients. The most common presenting feature was bleeding per vagina in 38 patients. The passage of grape like vesicles was present in six patients. Other features at presentation included hemoptysis (five patients) and pain abdomen (five patients), and excessive vomiting in two patients.

On examination, the most common finding was pallor which was noted in 22 patients. In one patient, there was mild abdominal tenderness, while the examination showed normal features in rest of patients. Of the 41 patients, 24 belonged to high-risk category and 17 belonged to low-risk category. The median age of our patients was 29.5 years (range 20–46 years). Only three patients were more than

Table 1 Summaries the demographic baseline characteristics

Patient characteristics	Low risk	High risk
Age (in years)		
<40	17	21
≥40	0	3
FIGO stage		
I	12	8
II	4	3
III	1	9
IV	0	4
Antecedent pregnancy		
Mole	13	11
Abortion	4	10
Term	0	3
Interval from antecedent pregnancy		
<4 months	7	6
4–7 months	6	12
7–12 months	4	2
>12 months	0	4
Mean pre-evacuation β-hCG (IU/l)	78,347	274,523.5
Mean post-evacuation β-hCG (IU/l)	47,933	128,809
Site of metastasis		
Lung	1	9
CNS	0	4
Tumor size (in cm)		
<3	8	5
3–5	9	12
>5	0	7
Number of metastasis		
0	17	19
1–4	0	4
>4	0	1
Imaging evidence of metastasis		
Chest X-ray	0	5
CECT	1	9
Previous failed chemo		
Single drug	0	2
≥2 drugs	0	0
Average number of chemo cycles received for β-hCG normalization	4.82	5.1
Total chemotherapy cycles received	6.13	7.6
Survival		
Complete remission	17	22
Relapse	0	1
Death	0	1
Fertility		
Number of patients delivered healthy babies	3	4

40 years of age, and all of them belonged to high-risk group. The FIGO stage 1 comprised the largest staging group among our patients (20 patients), and FIGO 4, the smallest group, only four patients. All stage 4 patients belonged to high-risk group only. The antecedent pregnancy was term in three, abortion in 14, and molar in 24. Interval from antecedent pregnancy to initiation of chemotherapy was less than 4 months in 13 patients, between 4 and 7 months in 18 patients, between 7 and 12 months in six patients, and more than 12 months in four patients. The overall average pre-evacuation serum β-hCG was 174,461.5 IU/l: in high-risk patients, the average pre-evacuation serum β-hCG was 274,523 IU/l (19,000–1,410,000 IU/l). The cycle was repeated 10,000 IU/l), while in low-risk patients, it was 78 347 IU/l (4500–462 417 IU/l).The overall average post-evacuation serum β-hCG level was 88,085 IU/l (2800–726,151 IU/l): in high-risk patients, the average post-evacuation serum β-hCG was 128,809 IU/l (3620–726,151 IU/l), while in low-risk patients, it was 47,933 IU/l (2800–509,991 IU/l). The lung metastases were found in ten patients; CNS was involved in four patients; one patient had MRI-documented brain metastasis; and the other three had high CSF/serum β-hCG. Among high-risk patients, lung metastasis were found in nine patients, and CNS involvement was found in four patients. Among low-risk patients, only one patient had lung metastasis. The size of largest tumor was <3 cm in 13 patients, 3–5 cm in 21 patients, and >5 cm in seven patients. Among high-risk patients, the largest tumor was less than 3 cm in five patients, 3–5 cm in 12 patients, and >5 cm in seven patients. Among low-risk patients, the largest tumor size was <3 cm in eight patients, and 3–5 cm in nine patients. The number of metastases was 1–4 in four patients of high-risk group, and more than four in one patient of high-risk group. In low-risk group, the number of metastases was zero in all patients [as per ESMO guidelines, the lung metastases were counted on chest X-ray only and not on chest Contrast enhanced computed tomography (CECT)].

Only two patients had history of prior failed chemotherapy, and both of them belonged to high-risk group. The average number of chemotherapy cycles received for normalization of serum β-hCG levels was 4.82 (2–12).In high-risk group, patients received on average 5.1 cycles (3–8), while in low-risk group, patients received on average 4.46 cycles (2–12) for normalization of serum β-hCG levels.

