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Analyze the Treatment Protocols for Choriocarcinoma Focusing on Chemotherapy Regimens and Their Outcome

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ABSTRACT

Background: The most prevalent type of gestational trophoblastic neoplasia that medical oncologists see is choriocarcinoma. It is an uncommon ailment, and there is little information available about its long-term effects from Pakistan. **Objective:** The main goal of this study was to evaluate the clinical outcomes and clinicopathological features of patients with choriocarcinoma. The secondary goal was to evaluate the relationship between outcomes and risk classification. **Materials and Methods:** The People's University of Medical and Health Sciences for Women, Shaheed Benazirabad, Sindh, served as the site of this single-center study. The study included all individuals between the ages of 18 and 70 who had been diagnosed with choriocarcinoma, either by histological diagnosis, serum beta human chorionic gonadotropin [HCG] levels, radiological image, or a combination of clinical characteristics. Patients who did not receive treatment but merely came to the hospital for an opinion were not included. We next took note of the patients' baseline features, treatment information, and clinical results. Baseline variables were analyzed using descriptive statistics, and the survival analysis was conducted using the Kaplan–Meier technique. **Results:** The study had a total of 24 patients. The patients were 29 years old on average. Eight individuals had low WHO risk scores (33.3%), while sixteen patients had high WHO risk scores (66.7%). Six patients (25 percent) received single-agent chemotherapy, 14 patients (66.7 percent) received the EMA-CO regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine), and one patient (4.7 percent) received the VIP regimen (etoposide, ifosfamide, and cisplatin). Only high-risk patients were administered the latter two regimens. **Conclusion:** In conclusion, our research supports the notion that choriocarcinoma is a very curable disease and offers real-world evidence for this uncommon cancer. The long-term results are positive in spite of the clinicopathological differences across the nation.

INTRODUCTION

One type of malignant gestational trophoblastic neoplasia is choriocarcinoma. Between 1 in 19,000 and 1 in 24,000 people are affected in the United States.[1] As the mother becomes older, the incidence rises. In addition, there are notable ethnic disparities, with African Americans and Asians having greater incidences than Caucasians and non-Asians, respectively.[2] According to reports, the 5-year survival rate for choriocarcinoma is approximately 90%.[2] Older people with severe disease and African Americans have poorer survival rates. HCG is high in invasive moles and choriocarcinomas, and the response to chemotherapy is suitable; however, HCG is low in PSTT and ETT, and greater chemotherapy resistance is seen.[3] The International Federation of Gynecology and Obstetrics (FIGO) staging system and the more widely used World Health Organization (WHO) risk stratification are the two staging methods used for choriocarcinoma prognostication.[3] FIGO only classifies gestational choriocarcinoma and invasive moles as GTN.[4] The location of metastases determines the classification of gestational trophoblastic tumors. Patients in Stage I only have uterine illness; in Stage II, it travels outside the uterus but only affects genital structures; in Stage III, it spreads to the lungs; and in Stage IV, it has moved to other distant locations. While Stage 4 and scores above 7 in Stages 2 and 3 are categorized as high risk 4, Stage 1 and scores below 7 in Stages 2 and 3 are classified as low risk. FIGO has assigned Stages 2-3 ratings according to the following criteria: age, kind of prior pregnancy, period between the disease and prior pregnancy, quantity and location of metastases, and type of prior chemotherapy.[5]

The WHO classification divides patients into low risk (score <7) and high risk (score ≥7) groups based on the likelihood of medication resistance. Single-agent regimens such as methotrexate or actinomycin D are used to treat low-risk patients.[6] Compared to actinomycin D, methotrexate has been linked to a considerably higher rate of treatment failure. In high-risk instances, on the other hand, the most successful treatment is multi-agent chemotherapy, such as EMA-CO (etoposide, methotrexate, actinomycin D-cyclophosphamide, and vincristine) or EMA-EP (etoposide, methotrexate, actinomycin D-etoposide, and cisplatin).[7] According to reports, 86% of patients who receive multi-agent chemotherapy survive for five years.[8] The results of choriocarcinoma have not been extensively studied. A retrospective analysis of 128 choriocarcinoma patients was reported by Bafna et al., but no patients had long-term survival.[9] According to a different study by Gulia et al., at a median follow-up of 16.6 months, overall survival (OS) was 100% in the low-risk group and 88.8% in the high-risk group.[10] Hussain et al. conducted another retrospective analysis that documented the clinicopathological characteristics of choriocarcinoma patients, but not their survival information.[11]

The majority of the evidence is based on retrospective data because the disease is so uncommon. Furthermore, there is no information about choriocarcinoma from Pakistan. Therefore, we share our institutional experience and choriocarcinoma patient survival results.

METHODOLOGY

From July 2024 to December 2024, this case series study was carried out at the People's University of Medical and Health Sciences for Women, Shaheed Benazirabad, Sindh. Every patient with a choriocarcinoma diagnosis who was treated there was included. According to our institutional protocol, a waiver of the requirement to seek informed consent was granted because this study was descriptive. The study was carried out in compliance with ethical standards.

