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Outcome of chemotherapy for gestational trophoblastic disease in Aminu Kano teaching hospital: A 5-year review

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Abstract
Background: Gestational trophoblastic diseases are the first and only disseminated solid tumours that have proved to be highly curable by chemotherapy. Chemotherapy can be used for both the premalignant and malignant forms with cure rates of upto 100% in hydatidiform moles and low risk GTD while in high risk GTDs, cure rates of 80 -90% have been achieved.
Objectives: To determine the outcome of chemotherapy for gestational trophoblastic disease in Aminu Kano Teaching Hospital, Kano.
Study design: Retrospective study of the outcome of chemotherapy for gestational trophoblastic disease in Aminu Kano Teaching Hospital between 1st January 2013 and 31st December 2017.
Results: The prevalence of GTD was 6.2/1000 (1 in 160) deliveries and it accounted for 2.8% of gynaecological admissions over the study period. The indications for chemotherapy for GTD in Aminu Kano Teaching Hospital were persistent GTD, choriocarcinoma and invasive mole. Complete remission was achieved in 83.4% of cases and this falls within the 80-100% reported by the American cancer society while relapse and refractory disease were observed in 8.3% each. Overall, the default rate was high (68.5%) for all the treatment modalities and a case fatality rate of 2.9% was observed.
Conclusion: The cure rate of 83.4% found in this study is within the 80-90% cure rates reported for high-risk gestational trophoblastic disease. However, the default rate was high (68.5%) for the various treatment modalities and needs to be improved upon.

Keywords: gestational trophoblastic diseases, chemotherapy, outcome

Introduction
Gestational trophoblastic disease (GTD) includes the tumour spectrum of hydatidiform mole (complete and partial), invasive mole (chorioadenoma destruens), choriocarcinoma and placental site trophoblastic disease (PSTT). They develop from an aberrant fertilization event and hence from fetal tissue within the maternal lhost [1]. They are the first and only disseminated solid tumours that have proved to be highly curable by chemotherapy. The World Health Organization classifies gestational trophoblastic tumours into premalignant (partial or complete moles) and malignant (Invasive mole, choriocarcinoma and PSTT) [2].
The incidence of GTD varies worldwide. It being lowest in Europe and North America where it occurs in 0.2-1.5/1000 live births and highest amongst East Asians at 1 in 125 deliveries. In Nigeria, Yakasai *et al* reported a prevalence of 4.5/1000 deliveries [3] in Kano, Mbamara reported 4.6/1000 deliveries [4] in the South East and the highest was 7.2/1000 [5] deliveries in Zaria where it accounts for 2.4% [5] of gynaecological admissions.
The documented risk factors for GTD are ethnicity, extremes of maternal age and previous molar pregnancy [2, 3] The disease is commonest amongst the Koreans and Japanese. Prevalence is higher amongst younger teenagers and those >45years when the overall risk of molar pregnancy is highest at 1 in 96/ 1 in 6 deliveries. The risk increases by 10 folds in those with a previous molar pregnancy.
Diagnosis of GTD is suspected on clinical presentation with suggestive ultrasound findings, raised B-hCG and ultimately confirmed by histological examination of products of conception. Symptoms and signs of the disease include recurrent 1st trimester vaginal bleeding, abdominal pain from theca lutein cysts, passage of vesicles, exaggerated pregnancy symptoms such as hyperemesis in 10%, hyperthyroidism in 5% and early pre-eclampsia in 5% of patients [3]. The characteristic snow storm appearance of complete mole is only seen in the second trimester. B-

hCG is used for diagnosis and monitoring during treatment. The distinguishing histological feature of choriocarcinoma is the presence of intermediate trophoblasts and absence of villi. The treatment modalities for GTD include suction evacuation, chemotherapy, surgery and irradiation [6]. The choice of treatment depends on the histological type. The treatment of choice for hydatidiform mole is suction evacuation while choriocarcinoma is treated with chemotherapy. Invasive mole, PSTT and metastatic lesions are treated by surgery / chemotherapy. Indications for chemotherapy include serum B-hCG >20,000IU at 4 weeks post evacuation, static or rising hCG after evacuation in the absence of a new pregnancy, persistent symptoms, evidence of metastasis and histological diagnosis of choriocarcinoma [4]. while only 0.5% of patients treated for partial mole will require chemotherapy, upto 15% of complete molar pregnancies will require chemotherapy [4]. It is also indicated in recurrent disease and relapse [7].

