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Is chemotherapy always necessary for patients with nonmetastatic gestational trophoblastic neoplasia with histopathological diagnosis of choriocarcinoma?

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HIGHLIGHTS

- 90% with nonmetastatic choriocarcinoma and elevated hCG needed chemotherapy.
- 8% with nonmetastatic choriocarcinoma and normal or falling hCG needed chemotherapy.
- All patients treated with immediate or delayed chemotherapy were cured.

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ABSTRACT

Objective. To evaluate expectant management versus immediate chemotherapy following pathological diagnosis of gestational choriocarcinoma (GCC) in patients with nonmetastatic disease.

Methods. Multicenter retrospective cohort that included patients with histological diagnosis of GCC with nonmetastatic disease followed at one of thirteen Brazilian referral centers for gestational trophoblastic disease from January 2000 to December 2016.

Results. Among 3191 patients with gestational trophoblastic neoplasia, 199 patients with nonmetastatic GCC were identified. Chemotherapy was initiated immediately in 152 (76.4%) patients per FIGO 2000 guideline, while 47 (23.6%) were managed expectantly. Both groups presented with similar characteristics and outcomes. All patients ($n = 12$) who had normal human chorionic gonadotropin (hCG) in the first 2–3 weeks of expectant management achieved complete sustained remission with no chemotherapy. Only 44.7% (21 patients) of patients who were expectantly managed needed to receive chemotherapy due to plateauing or rising hCG level in the first 2–3 weeks of follow up. The outcome of patients receiving chemotherapy after initial expectant

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management was similar to those who received chemotherapy immediately after the diagnosis in terms of need for multi-agent chemotherapy or number of cycles of chemotherapy. There was no case of relapse or death in either group. Logistic regression analysis showed that age ≥ 40 years and hCG ≥ 92,428 IU/L at GCC diagnosis were risk factors for needing chemotherapy after initial expectant management of nonmetastatic GCC.

Conclusion. In order to avoid exposing patients unnecessarily to chemotherapy, close surveillance of women with pathological diagnosis of nonmetastatic GCC seems to be a safe practice, particularly for those who have a normal hCG at the time of diagnosis. If confirmed by other studies, the FIGO guidelines may need to be revised.

1. Introduction

Choriocarcinoma is a highly aggressive malignancy with a potential to produce early metastasis [1]. Although it rarely presents as a gonadal or non-gonadal germ-cell tumor (either pure or as part of a mixed germ cell tumor), the most common presentation of a choriocarcinoma is when it arises from a pregnancy. These pregnancy events are not only molar pregnancies, but can also arise after abortions, ectopic pregnancies and term or pre-term deliveries [2]. The incidence of gestational choriocarcinoma (GCC) has been estimated to be 1:40,000–50,000 pregnancies, and 1:40 hydatidiform mole cases [3,4]. Even though GCC presents with extremely invasive behavior, over 90% of patients are cured by treatment, since this malignancy is highly sensitive to chemotherapy and exhibits a very reliable tumor marker – human chorionic gonadotropin (hCG) – which allows proper treatment monitoring [5].

In Brazil, despite many difficulties, patients with GCC receive care, generally, in one of the 44 Brazilian referral centers for gestational trophoblastic disease (BRCGTD), spread throughout this country of continental dimensions [6–8]. Since 2000, the BRCGTD have adopted the criteria established by the International Federation of Gynecology and Obstetrics (FIGO) for the diagnosis and treatment of postmolar gestational trophoblastic neoplasia (GTN): rising (>10%) hCG levels for three consecutive weeks or plateaued for four weeks, if there is a histological diagnosis of choriocarcinoma, or when the hCG level remains elevated for 6 months or more following uterine evacuation of a molar pregnancy [9].

