ORIGINAL ARTICLE

TREATMENT OUTCOMES OF GESTATIONAL TROPHOBLASTIC DISEASE, EXPERIENCE FROM SAUDI ARABIA

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Background: This research aims to assess the treatment outcomes and chemotherapy duration required for the normalization of Human chorionic gonadotropin (HCG) levels in patients diagnosed with Gestational Trophoblastic Neoplasia (GTN), encompassing both benign and malignant forms of the condition. **Methods:** This retrospective study included GTD patients treated with chemotherapy in a single oncology clinic from January 2016 to May 2022. Clinical data were gathered from electronic records of the patients. **Results:** During the study period, a total of 24 patients diagnosed with GTD underwent chemotherapy, with a median age of 32 years (range: 18–51). Intramuscular Methotrexate was the primary single-agent chemotherapy utilized in 20 cases (83%) for low-risk disease, while the EMA-CO regimen was the predominant combination chemotherapy employed in 3 cases (13%) for high-risk disease. The median number of chemotherapy cycles administered was 2 (range: 1–16), with a median duration of 4 weeks (range: 1–16) required for Human chorionic gonadotropin (HCG) normalization. Approximately half of the patients (n=10, 47.5%) transitioned to second-line combination chemotherapy, with a median normalization duration of 4 months. Four patients (40%) subsequently received third-line combination chemotherapy using the EMA-CO regimen. Initial complete response was achieved in 11 patients (47%) with first-line treatment, while 10 patients (43%) required second-line chemotherapy and 4 patients (17%) necessitated third-line EMACO chemotherapy. Of the 24 patients, 22 achieved complete response, while 2 patients are currently undergoing treatment. **Conclusion:** All patients successfully attained complete response with chemotherapy. The median duration of chemotherapy for achieving normalization of HCG was 4 weeks, equivalent to 2 cycles. Notably, only 4 patients necessitated third-line chemotherapy following single-agent chemotherapy in the first and second lines.

Keywords: Gestational trophoblastic neoplasia; Gestational trophoblastic disease; Methotrexate, chemotherapy

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INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a set of uncommon neoplasms resulting from abnormal trophoblastic tissue proliferation. The four histological subtypes include Invasive mole, choriocarcinoma, placental site trophoblastic tumour, and epithelioid trophoblastic tumours. While any molar pregnancy can progress to GTD, choriocarcinoma, placental site, and epithelioid trophoblastic tumour can arise from any antecedent pregnancy type.[1] About half of GTN cases stem from molar pregnancies, and the remainder from pregnancy loss, tubal pregnancy, term, or preterm pregnancies.[2,3] Trophoblastic cells produce human chorionic gonadotropin (HCG), and its levels in all GTD forms, except placental site and epithelioid trophoblastic tumour, correlate with disease volume. HCG serves as a valuable marker for disease progression, treatment response, and post-treatment surveillance.[4] Individuals diagnosed with GTD typically exhibit elevated HCG levels, amenorrhea, abnormal uterine bleeding, pelvic pain, or symptoms of metastatic disease. Common metastatic sites include the lung, liver, vagina, and central nervous system.[5–8]

The mainstay of treatment for post-molar GTD and choriocarcinoma is single or multi agent chemotherapy. International Federation of Gynaecology and Obstetrics (FIGO) staging or World Health Organization (WHO) risk scoring systems and Charing cross scoring commonly used to define the risk of progression and resistance to single agent chemotherapy. FIGO stage I, II or III GTD with WHO risk score <7 is considered low risk with 100% cure rate. There is no consensus regarding the first line chemotherapy regimen for low risk GTD and practice varies by clinicians' preference and geography. International guidelines support single agent therapy

and Methotrexate or Dactinomycin are preferred choices for most patients with low-risk GTD.[9,10]

High risk GTD can develop drug resistance with single agent therapy, hence these patients are treated with multi-agent regimens.[11] Combination of etoposide, methotrexate, plus actinomycin D, alternating with cyclophosphamide and vincristine (EMA-CO) results in complete response rates of up to 80 percent and long-term survival rates of 85 to 94 percent.[12] Time to HCG response and average number of chemotherapy cycles till HCG normalization varies depending upon disease risk.[13] Treatment is usually continued for 6 to 8 weeks after tumour markers normalization.

In this paper we present the demographics, disease stage, prognostic scores and treatment outcomes for 24 women treated for GTD at King Fahad Specialist hospital, a tertiary centre in Dammam, Saudi Arabia.

MATERIAL AND METHODS

In this retrospective study, the electronic medical records of patients with diagnosis of Gestational Trophoblastic disease who received systemic anticancer therapy at King Fahad specialist hospital, Dammam from January 2016 to May 2022 were reviewed. The hospital cancer registry does not list the diagnosis of GTD, hence patients for this study were identified from a single gynae-oncology clinic and the chemotherapy infusion center log. Ethical approval was obtained from the institutional review board.