Several chemotherapeutic agents are available for treatment of GTD. These include methotrexate, actinomycin D, etoposide, cyclophosphamide, vincristine, cis-platin, ifosfamide, bleomycin, paclitaxel, chlorambucil and 5-FU. Chemotherapy can be administered as single agent or multiple drug treatment [8]. Generally, single agent often cures early stage GTN while advanced disease requires multiple drug therapy. The most commonly used single drug treatment in Nigeria is methotrexate while EMA-CO is the most commonly used multiple drug regimen. Cure rates of 100% and 80-90% have been reported for low risk and high risk GTN respectively [9].

Treatment outcomes include complete remission, resistance, refractory disease and relapse. About 20-30% of low risk GTN will develop resistance to initial agent, 90% will be cured by sequential single agent while 5-15% will require multiagent chemotherapy [8, 9]. Approximately 30% of patients with high risk GTN develop an incomplete response to first line drugs or experience a relapse. Risk of relapse is 3% in the first year after completing treatment [9]. Risk factors for resistance include older age, higher hCG levels, choriocarcinoma, non-molar antecedent event, metastatic disease and increasing FIGO stage and prognostic score [10].

Fertility following chemotherapy is maintained. However, menopause occurs earlier by 1 year after single agent use and 3yrs after combination chemotherapy [2]. Pregnancy should be deferred for one year after completion of treatment to avoid teratogenic effect on developing oocyte as well as minimize confusion from the rising hCG between a new pregnancy and relapse of disease [2]. Long term health risks of chemotherapy include development of secondary malignancies e.g myeloid leukaemia, colon cancer, breast cancer and melanoma [2].

AIM

To determine the outcome of chemotherapy for treatment of GTD in Aminu Kano Teaching Hospital

Objectives

To determine the indications for chemotherapy in patients with GTD at Aminu Kano Teaching Hospital from 1st Jan 2013 to 31st Dec 2017 To determine the attrition rate in patients receiving chemotherapy for GTD at Aminu Kano Teaching Hospital 1st Jan 2013 to 31st Dec 2017 To determine the final outcome of chemotherapy in patients with GTD at Aminu Kano Teaching Hospital 1st Jan 2013 to 31st Dec 2017

Materials and Method

It was a 5-year retrospective study of the outcome of chemotherapy in patients with GTD in Aminu Kano Teaching Hospital from 1st Jan2013 to 31st Dec 2017. Their file numbers were extracted from the gynae ward and oncology registers. Their case notes were retrieved from the medical records department and case records analysed using excel sheet. Remission was defined as 3 consecutive negative B-hCG values [10]. Relapse was defined as 2 elevated and increasing serum B-hCG in the absence of a normal pregnancy, after achieving a complete serological remission with chemotherapy. Refractory disease was defined as increasing B-hCG or failure to decrease on EMA-CO i.e 2 or more abnormal or increasing plasma B-hCG levels, despite receiving standard EMA-CO chemotherapy for at least 3 weeks.

Result

During the 5-year period of study, there were 103 cases of GTD and 16,520 deliveries giving a period prevalence of 6.2/1000 deliveries (1 in 160 deliveries). Out of 3,712 gynaecological admissions that occurred during the study period, 103 were due to GTD accounting for 2.8% of gynaecological admissions. 70 out of 103 case notes were retrieved giving a retrieval rate of 68%. Table 1 shows the sociodemographic characteristics of the patients. The highest prevalence (31.4%) was seen among the 25-29 years while the least prevalence (2.9%) occurred among those >/ 45 years. Their ages ranged from 19-55 years with a mean age at presentation of 29.57 years. Nulliparity and multiparity were observed in 31.4% each while 37.2% of the women were grand multiparae.