The study included all individuals between the ages of 18 and 70 who had been diagnosed with choriocarcinoma, either by histological diagnosis, serum beta human chorionic gonadotropin [HCG] levels, radiological image, or a combination of clinical characteristics. Patients who did not receive treatment but merely came to the hospital for an opinion were not included. The study also excluded patients without follow-up data for longer than three months after treatment. The study's main goal was to evaluate the clinicopathological characteristics and prognoses of choriocarcinoma patients. Evaluating the relationship between outcomes and the various risk groups was the secondary goal.

The patients were categorized into high- and low-risk groups according to WHO risk stratification, based on their age, prior pregnancy interval in months, pre-treatment serum hCG levels, largest tumor size in centimeters, locations and quantity of metastases, and number of previous unsuccessful chemotherapy regimens. Individuals who scored between 0 and 6 were thought to be at little risk of developing resistance to treatment with just one drug. Combination treatment was administered to those who scored ≥7 because they were deemed to be at a high risk of developing resistance to single-agent chemotherapy. A full response was defined as beta(β)-hCG normalization. Progressive illness was defined as a rise in β-hCG in two or more consecutive samples. The time between the initiation of chemotherapy and the advancement of the disease was known as the progression-free survival (PFS), and the time between the initiation of chemotherapy and death from any cause was known as the OS.

The study encompassed all consecutive patients diagnosed with choriocarcinoma at our hospital or referred from other centers after initial treatment. All patients underwent radiological imaging, and their serum β-hCG levels along with other routine organ function measures were assessed. The WHO risk stratification score was used to put patients into groups based on how likely they were to get sick. Patients in the high-risk group were treated with EMA-CO, EMA-EP, or VIP (etoposide, ifosfamide, and cisplatin) regimens, while those in the low-risk group received methotrexate or actinomycin D. If clinically necessary, surgery was taken into consideration. The hospital's electronic medical records included information about the patients' clinicopathological traits, the treatments they received, and their results. Baseline demographic data were recorded, encompassing age, site and number of metastases, baseline β-hCG level, treatment interval since the last pregnancy, type of last pregnancy, chemotherapy regimen type and line, clinical and serological response, date of progression and date of death (if applicable), and status at the last follow-up.

The data was analyzed using SPSS 25. Clinical features and demographics were analyzed using descriptive statistics. Baseline demographics, clinical features, and treatment factors were expressed as absolute values and percentages. The degree of correlation between variables was examined using Pearson's correlation coefficient. The threshold for statistical significance was $P < 0.05$.

RESULTS

The analysis comprised 24 patients in total. The patients ranged in age from 19 to 53, with a median age of 29. Table 1 lists the symptoms that are currently present. Those with headaches at baseline had their brains imaged using magnetic resonance imaging. In 16 (66.5%) of the patients, a histopathological diagnosis was established. Abortions accounted for 12 (50%) of the antecedent pregnancies, with molar and term pregnancies following in 8 (33.3%) and 4 (16.7%) of the cases, respectively. At presentation, the median β-hCG level was 101030.5 IU/L (range: 5.67–1431800). Seventeen patients (70.8%) had distant metastases. Three metastases were the median (range: 0–13). Fourteen patients (82%) had metastases to the lung, while five patients (29.4%) had metastases to the brain. Eight patients (33.3%) had undergone chemotherapy prior to their arrival at our facility. The WHO risk stratification score indicated that 16 patients (66.67%) were at high risk. Six (25%) of the patients at our center were treated with single-agent chemotherapy, fourteen (66.7%) were treated with the EMA-CO regimen, and one (4.7%) was treated with the VIP regimen as a second-line treatment. In 19 (90.5%) patients, a dosage

intensity of 100% was maintained.

Six (28.5%) individuals experienced Grade 3 neutropenia, the most frequently reported hazard [Table 1]. No one died as a result of treatment.

Ten (66.6%) of the fifteen patients treated in the high-risk group experienced complete remission, whereas all of the patients in the low-risk group experienced a complete response. Following their visit to our facility, none of the patients had any cancer-directed surgeries. 4.9 months was the median follow-up period. Numerically, the low-risk group's PFS was superior than the high-risk group's (P = 0.14). Likewise, the low-risk group's OS outperformed the high-risk group quantitatively (P = 0.29).

Table 1

Distribution of Different Variables (n=24)

Variable		Frequency	%age
Presenting symptoms	Bleeding per vagina	19	79.17
	Abdominal pain	04	16.67
	Hemoptysis	06	25.0
	Dyspnea	02	8.33
	Headache	02	4.17
	Seizures	01	8.33
Histopathological confirmation	Yes	16	66.67
	No	08	33.33
Previously failed chemotherapy	Yes	08	33.33
	No	16	66.67
FIGO stage	1	06	25.0
	2	01	4.17
	3	07	29.17
	4	10	41.67
WHO risk category	Low	08	33.33
	High	16	66.67
Toxicity	Grade 3 neutropenia	06	25.0
	Grade 3 thrombocytopenia	02	4.17
	Grade 3 diarrhea	01	8.33

DISCUSSION

Nearly 70% of the choriocarcinoma patients in our study were classified as high-risk. Our patients' baseline β-hCG levels were higher than those found in other research. In our trial, every low-risk patient experienced a full remission. At a median follow-up of 4.9 months, our trial did not attain the median survival, either PFS or OS. The rates of toxicity associated with chemotherapy were similar to those documented in the literature.