Utilizing electronic medical records and the chemotherapy infusion center log, information on patients' demographics, serum human chorionic gonadotropin levels, histopathological evaluation of biopsy or curettage specimens, anticancer therapy regimen, treatment line, chemotherapy cycle count, laboratory reports, and pertinent clinical details was gathered. Subsequently, patients were classified into low or high risk based on the FIGO scoring system. Low risk was defined with a FIGO score <7, while those with a higher score were categorized as high risk. The therapeutic response was characterized as a complete response if HCG values normalized for three consecutive weeks, a partial response if there was a more than 50% decline in HCG levels compared with baseline, and no response if the decline was less than 50% from baseline values. Progressive disease was identified by an increase of at least 25% in the size of any measurable lesion or the appearance of any new lesion along with increasing HCG levels. Chemotherapy regimens used in the individual group were identified in the first, 2nd and 3rd line with the duration of therapy. We then looked at the time to normalization of HCG and the number of treatment cycles in low and high-risk populations as well as the line of therapy separately. Overall response rate and response rate in first, 2nd and 3rd line treatment was then calculated. Treatment toxicity was assessed using Common Terminology Criteria for Adverse Events (CTCAE v4.03). Data was analyzed using Microsoft Excel version 1808. Single agent intramuscular methotrexate was given either 50 mg intramuscularly on days 1,3,5,7 with folinic acid rescue orally on days 2,4,6, and 8 in 14 days cycle or Weekly 50 mg intramuscular injections.

RESULTS

During the study period, a total of 24 patients diagnosed with GTD received chemotherapy. Their median age was 32 years, ranging from 18 to 51 years. Among these cases, 12 (50%) were diagnosed with GTN following molar pregnancy, 9 (37.5%) were identified post-abortion, and 3 (12.5%) after surgical procedures. Utilizing the WHO prognostic scoring system, 21 patients (87.5%) were categorized as low risk, while 3 patients (12.5%) were classified as high risk. The majority of patients (71%) were diagnosed based on elevated HCG levels, with 7 patients (29%) diagnosed post-surgery. The median HCG level at diagnosis was 54,000 (ranging from 133 to 949,117). Histologically, the most common diagnoses were complete mole (54%), followed by partial mole (29%), choriocarcinoma (13%), and gestational trophoblastic epithelioid neoplasm (4%). [Table-1]

Intramuscular Methotrexate emerged as the primary first-line single-agent chemotherapy, administered to 20 patients (83%) for low-risk disease, with all patients receiving an 8-day regimen. Actinomycin was utilized as first-line therapy for only one patient (4%). For high-risk disease, the EMA-CO regimen was the predominant choice, administered to 3 patients (13%). The median number of chemotherapy cycles were 2 (1–16) and median duration of chemotherapy resulting in normalization of HCG was 4 (1–16) weeks. Subsequently, ten patients (47.5%) developed resistance to single-agent Methotrexate chemotherapy and transitioned to second-line therapy. Among these, five patients (50%) received actinomycin and the remaining five (50%) were treated with the EMA-CO regimen. Median duration for normalization of HCG was 4 months in 2nd line setting. [Table-2]

Four patients (40%) underwent third-line combination therapy with the EMA-CO regimen after experiencing progression on actinomycin, achieving a median duration for HCG normalization of 5 months following the chemotherapy switch. Among the patients treated with first-line therapy, eleven (47%) achieved complete response. In the second-line setting, six patients (60%) attained complete response, while four patients required third-line treatment. Overall, complete response was achieved in 22 patients, while treatment is ongoing for 2 patients

Table-1: Demographics of patients treated for GTN

Demographics (24 patients):	
Median Age	32 (18-51) years
Low risk	21 (87.5%)
High risk	3 (12.5%)
Histo-pathological diagnosis:	
Complete mole	13 (54%)
Partial mole	7 (29%)
Choriocarcinoma	3 (13%)
Gestational trophoblastic epitheloid	1 (4%)

Table-2: Details of chemotherapy regimens used and time to BHCG normalization.

Results:	
First Line chemotherapy (24 patients):	
Intramuscular MTX (weekly or 6 doses in 2 weekly cycles)	20 (83%)
Actinomycin	1 (4%)
EMA-CO	3 (13%)
Second line chemotherapy (10 patients):	
Actinomycin	5 (50%)
EMA-CO	5 (50%)
Third line chemotherapy (4 patients):	
EMA-CO	4 (100%)
Median duration for BHCG normalization after first line	4 weeks
Median duration for BHCG normalization after second line	16 weeks
Median duration for BHCG normalization after third line	20 weeks

DISCUSSION

GTN mainly affect women of reproductive age. Complete moles are usually the most common pathology. It is reported in 54% of patients in our study. Similarly studies from Pakistan, Nigeria and Oman reported complete mole in 65%, 57.3% and 43.8% patients respectively.[14–17] Our patients with GTD are mostly young in the 21-35 years age group which is similar to the studies from Pakistan, Oman and India but different from studies done in the western world with reported high prevalence in 31-40 years of age group.[14–18] The possible reason for this age group disparity might be the higher incidence of early marriages in the Eastern part of the world.