Table 2 shows the clinical presentation of the patients. Vaginal bleeding (85.7%) and amenorrhoea (82.6%) were the common presentations. Other presentations were abdominal swelling, abdominal pain and passage of vesicles. Only 2 patients had a past history of GTD. Anaemia was the commonest complication seen in 45.7% of cases while 14.3% presented with cardiac failure. Histological diagnosis was made in 37.1% of cases. Others had abdominopelvic ultrasound alone (34.3%), ultrasound combined with hCG (25.7%) and 2.9% patients had only serum B-hCG. Majority (68.6%) of the patients had hydatidiform mole while choriocarcinoma and invasive mole accounted for 22.9% and 8.5% respectively. Amongst those with GTN, only 36% had a FIGO clinical stage assigned. Stage 1 and 2 disease accounted for 50% each. 80% were high risk while 20% were low risk for developing resistance to chemotherapy.

Several treatment modalities were employed in the treatment of these patients as depicted in table 3. The commonest was suction evacuation alone that was performed in 34.3%. 5.71% had chemotherapy alone while others had combined treatments including suction evacuation + adjuvant chemotherapy, surgery (TAH) + adjuvant chemotherapy and suction evacuation + surgery + adjuvant chemotherapy. 25.7% requested and were discharged against medical advice (DAMA) while being worked up for treatment.

Table 4 shows the indications for chemotherapy and type of chemotherapy administered. Thirty six patients (51.4%) required chemotherapy. The commonest indication was choriocarcinoma (44.4%), 38.9% had persistent GTD while 16.7% had invasive mole. However, only 24 patients (66.6%) had the chemotherapy. Ten patients (27.8%) were discharged against medical advice while 5.6% (2) patients died while being worked up for chemotherapy. Among those that had chemotherapy, 66.7% were treated with a multiple agent regimen while 33.3% had single agent chemotherapy. Methotrexate/folinic acid was used in all cases of single agent chemotherapy. MAC regimen was used in 41.7% while 25.0% had EMA-CO as multiple agent

regimens.

Table 5 shows the outcome of chemotherapy. The rate of remission was 83.4%. Relapse and refractory disease accounted for 8.3% each. The average number of courses of chemotherapy after which B-hCG was undetectable was 3 for single agent and 4 for multiple agent regimens. Overall, 68.5% of the patients did not come for follow up at all. These patients were either DAMA or defaulted after initial treatment. 17.2% were followed up for at least one year. Two deaths were observed giving a case fatality rate of 2.9%. One patient conceived while on follow-up and had a normal pregnancy.

Table 1: Sociodemographic characteristics

	Frequency	%
Age distribution (yrs)		
15-19	6	8.6
20-24	18	25.7
25-29	22	31.4
30-34	4	5.7
35-39	4	5.7
40-44	14	20.0
>/45	2	2.9
Total	70	100
Mean Age	29.57	
Parity		
0	22	31.4
1-4	22	31.4
>/5	26	37.2
Total	70	100

Table 2: Clinical presentation of patients

Clinical feature	Frequency	%
Vaginal bleeding	60	85.7
Amenorrhoea	58	82.6
Abdominal swelling	34	48.6
Anaemia	32	45.7
Abdominal pain	30	42.9
Passage of vesicles	10	14.3
Cardiac failure	10	14.3
Previous molar	2	2.9

Table 3: Treatment modalities

Treatment	Frequency	%
Suction evacuation	24	34.3
SE + chemotherapy	18	25.7
Chemotherapy	4	5.71
Surgery + chemo	4	5.71
SE + surgery + chemo	2	2.9
DAMA	18	25.7
Total	70	100