The most common criteria for the start of chemotherapy for GTN are hCG plateau or rise in hCG values [10]. However, there is controversy as to whether chemotherapy should be initiated for patients with molar pregnancy whose hCG levels are raised but falling beyond the 6 months after uterine evacuation, since spontaneous remission will occur in most cases without treatment [10,11]. While there is no controversy to initiate chemotherapy for patients who present with metastatic GCC and an elevated hCG, some patients with pathological diagnosis of GCC are referred to the BRCGTD with normal hCG values and no evidence of metastasis. This finding is particularly challenging. Although these women meet histological diagnostic criteria to initiate chemotherapy for GTN, they have normal tumor marker levels and no evidence of disease [9]. The choice to treat these patients could be viewed as an over-treatment, since they do not show signs of active disease. Several small reports describing expectant management of patients with close clinical and hCG surveillance suggest that women with surgically evacuated choriocarcinoma may enter remission without receiving chemotherapy [12–20].

However, caution must be taken before dismissing this FIGO recommendation since postponing the chemotherapy in these patients with GCC could worsen GTN prognosis, due to the potential development of tumor mutations and consequent chemoresistance [7,11]. Furthermore, delayed treatment could also lead to more advanced disease and increase the FIGO prognostic risk scoring for these patients, which could potentially result in treatment with more aggressive and toxic multiagent chemotherapy [9,11,21].

This study aimed to investigate whether it is safe to monitor patients with nonmetastatic GCC without promptly initiating chemotherapy. The outcomes of Brazilian women with nonmetastatic GCC that received chemotherapy immediately after the diagnosis according to FIGO's recommendation [9] were compared to those of women who were expectantly managed with rigorous clinical and hormonal monitoring, without immediate start of chemotherapy.

2. Material and methods

2.1. Study design

This is a retrospective cohort study of patients with GTN followed at one of thirteen BRCGTD: in Rio de Janeiro (Maternity School of Rio de Janeiro Federal University, Antonio Pedro University Hospital of Fluminense Federal University, Maternity Ward of Santa Casa da Misericórdia do Rio de Janeiro – data entered by AB and audited by VC), in Sao Paulo (São Paulo Clinical Hospital of University of Sao Paulo and Sao Paulo Hospital of Sao Paulo Federal University – data entered by LHL and SYS and audited by VC), in Ribeirão Preto (Clinics Hospital of Ribeirão Preto – data entered by CBS and audited by VC), in Porto Velho (Ary Pinheiro Hospital of Base – data entered by RCAFS and audited by VC), in Rio Branco (in Clinics Hospital of Acre – data entered by EASL and audited by VC), in Santos (Guilherme Álvaro Hospital – data entered by ES and audited by VC), in Botucatu (Clinical Hospital of Sao Paulo State University – data entered by IM and audited by VC), in Caxias do Sul (General Hospital of Caxias do Sul – data entered by JMM and audited by VC), in Porto Alegre (Mario Totta Maternity Ward at Irmandade da Santa Casa de Misericórdia Hospital – data entered by EHU and audited by VC) and in Goiania (Clinical Hospital of Goias Federal University – data entered by MV and audited by VC), and from January 2000 to December 2016.

This study was approved by the local Institutional Review Board of the Maternity School of the Federal University of Rio de Janeiro, associated with the Brazilian Research Ethics Committee, under protocol number 572,887 (CAAE 23129813.0.1001.5275).

2.2. Study participants

Patients had a histological diagnosis of choriocarcinoma, associated with a pregnancy, without prior chemotherapy treatment for GTN and were followed at one of the above-mentioned centers during the study period. All pathological specimens were obtained by second curettage among patients with prior hydatidiform mole, by salpingectomy among patients with GCC diagnosed in association with ectopic pregnancy and by curettage among patients with postpartum abnormal uterine bleeding associated with an elevated hCG. All patients included in this study adhered to GTN follow-up and had complete medical records available for review.

All patients' pathological specimens were reviewed by an experienced pathologist affiliated with a BRCGTD. Immunohistochemistry aided the diagnosis in difficult cases. Patients with metastatic disease (47 patients) and with mixed choriocarcinoma and placental site trophoblastic tumor (1 patient) were not included in this study.

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