Intramuscular Methotrexate (IM MTX) is the preferred and most commonly used first line chemotherapy for low risk GTN. It was given to 20 (83%) patients in an 8-day regimen in our study. Actinomycin-D was used for only in 1(4%) patient in the 1st line. Although IM MTX is the preferred chemotherapy for the first line GTN, other single agent chemotherapy agents like Actinomycin D and VP-16 are equally or may be more effective for low risk GTN.[22,23] Four randomized, controlled trials have shown that Actinomycin-D is superior to weekly MTX. However, most oncologists do not use weekly MTX anymore and instead use either a 5-day MTX regimen or an alternating 8-day MTX regimen.[23–27] A phase III study comparing pulse Act-D (1.25 mg/m^2) versus a multi-day (5-day or 8-day with folinic acid) MTX regimen was closed due to a low accrual rate with the complete response rate of 88% with MTX and 79% with Act-D, which was not statistically significant.[28] After failing an IM MTX in low-risk patients, they can be treated with alternative single-agent regimen. We treated 50% with Actinomycin-D after failure on the first line IM MTX. Charing Cross Hospital recommends a 5 days actinomycin-D in patients with MTX resistance and beta–human chorionic gonadotropin (beta-HCG) level of less than 100 IU/L. However, if the beta-HCG level is more than 100 IU/L, then a combination chemotherapy regimen is more appropriate.[21]

EMA-CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and vincristine) regimen is the most frequently used combination chemotherapy for high risk disease, though other regimens like MAC and CHAMOCA regimens were also used. CHAMOCA (MTX, Act-D, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine) regimen is not recommended anymore due to significant myelotoxicity and similar efficacy to MAC (MTX, folinic acid, Act-D, and cyclophosphamide/ chlorambucil).[29] All of our patients with high risk GTN received EMA-CO chemotherapy. Hysterectomy as a first line treatment is not the preferred option and reserved for those patients who have completed family or refused chemotherapy. Makhathini et al. and Hussain et al in their studies reported hysterectomy as a primary treatment in 4.8% and 4.2% patients respectively.[14,19] None of our patients had hysterectomy.

Optimal duration of treatment is not known but it is recommended to continue chemotherapy till normalization of BHCG and then consolidation chemotherapy. The median number of chemotherapy cycles in our study were 2 (1–16) and the median duration of chemotherapy resulting in normalization of BHCG was 4 (1–16) weeks. Two cycles of consolidation chemotherapy were given for low risk patients and 3 cycles for high risk patients. Resistance to first line intramuscular methotrexate (IM MTX) in our study was unusually high with 10 (47.5%) out of 24 patients developed resistance and were switched to 2nd line therapy with actinomycin (50%) in those patients with BHCG of less than 100 and EMA-CO (50%) in those with BHCG of more than 100. Resistance to first line single agent chemotherapy reported in some studies is much less than ours. Hussein et al and Makhathini *et al*. reported resistance only in 1.7% and 3.2% respectively.[13,14,19]

While similar to our study, 2 other studies by Capobianco et al and I A McNeish reported resistance

to first line MTX in 25% and 31% patients respectively.[20,21] These results shall be interpreted with caution as the sample size of our study is small and patients represent population from a single cancer centre. Patients who received Actinomycin-D in the second line, 4 out of the 5 patients progressed and were treated with EMA-CO regimen with a median duration for normalization of BHCG of 5 months after chemotherapy switch over. Median duration for normalization of BHCG was 2 months with first line chemotherapy, 4 months with 2nd line and 5 months with third line chemotherapy. All 24 patients achieved complete response and are currently alive.

Limitations of our study are the retrospective nature of the study, small sample size and difficulties in getting the accurate number of patients from the hospital cancer registry.

CONCLUSION

Chemotherapy is highly effective treatment for GTN, with single-drug regimens curing most low-risk cases. High-risk GTN requires combination chemotherapy. Our study showed higher resistance to 1st line treatment. Despite study limitations, all patients in this study achieved complete response.

AUTHORS' CONTRIBUTION

FA: Literature search, conceptualization of study design, data collection, interpretation, write up and proof reading SHHT: Literature search, data interpretation, write up, proof reading Muhammad Farooq Latif, literature search, data interpretation, write up, proof reading. NB: Literature search, write up, proof reading

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