Table 4: Indications and type of chemotherapy

	Frequency	%
Indications n=36		
Persistent GTD	14	38.9
Choriocarcinoma	16	44.4
Invasive mole	6	16.7
Total	36	100
Type of chemorx n=24		
Single agent (MTX) 8 33.3		
MAC	10	41.7
EMA-CO	6	25.0
Total	24	100

Table 5: Outcome of chemotherapy

Outcome	Frequency	%
Remission	20	83.4
Relapse	2	8.3
Refractory disease	2	8.3
Total	24	100

Discussion

The prevalence of GTD was 6.2/1000 deliveries (1 in 160 deliveries). This is close to 7.2/1000 [5] reported in Zaria by Kolawole *et al*. but higher than 3.58/1000 [11] and 4.6/1000 [4] deliveries reported from Nnewi and Abakaliki all from South-eastern Nigeria. GTD accounted for 2.8% of gynaecological admissions. This is similar to 2.4%[5] found by Kolawole *et al* in ABUTH Zaria. The mean age of the patients was 29.5 years $\pm$ x. This is similar to 31 years reported by Mbamara *et al*. [4] from Nnewi and 32.5 years by Kolawole *et al*. [5] from Zaria. The peak incidence was found amongst the 25-29 years age group. This is the same as the finding of Dauda *et al*. [13] who reported a peak incidence in the 2nd and 3rd decade in Jos but lower than 30-39 years reported by Anuma *et al*. [11] in Nnewi likely due to delayed child bearing compared to the Northern part of the country. The nulliparae were the most commonly affected (31.4%) in this study. This is similar to the 29% observed by Igwegbe *et al*. [16] in a study from South Eastern Nigeria but contrary to the findings of Anuma *et al*. [11] and Kolawole *et al*[5] where grandmultiparae and multiparae were frequently affected in South East and Northwestern Nigeria respectively.

The most frequent presentation was vaginal bleeding (85.7%). The same was reported by Mbamara *et al*. [4], Ocheke *et al*. [17] and Igwegbe *et al*. [16] from South East and North Central Nigeria. However, amenorrhoea was reported in 100% of patients in studies done by Nyengidiki *et al*. [15] in Port Harcourt and Kolawole *et al*. [5] in Zaria. Anaemia was the commonest complication and this is the same as the finding of Igwegbe *et al*. [6] In this study, a histological diagnosis was made in 37.1% of cases while B-hCG was done in 60% of the patients. This is higher than 28% histological diagnosis done in Ocheke *et al*. [17] study in Jos and B-hCG higher than 24.4% reported by Kolawole *et al*. [5] in Zaria. In this study, hydatidiform mole occurred more frequently (68.6%) than the malignant forms. This is similar to the finding of Yakasai *et al*. [3] from a previous study in the same centre (67%) and that of Obahiagbon *et al*. [14] from Benin who reported a benign to malignant ratio of 4:1. However, this is contrary to observations in studies by Mbamara *et al*. [4] and Kolawole *et al*. [5] where choriocarcinoma occurred more frequently than hydatidiform mole probably because the peak incidence in these studies was in the 4th decade.

The most commonly performed treatment modality was suction evacuation. This is because majority of the patients had hydatidiform mole and most of those with the malignant disease had prior suction evacuation or MVA on suspicion of miscarriage. This was also the finding in most other studies [11, 15, 16]. Out of the 36 patients that required chemotherapy in this study, only 24 patients had it. Ten patients were discharged against medical advice either due to financial constraint or declining chemotherapy while 2 patients with advanced disease died while being worked up for chemotherapy.