Since choriocarcinoma is an uncommon condition, the majority of the information that is currently accessible comes from retrospective analyses. Gulia et al.[10] carried out the largest study on choriocarcinoma in India, which involved 70 patients. About 70% of the patients in this trial were low-risk, while 30% were high-risk. The ratio of patients at low and high risk was inverted in our study. This may be because the two hospitals' referral patterns differ, with our center receiving more patients with pretreated cases and advanced disease. In Gulia et al.'s work, the median baseline β-hCG level was 50000 IU/L; whereas, in our investigation, it was approximately 100000 IU/ml. This is perhaps because our study included a larger percentage of high-risk subjects. The most frequent metastatic site in our study (82%) was the lung. Other studies have also reported this.[10-12] Abortion was the most frequent antecedent pregnancy event in our analysis. This contrasts with findings from previous research, where the most frequent occurrence was molar pregnancy.[12] What caused this discrepancy is unknown to us. The 5-month median period since the last pregnancy was comparable to what other research had shown.[10-12]

Every patient in the low-risk group experienced total remission. The lack of progressive sickness and the small number of events prevented a formal comparison between individuals who got methotrexate and those who received actinomycin D. Single-agent chemotherapy has demonstrated response rates of roughly 80% in other, larger studies. In our study, a large percentage of responses were complete. Eleven (81%) of the 14 patients in the high-risk group who got the EMA-CO regimen experienced a full remission. Since she had already undergone treatment with the EMA-CO and EMA-EP regimens, one of the high-risk patients was given the VIP regimen. Thankfully, the treatment had an effect on her. Our patients' EMA-CO response rate was about 80%, which is comparable to other research' findings.[8-14]

According to a related study[15], the rate of full response to methotrexate monotherapy was 81%, whereas the rate for actinomycin as a supplementary treatment was 75%. Overall, 94% of patients responded to monotherapy, whereas 6% required surgery or combined therapy. Higher BHCG levels, metastasis[15], choriocarcinoma occurrence, and a high FIGO score were all linked to resistance to first methotrexate treatment.[15] About 30% of patients did not respond to the initial chemotherapy regimen, according to a parallel study. Additionally, GTN patients did not respond appropriately to treatment following adjustments in the chemotherapy regimen, particularly in higher stages.[16]

The total response to treatment was 93.7% in another research that lasted 30 years. In particular, the response rate was higher in phases 3 and 4, with a 98.1% response to treatment during the second 15 years of the research and an 83.4% response during the first 15 years. In the first 15 years of research[17], the tumor recurrence rate was 2.7%, and in the second 15 years, it was 3.6%. The complete and appropriate response rate was found to be 71.1% in a parallel study[18] conducted in 2018 that treated 135 low-risk GTN patients after molar pregnancy with actinomycin in a pulse every two weeks. Additionally, it was determined that there was a correlation between appropriate response to treatment and drug resistance to actinomycin and the presence of an invasion to the uterus in the ultrasound prior to chemotherapy, FIGO scores greater than or equal to 5, and BHCG levels above 4000IU/L.

Our toxicity rates were similar to those found in other research that has been published.[19,20] None of the patients experienced febrile neutropenia, despite the fact that 30% of patients who received multi-agent chemotherapy (EMA-CO) experienced Grade 3 neutropenia. Less than 10% of the patients had diarrhea or mucositis, two other typical toxicities. In susceptible patients, primary growth factor prophylaxis could easily reduce the high risk of Grade 3 neutropenia.

Our study has certain limitations. This was a single-center analysis, to start. Secondly, we had a tiny sample size. However, due to the rarity of choriocarcinomas, the majority of published retrospective research on the subject have tiny sample sizes. Third, for a small number of patients, we lacked long-term data. Lastly, we were

unable to record all of the patients' specific effects.

All things considered, our research shows that our findings are consistent with those found in the published literature. Our research contributes to the body of knowledge regarding the consequences of this uncommon illness in Pakistan. Retrospective audits provide the majority of the information on a rare disease like choriocarcinoma. Our analysis is significant because of this. Well-planned prospective research, involving multi-centric conglomerate data exchange, are necessary in the future, though.

The study's main conclusions are that choriocarcinoma is a very curable disease with a high cure rate. Our patients should be accurately risk stratified because they have a significant disease burden when they first arrive. Pembrolizumab and cell-based antibody targets are two other recent medications that might provide some promise for the treatment of refractory cases.[20]

CONCLUSION

Our findings support the notion that choriocarcinoma is a highly treatable condition. Long-term results are positive despite the nation's clinicopathological differences. Developing efficient treatment strategies for individuals who are drug resistant is one of the biggest challenges of the future. New drugs, targeted molecular therapies, and developments in anti-angiogenesis therapy may all help these individuals respond better to treatment.

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