The total number of chemotherapy cycles received on average was 7.08 (4–14). In high-risk patients, average number of cycles received was 7.6 (4–11), while in low-risk patients, it was 6.13 (4–14).

The lung metastases on CECT were present in ten patients, among whom nine were in high-risk group and one patient was in low-risk group, whereas on chest X-ray, it was found that only five patients had lung metastases, and all of them were from the high-risk group.

Table 2 Toxicity of chemotherapy

Toxicity	EMA–CO	EMA–CO with higher dose MTX	MTX+D	EP+TP
Alopecia	19	4	14	0
Neutopenia	14	2	6	0
Anemia	7	2	0	0
Thrombocytopenia	4	2	0	0
Mucositis	0	4	2	0
Peripheral neuropathy	0	0	0	1
Transaminitis	2	0	0	0
Death	1	0	0	0

Discussion

There is no consensus on the best chemotherapy regimen for initial management of low-risk GTN, and first-line regimens vary by geography and institutional preference. Most regimens have not been compared head-to-head, and the level of evidence for efficacy is often limited.

As GTN is a highly curable disease, the aim of treatment should be to minimize the drug toxicity, but not at the cost of treatment efficacy. In our study patients, these goals were demonstrably achieved as shown in the Table 2. All the low-risk patients who were treated with MTX and dactinomycin combination (17 patients) achieved remission, and there was no relapse in this subset of patients. In another study from India, 92.9 % of post-molar GTN attained complete remission with MTX [7]. Other studies from developed countries have reported lower rates of remission (72 %) with MTX and higher requirement of second-line salvage regimens [8]. Although it is difficult to draw definitive conclusions, it is possible that there may not be proper risk stratification in developing countries, and patients with risk scores of five and six may be relapsing on single-agent chemotherapy. The two-drug regimen received by our patients has prevented relapses, but at the same time, it has caused minimal toxicity (Table 2). Only six patients developed neutropenia, and two patients developed low-grade mucositis. It is pertinent to mention here that no patient needed growth factor support, and there was no delay in chemotherapy because of neutropenia. The patients in our chemotherapy protocol received 300 mg/m^2 of MTX over 4 h with four doses of calcium leucovorin and single dose Actinomycin-D 0.5 mg, and they were discharged on same day. The cycle was repeated once in 2 weeks. This protocol could be a good option in low-risk patients especially in developing countries. Our treatment outcomes are comparable with national and international data in low-risk disease [9–12].

Among the high-risk patients in our study, a large majority (91.6 %) achieved complete remission with the first-line use of the EMA/CO regimen. The long-term survival was 96 %, which is in the same range as most other centers that treat high-risk disease [13].

The one high-risk patient who relapsed on EMA–CO attained remission with a second-line salvage chemotherapy.

Although the number of patients treated at our institute was small, the survival was at par with national and international data [12, 14–17]. The single patient that died had a high disease burden and died while receiving first cycle of chemotherapy likely due to pulmonary hemorrhage. These deaths in future could be avoided by starting with low-dose chemotherapy for 2–3 cycles and then changing to usual EMA/CO chemotherapy in patients with high disease load.

Thus, EMA/CO is appropriate for use in experienced centers in developing countries in appropriately risk-stratified patients.

The relatively low rate of documented fertility in our data is probably a reflection of the completion of a family at a young age in our community and effective adherence to contraceptive advice. It is also possible that there has been less than perfect long-term follow-up of these patients with respect to their reproductive outcomes. It may be concluded that 1 g/m^2 MTX is a good choice for patients with CNS disease.

In summary, our data show that very high rates of remission and survival are possible in both low- and high-risk GTN patients in developing countries. Such patients should preferably be referred to experienced centers that have capabilities for appropriate risk stratification and subsequent treatment, including good supportive care.

Compliance with Ethical Requirements and Conflict of Interests All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008, Informed consent was obtained from all patients for being included in the study. The authors Ansar Hussain, Shiekh Aejaz Aziz, Gul Mohd. Bhat, A. R. Lone, Imran Hussain, Burhan Wani, and Nadeem Qazi have no conflicts of interest.

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