In this study, choriocarcinoma was the commonest indication (44.4%) for chemotherapy, then persistent GTD (38.9%) and Invasive mole (16.7%). This defers from a previous study done by Yakasai *et al*. [3] in the same centre where only cases of choriocarcinoma had chemotherapy likely due to increased awareness on indications for chemotherapy for hydatidiform

mole. 29.2% of patients with hydatidiform mole required chemotherapy, this is much higher than 6.5% reported by Igwegbe *et al*. [16] from South East Nigeria. Additional indications reported by Essel *et al*. from Texas include placental site trophoblastic tumour and intermediate trophoblastic tumour. These tumours were not diagnosed in the patients over the study period. Methotrexate was the only agent used for single agent chemotherapy while MAC and EMA/CO were used for multiple agent regimens respectively. This is contrary to Lertkhachonsuk *et al*. [18] study in x where Actinomycin D was the most frequently used single agent possibly due to relative availability and cost of the drugs. Multiple agent regimens used for salvage chemotherapy include EMA-EP, BEP and ICE [7].

Disease remission was achieved in 83.4% of the patients following chemotherapy. This is similar to 82.6% [18] reported by Lertkhachonsuk *et al*. in Bangkok but lower than 94% remission to initial chemotherapy reported by Al-Hussain *et al*. [10] from Saudi Arabia. However, it falls within the cure rates reported by American Cancer Society of 100% for hydatidiform / low risk GTD and 80-90% for high risk GTD [8]. The average number of courses before undetectable hCG was 3 and 4 courses for single and multiple agent regimens. This is similar to the findings of RattanaburI *et al*. [19] in Thailand who reported 2nd and 4th courses for single and multiple agent regimens respectively. Lybol *et al*. [20] however reported normalization of hCG regression normograms after 3rd and 6th courses for single and multiple agents for patients with high risk GTN in Netherlands. Delattre *et al*. [21] found mean time to normalization of 14-15 weeks after evacuation for complete or partial molar pregnancy in his study in Flanders. Two patients had relapse after cure and 1 died while awaiting recommencement of chemotherapy for relapse after single agent chemotherapy with methotrexate. Gadduci *et al*. [22] reported relapse in 1 case during follow up in his study Italy. Alazzam *et al*. [23] in Ireland recommend use of sequential DAC for 5 days followed by MAC or EMA-CO for methotrexate resistance or recurrent low risk GTN [23]. One patient conceived during follow up and was found to have a normal pregnancy. Wong *et al*. [24] reported resumption of menses in 100% after chemotherapy, similar age of menopause, equivalent conception and live birth rates in his study of reproductive outcomes after multiagent chemotherapy for high risk GTN.

The default rate in this study was found to be 68.5%. This is similar to 60% [11] and 52.6% [15] reported by Nyengidiki *et al*. and Anuma *et al* from South Eastern Nigeria. This is quite high and may be attributed to ignorance, financial constraints, inadequate counselling by the doctors and lack of a call and recall system which are quite common in the developing world like ours. Ayangade O, reported a much lower default rate of 17% [25] in 1979. The observed case fatality rate during the study period was 2.9%. This is similar to 2.4% reported by Kolawole *et al*. [5] in Zaria and lower than 9.7%, [16] 10% [11] and 15.1% [7] reported from South Eastern Nigeria and Texas respectively.

Conclusion

The prevalence of GTD is high. The indications for chemotherapy for gestational trophoblastic disease in this study are choriocarcinoma, persistent GTD and invasive mole. Remission rate following chemotherapy was 83.4%. This falls within the 80-100% range reported by the American cancer society. Relapse and refractory disease occurred in 8.3% of each. The default rate was high (68.5%) and needs to be improved upon. The case fatality rate was 2.9%.

Recommendations

Doctors and other health care providers should provide adequate and continuous counselling to the patients through the various stages of management to improve compliance and follow up. The hospital management through the records department should establish a call and recall system in order to facilitate follow-up. The Federal government should subsidize the cost of serum B-hCG and chemotherapeutic agents as financial constraint serve as major obstacle sto uptake of chemotherapy and follow up.

Limitations

1. Difficulty retrieving case notes from record office and missing folders.
2. The high default rate limited the evaluation of outcome of chemotherapy.
3. Only two thirds of the patients who met the indication for chemotherapy actually had it.

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